Clinical Significance of Pneumococcal Resistance and Factors Influencing Outcomes

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Abstract

Despite increasing penicillin and macrolide resistance worldwide, the clinical relevance of this phenomenon is still unknown. Debate continues as to whether increasing resistance among pneumococci to β-lactam agents, macrolides, and fluoroquinolones has been accompanied by an increase in the rate of treatment failure. In vitro findings do not appear to be predictive of in vivo outcomes. Studies have failed to demonstrate significantly higher mortality for patients infected with penicillin-resistant rather than penicillin-susceptible pneumococcal strains. Treatment failures are associated solely with the highest levels of resistance. Antimicrobial resistance appears to affect other markers of morbidity, but only statistically nonsignificant trends toward increased mortality have been demonstrated. Whether macrolide resistance among invasive pneumococcal isolates is clinically relevant or a matter of limited influence remains to be determined.

Penicillin and macrolide resistance among clinical isolates of Streptococcus pneumoniae is increasing worldwide, raising concerns about the role of these agents for the treatment of respiratory tract infections (RTIs).[1] Despite worldwide decreased susceptibility of pneumococci to β-lactam antibiotics, an adverse effect on treatment outcomes has not been consistently demonstrated. Although increases in mortality from penicillin-non-susceptible (pen-NS) pneumococci compared with penicillin-susceptible (pen-S) pneumococci have been documented in many studies since the early 1990s, these increases have not been statistically significant.[2-8] Consequently, the clinical significance of antibiotic resistance for S. pneumoniae remains the subject of much debate. While some authorities have suggested that with rising penicillin minimum inhibitory concentrations (MICs) in pneumococci we will soon see a clearer effect of resistance on outcome, several recent studies refute the notion.

Yu et al.[9] conducted an international prospective study of 844 consecutive cases of hospitalized adults with pneumococcal bacteremia during the period 1998–2001. Risk factors for pen-NS infection included underlying disease and prior antibiotic therapy. Age >65 years, severity of illness, and underlying disease/immunosuppression were significantly associated with mortality, while penicillin resistance was not. Fever resolution curves were virtually no different in patients who had received discordant therapy (an antibiotic to which the patient’s isolate proved resistant) and in patients who had received concordant therapy (an antibiotic to which the isolate proved susceptible).

In Spain, Falcó and colleagues[10] compared outcomes in patients with pneumonia due to pen-S S. pneumoniae and patients with pneumonia due to penicillin-intermediate-level-resistant (pen-I) strains. They examined outcomes in patients who had pneumococcal pneumonia caused by a strain with an MIC of 0.12–1 μg/mL (pen-I) and who were treated empirically during the therapeutic window (within 48 hours) with a β-lactam antibiotic. Pneumonia-related deaths in pen-I and pen-S groups were comparable. The only factors associated with pneumonia caused by pen-I level strains were serotypes 14 and 19, hematologic malignancy or splenectomy, and human immunodeficiency virus (HIV) infection. There was a nonsignificant trend to higher mortality in pneumococcal pneumonia caused by pen-I strains; however, patients treated with amoxicillin did not have a poorer outcome. The investigators recommended redefining levels of penicillin susceptibility in patients with pneumococcal pneumonia to consider strains with MICs ≤1 μg/mL as pen-S. While the penicillin breakpoints established by the National Committee for Clinical Laboratory Standards (NCCLS) are predictive of pneumococcal meningitis outcomes for which they were established in the 1970s, they might not predict clinical outcomes of pneumococcal pneumonia.[11]
1. Impact of High-Level Penicillin Resistance

The first study demonstrating penicillin resistance as an independent predictor of mortality among patients with pneumococcal bacteremia was reported by Turett et al.,[12] who examined penicillin resistance and other predictors of mortality in patients with a high prevalence of HIV infection. High-level penicillin resistance accounted for 65% of pen-NS isolates with known MICs. HIV-positive patients were more likely to have pen-NS pneumococci (those with intermediate- and high-level penicillin resistance). The overall mortality rate of 17% was consistent with that previously described in other studies. Severe illness, high-level penicillin resistance, multilobar infiltrates and/or effusion(s) on chest roentgenogram, Hispanic ethnicity, and age as a continuous variable were significant predictors of mortality. Previous studies had not separated patients with high and intermediate levels of penicillin resistance when analyzing survival. In the Turett study, 65% of isolates had high-level penicillin resistance, which proved to be an independent and strong predictor of mortality. All 11 patients with pen-NS survived.

