RISK FACTORS AND CLINICAL OUTCOMES OF PENICILLIN-RESISTANT *S. PNEUMONIAE* COMMUNITY-ACQUIRED PNEUMONIA IN KHON KAEN, THAILAND

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Abstract. To determine the prevalence, risk factors and clinical outcomes of penicillin-resistant *S. pneumoniae* (PRSP) in community-acquired pneumonia (CAP), a cross-sectional study was conducted between January 1995 and December 2004 at Srinagarind Hospital, Khon Kaen, Thailand. Patients hospitalized with CAP and culture proved to be *S. pneumoniae* were included. PRSP was found in 22 of 64 (34.4%) patients. The MIC levels of penicillin non-susceptible strains ranged between 0.25 and 0.75 μg/ml. Resistance to other antibiotics ranked: cotrimoxazole (51.6%), tetracycline (26.6%), erythromycin (20.6%), lincomycin (18.7%), chloramphenicol (12.5%) and ampicillin (1.6%). None of the isolates was resistant to cephalothin. The significant risk factors for PRSP infection were previous antibiotic use within 3 months (Adjusted OR 40.83, 95% CI 3.71 to 449.41) and alcoholism (Adjusted OR 8.82, 95% 1.25 to 62.46). Bacteremia and empyema thoracis were found more commonly in PRSP than PSSP infection, but not statistically significant. Pneumonia-related mortality was nearly the same, PRSP 9.1% *vs* PSSP 9.5% (p = 0.96). The reason why the clinical outcomes of these two groups were not different may be the patients were infected with mildly resistant organisms. Thus, pneumonia caused by intermediate-level penicillin resistant *S. pneumoniae* appears to be adequately treated with β-lactams or aminopenicillin antibiotics. The MIC levels of penicillin resistance should be monitored further. The need for antibiotics active against drug-resistant *S. pneumoniae* was required if high-level penicillin resistance was detected.

INTRODUCTION

S. pneumoniae remains the most common bacterial cause of community-acquired pneumonia (CAP), and these infections are associated with significant morbidity and mortality worldwide (File, 2003). The increasing prevalence of pneumococcal resistance to penicillin and other drugs has considerably complicated the empirical treatment of CAP (Heffelfinger *et al*, 2000; Garau, 2002). 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, 26.9% were intermediately susceptible, and 26.9% were penicillin resistant (Song *et al*, 2004). The morbidity and mortality rates of patients with pneumococcal meningitis caused by penicillin-resistant strains were higher than those for penicillin-susceptible strains (Klugman *et al*, 1992). However, the clinical impact of drug-resistant *S. pneumoniae* in community-acquired pneumonia is controversial (Metlay *et al*, 2000). Studies have suggested that empyema thoracis and bacteremia were more common in penicillin-resistant *S. pneumoniae* (PRSP) pneumonia, but the mortality rate was not significantly higher compared to penicillin-sensitive *S. pneumoniae* (PSSP) pneumonia (Aspa *et al*, 2004).

Recognition of patients at increased risk for acquiring drug-resistant pneumococcal pneumonia is essential to control epidemic spread of these strains and the selection of appropriate initial antimicrobial treatment. The objective of this study was to determine the prevalence, risk factors and clinical outcomes of penicillin-resistant *S. pneumoniae* in community-acquired pneumonia.

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MATERIALS AND METHODS

Patients

A cross-sectional study was carried out between January 1, 1995 and December 31, 2004 at Srinagarind Hospital, Khon Kaen University, Khon Kaen, northeast Thailand. Patients age ≥15 years, hospitalized with CAP and culture proved to be *S. pneumoniae* were included. A diagnosis of CAP was based upon: 1) fever (>37.5ºC) *vs* WBC >10,000/mm^3 or bands >15%; 2) new and sudden onset of at least two of the following signs or symptoms: cough, dyspnea or tachypnea, chills, pleuritic chest pain, purulent sputum or change in sputum character, signs of consolidation or rales on physical examination; and 3) a new infiltration seen on chest radiograph. Pneumococcal pneumonia was diagnosed if a culture from sterile sites (*ie* blood, CSF, or pleural fluid) yielded *S. pneumoniae*. A sputum culture was considered pathogenic if it was positive for *S. pneumoniae* and a sputum Gram's stain demonstrated gram-positive diplococci. HIV-positive patients or those hospitalized within 3 weeks prior to admission were excluded.

