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Penicillin resistance in *Streptococcus pneumoniae*: Threat, Treatment, and Future trends in Management

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ABSTRACT

Emergence of antibiotic resistance is a global concern in this era to combat infectious diseases. *Streptococcus pneumoniae* is one of the most common causes of community-acquired respiratory tract infections and the drug of choice for treatment was penicillin. However, the first clinically significant penicillin-non-susceptible pneumococcus (PNSP) was documented in 1967. Since then, penicillin resistance strain had been identified in different continents of the world. Among 94 serotypes of *S. pneumoniae*, "paediatric serotypes" (6A, 6B, 9V, 14, 15A, 19A, 19F and 23F) were found to have the highest resistance to penicillin and erythromycin globally. The mechanism of penicillin resistance in *S. pneumoniae* is conveyed by the alternation of the structure of penicillin binding proteins (PBPs), which leads to reducing the affinity for penicillin. There is a relationship between antibiotic consumption and dissemination of antibiotic resistant pneumococcal clones in Southern and Eastern Europe, America, and Asia. Therefore, rational use of antibiotics is important in order to decrease the development and spread of resistant strains. After the introduction of Pneumococcal conjugate vaccine (PCV) 7 vaccines, non-vaccine serotypes like 6C, 11A, 15A, and 15B/C have increased in prevalence. Since the changes in serotype prevalence due to selective pressure have been observed, it is necessary to monitor the prevalent serotypes. Optimal coverage may be achieved by using vaccines with a wide range of serotype coverage in the future. In managing pneumococcal infections, sensitivity tests are important to choose the appropriate antibiotics. In severe pneumonia or hospital-acquired pneumonia patients at the area of high prevalence of PNSP, the initial antibiotics must include intravenous carbapenems, ceftriaxone, cefotaxime or newer quinolones, meanwhile, penicillin-resistant pneumococcal meningitis (≥ 2 μg/ml) is vancomycin and ceftriaxone or cefotaxime. Judicious use of antibiotics, modification of the treatment duration and encouragement for adherence by patients are recommended to prevent antibiotic resistance. Development of new classes of drugs and novel therapeutic regimen is essential to overcome the hazard of penicillin resistance pneumococcal infection in future.

Keywords: Penicillin resistance, β-Lactams, *Streptococcus pneumoniae*, Community-acquired respiratory tract infections.

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INTRODUCTION

Streptococcus pneumoniae is one of the most common causes of community-acquired respiratory tract infections such as sinusitis, otitis media, pneumonia and invasive diseases (Ishida et al., 2008)[1]. Global mortality from pneumococcal diseases is about 1 to 2 million annually especially in the extreme of ages (Mulholland, 1999)[2]. Penicillin was the drug of choice for all pneumococcus diseases before the 1960s. However, the first clinically significant penicillin-non-susceptible pneumococcus (PNSP) was documented in 1967 (Hansman D, 1967)[3] and later, in the early 1970s with the reports from Australia, England, United States and New Guinea (Kislak et al., 1965, Hansman et al., 1971, Hansman et al., 1974)[4-6].

The emergence and global spread of β- lactam antibiotic resistance became a major public health concern as it has led to increased treatment failures; prolonged hospital stay and increased morbidity and mortality (Chawla et al., 2010)[7]. Therefore, it is vital to understand the mechanism of penicillin resistance in *S. pneumoniae*, its epidemiology, and subsequent interventions to reduce the spread of the resistance and prophylactic measures. This review focused on the understanding of the mechanism as well as the driving factors in the spread of penicillin resistance in S. *pneumoniae* in order to modify the management and related preventive measures.

Epidemiology

Penicillin resistance in *S. pneumoniae* was first identified in 1967 in Australia. Later, it was identified in New Guinea, South Africa, Spain, America, Southern and Eastern Europe, Africa and Asia from the 1970s onwards. Currently, 94 serotypes of *S. pneumoniae* with great geographic variability have been identified. Among them, "paediatric serotypes" (6A, 6B, 9V, 14, 15A, 19A, 19F and 23F) were found to have the highest resistance to penicillin and erythromycin globally (Linares et al., 2010)[8].

Drug-resistant strains may be spread to wide geographic areas by (1) the dissemination of resistant bacteria, i.e., clonal spread or (2) dissemination of genes (horizontal spread). Most of the antibiotic resistance is caused by the expansion of limited number of pneumococcal clones detected in most of the countries all around the world (MATS KALIN, 1999)[9].

