RISK FACTORS FOR PENICILLIN-RESISTANT *STREPTOCOCCUS PNEUMONIAE* ACQUISITION IN PATIENTS IN BANGKOK

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Abstract. To identify risk factors for acquisition of penicillin-resistant *Streptococcus pneumoniae* (PRSP) in patients in Bangkok, using a case-control study, the study included patients with clinical specimens which grew *S. pneumoniae* during January to December 1997, treated at a teaching hospital in Bangkok. Penicillin susceptibility was determined by E-test and strains with MIC of >0.1µg/ml were considered resistant. Cases were the patients who had PRSP, and patients who had penicillin-susceptible *S. pneumoniae* (PSSP) were controls. The study variables included age 15 years or younger, immunocompromised status, ventilatory support, and antibiotic use or hospitalization within the previous 3 months. There were 73 cases and 51 controls. Their ages were 0 to 87 years, with median age of cases 4 and controls 49 years. Pneumonia was the most common type of infection, being 47% in cases and 45% in controls. Univariate analysis revealed significant association of PRSP acquisition with previous antibiotic use (p<0.0001), age ≤15 years (p=0.001) and previous hospitalization (p=0.002). Logistic regression analysis in order to adjust for confounding effects showed that the only significant risk factor was previous antibiotic use (OR 18.4; 95% Cl 6.2-54.6). The major risk factor for acquisition of PRSP in this study population is recent antibiotic use. Decreased antibiotic use would reduce risk of acquisition of PRSP.

INTRODUCTION

Streptococcus pneumoniae is a common cause of bacterial pneumonia, bacterial meningitis, and acute otitis media (Allen, 1991). Children (Appelbaum, 1987; Chesney, 1992) and the institutionalized elderly (Chesney, 1992) are particularly susceptible to *S. pneumoniae* infection. The emergence of penicillin resistance has posed serious problems in the treatment of pneumococcal diseases, especially meningitis. Clinical resistance to penicillin in *S. pneumoniae* was first reported from Boston in 1965 (Kislak *et al*,1965). Subseqntly, this phenomenon was reported from Australia in 1967 and South Africa in 1977 (Appelbaum, 1992). The problem of penicillin resistance has spread throughout the world (Appelbaum, 1992). Not only are penicillin-resistant *Streptococcus pneumoniae* (PRSP) resistant to other beta-lactams but they can also be resistant to erythroycin, tetracycline, rifampicin and trime-thoprim/sulfamethoxazole as well (M c C r a c k e n ,

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1995).

The frequency and severity of pneumococcal infections together with the increasingly rapid discovery of pneumococcal strains resistant to antimicrobial agents, underscore the need for developing more effective therapeutic, preventive and control measures (Clavo-S'anchez *et al*, 1997). Although PRSP infection may occur more often in the patients with identifiable predisposing conditions, Nava *et al* (1994) considered age 0-4 years, presence of immunosuppressive underlying disease, and previous use of beta-lactam antibiotics as factors for invasive infection by PRSP. Previously reported risk factors for infections by PRSP also include staying in the day care center or other closed environments in which antimicrobial use is common, nosocomial acquisition and underlying diseases in adults such as lymphoma, multiple myeloma, chronic lymphocytic leukemia, HIV infection, diabetes mellitus, renal insufficiency, hepatic cirrhosis (Musher, 1995). One study showed that patients with PRSP infections were more likely to have taken an antibiotic in the 3 months before their illness than those infected with penicillin-susceptible *S. pneumoniae* (PSSP) (Kronenberger *et al*, 1996). A study in Spain also showed that previous use of beta-lactam antibiotics, alcoholism, and noninvasive *S. pneumonia* disease were

associated with PRSP (Clavo-S'anchez *et al*, 1997).

In Thailand, PRSP is also an increasing problem. The risk factors for acquisition of PRSP in population in Thailand may be different from other countries. We conducted a case-control study to identify risk factors for PRSP infection in Thai patients treated at a medical school hospital in Bangkok, Thailand.