Microbiology

Gram-stained smears and quantitative cultures of adequate sputum samples were performed by standard methods. Optochin sensitivity, bile solubility and latex agglutination tests were performed to confirm suspected *S. pneumoniae* colonies. Blood cultures were performed in patients with high fever, and pleural fluid cultures in patients with pleural effusion.

Antibiotic susceptibility was tested by the disk-diffusion technique with Mueller-Hinton agar supplemented with 5% sheep blood and incubated overnight in 5% CO_2 at 35ºC. A 1 μg oxacillin disk (Oxoid, UK) was used to reveal resistance to penicillin and was positive if the diameter of the inhibition zone was <20 mm. The other antimicrobial agents tested for by disk diffusion were ampicillin, cephalothin, chloramphenicol, cotrimoxazole, erythromycin, tetracycline, and lincomycin. The zone diameter interpretative standards used were defined according to NCCLS guidelines (1997).

The minimum inhibitory concentration (MIC) of oxacillin resistant strains for penicillin was determined by E-testing (AB Biodisk, Sweden) done at our hospital since 2001. The isolates were classified as susceptible to penicillin if the MIC was ≤0.06 μg/ml, intermediately resistant if the MIC was 0.12-1 μg/ml, and resistant if the MIC was ≥2.0 μg/ml. Intermediate and resistant isolates were considered to be non-susceptible (NCCLS, 2002).

Data collection

The demographic data collected included: age, gender, occupation, underlying diseases, smoking and alcohol use. Initial clinical signs and symptoms, complete blood count (CBC), sputum Gram's stain, and chest radiograph results were also recorded. The severity of CAP was classified according to American Thoracic Society (ATS) guidelines (Niederman *et al*, 2001). Patients were classified as having severe CAP if they presented with shock, needed mechanical ventilation, or had 2 of 3 of the following criteria: 1) systolic blood pressure <90 mmHg, 2) multilobar involvement, and 3) PaO_2/FiO_2 <250. The following risk factors were assessed in each patient: older age (>65 years), comorbidities, previous antibiotic use within 3 months, steroid use (>10 mg prednisolone/day) and alcoholism.

The outcomes of treatment with penicillin-resistant *S. pneumoniae* (PRSP) were compared with penicillin-sensitive *S. pneumoniae* (PSSP) pneumonia. Complications following pneumonia, such as bacteremia, shock, requiring mechanical ventilation, empyema thoracis, and acute renal failure, were recorded. The length of hospital stay was also evaluated. Mortality was defined as death during the hospital stay. Pneumonia-related deaths were defined as those in which pneumonia was the major contributing cause. In those cases in which the cause of death was not clearly documented, death within 7 days following admission was also considered pneumonia-related.

Ethics

The study was approved by the Ethics Committee of the Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.

Statistical analysis

Descriptive statistics were used to describe characteristics, clinical presentations, and the

drug-susceptibility patterns of the *S. pneumoniae* isolates. Means and standard deviations were calculated for continuous variables, and number and percentage for categorical variables. Analysis of risk factors of PRSP infection was initially assessed by univariate analysis. Odds ratios (Crude OR) were then determined using a logistic regression model. An adjusted analysis for confounders was performed with the model constructed by multiple logistic regression. Adjusted odds ratios (Adjusted OR) and 95% confidence intervals (CI) were calculated. Complications, lengths of hospital stay, and mortality rates were compared between patients infected with PRSP and PSSP pneumonia. The χ^2 test or Fisher's exact test was used to compare categorical variables and the Student's *t*-test to compare continuous variables. A p-value of ≤ 0.05 was considered to be of statistical significance in all analyses.