In Europe, only Finland and Ireland have significantly increased the prevalence of drug-resistant pneumococcal infections from 2005 to 2008 while France, Spain, Belgium and Israel showed decreasing rate of drug-resistant pneumococcal infections from 2000 onwards (Linares et al., 2010)[8]. The serotypes 19F, 23 F, 6A, 6B were commonest among children under 5 years of age and serotypes 3 and 23F were common in adults before the first vaccine pneumococcal vaccine (PCV7) (Table 1) was introduced in the US in 2000 and now also

currently used in different parts of the world. After the introduction of PCV7, non-vaccine serotypes like 19A, 6C, 11A, 15A, and 15B/C have increased in prevalence (Song et al., 2013)[10].

Pneumococcal meningitis in the African meningitis belt is quite different from the US and Europe. In Africa, serotype 1 is the main cause of pneumococcal meningitis so that travellers to that area are recommended to have the PCV13 vaccination in addition to the meningococcal vaccine required (Brueggemann and Spratt, 2003)[11].

Table 1: Vaccines and serotype coverage

Vaccine	Serotypes covered by vaccine
PCV 7	4, 6B, 9V, 14, 18C, 19F and 23F
PCV 13	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

Although *S. pneumoniae* is a well-known agent of community – acquired infections, it also has a role in nosocomial infections. Serotype 3, 6, 9, 14 and 23 F were identified as causal organisms of nosocomial infections, which mainly occurred in elderly patients, oncologic patients, and patients with ultimately fatal diseases. In particular, *S. pneumoniae* is accounted for 5% -20% of early onset of ventilator-associated pneumonia (Paradisi et al., 2001)[12.]

Resistance and susceptibility mechanisms

Penicillin binding proteins (PBPs) are a group of enzymes in the bacterial cell wall synthesis and contribute to "cross-linking" at the peptidoglycan layer. The beta-lactam ring of penicillin targets to bind PBPs and inhibit the bacteria cell wall synthesis leading to the cell lysis (bactericidal) (Yocum et al., 1980)[13]. The PBPs are known to have six different variants, i.e, PBP 1a, 1b, 2x, 2a, 2b and 3 (Kotevska et al., 2009)[14].

The mechanism of penicillin resistance in *S. pneumoniae* is conveyed by the alternation of the structure of penicillin binding proteins (PBPs), which leads to reducing the affinity for penicillin (Hakenbeck et al., 1980)[15]. Alternations in high molecular weight PBPs which have high penicillin binding affinities such as PBP 2x and 2b, cause low resistance and are responsible for the high level of resistance mediated by the other PBP mutations (Figure 1) (Grebe and Hakenbeck, 1996)[16].

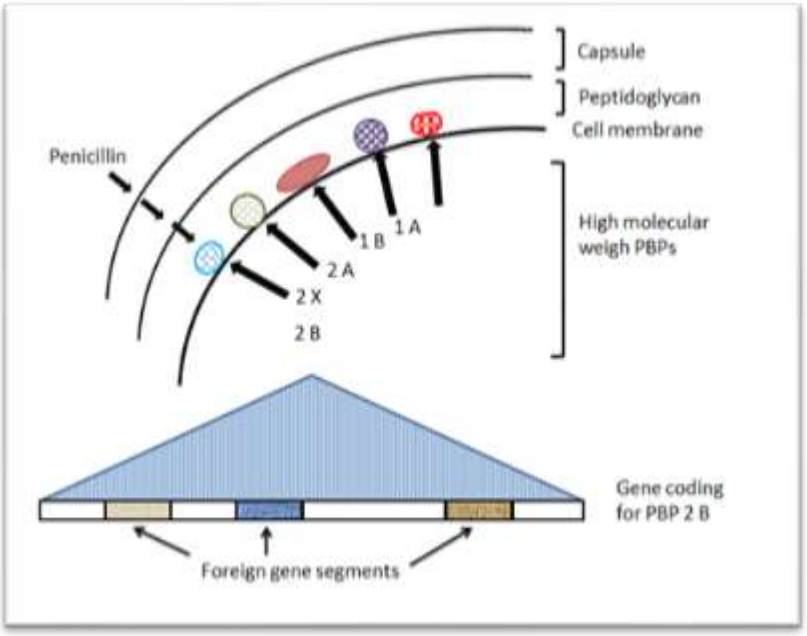

Figure 1: Schematic diagram of the molecular basis of penicillin resistance in *S. pneumoniae* (Reproduced from (MATS KALIN, 1999))[9]

Pneumococci strains with limited alternations in one or two PBPs with MIC 10-100 times that of fully susceptible strains are classified as "intermediate resistant" strains while those with extensive alternations in three or more PBPs with MICs more than 1000 times that of the susceptible strains are classified as "resistant" strains.

