



Pneumococcal Resistance to Beta-Lactams and Macrolides

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Introduction

Antimicrobial resistance among *Streptococcus pneumoniae* has been a major issue since the 1980s because it can affect the outcome of community-acquired pneumonia, otitis media, bacterial meningitis, and sinusitis. Epidemiologic reports during the past 2 decades consistently showed that prevalence and level of pneumococcal resistance have been sharply increasing in many parts of the world, especially in the 1990s. International spread of resistant clones such as the Spanish 23F, 19F or 6B contributed to the globalization of pneumococcal resistance in a short period. Based on the published reports, pneumococcal resistance is particularly serious in some Asian countries (Vietnam, Korea, Hong Kong, Taiwan and Japan), Western Europe (Spain, Hungary and France), South Africa and the southeast part of the United States. Increasing prevalence of pneumococcal resistance also contributes to increasing incidence of invasive pneumococcal diseases in children.¹

Epidemiology of beta-lactam and macrolide resistance

1. Beta-lactam resistance among *S. pneumoniae*

Pneumococcal resistance to beta-lactam agents results either from mosaic mutation of penicillin-binding protein genes of pneumococci by interspecies recombinational events or from alterations in *MurM*, the histidine protein kinase *CiaH*, or glycosyltransferase *CpoA*.² Penicillin resistance can be defined when the penicillin MIC is $\geq 2 \mu\text{g/mL}$, while strains with MIC between 0.1 and $1 \mu\text{g/mL}$ are intermediate to penicillin. Penicillin resistance, which had been first reported in the clinical specimen in 1967, was not popular among clinical isolates of pneumococci until the 1970s. In the 1980s, Spain and Hungary have reported very high rates of penicillin resistance, which were 52.7% (1984-6) and 57.8% (1988-9) among clinical isolates, respectively.^{3,4} In the 1990s, however, many countries have reported the increasing prevalence of penicillin resistance. Data from serial studies done by the Asian Network for Surveillance of Resistant Pathogens (ANSORP) Study Group from 1996 to 2002 revealed that some Asian countries had much higher prevalence of penicillin, macrolide, and multidrug resistance among pneumococcal isolates than western countries. The most recent ANSORP study from 2000 to 2002 with invasive pathogens from 12 countries in Asia showed that 71.4% of invasive isolates from a hospital in Ho Chi Minh city, Vietnam were fully resistant to penicillin with MIC $\geq 2 \mu\text{g/mL}$.⁵ Only 7.9% of invasive strains from this hospital

were susceptible to penicillin. Next to Vietnam, Korea (R 54.8%, I 9.7%), Hong Kong (R 43.8%, I 24.1%), Taiwan (R 38.6%, I 24.6%), Malaysia (R 29.5%, I 9.1%) and Thailand (R 26.9%, I 26.9%) also showed very high rates of penicillin resistance. MIC₉₀ values for penicillin among isolates from these countries have also increased to 4 µg/mL. Notable finding from this surveillance was a rapid increase in penicillin resistance in China (R 23.4%, I 19.8%) compared with previous data in 1996-1997. These data from Asian countries indicate that pneumococcal resistance has been progressively aggravating in this region. Penicillin resistance among pneumococci is more prevalent in young children < 5 years of age, among isolates from non-sterile site specimens, and among strains with serotypes 23F, 19F, 19A, 6, 14 and 9V.

Clinical relevance of in vitro resistance is different between non-meningeal and meningeal infections. In meningitis and otitis media, penicillin non-susceptibility of infecting pathogen results in therapeutic failure of penicillin.⁶ However, clinical implication of penicillin resistance in pneumococcal pneumonia is not clear at the current level of resistance.⁷ Most studies documented that mortality rate from pneumococcal pneumonia caused by penicillin-resistant strains was not higher than that from pneumonia by susceptible strains. Recently, some clinical data suggested worse clinical outcome or more severe clinical features in pneumococcal pneumonia caused by resistant strains.^{8,9} Clinical analysis with more cases by high-level resistant strains is required to clarify this issue.

2. Macrolide resistance among *S. pneumoniae*

Erythromycin resistance was a relatively rare phenomenon until the early 1980s in many countries in the world. However, since the late 1980s, increasing prevalence of erythromycin-resistant strains associated with multidrug resistance among pneumococci have been reported from various parts of the world. Penicillin-resistant strains are more frequently resistant to macrolides than penicillin-susceptible strains. Therefore, areas with prevalence of penicillin resistance also show high rates of macrolide resistance. Not only popular use of erythromycin but also introduction of new macrolide (clarithromycin) and azalide (azithromycin) in the clinical practice contributed to the rapid increase in macrolide resistance among pneumococci.

Major mechanisms of macrolide resistance include alteration of the ribosomal target site and the production and utilization of active efflux mechanisms.¹⁰ Ribosomal target modification by 23S rRNA methylases, which is encoded by *ermB* gene, conveys cross-resistance to macrolides, lincosamides, and streptogramins (MLS_B phenotype). This is usually manifested as high-level resistance to macrolide. A new phenotype designated M type, consisting of resistance to 14- and 15-membered macrolides, but susceptibility to 16-membered macrolides, lincosamides and type B streptogramins is induced by a proton-dependent efflux system encoded by *mefE* gene. In Canada and the USA, the M phenotype specified by the *mefE* gene, which shows low-level macrolide resistance, represent the prevailing mechanism, while in Spain, an MLS_B phenotype with very high-level resistance is observed almost exclusively.¹¹ According to the ANSORP study in 2001 with invasive pneumococcal isolates from Asian countries, isolates from Korea, China, Taiwan, Hong Kong, Vietnam, and Singapore showed very high MIC₉₀s for erythromycin (≥ 32 µg/mL) which were harboring *ermB* gene.¹² This ANSORP surveillance study and the Alexander Project data confirmed that Asian countries had more serious problem of macrolide resistance than western part. More than 70% of invasive isolates from Vietnam (91%), Taiwan (86%), Korea (80%), Hong Kong (77%) and China (73%) were resistant to erythromycin in ANSORP surveillance in 2001.

It is clear that failure is predictable if a macrolide is used against pneumococcal pneumonia caused by strains harboring the *ermB* gene. Given the high rates of high-level macrolide resistance among pneumococci in Asian countries, macrolide monotherapy may not be recommended as an empirical therapy for suspected pneumococcal

pneumonia in the region.

3. Multidrug resistance among *S. pneumoniae*

Multidrug resistance to ≥ 3 classes of antibiotics is restricting the options of antimicrobial therapy for pneumococcal infections. Penicillin resistance is frequently associated with multiple resistance to other classes of antibiotics, although mechanism of this multiresistance is unclear. The most common pattern of multidrug-resistance is resistance to penicillin, erythromycin, and trimethoprim-sulfamethoxazole. Prevalence of multidrug-resistance is also highest in some Asian countries. Among invasive pneumococcal isolates, 77% of isolates from Vietnam, 59% from Hong Kong, and 55% from Korea were multi-resistant.⁵

Summary

Current epidemiologic data demonstrate the rapid escalation of pneumococcal resistance to many classes of antimicrobial agents in most continents, particularly in the Asian region. Given the epidemiologic trend in pneumococcal resistance and the spread of resistant clones in many parts of the world during the past decades, pneumococcal resistance will be one of the most serious problems in the clinical medicine. Future studies should focus on the clinical impact of in vitro resistance as well as potential measures to prevent further emergence of high-level resistance among invasive pathogens.

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