Global Epidemiology of Pneumococcal Resistance

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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. Such dramatic increase of antibiotic resistance in *S. pneumoniae* is one of the most remarkable examples of the emergence of antibiotic resistance in major human pathogens. Rapid emergence of pneumococcal resistance in many parts of the world is due to antimicrobial abuse and the international spread of resistant clones. Although increasing prevalence of pneumococcal resistance is a universal phenomenon in the world, situation of increasing resistance in Asian countries since the 1990s is particularly alarming.

Pneumococcal resistance to major antibiotic class

Since the first report on a penicillin-intermediate strain in 1967, antimicrobial resistance to various classes of antibiotics in *S. pneumoniae* has rapidly developed for the past 3 decades. Multidrug resistance in *S. pneumoniae* was first reported in South Africa in 1977. Particularly, since the 1990s, resistance to penicillin and beta-lactams, macrolides, and fluoroquinolones has become a full-blown concern in many parts of the world. Among the major antibiotic classes, macrolide resistance is the most prominent type of pneumococcal resistance in Asian countries and some European countries. Fluoroquinolone resistance is an emerging issue especially in Hong Kong and some Asian countries. Vancomycin tolerance in *S. pneumoniae* was also reported with experimental evidence of vancomycin failures in rabbit meningitis. However, vancomycin resistance has not been reported yet. Multidrug-resistance to more than 3 classes of antibiotics is very prevalent (>30%) in some Asian countries including Vietnam, Korea, Hong Kong and Taiwan.

Regional epidemiology of pneumococcal resistance

Based on the epidemiological reports, the hot spots of *in vitro* pneumococcal resistance include Asian countries, some Western European countries, South Africa, and southern part of the United States.

1. Asia

International surveillance studies by the Asian Network for Surveillance of Resistant Pathogens (ANSORP) Study Group have documented distinctive increases in the prevalence rates and the level of antimicrobial resistance in *S. pneumoniae* in the Asian region.[1] In some Asian countries, more than 50% of pneumococcal isolates were not susceptible to penicillin. Particularly, in Vietnam and Korea, more than 70% of clinical isolates were not susceptible to penicillin. Hong Kong and Taiwan also showed high prevalence of penicillin resistance. Penicillin resistance has been rapidly increasing in China and Malaysia for the past few years. Pulsed-field gel electrophoresis showed that the Spanish^{23F} penicillin-resistant clone had been introduced into Asian countries.[2] Penicillin-non-susceptible strains are usually not susceptible to other antimicrobial agents. Macrolide resistance is a more prominent problem than penicillin resistance in many Asian countries. For instance, in Vietnam, Taiwan, Korea, Hong Kong and China, more than 70% of pneumococcal isolates are resistant to erythromycin with very high MIC level (>128 mg/L).[3] 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 analysis.[4] Fluoroquinolone resistance is relatively prominent in Hong Kong, where more than 10% of pneumococcal isolates were resistant to ciprofloxacin, levofloxacin, and gatifloxacin.[5] A report from Hong Kong documented that the Spanish clone with fluoroquinolone resistance was circulating in Hong Kong, which could be a potential reason for rapid increase in fluoroquinolone resistance in this area.

2. United States of America

According to the SENTRY surveillance program, penicillin resistance rate among *S. pneumoniae* isolates causing bloodstream infections in North America was less than 20%.[6] Recent PROTEKT surveillance program reported that about 30% of pneumococcal isolates were resistant to erythromycin and 0.8% were resistant to levofloxacin.[7] In contrast to Asian strains, the *mef*(A) gene is the main mechanism of macrolide resistance in 70% of the erythromycin-resistant pneumococcal isolates from the United States. Recent reports suggested the dissemination of fluoroquinolone-resistant clones including Spain^{23F}-1 within the United States.

3. Europe

In the 1980s, Spain and Hungary were the classic focus of penicillin resistance in *S. pneumoniae*. During the 1990s, the Spanish23^{F} penicillin-resistant clone has disseminated to all over the world. According to the recent Alexander Project, France (57%) and Spain (40%) showed high prevalence of penicillin resistance.[8] In France, more than 50% of clinical isolates were resistant to erythromycin. France had the highest prevalence of penicillin resistance and erythromycin resistance as well as the highest total antimicrobial usage, broad-spectrum penicillin and macrolide usage, and second highest cephalosporin usage of the European countries.[8] In contrast, Italy showed relatively low prevalence of penicillin resistance despite high levels of both penicillin and cephalosporin usage. This may be due to the widespread use of parenteral rather than oral cephalosporin in this country.

Clinical impact of resistance

Clinical implications of *in vitro* pneumococcal resistance may vary by disease category. Treatment failure associated with antibiotic-resistant pneumococci has been reported in patients with meningitis or

otitis media. Antimicrobial options for the treatment of pneumococcal meningitis or otitis media caused by resistant strains were changed. 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 pneumococal pneumonia at the current level of resistance. A recent ANSORP study also showed that penicillin-resistant *S. pneumoniae* strains did not result in increased mortality or disease severity.[9] However, a few studies reported an increased mortality in patients with pneumococcal pneumonia caused by high-level resistant strains to penicillin.[10] Macrolide resistance may be more directly associated with clinical failures of antimicrobial treatment than penicillin resistance. Case reports of treatment failures with macrolides in pneumococcal pneumonia suggested that either high-level or 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 would result in treatment failures. Emergence of macrolide resistance during antimicrobial therapy and subsequent treatment failure was also reported. But, data from controlled clinical studies to document the clinical impact of macrolide resistance in the treatment of pneumococcal pneumonia are still lacking. Fluoroquinolone failures in pneumococcal pneumonia have been reported in a few cases. These cases were treated with ciprofloxacin or levofloxacin and resistance was induced by mutations in *par*C and *gyr*A genes.

References

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