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Risk Factors for Penicillin Resistance and Mortality in Korean Adults with *Streptococcus pneumoniae* Bacteremia

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Abstract A retrospective analysis was performed to measure the incidence of pneumococcal bacteremia and to identify risk factors for penicillin resistance and prognostic factors for outcome in adults. A total of 151 cases of pneumococcal bacteremia were identified from 149 adults during the period 1996–2000. The overall rate of penicillin resistance was 49%, ranging from 54.2% in 1996 to 48.5% in 2000 (P=0.93). Rates of resistance to ceftriaxone, clindamycin, erythromycin, and trimethoprim-sulfamethoxazole were 21.6%, 51%, 62%, and 44.7%, respectively. Multidrug resistance was documented in 47.7% of the cases. Penicillin resistance was significantly associated with solid tumor, biliary drainage catheter, and previous β-lactam therapy in the univariate analysis. However, the associations were not as significant as independent risk factors in the multivariate analysis. Mortality was 23.8% and did not change significantly during the study period (P=0.06). Mortality rates in cases caused by penicillin-susceptible *Streptococcus pneumoniae* and penicillin-resistant *Streptococcus pneumoniae* were 23% and 24.7%, respectively (P=0.81). Mortality was not significantly influenced by penicillin resistance, even high-level resistance (24.4% vs. 20%; P=0.64). Multivariate analysis revealed that antineoplastic chemotherapy, respiratory failure, and acute renal failure were independent prognostic factors for mortality. In conclusion, the rate of penicillin resistance among pneumococcal blood isolates was high in the late 1990s, but penicillin resistance, and even high-level penicillin resistance, was not significantly associated with increased mortality in adults with pneumococcal bacteremia.

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Introduction

Resistance of *Streptococcus pneumoniae* to penicillin is now widespread and rapidly increasing worldwide [1]. Although the incidence of penicillin-resistant *Streptococcus pneumoniae* (PRSP) strains varies considerably, it is extremely high in some areas [2, 3, 4, 5, 6, 7]. In Korea, penicillin resistance showed a sharp increase at the beginning of the 1990s, peaking at 78% in 1998 [8]. Studies document an increasing trend in multidrug resistance among PRSP strains; increasing levels of resistance to β-lactam antibiotics correspond with increasing resistance to other antibiotics, such as the macrolides, tetracyclines, and trimethoprim-sulfamethoxazole (TMP-SMX) [2, 3, 4, 5, 6, 7, 8, 9].

The emergence of penicillin resistance and resistance to other antibiotics has important implications for treatment, because infections due to PRSP strains pose serious problems for therapy [10]. The clinical impact of PRSP strains has not been clearly defined, although invasive systemic infections due to PRSP strains have been reviewed [11, 12, 13, 14, 15, 16, 17, 18, 19]. However, these reports were mainly from Western countries, where rates of penicillin resistance in pneumococci were relatively low. There have been few detailed reports from areas with high rates of penicillin resistance, especially from Asian countries [20].

We conducted a retrospective analysis to measure the incidence of pneumococcal bacteremia and to identify risk factors for penicillin resistance and prognostic factors for outcome in adults in Korea, which is known to have the highest rate of pneumococcal resistance to penicillin in the world.

Materials and Methods

This study was carried out in the Asan Medical Center, a 2,200-bed tertiary-care university-affiliated hospital in Seoul, Korea, with approximately 60,000 admissions annually. Patients with pneumococcal bacteremia were identified by reviewing the blood culture logbook at the clinical microbiology laboratory. We reviewed the medical records of all patients who had pneumococcal bacteremia between January 1996 and December 2001. Demographic, clinical, and microbiologic data were obtained according to a standardized protocol. Pediatric patients under 15 years of age were excluded.

Identification and Antimicrobial Susceptibility Testing of Blood Isolates

Blood cultures were processed using the Bactec 9240 system (Becton Dickinson, USA). *Streptococcus pneumoniae* was identified by standard methods. All isolates were screened for penicillin resistance using 1 μg oxacillin disks. Susceptibility to penicillin and ceftriaxone was defined by an inhibition zone diameter of ≥20 mm. MICs of penicillin and ceftriaxone were determined by the E test (AB Biodisk, USA) beginning in July 1996 but were not determined for isolates obtained before June 1996. Pneumococcal isolates were defined as penicillin susceptible (PSSP) when MICs were <0.1 μg/ml, as intermediately resistant when MICs were 0.1–1.0 μg/ml, and as highly resistant when MICs were ≥2.0 μg/ml [21]. Susceptibility to other antibiotics was determined by the disk diffusion method, and results were interpreted by NCCLS criteria [22]. To clarify the terminology used in the present study, we classified all strains that were not susceptible to penicillin as penicillin-resistant *Streptococcus pneumoniae* (PRSP). Pneumococcal strains resistant to three or more classes of antibiotic were considered multidrug resistant [1].

