

Clinical Characteristics of Pneumonia Caused by Penicillin Resistant and Sensitive *Streptococcus pneumoniae* in Japan

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Abstract

Background *S. pneumoniae* is the leading cause of morbidity and mortality worldwide. β -lactam antibiotics were very effective against *S. pneumoniae*, however resistance to this class of antibiotic has become an increasing problem.

Objectives To assess the clinical differences between penicillin-sensitive and penicillin-resistant pneumococcal pneumonia.

Methods The medical records of 306 patients with pneumococcal pneumonia who visited Nagasaki University Hospital or affiliated institutions between January 1997 and December 2001 were retrospectively reviewed. The Pneumonia Severity Index (PSI), sensitivity of *S. pneumoniae*, antibiotic choices and information on clinical outcome were evaluated.

Results Penicillin sensitive and resistant organisms were responsible for 177 (57.7%) and 129 (42.0%) cases of pneumonia, respectively. The median age of patients was 65.5 years, and 72.3% (222) were males. There were no significant differences in the resistance rate between elderly (>65 years) and young patients. The median PSI score was 76. No significant association was observed between the severity of illness and sensitivities of *S. pneumoniae*. Previous use of beta-lactams in the last 3 months and chronic obstructive pulmonary disease were associated with penicillin resistance. The failure rate of first line antibiotics was significantly higher in the resistant group (22.5%) than in the sensitive group (9.0%). Four of 306 patients died (mortality, 1.3%).

Conclusion There were no significant differences cli-

nically between the penicillin-sensitive and penicillin-resistant groups. The failure rate of first line antibiotics was higher in the resistant than in the sensitive group. Thus, the selection of antimicrobial agents should be carefully considered in the context of the patient's risk factors.

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Key words: *Streptococcus pneumoniae*, penicillin-resistance, COPD, risk factor

Introduction

Streptococcus pneumoniae is an important pathogen in many community-acquired respiratory infections, including community-acquired pneumonia, acute bacterial sinusitis, acute otitis media, and in more invasive infections, such as meningitis and bacteremia. *S. pneumoniae* is the leading cause of morbidity and mortality worldwide. β -lactam antibiotics were very effective against *S. pneumoniae*, however resistance to this class of antibiotic has become an increasing problem. The first isolate of penicillin-resistant *S. pneumoniae* (PRSP) of recognized clinical significance [minimum inhibitory concentration (MIC) = 0.5 μ g/ml] was recovered in Australia (1). PRSP became widespread in many parts of the world during the 1980s (2). In Japan, the reported rate of penicillin resistance among the pneumococci ranges from 30 to 46% (3, 4). Furthermore, the resistance rate is as high as 60% in some parts of Latin America (5) and 80% in Korea (6). Given the high incidence of both pneumococcal pneu-

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monia and drug resistance, the importance of studying the effects of resistance to antibiotics on mortality and other important clinical outcome variables in this disease is obvious.

Previous comparative clinical studies of penicillin resistant and sensitive pneumococcal pneumonia (7, 8) revealed some new aspects of this association. However, there are no comprehensive comparative studies in Asian countries, including Japan, although PRSP pneumonia is prevalent in this region. The purpose of the present study was to determine the clinical differences between pneumonia caused by PRSP and penicillin-sensitive *S. pneumoniae* (PSSP) and to identify risk factors for PRSP pneumonia.

Materials and Methods

The medical records of all patients who visited Nagasaki University Hospital and affiliated institutions from January 1997 to December 2001 were reviewed. All patients with pneumococcal pneumonia were retrospectively evaluated. One hundred and twenty-nine cases of PRSP-induced pneumonia were compared with 177 cases of PSSP. Age, sex, underlying diseases, clinical features, antibiotic use (obtained from clinical notes), treatment, clinical results, bacteriological effects and complications were compared.

In addition to demographic data, the selected antibiotics, subsequent changes of antibiotics, frequency of antibiotic change, complications and outcome were recorded. The Pneumonia Severity Index (PSI) score as defined by Fine et al (9) was also calculated.

Diagnostic criteria

Pneumonia was defined as the presence of symptoms of lower respiratory tract infection along with a new infiltrate on chest radiography and no emerging alternative diagnosis during follow-up. The diagnosis of pneumococcal pneumonia was considered probable in patients with sputum culture positive for *S. pneumoniae*. It was classified as definite if one of the following criteria was met: a culture yielding *S. pneumoniae* exclusively, or the presence of the organism in: 1) blood culture; 2) pleural fluid; 3) a transthoracic needle aspirate; 4) a tracheobronchial aspirate with $\geq 10^5$ cfu/ml; 5) a protected specimen brush (PSB) sample with $\geq 10^3$ cfu/ml; 6) a bronchoalveolar lavage fluid (BALF) specimen with $\geq 10^4$ cfu/ml; or 7) sputum with $\geq 10^7$ cfu/ml (7).