RESULTS

Patient characteristics and clinical features

During a 10-year study period, 64 patients were hospitalized with CAP caused by *S. pneumoniae*. The demographic data are shown in Table 1. The mean age was 51.9 years (range, 15-94 years), with a male to female ratio of 1.8:1. One-third of the patients were farmers. Most of them (87.5%) had underlying diseases. The most common comorbidity was autoimmune disease (26.6%), follow by cardiovascular disease (23.4%), diabetes mellitus (15.6%), chronic obstructive lung disease (12.5%), neurologic disease (12.5%), renal disease (10.9%), and hematologic disease (7.8%).

Over one-third of community-acquired *S. pneumoniae* pneumonia patients needing hospitalization presented with severe CAP. The mean incubation period was 4.6 days. The initial laboratory studies were: CBC, sputum Gram's stain, and chest radiographs, which are summarized in Table 2. About 70% of the patients had >70% PMN, with a mean white blood cell count of 13,947.6 cells/mm^3 (SD 6,379.1 cells/mm^3). Seventeen percent had no sputum production or inadequate sputum examination. In cases with adequate sputum, 68% had gram-positive diplo-

Table 1
Demographic data of *S. pneumoniae* pneumonia patients.

Characteristics	N = 64
Age, year (mean, SD)	51.9 (20.2)
Male to female ratio	1.8:1
Occupation (N, %)	
Farmer	23 (35.9)
Government service	12 (18.8)
Business	6 (9.4)
Healthy (N, %)	8 (12.5)
Underlying disease[a] (N,%)	56 (87.5)
Autoimmune disease	17 (26.6)
Cardiovascular disease	15 (23.4)
Diabetes mellitus	10 (15.6)
Chronic obstructive lung disease	8 (12.5)
Neurologic disease	8 (12.5)
Renal disease	7 (10.9)
Hematologic disease	5 (7.8)
Smoking (N, %)	25 (39.1)
Alcoholism	7 (10.9)
Steroid use	11 (17.2)
Previous antibiotics	9 (14.1)

[a]Some patients had more than one underlying disease

Table 2
Clinical presentation.

Clinical presentation	N = 64
Incubation, days (mean, SD)	4.6 (5.8)
Severe CAP (N, %)	24 (37.5)
White blood cell count, cell/mm^3 (mean, SD)	13,947.6 (6,379.1)
Patients with PMN >70% (N, %)	44 (68.8)
Patients with no sputum production (N, %)	11 (17.2)
Results of sputum Gram's staining (N, %)	
Gram-positive diplococci	44 (68.8)
No organism	3 (4.7)
Gram-positive cocci in chain	2 (3.1)
Gram-negative coccobacilli	2 (3.1)
Mixed organism	2 (3.1)
Results of chest radiographs (N, %)	
Localized patchy alveolar infiltration	40 (62.5)
Bilateral interstitial infiltration	13 (20.3)
Lobar infiltration	9 (14.1)
Multilobar infiltration	2 (3.1)
Pleural effusion	6 (9.4)
Positive sputum culture (N, %)	47 (73.4)
Positive hemoculture (N, %)	22 (34.4)

cocci, while the remainder had no organisms (4.7%), gram-positive cocci in chains (3.1%), gram-negative coccobacilli (3.1%), or mixed organisms (3.1%). The major finding on chest radiograph was localized patchy alveolar infiltration (62.5%). The other findings were bilateral interstitial infiltration (20.3%), lobar infiltration (14.1%), multilobar infiltration (3.1%), and pleural effusion (9.4%). *S. pneumoniae* was isolated from sputum in 73.4% and from blood in 34.4% of patients.

Antimicrobial susceptibility

Penicillin-resistant *S. pneumoniae* was found in 22 of 64 (34.4%) cases. Resistance to other antimicrobial agents was: 51.6% to cotrimoxazole, 26.6% to tetracycline, 20.6% to erythromycin, 18.7% to lincomycin, 12.5% to chloramphenicol, and 1.6% to ampicillin. All of the *S. pneumoniae* isolates were sensitive to cephalothin (Table 3). The MICs of oxacillin resistant strains ranged between 0.25 and 0.75 μg/ml.

