Capsular Types and Predicting Patient Outcomes in Pneumococcal Bacteremia

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(See the article by Alane et al. on pages 46–51)

In the 1910s, Dochez and Avery [1] made a number of observations that formed the basis for the scientific bridge between the pneumococcus world and the carbohydrate world. They reported the presence of a type-specific soluble substance in filtrates of pneumococcal cultures and in serum and urine specimens obtained from infected humans and rabbits. The specific soluble substances turned out to be type-specific capsular polysaccharides [2]. Of high importance was the antigenicity of these polysaccharides—a finding that paved the way for the use of pneumococcal polysaccharides as vaccines. It has been said that the capsules of the pneumococcus were the first nonprotein substances that were shown to be antigenic to humans [3].

The polysaccharide capsule, a highly hydrated shell around the bacterium, modulates the passage of molecules and ions to the bacterium cell envelope, the adherence of the bacterium to biological and inorganic surfaces, and the formation of biofilms and microcolonies [4]. At present, 92 immunologically distinct polysaccharide types have been described in the literature [5]. They are distinguished by chemical differences in their capsular polysaccharides and, in turn, on the ability of the immune system of rabbits to recognize these structural differences and to respond with specific antibodies against the antigens of each different type. The polysaccharide capsule represents the major virulence determinant of Streptococcus pneumoniae. It permits the bacteria to resist phagocytosis, and opsonizing antibodies to capsular polysaccharide are protective against invasive disease. Different serotypes exhibit variations in resistance to phagocytosis [6], in activation of the alternative pathway of complement [7], in deposition and degradation of complement fragment of C3b [8], and in penetration into tissues. Variations in the frequency of the capsular types over time, geographic areas, different types of infection, and age groups remain unexplained [9, 10].

Many studies have explored the relationship among serotypes and mortality in invasive pneumococcal disease. In the often-cited study by Austrian and Gold [11], the authors correlated the serotype, age, presence of preexisting illness, and extent of pulmonary consolidation with mortality in bacteremic pneumococcal infection. Mortality due to infection with different capsular types was shown to have considerable variation. The fatality rate for type 1 pneumococcal bacteremia was 8%, whereas it was 55% for type 3 infection. The rate of mortality due to infection with other capsular types seen in significant numbers was in the range of 15%–25%. Even when adjustments were made for age, the mortality after infection with pneumococcus type 3 was several-fold higher than that for infection with any other pneumococcal type. However, among serotype 3–infected patients, the deaths were concentrated among older patients with comorbidities; thus, 72% of deaths in this group involved persons aged >50 years and patients with preexisting illness. However, no special predilection for any specific capsular type was observed among patients with comorbidities, suggesting that both the serotype and the host played a role in the fatal outcome.

In the 1990s, the remarkable differences in the case-fatality rates among patients with bacteremic pneumococcal pneumonia at different health care centers in Huntington, West Virginia, and Stockholm, Sweden (26% vs. 5%) [12] stimulated researchers to conduct additional studies to elucidate the reasons for these differences in outcome. A multicenter study was performed during 1993–1995 to prospectively investigate the influence of several prognostic factors for predicting the risk of death among patients with pneumococcal bacteremia [9]. Five health
care centers from 5 different countries participated. The study revealed a possible reason for the differences noted in case-fatality rates between countries: the non-equal spread of certain clones/serotypes in the countries. Higher case-fatality rates were observed for infections caused by serotypes 3, 6B, and 19F than for infections caused by other serotypes. The higher case-fatality rate for type 3, compared with type 14, was in concordance with the results of previous studies [10, 13, 14]; this difference could be a contributing factor to the higher mortality rate found in Spain and the United States, where type 3 was the most common serotype, compared with Sweden, where type 14 was the most common serotype.

In the same vein, in their retrospective review of 464 adult patients with invasive disease, Martens et al. [15] also found a correlation between serotype 3 infection and a higher mortality rate, after adjusting for age, comorbidity, alcoholism, temperature, and leukocyte count. More recently, Sjöström et al. [16] suggested that clones with capsular types 1 and 7F, which are known to have high invasive potential, behave as primary pathogens and are associated with lower mortality, whereas clones with other capsular types that have a lower relative risk of causing invasive disease (serotypes 3, 6A, 6B, 8, 19F, and 23) are more opportunistic, primarily affect patients with underlying disease, and were associated with more-severe disease and significant mortality [16]. Thus, there is mounting evidence that capsular types are not only the main virulence factor for invasive disease, but that the severity of disease and mortality also involve capsular types. The evidence to have been generated thus far seems to indicate that serotype 3 (and perhaps serotypes 6B and 19) may be an independent predictor of increased mortality in certain populations, although this finding has not been consistently found across all studies.