MATERIALS AND METHODS

Patients

A case-control study was performed at Ramathibodi Hospital which is a 900-bed teaching hospital in Bangkok. All patients with positive cultures for *S. pneumoniae* treated at this hospital during January to December 1997 were included in the study. Cases were patients with positive cultures for PRSP, and controls included patients with positive cultures for PSSP.

Microbiology

Clinical specimen cultures were performed by standard microbiology methods at the hospital microbiology laboratory. Susceptibility test for penicillin was assessed by using E-test and the organisms with minimum inhibitory concentration to penicillin G of > 0.1 μg/ml was diagnosed as PRSP (Clavo-S'anchez *et al,* 1997; Baquero *et al* 1991).

Data collecfion

The medical records of the study patients were reviewed and information was extracted in data extraction forms. The study factors included age, underlying diseases, previous antibiotic use, use of mechanical ventilator, and previous hospitalization.

Definition

The patients were classified as immuno-compromised hosts if they had any conditions or diseases such as infection with human immuno-deficiency virus, diabetic mellitus, alcoholism, chronic airway diseases, hepatic cirrhosis, malignancy, steroid therapy, connective tissue diseases, or immuno-suppressive drug use. Previous antibiotic use was defined as any records in the medical records of antimicrobial prescription during the previous three months. Previous hospitalization was an admission to any hospital during the immediate three months prior to this admission. Bacteremia was defined as positive blood cultures for *S. pneumoniae* with no evidence of focal infection. Pneumococal pneumonia was diagnosed when a patient had clinical evidence of lower respiratory tract infection, as well as a pulmonary infiltrate on chest radiography, and when *S. pneumoniae* was isolated from cultures of one or more of the following specimens: sputum, blood, pleural fluid, specimens obtained by transthoracic needle aspiration or bronchoalveolar lavage. Meningitis was defined as having compatible clinical picture together with positive cerebrospinal fluid (CSF) cultures for *S. pneumoniae*. Invasive pneumococcal disease was defined as clinical evidence of infection and isolation of *S. pneumoniae* from clinical specimens obtained from blood, CSF, pus, pleural fluid, and sputum. Nosocomial infection was defined as any infection that developed after three days of hospitalization.

Analysis

The Student unpaired *t*-test and chi-square test were applied in the univariate analysis for continuous and categorical data, respectively. Logistic regression analysis was used to determine the risk factors of PRSP adjusting for confounders. STATA software version 5.0 was used for all analysis (Stata Crop, 1997). The type I error (α error) was set at 0.05

RESULTS

Clinical characteristics of patients

A total of 160 patients who had positive cultures for *S. pneumoniae* were identified from the microbiological laboratory records, and the medical records were available for 124 of those patients. Seventy-three (59%) patients had PRSP and fifty-one (41%) patients had PSSP. Clinical characteristics of the study patients are shown in Table1. Ages of the study population ranged from 3 months to 87 years with a median of 21 years. Sixty patients (48%) were children 0-15 years old with a median of 1.5 years, and sixty-four patients (52%) were adults whose ages were 16-87 years with a median of 58 years. The median ages of cases and controls were 4 and 49 years, respectively. Seventy-one percent of patients lived in Bangkok.

Thirty-seven percent of the clinical specimens from the study patients were sputum fol-

lowed by nasopharyngeal secretion (23%), blood (11%), tracheal suction (7%), and pus (7%). In addition, 7% of the patients had positive culture specimens from multiple sites. Sites of pneumococcal infection included pneumonia (46%), sinusitis (5%), bacteremia (5%), bronchiectasis (4%), meningitis (3%), otitis media (3%), and bronchitis (3%). Respiratory tract was the most common system (70%), and pneumonia was the most common type of infection being 47% in cases and 45% in controls. One hundred patients (81%) had invasive diseases, and 104 (84%) patients had community-acquired

infection. Death occurred in 7/73 (10%) of cases and 3/51 (6%) of controls, which did not achieve statistically significant difference (p=0.42).

