Penicillin and Macrolide Resistance in Pneumococcal Pneumonia: Does In Vitro Resistance Affect Clinical Outcomes?

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In vitro resistance to antimicrobial agents is escalating among pathogens responsible for the most serious respiratory tract infections. Some reports have suggested that this has direct clinical implications. Because of penicillin and macrolide resistance in *Streptococcus pneumoniae*, current guidelines for the initial treatment of respiratory tract infections advocate less reliance on the use of either of these classes of drugs in single-agent therapy. Recent studies that have assessed the impact of \(\beta\)-lactam and macrolide resistance on clinical outcomes in community-acquired pneumonia fail to provide incontrovertible evidence for a direct link between in vitro resistance and treatment failure. However, there are anecdotal reports of breakthrough bacteremia due to macrolide-resistant pneumococci among patients receiving macrolide therapy, unlike the situation for \(\beta\)-lactams and penicillin-resistant pneumococci. Continued efforts, including in vitro surveillance, appropriate antibiotic use campaigns, and immunization programs, will be important in limiting the spread of drug-resistant *S. pneumoniae*.

There are >5 million cases of community-acquired pneumonia (CAP) per year in the United States [1]. *Streptococcus pneumoniae* is the most commonly identified cause, accounting for up to one-third of all cases, as well as two-thirds of all cases of bacteremic pneumonia [2]. Pneumococcal pneumonia is associated with an overall mortality rate of \(~\frac{1}{8}\%\) [3, 4]. The emergence of resistance to a wide variety of antimicrobial agents among pneumococci has been well documented. This phenomenon has surprised many, despite the warning from early pioneers in antimicrobial chemotherapy that prescribers must “do [their] utmost to destroy the whole of the parasites all at once by means of drugs, as owing to their great power of adaptation a single germ surviving may perhaps be the cause of the infection breaking out afresh” [5]. Yet, in the face of increasing in vitro resistance, the overall mortality rate for CAP has remained stable [4, 6, 7]. Additionally, the question of whether in vitro resistance data are predictive of treatment outcomes is controversial, especially in the case of CAP. Here I review recently published studies that have investigated the potential link between pneumococcal drug resistance and adverse clinical outcomes.

\(\beta\)-LACTAM RESISTANCE AND CLINICAL OUTCOMES

Despite reports of high rates of resistance to \(\beta\)-lactams among pneumococci [8, 9], convincing evidence of a corresponding increase in the number of treatment failures in pneumococcal pneumonia is lacking. A number of studies in the 1990s compared outcomes among patients infected with penicillin-susceptible *S. pneumoniae* with those among patients infected with strains with intermediate susceptibility to penicillin. Although these studies were limited by relatively small sample sizes, and few of them adjusted for important confounders, they provided strong evidence that infection due to
intermediately susceptible strains is not associated with either treatment failure or increased mortality [2].

More recently, 2 controlled studies noted adverse outcomes among patients with CAP due to penicillin-resistant *S. pneumoniae*. Feikin et al. [4] reported a significant risk of death associated with infection due to pneumococci with penicillin MICs of $\geq 4 \mu g/mL$, after excluding deaths that occurred after the first 4 days of hospitalization. Metlay et al. [10] found no increased risk of death but noted an increased risk of suppurative complications among patients with pneumonia due to nonsusceptible *S. pneumoniae* (which included both intermediately resistant and resistant categories) compared with patients who had infections with penicillin-susceptible *S. pneumoniae*. However, neither study was able to demonstrate that discordant therapy (i.e., treatment with an agent that had reduced in vitro activity against the pathogen) for patients with drug-resistant isolates led to adverse outcomes. In a recent review, Metlay [11] emphasized that the impact of in vitro resistance on outcomes can be presumed only if the drug found to have reduced in vitro activity is the drug actually administered to the patient. Another limitation of many of these outcomes studies is a failure to adjust results for any baseline differences in severity of illness or comorbid conditions.