Genetic background to β-Lactam resistance

Examination of the nucleotide sequence of PBP encoding genes of the reduced susceptible pneumococcal strains revealed that only 14-23 % of the base pairs have changed (Maiden, 1998)[15]. When these mutant genes of penicillin resistant pneumococci were compared with the genetic sequence of oral α- haemolytic streptococci, a high degree of similarity occurred among them. The possible explanation is that the penicillin sensitive commensal streptococci are exposed to antibiotics and develop resistance by acquiring point mutations in their PBL gene. These mutant genetic segments have been transferred from the commensal streptococci to the *S. pneumoniae* (Chi et al., 2007)[13]. α- haemolytic streptococcal species such as *Streptococcus mitis, Streptococcus oralis* and *Streptococcus sanguis* can involve in the genetic transfer process with *S. pneumoniae* (Potgieter and Chalkley, 1995)[14].

Factors driving the development and spread of resistance

Penicillin resistance in *S. pneumoniae* has been associated with the following risk factors:

- Prior antimicrobial usage
- Carriage of S. pneumonia
- Day care attendance (Reichler et al., 1992)[20]
- Exposure to children who attend day-care

- Immunosuppression (Taylor and Sanders, 1999)[21]
- Medical comorbidities (Taylor and Sanders, 1999)
- Alcoholism (Taylor and Sanders, 1999) and
- Hospitalization (Lee et al., 1995)[22]

There is a relationship between antibiotic consumption and dissemination of antibiotic resistant pneumococcal clones in Southern and Eastern Europe, America, and Asia (Low, 2005, Goossens H1, 2007)[23-24]. High prevalence rates of penicillin-resistant pneumococci have been reported in Spain and France, where antibiotics are widely prescribed while lower prevalence rates were observed in Germany and UK where antibiotic consumption is lower and there is better treatment compliance (Pradier et al., 1997)[25]

Resistance is usually associated with the usage of β-lactam antibiotics, tetracycline, co-trimoxazole and chloramphenicol (Reichler et al., 1995, Klugman, 1990, Tamayo et al., 1999)[25-27]. So that rational use of antibiotics is important in order to decrease the development and spread of resistant strains.

Clinical implication

S. pneumoniae can only colonize in the human nasopharynx and there is no other natural reservoir in animals. Carrier state usually occurs in early life and prevalence is highest among infants. Children and adults usually contracted pneumococcal infection from the carriers. A meta-analysis had shown the different percentages of carriers at different ages (Table 2) (Song et al., 2013)[10].

Table 2: Pneumococcal carriage rate by age groups

	Kenya	Australia	Gambia	Nigeria	USA	Korea
Study period	2004	2002-2004	2005	2006	2006-2008	2009-2010
Prevalence of carrier and age	59% (<1 yr) 61% (1-2 yr) 7.8% (20-29yr)	82.4% (2-4 yr) 19.8% (16-34yr)	97% (< 1yr) 90% (1-4 yr) 65%(15-39yr)	74.4% (<2 yr) 10.8% (15-39yr)	54.8% (<2yr) 55.8% (2-4yr) 11.1 %(17-40yr)	16.3% (<2yr) 9.6 (5-18 yr)

Pneumococcus can asymptomatically colonize in the nasopharynx and can cause different clinical forms. The estimated incidence of invasive pneumococcal diseases (IPD) is 8-34 cases per 100,000 inhabitants with geographical variance and the mortality is ranging from 10% to 30% (WHO, 2008)[28]. Different serotypes are responsible for different clinical diseases as shown in Table 3 (Song et al., 2013).

Table 3: Clinical presentations and serotypes of pneumococci

Diseases	Serotypes
Highly invasive diseases	1, 4, 5, 7F, 8, 12F, 14, 18C and 19A
Less invasive diseases	6A, 6B, 11A, 15B/C and 23F
Acute otitis media in young children	3, 6A, 6B, 9V, 14, 19A, 19F, and 23F
Acute conjunctivitis	3, 11A and non-typeable pneumococci (NT)

Community acquired pneumonia (in Latin America and the Caribbean)	1, 19A, 5, 14
Empyema	1, 3, 7F, 14 and 19A
Meningitis (children <5 yr)	6A/6B, 22A, 23F, 14, 19A
African meningitis belt	1 (60% -80%)

Treatment

In managing pneumococcal infections, sensitivity tests are important to choose the appropriate antibiotics. In outpatients with infections strongly suggestive of pneumococcal infection and where PNSP are not significantly prevalent, high dosage of oral amoxicillin (50 mg/kg/day) may be the therapy of choice. In patients with severe pneumonia or hospital-acquired pneumonia at the area of high prevalence of PNSP, the initial antibiotics must include intravenous carbapenems, ceftriaxone, cefotaxime or newer quinolones. When the antimicrobial susceptibility is available, treatment should be switched to the narrowest-spectrum antibiotics according to the susceptibility profile (Paradisi et al., 2001)[12].