Risk factors for PRSP infection

The potential risk factors tested for association with PRSP infection were: age >65 years, multiple comorbidities, previous antibiotic use within 3 months, steroid use (>10 mg prednisolone/day), and alcoholism. Pencillin-resistant isolates were significantly associated with previous antibiotic use within 3 months and alcoholism (Table 4). On multivariate analysis to adjust for confounding factors, these two factors were still significantly correlated with PRSP infection, previous antibiotic use within 3 months (Adjusted OR 40.83, 95% CI 3.71 to 449.41) and alcoholism (Adjusted OR 8.82, 95% CI 1.25 to 62.46).

Prognosis and outcomes

The prognosis and outcomes of patients infected with PRSP and PSSP pneumonia were compared (Table 5). We could not demonstrate any difference in outcomes between these two groups. Bacteremia (PRSP 36.4%, PSSP 33.3%) and empyema thoracis (PRSP 9.1%, PSSP 7.1%) were more common complications in PRSP infection, but not statistically significant. Other complications, such as shock, need for mechanical ventilation and acute renal failure were not different. The length of stay, overall mortality, and pneumonia-related mortality were also nearly the same. Pneumonia-related deaths occurred in 9.1% of PRSP and 9.5% of PSSP patients (p = 0.96).

Table 3
Drug-susceptibility pattern of *S. pneumoniae* isolated from patients with CAP.

Drug	No. resistant strain (%)
Penicillin	22 (34.4)
Ampicillin	1 (1.6)
Cephalothin	0 (0)
Chloramphenical	8 (12.5)
Cotrimoxazole	33 (51.6)
Erythromycin	13 (20.6)
Tetracycline	17 (26.6)
Lincomycin	12 (18.7)

Table 4
Univariate and multivariate analysis of risk factors associated with PRSP pneumonia.

Variable	Cruded OR	Adjusted OR	95% CI	p-value
Age >65 years	0.36	0.23	0.04 to 1.21	0.08
Co-morbidity ≥2 diseases	1.03	3.70	0.87 to 15.80	0.08
Previous antibiotic use within 3 months	23.43	40.83	3.71 to 449.41	0.002[a]
Steroid use (>10 mg pred/day)	0.37	0.45	0.07 to 2.93	0.41
Alcoholism	5.88	8.82	1.25 to 62.46	0.03[a]

[a]p-value < 0.05

Table 5
Outcome of PRSP compared with PSSP pneumonia.

Outcome	PRSP (N=22)	PSSP (N=42)	p-value
Bacteremia, N (%)	8 (36.4)	14 (33.3)	0.81
Shock, N (%)	5 (22.7)	12 (28.6)	0.61
Mechanical ventilator, N (%)	7 (31.8)	20 (47.6)	0.22
Empyema thoracis, N (%)	2 (9.1)	3 (7.1)	0.78
Acute renal failure, N (%)	3 (13.6)	5 (11.9)	0.84
Length of stay, days (mean, SD)	12.2 (9.0)	15.5 (17.8)	0.43
Overall mortality, N (%)	2 (9.1)	5 (11.9)	0.73
Pneumonia-related mortality, (7 days), N (%)	2 (9.1)	4 (9.5)	0.96

DISCUSSION

S. pneumoniae was the major cause of hospitalized CAP (File, 2004), and affects a wide range of ages. Most of the patients had predisposed medical comorbidity. Severe CAP occurred in one-third of them. The clinical presentation and initial laboratory findings were indistinguishable from other bacterial pathogens (Niederman *et al*, 2001; Mandell *et al*, 2003). However, an attempt to collect adequate sputum should be performed (Musher *et al*, 2004). Microscopic examination of sputum samples before antibiotics were administered and the performance of culture within 24 hours yielded the diagnosis in about 70% of cases. The blood culture was positive in one-third of pneumococcal pneumonia cases.

Penicillin resistant pneumococci has become widespread and is a worldwide occurrence. Resistance to other classes of antibiotics traditionally used as alternatives in the treatment of pneumococcal infections has also increased markedly during recent years. β-lactam and macrolide antimicrobial agents are questionable in this situation (Feldman, 2004). Fluoroquinolones with enhanced anti-pneumococcal activity represent an attractive antimicrobial treatment option for community-acquired respiratory tract infections in adults (Zhanel *et al*, 2002).