In the same article [11], Metlay reviewed the results of several recent studies that evaluated the impact of $\beta$-lactam resistance on outcomes among patients with pneumococcal pneumonia, including 4 cohort studies [12–15] and 1 randomized clinical trial [16]. In the cohort studies, patients with CAP were identified and were classified according to susceptibility of the pathogen. Clinical outcomes among the different groups were then compared. The 4 cohort studies included 466 patients with pneumococcal pneumonia, of whom 127 were infected with penicillin- or cephalosporin-nonsusceptible isolates. The randomized clinical trial included 116 patients with pneumococcal pneumonia, of whom 10 were infected with penicillin-nonsusceptible isolates. In these 5 studies, no increase in mortality rates or other adverse outcomes was noted among patients infected with nonsusceptible pneumococci. This was also the case in those studies that specifically assessed the impact of $\beta$-lactam therapy in patients infected with $\beta$-lactam–resistant isolates. Of importance, however, the penicillin MICs for the vast majority of pneumococci in these studies were $\leq 4 \mu g/mL$.

Metlay [11] also reviewed the results of a recent case-based study of CAP from a university hospital in Spain [17]. In contrast to a cohort study, the case-based approach identifies the outcome first, that is, patients who experienced treatment failure, and then determines whether the pathogen is susceptible or resistant. In the study by Arancibia et al. [17], 5 of 444 patients with CAP were identified as having experienced treatment failure, defined as persistence of a resistant pathogen. *S. pneumoniae* was the pathogen in only 2 of the 5 patients; both received initial therapy with a third-generation cephalosporin plus a macrolide. However, only 1 of the 2 isolates was resistant to the drugs that were used as initial therapy.

More recently, Yu et al. [18] conducted an international study of 844 hospitalized patients with pneumococcal bacteremia from 21 hospitals in 10 countries. The authors evaluated the association between in vitro resistance, antibiotics administered, and clinical outcome (14-day mortality rate). In contrast with previous reports, this study was prospective in design, and data collection included specific details of antibiotic therapy administered, including dose, route of administration, and duration, as well as clinical response to therapy. Age, severity of illness, and underlying disease with immunosuppression were significantly associated with mortality, whereas penicillin nonsusceptibility was not. For 360 patients receiving monotherapy, the study found that use of discordant therapy with penicillins, cefotaxime, and ceftriaxone (but not cefuroxime) was not associated with a higher mortality rate, regardless of severity of illness. The authors concluded that, with the exception of those for cefuroxime, the current NCCLS breakpoints for antimicrobial susceptibility in *S. pneumoniae* were not predictive of clinical outcome in pneumococcal pneumonia.

**MACROLIDE RESISTANCE AND CLINICAL OUTCOMES**

A number of recent anecdotal reports have cited an association between macrolide resistance and treatment failure. Waterer and Wunderink [19] reported a case of fatal bactereamic pneumococcal pneumonia in a patient treated with intravenous azithromycin monotherapy. Macrolide-resistant *S. pneumoniae* (erythromycin MIC, 16 $\mu g/mL$) was recovered from blood and sputum cultures. Fogarty et al. [20] described 3 outpatients who had received orally administered azithromycin to treat community-acquired respiratory tract infections during a 9-month period. All 3 patients were subsequently hospitalized because of bactereamic pneumonia due to macrolide-resistant *S. pneumoniae* (isolates from 2 patients had erythromycin MICs of 8 $\mu g/mL$; the isolate from the other patient had an erythromycin MIC of $\geq 128 \mu g/mL$). However, no data were provided on the number of patients with pneumococcal pneumonia who had been treated successfully with macrolides at their institution during the same time period. Musher et al. [21] documented the emergence of macrolide resistance in a patient with severe pneumonia who had received intravenous azithromycin monotherapy. After initial improvement, the patient’s condition suddenly deteriorated; multiorgan failure developed, and the patient died. Isolates of *S. pneumoniae* from the initial sputum sample and from pleural fluid obtained at the time of relapse were both serotype 3 and were genotypically identical. The initial isolate was susceptible to azithromycin.
(MIC, 0.008 μg/mL), whereas the later isolate was azithromycin-resistant (MIC, 2–4 μg/mL) and contained a mutation in the gene encoding ribosomal protein L22.

Using a case-based approach, Kelley et al. [22] reviewed the medical records for all 41 patients with pneumococcal bacteremia admitted to a university hospital between 1998 and 1999. The authors identified 7 patients who had been treated as outpatients and had received antibiotics before admission. Of these, 4 had received oral macrolide therapy, and erythromycin-resistant pneumococci (MICs of 8–16 μg/mL) were recovered from the blood of all 4 patients. These findings suggested that macrolide resistance increased the risk of outpatient treatment failure. However, the ability to quantify the risk is limited by the small sample size and uncontrolled design of the study.