For beta-lactam resistant infections, especially in respiratory tract infections, it is highly dose dependent. Moreover, the consequences of resistance are much greater in meningitis because beta-lactams have poor ability to cross the blood brain barrier. The recommended therapy for penicillin resistant pneumococcal meningitis (≥ 2 μg/ml) is vancomycin and ceftriaxone or cefotaxime.

In pneumococcal infection, the asymptomatic carriers play an important role so that reducing the carrier state by using antibiotics might play a role in prevention. A study in Sweden has shown that eradication therapy with rifampicin and erythromycin or clindamycin for 7 days was achieved in 91.5% of the participant children (Hellberg et al., 2012)[29].

Potential drugs for the management

Daptomycin is a lipopeptide antibiotic with a structure of 13 amino acid peptide having a hydrophilic core and a lipophilic tail (Banwan, Senok and Rotimi, 2009; Hanberger et al., 1991)[30,31]. It is a bactericidal antibiotics and potent against the Gram-positive pathogen including the penicillin-resistant *S. pneumoniae* (Lee et al., 2006)[32]. The half-life of daptomycin is 8 hours and has poor absorption in the gastrointestinal tract, and therefore, it is recommended to give through parenteral route to achieve the target serum concentration (Banwan, Senok and Rotimi, 2009)[31]. *In vivo* murine study found out that it is highly potent to prevent *S. pneumoniae*-induced septic death (Henken et al., 2010)[33].

Dalbavancin is a semisynthetic glycopeptide, engineered as an alternative of naturally occurring glycopeptides such as teicoplanin and vancomycin (Chen, Zervos and Vazquez, 2007)[34]. It is a bactericidal antibiotic that blocks the enzymes involved in the bacterial cell wall synthesis (Chen, Zervos and Vazquez, 2007) [34]. The parenteral route of administration is

recommended for the reason of poor absorption in the gastrointestinal tract (Leighton et al., 2004)[35]. *In vitro* studies have been proven that it has the efficacy against both antibiotic sensitive and resistance pathogens, including *S. pneumoniae* (Chen, Zervos and Vazquez, 2007; Streit et al., 2004; Mushtaq, 2004)[34,36,37].

Ceftaroline Fosamil is a new cephalosporin drug, which has a bactericidal action and recommended to be administered parentally (El Hajj MS, 2017). It is potent against antibiotic-resistant Gram-positive pathogens including penicillin-resistant *S. pneumoniae* (P. Cottagnoud, 2013). *In vivo* study in an experimental Rabbit Meningitis Model had shown that ceftaroline fosamil has significant superior efficacy against penicillin-resistant *S. pneumoniae* compared to the ceftriaxone and vancomycin combination therapy (P. Cottagnoud, 2013).

Quinupristin—dalfopristin is the (30:70) ratio combination of type A and type B streptogramin (Lamb, Figgitt and Faulds, 1999)[41]. Each of the streptogramins has bacteriostatic effect; however, the combination of the two has a synergistic effect and achieve bactericidal action (Hancock, 2005)[43]. Because of its poor absorption in oral administration, the intravenous route is recommended in treating the patients (Johnston, Mukhtar and Wright, 2002)[40]. Some studies had demonstrated that this combination therapy was effective against penicillin-resistant *S. pneumoniae* (Jones et al., 1998; Jones, Low and Pfaller, 1999)[38,39].

CONCLUSION

Penicillin resistance in *S. pneumoniae* is a challenging issue in clinical management and has the high impact on morbidity and mortality. Judicious use of antibiotics, modification of the treatment duration and encouragement for adherence by patients are recommended to prevent antibiotic resistance. Additionally, widespread use of PCV is an effective way of reducing the burden of disease and prevalence of penicillin-resistant pneumococci infections. Since the changes in serotype prevalence due to selective pressure have been observed, it is necessary to monitor the prevalent serotypes (Schrag et al., 2000)[42]. Optimal coverage may be achieved by using vaccines with a wide range of serotype coverage in the future. Moreover, development of new classes of drugs and novel therapeutic regimen is essential to overcome the hazard of penicillin resistant pneumococcal infection.

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