In this issue of Clinical Infectious Diseases, Alanee et al. [17] evaluated the risk factors for increased disease severity and mortality in adults with invasive pneumococcal disease, including patient-related variables and bacterial serotypes. To this end, they analyzed data collected from a prospective, international, large-scale study of adult patients with pneumococcal bacteremia. The study’s end point was mortality at 14 days after the first blood culture positive for S. pneumoniae was obtained. Three different comparisons of the severity of illness and mortality were performed, and each was defined on the basis of vaccine serotype. Three different groups of serotypes were considered: “invasive” serotypes (serogroups 1, 5, and 7), “pediatric” serotypes (serogroups 6, 9, 14, 19, and 23) and “conjugate vaccine serotypes” (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F). The authors were very careful in adjusting for the important variables that are known to be risk factors for increased mortality (namely, older age, the presence of comorbidities, immunosuppression, and severity of disease). The results were astounding: no significant association was found between the predefined groups of pneumococcal serotypes and invasive pneumococcal disease-related mortality. The independent risk factors that predicted increased mortality were older age (age, ≥65 years), the presence of comorbidities, immunosuppression, and severity of illness; these findings were concordant with the findings of previous studies that emphasized the importance of host factors in predicting the outcome of invasive pneumococcal disease.

Although it is clear that host factors are critical in determining the outcome of invasive pneumococcal disease, blurring any specific impact of a given serotype, it is also becoming clear that there are circumstances in which the weight lies on the bacterium. This is best exemplified in the young adult without comorbidities in whom the infecting serotype becomes the determinator factor of outcome.

The relationship between serotype and genome is complex and not well understood. Pneumococcal mutants that differ only in the type of capsular polysaccharide expressed have been constructed [18]. The virulence of the mutants in relation to the parental strain was shown to be determined mainly by the capsular type. However, the genetic background of the recipient strains was also of considerable importance, showing that other components besides the capsule are required for full virulence of pneumococci. Thus, for each serotype a distinct set of genetic requirements may be required to cause invasive pneumococcal disease. Molecular typing has refined these observations, determining that within invasive serotypes, invasive and noninvasive clones exist [19, 20]. Thus, the propensity of an isolate to cause invasive disease and increased severity is dependent on its serotype and its genomic content.

In fact, many other elements must be taken into account. It is well known that cell wall components are able to induce an inflammatory response several-fold more potent than that of the capsule [21], and the virulence of pneumolysin [22], neuraminidase, and autolysin has been described as important [23]. Perhaps more pertinent to this discussion is the recent description of pilus-like structures in S. pneumoniae that project from the bacterial cell surface [24]. The pilus is encoded by the rlrA pilus islet [25] and is found in some—but not all—pneumococcal strains. In capsulated pneumococci, pil contribute to adhesion, colonization, and invasion in murine models of infection. Of considerable interest is the fact that pili expression also augments the host’s inflammatory response. Thus, strains that lack pili (i.e., strains that belong to clones of serotypes 1 and 7F) are rarely found in healthy carriers, but they may cause invasive disease of a relatively mild character. In contrast, rlrA-positive pneumococcal strains of type 4 and 19F elicit a high cytokine response. In other words, presence or absence of the pneumococcal pilus may have a profound effect on the severity of disease.

The interplay of the different virulence factors described here and how they work
in concert to cause lung injury and invasion are complex. It has been suggested that virulence factors may be divided into 2 separate groups: one consists of factors present on the surface of intact pneumococci that seem to act at the beginning of the infection, mainly by impeding phagocytosis via complement inhibition; and the second consists of factors that act at the stage of pneumococcal disintegration and lysis. At this stage, complement activation enhances the inflammation. Perhaps capsular polysaccharides are the main virulence determinants that govern initial lung injury and bloodstream invasion. Beyond this point, other virulence factors that generate an inflammatory response will be responsible for the severity of disease and the final outcome. In the study reported by Alane et al. [17], the common denominator of the group was the presence of bacteremia. It appears that, at this stage of infection, the importance of the different serotypes is no longer predictive of mortality, and other virulence factors and host response become critical.

To conclude, host factors—and, more specifically, the intrinsic relationship between the innate immune system and the pathogen—are critical in the explanation of early mortality in invasive pneumococcal disease. It remains to be elucidated to what extent the significant differences in invasive disease potential and severity of disease for different serotypes should be attributed to the capsular type, to the clonal type, or to both. The study of the recently described pathogenicity islands within different clonal types and different serotypes should provide new information regarding the genetic properties of pneumococci that are important for invasive disease severity [16]. Despite its intensive study for more than a century, more continues to be learned about pneumococcal disease.

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References