Lonks et al. [23] conducted a retrospective case-control study of patients with pneumococcal bacteremia to assess the relationship between macrolide resistance and treatment failure. Data were collected from 4 hospitals (3 in the United States, 1 in Spain) over a 13-year period, 1987–2000. The authors demonstrated an association between receipt of a macrolide at the time blood was drawn for culture and recovery of erythromycin-nonsusceptible S. pneumoniae from the blood. They also concluded that breakthrough bacteremia during macrolide or azalide therapy is more likely to occur among patients infected with macrolide-nonsusceptible S. pneumoniae than among those infected with a susceptible isolate. This conclusion recently has been questioned [24]. Whereas 1071 patients with pneumococcal blood isolates were initially identified, only 90 case-patients and 141 age- and sex-matched controls were selected; thus, an additional 840 cases of macrolide-susceptible pneumococcal bacteremia were not included in the analysis. As noted by Bishai [24], an analysis of these additional cases would be needed to provide a proper relative rate of breakthrough bacteremia due to resistant strains versus that due to susceptible strains among case-patients and controls receiving macrolide therapy. Other limitations include poor matching of patients with respect to race and underlying disease and the use of case-control methodology, which is typically used for hypothesis generation. A randomized, prospective trial is needed to establish a causal relationship between in vitro resistance and treatment failure.

**CURRENT STRATEGIES TO LIMIT PNEUMOCOCCAL DRUG RESISTANCE**

Although the link between in vitro resistance and treatment outcomes continues to be debated, recent efforts to control drug-resistant pneumococcal disease have begun to yield encouraging results. In response to the worldwide problem of drug-resistant pneumococci, programs have been developed to reduce antibiotic use [25]. Several educational programs aimed at physicians and patients have achieved significant reductions in antibiotic use [26–29]; however, a direct effect on resistance rates has yet to be demonstrated. Another strategy, the introduction of conjugate pneumococcal vaccines, appears to be an extremely effective tool for preventing disease due to resistant pneumococci [30, 31]. Continued success in controlling pneumococcal resistance will require sustained efforts to monitor resistance trends, reduce unnecessary antibiotic use, and expand immunization programs.

**CONCLUSIONS**

This review summarizes the results of studies that addressed the impact of antimicrobial resistance on outcomes for patients with pneumococcal pneumonia. In the reports that focused on penicillin resistance, pneumonia due to penicillin-nonsusceptible pneumococci (defined as those with MICs of <4 μg/mL) was not associated with an increased rate of mortality or other adverse outcomes. This was true even among patients infected with β-lactam–nonsusceptible organisms who were treated with a β-lactam antibiotic.

For the macrolides, the body of published literature on the impact of resistance on outcomes is much less extensive than for the β-lactams. Besides several anecdotal reports, the 2 case-based studies reviewed above suggested an association between macrolide resistance and breakthrough bacteremia. However, because of the retrospective design and other limitations of these studies, it was not possible to establish a specific risk associated with macrolide resistance. In addition, because macrolide monotherapy is typically used for treating mild to moderate CAP in outpatients, it is likely that treatment failure due to macrolide resistance will remain relatively uncommon [11].

As noted by Bishai [7] and Lynch and Martinez [32], a certain proportion of patients with pneumococcal pneumonia—including those infected with a drug-susceptible pathogen—fail to respond to therapy, even with appropriate antibiotics. Clinical failures often reflect factors other than the susceptibility of the infecting pathogen. These include patient-related factors, such as age, underlying illness, and comorbidities, as well as pathogen-specific factors, such as virulence determinants. Thus, interpretation of the results of retrospective studies can prove difficult. To directly assess the impact of resistance on clinical outcomes, prospective, randomized, well-powered studies are optimal. However logistical and ethical challenges make it unlikely that such studies will be performed.

Strategies for controlling antimicrobial resistance include active in vitro surveillance, interventions to promote appropriate antibiotic use, and broad implementation of immunization programs. Continued vigilance will be required to reduce the burden of drug-resistant disease and to ensure the continued effectiveness of antimicrobial agents.
References