



Symposium 1.1

Pneumococcal resistance & its clinical implications : an update

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Introduction

Global emergence of in vitro antimicrobial resistance in *Streptococcus pneumoniae* has become a serious clinical concern since the 1980s. During the past 2 decades, antibiotic resistance to penicillin, other beta-lactams, and non-beta-lactam agents has been increasing rapidly in many parts of the world. With increasing prevalence of pneumococcal resistance, especially in Asian countries, clinical implications of in vitro pneumococcal resistance are also becoming more important.

1. Penicillin and beta-lactam resistance

Since the first report on a penicillin-intermediate strain in 1967, penicillin resistance has been used as a representative marker for antimicrobial resistance in *S. pneumoniae*.

1) Recent trends in regional epidemiology

Some Asian countries showed the highest rate of penicillin resistance in the world. According to the data from multinational ANSORP (Asian Network for Surveillance of Resistant Pathogens) surveillance studies, more than 70% of invasive pneumococcal isolates from Ho Chi Minh city hospitals in Vietnam were fully resistant to penicillin¹. Korea (55%), Hong Kong (43%) and Taiwan (38%) also showed high prevalence of penicillin resistance in this study. Another recent surveillance study in Taiwan showed a decreasing trend in penicillin resistance from 25% in 1998-1999 to 9% in 2001 associated with a 46% decrease in total penicillin and other cephalosporin usage². Rapid emergence of penicillin resistance in *S. pneumoniae* in some Asian countries was partly due to the clonal spread of the Spanish^{23F} penicillin-resistant clone in the region¹. In the United States, a recent surveillance study in 2002-2003 showed that 34.2% of pneumococcal isolates were not susceptible to penicillin (intermediate 15.7%, resistant 18.5%). The rate of penicillin resistance has plateaued during the past 5 years in the United States. In 8 European countries, overall rate of penicillin non-susceptibility was 24.6% (R 12.1%), while Spain (61.9%) and France (47.6%) showed very high prevalence of penicillin non-susceptibility⁴.

2) Clinical implications of penicillin and beta-lactam resistance

Clinical implications of in vitro pneumococcal resistance may vary by disease category or antibiotic class. Clinical implications of antibiotic resistance are relatively obvious in meningitis or otitis media because in vitro resistance could match with in vivo clinical response to antibiotic treatment. However, the clinical significance of antimicrobial resistance in patients with pneumococcal pneumonia is still controversial. Most of the studies suggested that in vitro resistance to beta-lactam agents is not associated with increased mortality in patients with pneumococcal pneumonia at the current level of resistance. But, a recent meta-analysis showed that penicillin resistance is associated with a higher mortality rate than is penicillin susceptibility in hospitalized patients with pneumococcal pneumonia⁵.

2. Macrolide resistance

Macrolide resistance became a major problem of pneumococcal resistance in many countries since the 1990s.

1) Recent trends in regional epidemiology

Macrolide resistance is particularly a serious problem in many Asian countries. ANSORP surveillance study showed that more than 70% of pneumococcal isolates are resistant to erythromycin with very high MIC level (> 128 mg/L) in Vietnam, Taiwan, Korea, Hong Kong, and China¹. Molecular analysis of the mechanism of macrolide resistance in these Asian strains showed that *erm(B)* gene-mediated resistance is a major mechanism, while

dual presence of *erm(B)* and *mef(A)* gene was very frequent in Korea and Vietnam. This might be due to the dissemination of Taiwan^{19F} clone and its variants according to MLST analysis⁶. The most recent data from the United States in the multicenter GRASP (Global Resistance to Antimicrobials with *Streptococcus pneumoniae*) surveillance project during 2004-2005 showed that 29.6 % of pneumococcal isolates were resistant to erythromycin⁷. The rate of increase in the overall prevalence of macrolide resistance with *S. pneumoniae* seems to have plateaued during the past 5-6 years. Approximately two thirds of resistant strains from the United States have efflux encoded by *mefA* gene as their resistance mechanism; the remainder express high-level MLSB resistance encoded by *ermB* gene. Macrolide resistance was also prominent in France (46.1%), Spain (43.6%), and Italy (35.5%)⁴. While ketolide resistance may ultimately become a problem with *S. pneumoniae*, it has not become a problem yet and it is unlikely to emerge as quickly as has occurred with certain other agents in the past.

2) Clinical implications of macrolide resistance

Increasing number of reports suggested that macrolide resistance may be more directly associated with clinical failures of antimicrobial treatment and worse clinical outcomes. Both high-level and low-level resistance to macrolides could be associated with clinical failures of antimicrobial treatment. Particularly, high-level resistant strains in Asian countries with erythromycin MIC of > 128 mg/L could result in treatment failures. Emergence of macrolide resistance during antimicrobial therapy and subsequent treatment failure was also reported. Although data from controlled clinical studies to document the clinical impact of macrolide resistance in the treatment of pneumococcal pneumonia are still lacking, physicians should not use macrolides as an initial empiric agents for treating pneumococcal infections, especially for patients in areas with high prevalence of high-level resistance and patients with a recent history of macrolide use.

3. Fluoroquinolone resistance

1) Recent trends in regional epidemiology

A recent PROTEKT surveillance study showed that 14.3% of pneumococcal isolates from Hong Kong were resistant to levofloxacin followed by Korea (2.9%) and USA (1.8%)⁸. ANSORP surveillance also showed that ciprofloxacin resistance (MIC \geq 4 mg/L) is emerging in Hong Kong (11.8%), Sri Lanka (9.5%), Philippines (9.1%), and Korea (6.5%)¹. Another surveillance study in the United States also reported that the rate of pneumococcal isolates with ciprofloxacin MIC of \geq 4 mg/L has been increasing to higher than 2% since 2001 compared with 1994-1994 surveillance³. Increasing prevalence of fluoroquinolone resistance in Hong Kong and USA is partly due to the clonal spread of the fluoroquinolone-resistant clones, especially the Spanish^{23F} clone.

2) Clinical implications of fluoroquinolone resistance

There were 20 cases of treatment failures with ciprofloxacin and levofloxacin to date⁹. These cases were treated with ciprofloxacin or levofloxacin and resistance was induced by mutations in *parC* and *gyrA* genes. Physicians should be aware that clinical failures may occur, when treating pneumococcal pneumonia with fluoroquinolones, especially in patients with comorbid illnesses and a history of recent fluoroquinolone use.

Conclusion

Not only classic resistance to penicillin and macrolide but also emerging resistance to fluoroquinolones and multiple antibiotics has become a serious concern in the clinical practice. Continued surveillance of resistance and more prospective large-scale clinical data are needed to clarify the epidemiologic and clinical meaning of pneumococcal resistance.

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