In our study, the rate of penicillin resistant *S. pneumoniae* in community acquired pneumonia was 34.4%. When the MICs in the resistant cases was tested in the year 2001, all of them had intermediate resistance to penicillin. A previous study in Thailand found high resistance rates to penicillin were infrequent in CAP; 37% had intermediate resistance and 4.3% had high resistance (Sangthawan *et al*, 2003). At that time, *S. pneumoniae* was still susceptible to β-lactam and the amino-penicillin groups. In cases infected with intermediate resistant *S. pneumoniae*, high-dose of β-lactams or amino-penicillins could be used in our region. This administration was based on the time-dependent antibacterial property of the drugs to achieve serum concentrations exceeding the MIC (T>MIC), when the MIC of resistant strains was increased. However, the resistance rate of *S. pneumoniae* to cotrimoxazole, tetracycline, and erythromycin was high. These antimicrobial agents were not recommended as monotherapy, especially in patients with suspected *S. pneumoniae* infection (Cunha, 2002). In addition, the newer fluoroquinolones, effective against drug-resistant *S. pneumoniae*, should be reserved for use in patients with high-levels resistance strains. This can help limit the mutation of fluoroquinolone-resistant strains for *S. pneumoniae*, which have already been documented (Ho *et al*, 2001).

The two significant risks for PRSP infection on both univariate and multivariate analyses in our study were previous antibiotic use within 3 months and alcoholism. This finding was the same as a previous study by Clavo-Sanchez *et al* (1997). Other studies from Thailand (Dejthevaporn *et al*, 2000) and Japan (Yanagihara *et al*, 2004) showed that the only significant risk

factor was previous antibiotic use. According to the ATS guidelines (Niederman *et al*, 2001), aging, multiple comorbidities and steroid use are other risk factors for PRSP infection, but these were not significant risk factors in our study. Education regarding the inappropriate use of antibiotics should decrease the number of resistant strains of *S. pneumoniae*. Initial empirical therapy in patients with previous antibiotic use during the previous 3 months should cover drug-resistant *S. pneumoniae*.

The outcomes in pneumococcal pneumonia were not significantly affected by drug resistance. The percentages of bacteremia and empyema thoracis were higher in PRSP than PSSP. The pneumonia-related mortality rate was nearly the same. These outcomes may be due to intermediately resistant strains of PRSP. Falco *et al* (2004) reported that mortality in patients with pneumonia caused by penicillin intermediately resistant to pneumococci was not higher than with the susceptible strains. However, several studies have shown a significant association between mortality and high-levels of penicillin resistance (MIC >4 μg/ml) in *S. pneumoniae* (Feikin *et al*, 2000; Metlay *et al*, 2000; File, 2004). Therefore, monitoring the MIC levels of resistant *S. pneumoniae* to penicillin is very important, and antimicrobial agents active against highly penicillin resistant *S. pneumoniae* are required. This includes new generation fluoroquinolones, ketolides, vancomycin and linezolid (Jacobs, 1999). In the future, the interventions to limit the further emergence and spread of DRSP must included campaigns on the appropriate use of antibiotics and the introduction of pneumococcal conjugate vaccines (Nuermberger and Bishai, 2004).

In conclusion, previous antibiotic use within 3 months and alcoholism were the two significant risk factors for PRSP infection. In order to lessen this problem in Thailand, efforts should be made to improve correct antibiotic use. Morbidity, mortality, and length of stay were not significantly different in community-acquired pneumonia due to PRSP *vs* PSSP; perhaps because the *S. pneumoniae* had a low-level of resistance. β-lactams and aminopenicillins are still the antibiotics of choice for *S. pneumoniae* community-acquired pneumonia, and the overuse of fluoroquinolones may promote quinolone resistance in the future. Local regular surveillance of susceptibility pattern(s) of *S. pneumoniae* are required in order to develop local management guidelines.

ACKNOWLEDGEMENTS

The authors thank Mr Bryan Roderick Hamman for assistance with the English-language presentation of the manuscript.

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