# MACROLIDE RESISTANT *STREPTOCOCCUS PNEUMONIAE* IN CHAROENKRUNG PRACHARAK HOSPITAL, THAILAND

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**Abstract**. Macrolide resistant *Streptococcus pneumoniae* has been increasing rapidly in Southeast Asia. A review from 2000 through 2011 at Charoenkrung Pracharak Hospital that evaluated drug resistance to erythromycin found *S. pneumoniae* from 158 of the 390 (40.5%) patients: 3.6% intermediate, 36.9% highly resistant. A significant correlation was found between macrolide resistant *S. pneumoniae* and penicillin resistance ($p<0.001$), macrolide susceptible pneumococci and penicillin susceptibility ($p<0.001$). Trends of macrolide resistant *S. pneumoniae* at Charoenkrung Pracharak Hospital were found to have increased. Therefore, macrolide monotherapy should be avoided or care should be taken for prophylaxis or treatment in the patient suspected of *S. pneumoniae* infection.

**Keywords:** *Streptococcus pneumoniae*, macrolide resistance, Thailand

## INTRODUCTION

*Streptococcus pneumoniae* is one of the most common bacterial pathogen in patients with upper respiratory tract infections. It also causes severe infections, such as pneumonia, septicemia, and meningitis, especially in community-acquired pneumonia (Pihlajamaki *et al*, 2001). Up to over half (9-55%) of community-acquired pneumonia (CAP) patients require hospitalization, and this is the most common cause of death (Lynch and Martinez, 2002). Macrolides are recommended as drugs of choice for empiric treatment of CAP in low-risk patients. For patients requiring hospitalization, but not requiring intensive care, a β-lactam with or without a macrolide is advocated (Lynch and Martinez, 2002). There has been concern that the increasing use of macrolides might select for macrolide resistance in pneumococci. A Spanish study that assessed prescribing habits for antimicrobial agents and resistance patterns of pneumococci supports such a suggestion (Pihlajamaki *et al*, 2001).

*S. pneumoniae* developed resistance to macrolides has been increasing rapidly in Southeast Asia. The increasing prevalence of drugs resistant *S. pneumoniae* (DRSP) has been reported over the past two decades (Bamrungtrakul *et al*, 1994; Chokephaibulkit *et al*, 2000; Pancharoen *et al*, 2001; Critchley *et al*, 2002; Sangthawan *et al*, 2003; Srifeungfung and Thamlikitkul, 2004).

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Table 1
Criteria for interpretation of zone diameters of studied antibiotics against *S. pneumoniae*.[a]

| Antibiotic | Disk content (μg) | Zone diameter (mm) | | |
|---|---|---|---|---|
| | | Resistant | Intermediate | Susceptible |
| Erythromycin | 15 | ≤ 15 | 16-20 | ≥ 21 |
| Clindamycin | 2 | ≤ 15 | 16-18 | ≥ 19 |
| Tetracycline | 30 | ≤ 18 | 19-22 | ≥ 23 |
| Vancomycin | 30 | - | - | ≥ 17 |

[a]National Committee for Clinical Laboratory Standards, 2002.

In 2005, WHO estimated that 1.6 million people die of pneumococcal disease every year (Siripongpreeda *et al*, 2009). International surveillance studies in Asian countries by the Asian Network for Surveillance of Resistant Pathogens (ANSORP) documented that 28 of 52 (53.8%) strains of *S. pneumoniae* isolated from clinical specimens in Thailand were not susceptible to penicillin, 26.90% were intermediately susceptible, and 26.95% were penicillin resistant (Reechaipichitkul *et al*, 2006). The objective of our study was to determine the incidence of drug resistance of *S. pneumoniae* and its impact on the outcome of patients who were *S. pneumoniae* infected.

## MATERIALS AND METHODS

From January 1, 2000 through December 2011, 390 *S. pneumoniae* were isolated from blood, sputum, tracheal suction, and body fluid of patients in different departments of Charoenkrung Pracharak Hospital. Identification of *S. pneumoniae* was performed using standard microbiological method (morphology and optochin susceptibility as shown by a diameter of inhibition zone ≥14 mm.)

The susceptibility to penicillin was performed by Epsilometer-test (Etest) using a 90 mm agar plate containing cation-adjusted Mueller Hinton agar with 5% sheep blood. The susceptibility to erythromycin was performed by disk diffusion according to the National Committee for Clinical Laboratory Standard (NCCLS) 2000 procedures (NCCLS, 2000). *S. pneumoniae* ATCC 49619 was used as quality control strain in every batch tested. All plates were incubated at 35°C in 5% $CO_2$ for 20-24 hours. Interpretation of the test results for susceptible, intermediate, or resistant to erythromycin was made according to the criteria in Table 1 (NCCLS, 2000).

**Statistical analysis**

Data were analyzed by SPSS® (version 14; IBM, Armonk, NY). Descriptive statistics were used for demographic baseline data and summarized as number, percent, mean with standard variation, or median with range. The comparisons of differences between categorical variables were evaluated by chi-square, and the primary outcome was significant if $p<0.05$.