Risk and risk factors for PRSP infection/colonization

Univariate analysis: Table 2 demonstrates results of univariate analysis comparing characteristics of cases and controls. Fifteen patients (29.4%) of PSSP group and 45 (61.6%) patients of PRSP

Table 1

General characteristics of patients with pneumococcal infection and susceptibility of the isolates to penicillin.

Characteristic	Penicillin susceptibility		Total	p-value
	Susceptible	Resistant		
Sex				0.92
Male	34 (66.7)	48 (65.7)	82 (66.1)	
Female	17 (33.3)	25 (34.2)	42 (33.9)	
Age				<0.0001
≤ 15 years	15 (29.4)	45 (61.6)	60 (48.4)	
> 15 years	36 (70.6)	28 (38.4)	64 (51.6)	
Province				0.09
Bangkok	32 (62.7)	56 (76.7)	88 (71.0)	
Rural	19 (37.3)	17 (23.3)	36 (29.0)	
Culture specimens				0.31[a]
Respiratory secretion	31 (60.8)	56 (76.7)	87 (70.2)	
Blood	10 (19.6)	10 (13.7)	20 (16.1)	
Pus	6 (11.8)	3 (4.1)	9 (7.3)	
Cerebrospinal fluid	2 (3.9)	2 (2.7)	4 (3.2)	
Others	2 (3.9)	2 (2.7)	4 (3.2)	
Types of infection				0.87[a]
Lower respiratory infection	29 (56.9)	45 (61.6)	74 (59.7)	
Upper respiratory infection	4 (7.8)	6 (8.2)	10 (8.1)	
Meningitis	2 (3.9)	2 (2.7)	4 (3.2)	
Abscess	1 (2.0)	0 (0.0)	1 (0.8)	
Bacteremia	3 (5.9)	3 (4.1)	6 (4.8)	
Other infections[b]	3 (5.9)	2 (2.7)	5 (4.0)	
Colonization	9 (17.6)	15 (20.5)	24 (19.3)	
Invasive diseases				0.69
Yes	42 (82.3)	58 (79.4)	100 (80.6)	
No	9 (17.7)	15 (20.6)	24 (19.4)	
Modes of acquisition				0.54
Community	44 (86.3)	60 (82.2)	104 (83.9)	
Nosocomial	7 (13.7)	13 (17.8)	20 (16.1)	
Clinical outcomes				0.42
Cure	48 (94.1)	66 (90.4)	114 (91.9)	
Death	3 (5.9)	7 (9.6)	10 (8.1)	

[a]Exact test

[b]Cholangitis 1, corneal ulcer 3, septic arthritis 1

Table 2

Univariate analysis of risk factors associated with penicillin-resistant *Streptococcus pneumoniae*.

Variables	Penicillin-susceptibility		Total	OR (95%CI)	p-value
	Susceptible	Resistant			
Age					
≤ 15 years	15 (29.4)	45 (61.6)	60 (48.4)	3.86 (1.79-8.29)	
> 15 years	36 (70.6)	28 (38.4)	64 (51.6)	1	0.001
Compromised host status					
Yes	33 (64.7)	51 (69.9)	84 (67.7)	1.26 (0.59-2.71)	0.55
No	18 (35.3)	22 (30.1)	40 (32.3)	1	
Invasive disease					
Yes	42 (82.4)	58 (79.4)	100 (80.6)	0.83 (0.33-2.07)	0.69
No	9 (17.6)	15 (20.6)	24 (19.4)	1	
On mechanical ventilator					
Yes	5 (9.8)	11 (15.1)	16 (12.9)	1.63 (0.53-5.02)	0.40
No	46 (90.2)	62 (84.9)	108 (87.1)	1	
Previous antibiotic use					
Yes	6 (11.8)	57 (78.1)	63 (50.8)	26.72 (9.67-73.83)	<0.0001
No	45 (88.2)	16 (21.9)	61 (49.2)	1	
Previous hospitalization					
Yes	4 (7.8)	24 (32.9)	28 (22.6)	5.76 (1.86-17.84)	0.002
No	47 (92.2)	49 (67.1)	96 (77.4)	1	