2. Community-Acquired Pneumonia Outcomes with Macrolide-Resistant S. pneumoniae

Over the past 15 years, macrolide resistance has emerged in S. pneumoniae; current rates of resistance in the US are approximately 30%.[13] Studies have also documented increased levels of macrolide resistance in Europe, Canada, and Asia.[14-17] Several studies on community-acquired pneumonia (CAP) have assessed the effect of macrolide resistance on outcomes.

A multicenter study in Spain of 683 patients with CAP showed that 10% of isolates were pen-R (MIC ≥2 µg/mL) and 27% of isolates were macrolide resistant (mac-R; MIC ≥1 µg/mL).[18] Of the mac-R strains, 87% were highly resistant strains (i.e. MIC ≥128 µg/mL). The overall mortality rate was 14.4%; however, despite penicillin resistance and high-level macrolide resistance, there was no significant impact on mortality. Penicillin resistance in this study was associated with chronic pulmonary disease, HIV infection, suspected aspiration, or admission to hospital within the previous 3 months. Drug-susceptible pneumococcal CAP was commonly associated with disseminated intravascular coagulation, empyema, and bacteremia. Serotype 19 was predominant among isolates with penicillin MICs ≥12 µg/mL and was associated with increased mortality. In other studies, high case fatalities have been observed with infections caused by serotypes 3, 6B, and 19F. It has been postulated that serotype may be a more important factor than antibiotic susceptibility in mortality resulting from pneumococcal infection.[12,19]

Prompted by increasing reports of clinical failures using macrolides, Rzeszutek et al.[20] conducted a review of clinical failures associated with macrolide-resistant S. pneumoniae. Among 33 cases of reported macrolide failure during treatment for pneumococcal infection, CAP accounted for 89% (24/27) of available diagnoses. Eight patients (24%) had a medical history of cardiopulmonary disease and five (15%) were immunocompromised. Most patients (94%) had received an oral macrolide in an outpatient setting. A macrolide-resistant S. pneumoniae genotype was confirmed in 19 of 29 patients: erm-based resistance (erythromycin ribosomal methylation) only in 63%, erm + mef in 5%, and mef-based resistance (macrolide efflux) only in 26%. The majority of patients (88%) with documented treatment failure survived. Three patients (9%) died as a result of S. pneumoniae infection: a 27-month-old child after failure of 7-day clarithromycin therapy, a 49-year-old woman who had been hospitalized with CAP and treated with intravenous azithromycin, and a 28-year-old man with a 5-day history of lower RTI who was treated with azithromycin for 4 days.[21-23]

The authors of the review noted that macrolide treatment failure occurred predominantly in pediatric and geriatric cases, and equally in both sexes. Although the three fatal cases spanned several age groups, the sample was too small to draw meaningful conclusions. It was disturbing, however, to observe that treatment failure can occur despite appropriate therapy and, in some cases, in the absence of bacterial resistance. The presence of risk factors for pneumococcal disease has been blamed for treatment failures, but since high mortality rates have been observed in drug-susceptible pneumococcal pneumonia in patients with severe disease,[19] this theory is weakened. Susceptibility data on 40% of isolates involved in the study by Rzeszutek et al.[20] were uncharacterized, preventing conclusions from being drawn on phenotypic or genotypic data.

Bacteremia associated with drug-resistant pneumococcal pneumonia tends to be relatively rare. Lonks et al.[24] conducted a 13-year, matched, case-control study of patients (86 cases, 141 controls) with bacteremic pneumococcal infection at four hospitals (one in Spain and three in the US). The authors attempted to ascertain if macrolide susceptibility of pneumococcal isolates was associated with breakthrough bacteremia during macrolide treatment. The case patients had pneumococcal bacteremia and an isolate that was resistant or intermediate resistant to erythromycin. As shown in figure 1, looking at strains for which genotypic data were available, breakthrough bacteremia with a macrolide-non-susceptible (mac-NS) pneumococcus while on macrolide therapy was rare when mef was the resistance mechanism; only three instances were documented (one with an MIC of 4 µg/mL and two with MICs of 16 µg/mL). Mef-based resistance leading to treatment failure occurred in patients taking azithromycin and erythromycin, agents that have higher S. pneumoniae MIC90 values than clarithromycin and do not achieve epithelial lining fluid concentrations as high as clarithromycin. In contrast, 11 of 14 break-