## RESULTS

A total of 390 specimens were col-

Table 2
Correlation between penicillin susceptible or resistant *S. pneumoniae* and age, sex and survival.

| Characteristic | Susceptible to penicillin *n* (%) | Resistant to penicillin *n* (%) | *p*-value |
|---|---|---|---|
| Age (years) | | | |
| 1-35 | 23 (39.0) | 36 (61.0) | 0.174 |
| 36-60 | 36 (25.7) | 104 (74.3) | |
| >60 | 57 (29.8) | 134 (70.2) | |
| Gender | | | |
| Male | 82 (30.6) | 186 (69.4) | 0.585 |
| Female | 34 (27.9) | 88 (72.1) | |
| Survival study | | | |
| Survive | 87 (31.2) | 192 (68.8) | 0.324 |
| Death | 29 (26.1) | 82 (73.9) | |

Table 3
Correlation between erythromycin susceptible or resistant *S. pneumoniae* and age, sex and survival.

| Characteristic | Susceptible to erythromycin *n* (%) | Resistant to erythromycin *n* (%) | *p*-value |
|---|---|---|---|
| Age (years) | | | |
| 1-35 | 23 (39.0) | 36 (61.0) | 0.444 |
| 36-60 | 53 (37.9) | 87 (62.1) | |
| > 60 | 85 (44.5) | 106 (55.5) | |
| Gender | | | |
| Male | 111 (41.4) | 157 (58.6) | 0.936 |
| Female | 50 (41.0) | 72 (59.0) | |
| Survival study | | | |
| Survive | 122 (43.7) | 157 (56.3) | 0.120 |
| Death | 39 (35.1) | 72 (64.9) | |

lected from 268 male and 122 female patients. The mean age was 60±18.87 years and the median age was 57.97±18.87 years. The death rate was 28.5%. Resistance to penicillin was found in 113 (28.97%) *S. pneumoniae* (20.0% were intermediate and 8.97% were highly resistant), and drug resistance to erythromycin was found in 158 of the 390 (40.50%) patients (3.59% intermediately, 36.92% highly resistant). A significant correlation was found between macrolide resistance and penicillin resistant pneumococci ($p<0.001$) and between macrolide susceptible and penicillin susceptible pneumococci ($p<0.0001$). No significant correlation between susceptibility or resistance of *S. pneumoniae* and age, sex and survival ($p>0.05$) (Tables 2, 3).

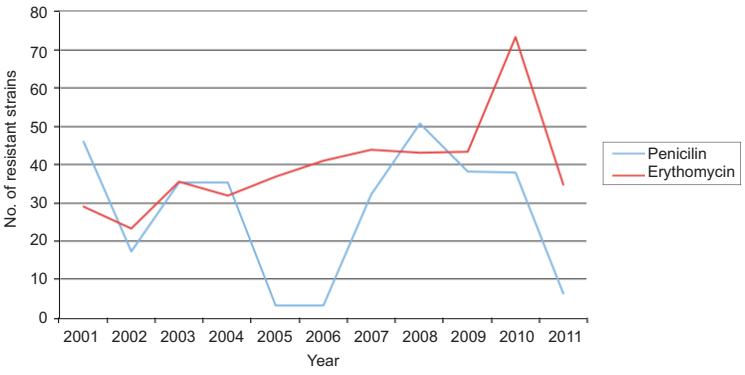


Fig 1–Trend of penicillin/erythromycin resistant *S. pneumoniae* at Charoenkrung Pracharak Hospital during 2001-2011.

## DISCUSSION

The prevalence of penicillin and macrolide resistant *S. pneumoniae* in patients at Charoenkrung Pracharak Hospital during 2001 to 2011 was high and continuing to increase (from 8.97% to 36.92%, respectively) (Fig 1).

The proportion of erythromycin resistance varied from 7.7% in the Republic of Ireland to 97.0% in Hong Kong and Singapore (Jacobs *et al*, 2003). Our observation is similar to a previous study at Phramongkutklao Hospital, Bangkok Thailand where there were 39% resistant strains to erythromycin (Wongsricharnalai, 2010). Our study indicates that there is a significant correlation between penicillin susceptible *S. pneumoniae* and erythromycin susceptible *S. pneumoniae* ($p<0.0001$), but no correlation between drug resistant *S. pneumoniae* and age, sex and survival of patients ($p>0.05$).

Clinical failure of macrolide treatment in *S. pneumoniae* infection caused by macrolide resistant strains has been reported in various parts of the world (Song *et al*, 2004). Such failures of treatment were not confined to pneumococcal disease caused by highly resistant strains but was also evident in those caused by low-level resistance to erythromycin in pneumococci in the Asian region (Song *et al*, 2004).

Macrolide use is steadily increasing across the developing world from 2005 to 2010 (Titus, 2012). Antibiotic use has been shown to be an important contributing factor in the development of pneumococcal resistance (Hicks *et al*, 2011). A positive connection was found between macrolide resistance in *S. pneumoniae* and total macrolide consumption (Bergman *et al*, 2006). Increase in macrolide consumption was associated with increase in macrolide resistant *S. pneumoniae* (Cizman *et al*, 2001).

Trends of macrolide resistant *S. pneumoniae* at Charoenkrung Pracharak Hospital were increased. So macrolide monotherapy should be avoided or care should be taken for prophylaxis or treatment in the patient suspected of *S. pneumoniae* infection.

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