group were 15 years and younger (OR 3.9; 95% Cl 1.8, 8.3). The proportion of patients with previous antibiotic use was much higher in PRSP group than in PSSP group (78.1% *vs* 11.8%: OR 26.7; 95% CI 9.7, 73.8). It was also found that the proportion of patients in PRSP group that had ever been admitted to a hospital during the previous three months was more than those of PSSP group (32.9% *vs* 7.8%; OR 5.8; 95% Cl 1.9, 17.8). The proportion of patients with immunocompromising status or using mechanical ventilator were not differerent between groups (p=0.55 and 0.40 respectively).

Mulivariate analysis: Multivariate analysis to adjust for confounding factors was performed. Three variables that were found significantly different between groups in univariate analysis were included in the logistic model. The goodness of fit of this model was assessed and it was found that the model fitted well (p=0.15). In addition, the interaction among the immunocompromising status and the other four factors were determined. Since their effects did not improve explanation of risk for PRSP acquisition, they were not included in the final model. After controlling for confounding

variables, only previous antibiotic use was a significant risk for PRSP acquisition: the patients with PRSP had the odds of antibiotic use 18.4 (95% Cl 6.2-54.6) times compared to the patients with PSSP. Age15 years and younger, and previous hospitalization were not detected as risk factors for PRSP acquisition (OR 1.7; 95%CI 0.6, 4.7)

DISCUSSION

It was shown by univariate analysis in this study in Thai population that there is statistically significant difference between cases and controls for proportions of patients who were aged 15 years and younger, previous antibiotic use, and previous hospital admission; but not for immunocompromising status or the use of a mechanical ventilator. However, the only adjusted risk factor was the previous use of antibiotics.

It was found among the patients who acquired *S. pneumoniae* in this study that children 15 years of age and younger have a higher proportion of PRSP infection. This suggests that PRSP problem is more important in children than in adults in this population. The data also shows that

children had previously received antibiotics more often than adults (68% *vs* 28%). Age was not detected as a risk factor for PRSP acquisition after adjusting for confounding variables, especially previous antibiotic use.

It was found in univariate analysis that previous hospitalization within 3 months is associated with PRSP acquisition, but not after adjusting for confounding factors in multivariate analysis. One explanation is that previous hospitalization had statistical association with previous antibiotic usage (36% *vs* 8%, p< 0.001). This study also showed that the patients with invasive pneumococcal disease did not have lower risk of infection by PRSP than those with noninvasive diseases, which agrees with a previous report (Clavo-S'anchez *et al*, 1997). Immunocompromising status was not found to be associated with PRSP acquisition in this study. Although immunocompromised hosts were susceptible to invasive *S. pneumoniae* infection (Baquero *et al*, 1991), it was not found in this study that they have increased risk for acquisition of penicillin-resistant strains.

The only factor that shows statistically significant association with PRSP acquisition after adjusting for confounding factors in multivariate analysis is the previous use of antibiotic. Baquero *et al* (1991) mentioned that the repetitive use of beta-lactam agents exerted a selection effect on the pneumococcal strains in carriers, therefore leading to the emergence of resistant strains. Limitation of this study is that the data was retrospectively obtained from medical records. There is possibility that antibiotic use may be underestimated, but underestimation would likely occur similarly in both cases and controls.

It was concluded from this case-control study in Thai patients that there is strong association between previous antibiotic use and acquisition of PRSP. In order to lessen problems from rapid rising of PRSP strains in Thailand, efforts should be placed on improving use of antibiotics.

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