Identification of bacteria

Gram-stained smears and quantitative cultures of adequate sputum samples according to the criteria of Bartlett (10) were performed by standard methods. Culture plates were incubated overnight in a 50% CO₂ incubator. Optochin sensitivity and bile solubility tests were performed for confirmation of suspected colonies of *S. pneumoniae*.

Microbiological data regarding all pneumococcal isolates during the period of interest were obtained from laboratory records. Isolates were classified as PSSP if the MIC was < 0.12 $\mu\text{g/ml}$, or as PRSP if the MIC was ≥ 0.12 $\mu\text{g/ml}$.

Table 1. Clinical Characteristics and Laboratory Finding in Patients Infected with Penicillin-sensitive (PSSP) and Penicillin-resistant *S. pneumoniae* (PRSP)

	PSSP	PRSP
n	177 (57.8%)	129 (42.2%)
Mean age (years)*	67.1 \pm 1.2	65.7 \pm 1.6
Sex (male/female)	131/46	91/38
(%)	(74.0/26.0)	(70.5/29.5)
Over 65 years of age	118 (66.7%)	82 (64.1%)
Death	1	3
Underlying disease		
COPD	26 (14.7%)	33 (25.6%)**
Cerebrovascular damage	10 (6.8%)	12 (9.3%)
Malignant disease	19 (10.7%)	10 (7.8%)
Old tuberculosis	17 (9.6%)	9 (7.0%)
Diabetes mellitus	14 (7.9%)	10 (7.8%)
Heart disease	17 (10.7%)	17 (13.2%)
Others	43 (24.3%)	28 (21.7%)
None	50 (28.2%)	33 (25.6%)
Body temperature ($^{\circ}\text{C}$)*	37.8 \pm 0.1	38.1 \pm 0.1
Leukocyte count*	11,824 \pm 373	11,410 \pm 405
CRP*	13.4 \pm 0.7	12.1 \pm 0.7

*Data are mean \pm SEM. **p<0.05, compared with the PSSP group.

Antimicrobial treatment

The exact design of the initial antimicrobial treatment regimen was the responsibility of the physician in charge. The first antibiotic was changed only in the case of clinical non-response to this treatment.

Statistical analysis

All data were expressed as mean \pm SEM. Differences between qualitative variables were examined for statistical significance using both the χ^2 test and Fisher's exact test. A *P* value of less than 0.05 denoted the presence of a statistically significant difference.

Results

Epidemiological characteristics and risk factors

The number of episodes, ratio of males to females, mean age and laboratory data (leukocyte counts and C reactive protein) did not differ between PRSP group and PSSP group (Table 1). Chronic obstructive pulmonary disease (COPD) was associated with penicillin resistance. Four patients (three patients with PRSP and one patient with PSSP) of 306 (1.3%) patients died as a result of the infection (Table 1). None of the patients received pneumococcal vaccination.

We also examined previously reported risk factors for infection caused by PRSP (8, 11). Previous use of beta-lactams was associated with penicillin resistance, whereas age of 65 years, alcoholism, immunosuppressive illness, multiple medical co-morbidities and exposure to a child in a day care center were not (Table 2).

Table 2. Comparison between PSSP and PRSP Pneumonia with Regard to Risk Factors of Infection with Penicillin Resistant *S. pneumoniae*

	PSSP	PRSP	P value
n	177	129	
Age >65 years	114 (65.5%)	79 (61.2%)	N.S.
β -lactam therapy within the past 3 month	12 (6.9%)	21 (16.3%)	p<0.01
Alcoholism	5 (2.9%)	4 (3.1%)	N.S.
Immunosuppressive illness	25 (14.4%)	18 (14.0%)	N.S.
Multiple medical comorbidities	45 (25.9%)	42 (32.6%)	N.S.
Exposure to a child in a day care center	13 (7.5%)	14 (10.9%)	N.S.
Smoking	60 (34.5%)	46 (35.7%)	N.S.

Table 3. PSI Scores by Penicillin Resistance Status

Resistance	PSI Grade					Total
	I	II	III	IV	V	
PRSP	26	28	34	35	6	129
PSSP	25	54	52	39	7	177
Total	51	82	86	74	13	306

The PSI scores of all patients, with and without PRSP, are shown in Table 3. The median PSI score was 76 (class I: 51; 16.6%, class II: 82; 26.8%, class III: 86; 28.1%, class IV: 74; 24.2%, class V: 13; 4.2%). No significant association was observed between the severity of illness and sensitivities of *S. pneumoniae*. There was no difference between the two groups with regard to the mean total number of points on the PSI.

Treatment

Table 4 lists various features of chemotherapy for patients with pneumococcal pneumonia. The response rate to first choice antibiotic was significantly higher in the PSSP group (90.0%) than in the PRSP group (79.1%) (p<0.01). The number of cases that received antibiotics for more than 7 days tended to be greater in the PRSP than the PSSP group, but the difference was not statistically significant. A higher proportion of patients with PSSP had a short duration of fever than those with PRSP (p<0.01) (Table 4).

