The Clinical Relevance of Penicillin-Resistant *Streptococcus pneumoniae*: A New Perspective

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(See the article by Tleyjeh et al. on pages 788–97)

*Streptococcus pneumoniae* remains the most commonly identified cause of community-acquired pneumonia (CAP), despite the emergence of newly identified pathogens. It accounts for approximately two-thirds of cases in which an etiological diagnosis has been made, as well as for two-thirds of the cases of bacteremia [1]. It is paramount, therefore, that empirical therapy for CAP be optimal for *S. pneumoniae*. The approach to empirical therapy for CAP has changed over the past decade because of the emergence of strains of *S. pneumoniae* that are resistant to penicillin and other antimicrobials. However, the relevance of penicillin-resistant *S. pneumoniae* in relation to the clinical outcome of CAP is controversial.

Historically, clinicians prescribed penicillin for empirical treatment of *S. pneumoniae* infection with little concern about the susceptibility of the pneumococcus to the chosen antimicrobial. However, a sharp increase in the prevalence of penicillin-resistant *S. pneumoniae* occurred in the United States in the early 1990s. The results of antimicrobial surveillance studies demonstrated that the prevalence of penicillin-nonsusceptible *S. pneumoniae* (PNSP) in the United States was ~18% in 1990–1991 and was almost 34% by 2003 [2]. “High-level” penicillin resistance (MIC of penicillin, ≥2.0 μg/mL) among *S. pneumoniae* has increased to a greater degree during the past 10 years than has intermediate resistance (MIC, 0.12–1.0 μg/mL). Most (71%) PNSP strains in the United States are caused by 8 different serotypes, and the dominant factor associated with PNSP in the United States has been the human-to-human spread of a few clonal groups [3].

Despite the decreasing susceptibility of pneumococci to penicillin, convincing evidence that resistance has an adverse effect on clinical outcomes, particularly mortality, is lacking. This was illustrated in a prospective 10-year study from Spain, in which mortality was not found to correlate with drug resistance, even though rates of resistance to penicillin, cephalosporins, and erythromycin increased during the study period [4]. Since then, several studies have attempted to evaluate this relationship. In a recent review of the implications of antibacterial resistance for the treatment of CAP, Metlay [5] evaluated 15 published reports assessing the impact of PNSP on outcomes for pneumococcal pneumonia, which represented the outcomes of >7500 patients. Twelve of these studies concluded that there was no impact of PNSP on mortality. In one study from the Centers for Disease Control and Prevention, which did show an impact, investigators found that, after day 4 of hospitalization, the risk of death was 7 times greater in patients infected with high-level PNSP (MIC, ≥4.0 μg/mL; 19 of 1151 patients) than in patients infected with intermediate isolates (MIC, 0.012–1.0 μg/mL; 81 of 1151 patients) [6]. However, treatment and severity of disease were not recorded. Similar results were found in a follow-up case-control study of patients with bacteremic pneumococcal pneumonia [7], which addressed the limitations of the trial by Feikin et al. [6] and controlled for risk factors, severity of illness, and treatment. The findings of this multivariate analysis revealed that antimicrobial resistance did not contribute to mortality or to a requirement for intensive care unit stay, but determined that more important predictors of outcome included severity of illness and whether there was a “do not resuscitate” order on the patient’s chart. An additional international, prospective, observational study of 844 patients with pneumococcal bacteremia that age, severity of illness, and comorbidity were associated with mortality but not with whether the isolates were PNSP [8]. Although many of these studies attempted to control for confounding variables (such as comorbidities, which will also affect mortality), Metlay [5] concluded that the heterogeneity of the inclusion criteria, outcome measures (other than mortality), and statistical analyses precluded a meta-analysis of the results.

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Thus, the prevailing view has been that current levels of penicillin resistance do not adversely affect outcomes for CAP in immunocompetent patients as long as the MIC is <4.0 µg/mL (the majority of non-susceptible isolates). This view has also been supported by pharmacokinetic/pharmacodynamic principles, which suggest that adequate serum and tissue levels should be achieved with appropriate doses of parenteral β-lactams or oral amoxicillin to effectively treat the great majority of pneumococcal strains, which are considered “nonsusceptible” to penicillin on the basis of the present criteria [9, 10]. In part because of these data, the Clinical Laboratory Standards Institute (formerly the NCCLS) increased the MIC breakpoints for cefotaxime, ceftriaxone, and amoxicillin for nonmeningeal infections, recognizing that infections (such as pneumonia due to strains formerly considered nonsusceptible) can be treated successfully with the usual doses of these β-lactam drugs.

In this issue of Clinical Infectious Diseases, Tleyjeh et al. [11] evaluate 10 studies that examined the association between PNSP and short-term mortality in pneumococcal pneumonia, and they find a significant difference in the mortality rate (19.4% in the PNSP group and 15.7% in the penicillin-susceptible S. pneumoniae group). They conclude that penicillin nonsusceptibility is a prognostic factor and should be included as a risk factor for mortality. If this observation is correct, it suggests a change in our view of PNSP and implies an increased need to address this issue of penicillin resistance, to lessen its effect on our patients and, furthermore, to explore the relationship between resistance and outcome.

