The Continuing Challenge of Lower Respiratory Tract Infections

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The discovery and clinical application of antibiotics has markedly changed the management of a wide variety of respiratory tract infections, including community-acquired pneumonia (CAP), during the past half-century. However, despite earlier predictions, these infections have not disappeared as significant clinical problems, and lower respiratory tract infections continue to take a major toll in terms of morbidity and mortality throughout the world.

One of the factors that could account for the persistence of problematic respiratory tract infections is the development of resistance to antimicrobial agents by a number of respiratory tract pathogens, most prominently *Streptococcus pneumoniae*. To monitor the development of antimicrobial resistance, a large number of bacterial surveillance studies have been undertaken in the past decade, some conducted by federal and state agencies, but the majority privately sponsored. These studies are fairly consistent in demonstrating a worldwide increase in resistance to antimicrobial agents (especially the β-lactams and macrolides and, to a lesser degree, the tetracyclines and fluoroquinolones) among pneumococci. Given this fact, it is somewhat surprising that there appears to be considerable difficulty in identifying patients with CAP caused by pneumococci resistant to β-lactams and/or macrolides in phase II and phase III clinical trials of new antimicrobial agents. There are a number of plausible explanations for this phenomenon, including the possibility that current surveillance studies overestimate the prevalence of antibiotic resistance among pneumococci. It is also possible that the prevalence of pneumococcal pneumonia is decreasing, perhaps in partial response to immunization programs or to other unknown factors. Finally, in vitro resistance may not always predict antimicrobial failure against *S. pneumoniae* when it causes respiratory tract infections.

As noted above, numerous surveillance studies have addressed the topic of resistance to β-lactams, macrolides, and other antimicrobial agents in *S. pneumoniae* during the past decades. On the basis of these studies, there appears to be an ongoing worldwide increase in resistance among pneumococci. A recent study by Lynch and Martinez [1] documented a significant increase in resistance to macrolides among pneumococci from a variety of European countries and Hong Kong. A separate study from the United States demonstrated that much of the increase in macrolide resistance among pneumococci is seen in isolates obtained from young children, as opposed to those obtained from adults [2]. These findings are consistent with known patterns of antimicrobial use in outpatients.

Historically, *S. pneumoniae* has been considered the most frequent cause of CAP in adults. Studies in the 1960s and 1970s regularly demonstrated that pneumococci could be isolated from appropriate specimens from 60%–75% of adults admitted to the hospital with CAP [3]. More recently, however, the frequency of CAP due to pneumococci among such patients has apparently been decreasing. For instance, in 1989, Marrie et al. [4] isolated pneumococci from 8% of their patients with CAP in a rigorous study in Nova Scotia, whereas in Berlin, Steinhoff and Lode [5] found pneumococci as the etiologic agent in only 12.7% of patients hospitalized because of CAP. Whether there has truly been a decrease in the overall incidence of CAP due to pneumococci (compared with lower respiratory tract disease due to atypical pathogens, including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*) remains to be determined. It is possible that the apparent decrease found in the studies cited above is simply due to chance or regional variation. Of note, however, it is very difficult to document patients with pneumonia due to penicillin-resistant pneumococci who have truly experienced treatment failure with appropriate dosage of β-lactams (i.e., patients with cultures that yield persistently positive results during or after therapy). There are studies that
have shown patients died because of infection with penicillin-resistant pneumococci \[6\], but, even in these studies, the authors do not demonstrate persistence of viable bacteria during or after treatment.

It is also recognized that the mortality rate among patients with documented pneumococcal pneumonia is not influenced by receipt of antibiotic therapy during the first 4–5 days of treatment \[7\]. Indeed, this observation forms one of the bases for recommendations for the widespread use of pneumococcal vaccines. Reported cases of antibiotic treatment failure in patients infected with macrolide-resistant pneumococci are relatively common, but the recent study by Lonks et al. \[8\] clearly suggests that there is a significant treatment failure rate among patients treated with macrolides who have pneumococcal bacteremia due to macrolide-resistant organisms. Unfortunately, the retrospective design of this study does not allow the reader to determine whether any (or how many) of the patients infected with a macrolide-resistant \emph{S. pneumoniae} strain may have responded to macrolide therapy despite the resistance of the infecting strain.

A recent publication by Wester et al. \[9\] raises some interesting questions about the identification of pneumococci in surveillance studies. When they used standard criteria (optochin susceptibility and bile solubility) to identify pneumococci and then confirmed this identification with DNA probes, 70% of the organisms identified from their study of \emph{S. pneumoniae} oropharyngeal colonization were not pneumococci (presumably they were \emph{S. mitis} and other viridans streptococci). Moreover, they demonstrated that the prevalence of resistance to penicillin, macrolides, and other antimicrobial agents was much lower among the true pneumococci than among the viridans streptococci misidentified as pneumococci in this study.

Given these observations, I examined the methods used to identify pneumococci in 15 recent surveillance studies \[2, 10–23\]. The majority of these studies relied on optochin susceptibility and bile solubility testing alone to identify pneumococci. Serotyping was used in 2 of the studies \[2, 12\], and it was possibly used in another study, although the methods used were not stated \[11\]. PCR identification of pneumolysin was used to confirm the identity of the pneumococcal isolates in a fourth study \[23\]. Thus, in a number of these studies, it is possible that misidentification of viridans streptococci as pneumococci could account for a false elevation in the prevalence of resistance to the antimicrobial agents noted.

Whether this is a significant problem in surveillance studies is not clear at this point. It would be relatively simple to repeat identification by means of molecular methods for a subsample of isolates in these studies to verify whether there is a significant methodological problem. The magnitude of this problem may not be nearly as great as suggested by Wester et al. \[9\]. In a study in which a subset of isolates from the Tracking Resistance in the United States Today (TRUST) study were serotyped \[24\], >90% of these isolates could be serotyped with standard antisera, suggesting that they were indeed pneumococci. Nonetheless, it seems prudent to again address the issue of accurate identification of pneumococci in large-scale surveillance studies.

Clearly, resistance to antimicrobial agents has increased significantly among pneumococci in the past decades. The exact clinical implications of these findings remain to be determined. Even so, the perception that resistance is present is important, because it clearly drives therapeutic decisions by clinicians. These and a number of the important issues relating to antimicrobial resistance among pneumococci are addressed in detail in this supplement.

References


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