The first line antibiotics and the medication modifications are listed in Table 5. The antibiotic choice tended to be similar between the two groups. Only 10% of patients were treated with oral antibiotics. The main antibiotics used for treatment in both resistant and sensitive groups were penicillins, cephalosporins and carbapenems. Most antibiotics were administered in typical amounts. The number of cases with medication modifications was fewer in the PSSP group than in the PRSP group.

Discussion

Streptococcus pneumoniae remains a major cause of infection, annually resulting in significant morbidity and mortality. The past two decades have seen an alarming worldwide increase in the incidence of PRSP, and thus it is very important to treat patients with PRSP pneumonia.

In this study, we investigated the incidence of and risk factors for drug resistance in *S. pneumoniae*, and its impact on antimicrobial treatment and outcome. The important findings of our study were as follows: 1) The incidence of resistance to penicillin was very high (40%); 2) The severity of pneumonia and death rate were not affected by drug resistance; 3) COPD and previous antibiotic use were associated with drug resistance; 4) The response rates to first line antibiotics were significantly higher in the PSSP group than in the PRSP group, and the duration of fever was shorter in the PSSP group than in the PRSP group.

The incidence of PRSP pneumonia observed in our study was similar to that in other reports (7, 8). No difference was reported between the PSSP and PRSP group for the mean number of points on the PSI. Recently, a complex relationship was reported between acquisition of β -lactam resistance and loss of virulence in *S. pneumoniae* (12). However, other clinical investigations (7, 8), including the present report, have not supported this finding. There is a discrepancy between basic and clinical research. Risk factors for penicillin resistant *S. pneumoniae*, such as age <2 or >65 years, antibiotic therapy within 3 months, alcoholism, medical comorbidities, immunosuppressive illness or therapy, and exposure to a child in a day care center, have been identified

Table 4. Antibiotic Therapy for Pneumonia Caused by Penicillin-sensitive (PSSP) and Penicillin-resistant *S. pneumoniae* (PRSP)

	PSSP	PRSP	P value
n	177	129	
Response rate to first choice antibiotic	160 (90.0%)	102 (79.1%)	p<0.01
Duration of antibiotic therapy			
Up to 7days	67 (38.0%)	40 (31.0%)	N.S.
More than 7days	110 (62.0%)	89 (69.0%)	
Duration of fever			
Up to 3 days	123 (69.5%)	71 (55.0%)	p<0.01
More than 3 days	54 (30.5%)	58 (45.0%)	

Table 5. Changes of Antibiotics

	PSSP	PRSP
	change/cases (%)	change/cases (%)
Oral	3/24 (12.5%)	3/11 (27.2%)
penicillins	0/0	0/1
cephalosporins	1/7	1/2
macrolides	1/3	2/3
new-quinolones	1/12	0/5
others	0/2	0/0
Intravenous	13/153 (8.4%)	23/118 (19.8%)
penicillins	5/35	8/31
cephalosporins	4/61	13/49
carbapenems	2/50	0/29
new-quinolones	2/4	0/1
others	0/3	2/8
Total	16/177 (9.0%)	26/129 (20.2%)*

*p<0.05, compared with PSSP.

by other investigators (8). However, our study suggested that only one risk factor (previous use of antibiotics within 3 months) was associated with penicillin resistance. It is not yet clear that these risk factors are specific enough for individual patients to be clinically reliable. The possible reason is that the number of mild cases (PSI I or II) in our study is larger than that in other reports. A larger study is necessary to obtain more accurate data. We found that COPD was also a risk factor for penicillin resistance. To date, there have been no reports describing the relationship between COPD and PRSP. Recently, it was shown that the intra-alveolar immune response to pneumococcal infection was impaired in mice with experimental emphysema (13). This report may be consistent with our data. The frequent use of antibiotics in patients with COPD is considered as another reason.

The main antibiotics used for treatment in both groups were penicillins, cephalosporins and carbapenems. The response rates were significantly higher in the PSSP group (90.0%) than in the PRSP group (79.1%) (p<0.01) (Table 4). In particular, penicillins and cephalosporins failed to treat 8/31 and 13/49 patients, respectively. In contrast, the effica-

cy of carbapenems in the PRSP group was 100% (Table 5). These results suggest that it may be necessary to use carbapenems as first line antibiotics for patients with previous therapy of β -lactams or COPD. A higher dose of penicillins is another option (14). The number of patients with severe pneumonia (PSI=IV or V) that we observed was lower than in another report (15). Thus, the mortality rate (1.3%) of patients with pneumococcal pneumonia in our study was lower than the previously reported rate (7, 8, 15). The low mortality might be related to the fact that most hospitals in the present study did not have an emergent outpatient unit.

In conclusion, the present study suggested that there were no significant clinical differences between penicillin-sensitive and penicillin-resistant groups. Our study also showed that previous use of β -lactams and COPD were associated with penicillin resistance in *S. pneumoniae*. The failure rate of first line antibiotics was higher in the resistant group than in the sensitive group. Our findings indicate that the selection of antimicrobial agents should be considered in the context of patients' risk factors for penicillin resistance.

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