The analysis performed by Tleyjeh et al. [11] was a systematic review and meta-analysis of prospective cohort studies. They rigorously followed the Meta-Analysis of Observational Studies in Epidemiology protocol, proposed by Stroup et al. [12] in 2000. Many investigators regard randomized, controlled trials as the gold standard for experimentation, but such trials are often not feasible or ethical, requiring the use of quasi experimental or observational designs. Although systematic reviews and meta-analyses were initially principally conducted with controlled clinical trials, meta-analyses of observational studies have become as common as those of clinical trials, and the systematic review approach has spread beyond clinical studies to areas such as medical education [13] (http://www.bestevidenceducation.org) and the social sciences in general (http://www.campbellcollaboration.org).

A key issue in systematic reviews, such as the one by Tleyjeh et al. [11], which relies primarily on observational studies, is quality assessment. The authors of this study employed the Newcastle-Ottawa scale, which is recommended by the Cochrane Non-Randomized Studies Methods Work Group [14]. Heterogeneity can be another major concern when combining the results of several study designs, but Tleyjeh and colleagues included only prospective cohort studies in their analysis, and they tested the studies appropriately, reporting minimal and statistically non-significant between-study heterogeneity.

One limitation of the analysis by Tleyjeh et al. [11] is also found in the analysis by Metlay [5] and in all systematic reviews: both require their authors to depend on both the quality of the work of others (the authors of the studies they choose to include) and the editors of the journals in which they were published, as well as other, unknown editors who may have elected not to publish works of similar quality. Tleyjeh and colleagues have attempted to address the former limitation by, in some cases, directly contacting the authors of the 10 studies that met their final inclusion criteria. And although their search methodologies met or exceeded existing protocols, publication bias must continue to be an explicit concern when considering evidence from any systematic review.

Thus, the ability to control for confounding variables in each of the studies can be questioned. It is well recognized that mortality associated with pneumococcal pneumonia often reflect factors independent of antimicrobial susceptibility. Host factors (e.g., extremes of age, underlying immunosuppressive or debilitating disease, and comorbidities) [1, 15, 16] or factors of the organisms (e.g., capsular subtype) [17] influence mortality, irrespective of antimicrobial susceptibility profiles. Mortality rates are higher in the presence of multilobar involvement, renal insufficiency, need for intensive care unit stay, hypoxemia, severe derangement in physiological parameters, and other comorbidities. Furthermore, the variables of double-drug therapy (i.e., the addition of a macrolide to an effective β-lactam regimen), genetic variation of the host, and mixed infections may affect mortality, and these considerations may not be assessed in these studies or are poorly understood [18, 19]. Given these confounding factors, dissecting out the impact of antimicrobial resistance on clinical outcomes is difficult.

Despite our reservations, the findings of the meta-analysis by Tleyjeh et al. [11] are potentially significant, because of the impact PNSP infection has on antimicrobial prescribing and its potential consequences to our patients. The absolute difference in mortality of 4.7% is noteworthy, considering the number of cases of pneumococcal pneumonia that occur annually. Furthermore, studies have demonstrated that there are increased costs associated with pneumonia caused by PNSP, because of prolonged hospitalizations and use of more-expensive antimicrobial agents, which may be unwarranted [20, 21].

Tleyjeh and colleagues offer potential explanations for an association between penicillin susceptibility and mortality. In addition to concomitant comorbidities and severity of illness, they include considerations of organism virulence and discordant antibiotic therapy. However, as they indicate, resistance and virulence are not well linked. Although acquisition of resistance genes may be deleterious to the organism, adaptations compensating for these costs often evolve [22]. Furthermore, except for an association of clinical failure with cefuroxime for cefuroxime-resistant infections in the study by Yu et al. [8], discordant therapy has not been shown to...
affect mortality. Also, in the present study, there was no apparent difference in outcome for penicillin-nonsusceptible and -resistant strains.

So what are the implications of this meta-analysis? As the authors point out, it will not significantly affect our approach to empirical therapy of CAP. Because our present guidelines recommend antimicrobials effective against penicillin-resistant S. pneumoniae [23]. The findings suggest, however, that resistance may need to be reconsidered as an independent predictor of poor response. Thus, in addition to such factors as age and severity of illness, the presence of PNSP may be used to predict prognosis. In addition, it also reinforces the need to reduce the prevalence of resistant organisms. Continued surveillance studies, appropriate antimicrobial use campaigns, stratification of patients on the basis of known risk factors for resistance, and vaccination programs are needed to appropriately address concerns associated with PNSP and to limit its spread.

In conclusion, the methodology provided by Tleyjeh and colleagues is rigorous and presents a new perspective on the issue of PNSP. Whether levels of drug resistance will continue to increase or will decrease in the future is unknown. To better evaluate the impact of resistance on clinical outcomes, randomized, prospective controlled trials would be the best option. However, logistical considerations make it improbable that such studies will be performed. We may need to rely on future, carefully designed, observational (preferably prospective) studies to better assess the relationship between resistance and outcomes and to define optimal therapy for patients with CAP. Until then, strategies to control resistance through appropriate antimicrobial use need to be encouraged.

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