Definitions

Bacteremia was defined by the isolation of pneumococci from more than one blood culture. Each episode of bacteremia recorded on a separate admission was considered a new case. The date of collection of the first blood culture from which pneumococci were isolated was considered the date of onset of bacteremia. Bacteremia was considered nosocomial (i) if a positive blood culture was obtained after 48 h of admission and, additionally, there was no evidence of pneumococcal infection at the time of admission; or (ii) if infections were acquired at other hospitals before transfer to the study hospital. Otherwise, bacteremia was considered community acquired. Polymicrobial bacteremia was considered to occur when more than one organism was isolated from blood culture(s). Antineoplastic chemotherapy was defined as antineoplastic therapy for a solid tumor or hematologic malignancy within 2 weeks of the onset of bacteremia. Immunosuppressive therapy was defined as receipt of corticosteroids or other immunosuppressive agents except the above antineoplastic agents within the previous month. Invasive procedures included gastroscopy with or without sclerotherapy, bronchoscopy, endoscopic retrograde cholangiopancreatography, and insertion or dilatation of a percutaneous transhepatic biliary drainage catheter. Previous hospitalization was defined as admission to any hospital during the previous 6 months. Prior use of antibiotics was defined as the receipt of any antibiotics within the previous month. Leukopenia was defined as a leukocyte count of <4,000 cells/mm^3. Septic shock was defined as systolic blood pressure <90 mmHg or reduction of >40 mmHg from baseline with clinical signs of peripheral hypoperfusion. Adult respiratory distress syndrome was defined as diffuse pulmonary infiltrate in a patient with a PaO_2/FIO_2 ratio of <200 mmHg and without evidence of left ventricular dysfunction or fluid overload. Acute renal failure was defined as a serum creatinine level of >2 mg/dl in a patient with no known chronic renal insufficiency.

The primary site of infection was determined on the basis of clinical data and/or by a culture of tissue that was positive for pneumococci. Pneumococcal meningitis was defined as either a cerebrospinal fluid (CSF) culture that was positive for pneumococci or a CSF profile that was consistent with meningitis. Pneumococcal pneumonia was diagnosed if a patient had a clinically evident lower respiratory tract infection and a radiographically evident pulmonary infiltrate. The case was classified as primary bacteremia when no clear site of focal infection had been documented. Outcome was evaluated at discharge or 1 month after treatment was started. The death of a patient was considered unrelated to the bacteremia if the patient died of other conditions that were obviously documented to be the direct cause of death. Otherwise, death was considered related to the bacteremia.

Statistical Analysis

Univariate analyses were performed by using either the chi-square test or Fisher's two-tailed exact test (for small expected values) for categorical variables and Student's *t*-test for continuous variables. To demonstrate the relation of each variable to penicillin resistance and to poor outcome, multivariate analyses included all study variables and were performed with stepwise logistic regression. *P* values <0.05 were considered statistically significant. All statistical analyses were performed using SAS software version 6.12 (SAS Institute, USA).

Results

During the study period, 199 episodes of pneumococcal bacteremia were documented. Of the 199 episodes, 48 occurred in children under 15 years of age. The remaining 151 episodes in 149 adult patients were analyzed. Two patients had recurrent episodes of pneumococcal bacteremia on two separate admissions. The mean age of the patients was 55.7 years (range, 18–90 years), and 51 patients (33.8%) were ≥65 years of age. Of the 151 cases, 102 (67.5%) occurred in males.

Trends in Antibiotic Resistance Patterns

Of the 151 isolates, 77 (51%) were penicillin susceptible. The remaining 74 (49%) isolates were penicillin resistant, with 46 isolates exhibiting intermediate resistance and 25 exhibiting high-level resistance (MICs of penicillin were not determined for 3 isolates). Trends in antibiotic resistance are summarized in Table 1. Of the isolates tested, 21.6%, 51%, 62%, and 44.7% were resistant to ceftriaxone, clindamycin, erythromycin, and TMP-SMX, respectively. All isolates tested were susceptible to vancomycin. Multidrug resistance was documented in 47.7%. Over the 5-year study period, the incidence of penicillin-resistant pneumococcal bacteremia remained stable (P=0.93). There was an overall decrease in the proportion of ceftriaxone-resistant pneumococcal bacteremia from 38.1% in 1996 to 15.2% in 2000, although it was not statistically significant (P=0.08). The rate of resistance to clindamycin increased from 41.7% in 1996 to 63.6% in 2000. There also was a trend of increase in the rate of resistance to erythromycin, from 58.3% in 1996 to 78.8% in 2000. The incidence of pneu-

Table 1 Temporal trend of resistance to antibiotics among blood isolates during the period 1996–2000

Antibiotic[a]	No. of resistant isolates/total no. of isolates (%)						*P* value[b]
	Overall (%)	Year					
		1996	1997	1998	1999	2000	
Penicillin	74/151 (49.0)	13/24 (54.2)	12/29 (41.4)	15/28 (53.6)	18/37 (48.6)	16/33 (48.5)	0.93
Ceftriaxone	32/148 (21.6)	8/21 (38.1)	6/29 (20.7)	6/28 (21.4)	7/37 (18.9)	5/33 (15.2)	0.08
Clindamycin	76/149 (51.0)	10/24 (41.7)	14/29 (48.3)	12/26 (46.2)	19/37 (51.4)	21/33 (63.6)	0.10
Erythromycin	93/150 (62.0)	14/24 (58.3)	15/29 (51.7)	19/28 (67.9)	19/36 (52.8)	26/33 (78.8)	0.13
TMP-SMX	67/150 (44.7)	12/24 (50.0)	13/28 (46.4)	13/28 (46.4)	15/37 (40.5)	14/33 (42.4)	0.47
Multidrug	72/151 (47.7)	12/24 (50.0)	12/29 (41.4)	13/28 (46.4)	17/37 (45.9)	18/33 (54.5)	0.59

[a] Susceptibility to ceftriaxone in 3 isolates, to clindamycin in 2 isolates, to erythromycin in 1 isolate, and to TMP-SMX in 1 isolate was not tested

[b] Using the Cochran-Mantel-Haenszel trend test

Table 2 Demographic data and risk factors for penicillin resistance in 151 cases of pneumococcal bacteremia

Characteristic	No. (%) of cases			*P* value[a]
	Total (*n*=151)	PSSP (*n*=77)	PRSP (*n*=74)	
Age ≥65 years	51 (33.8)	29	22	–
Sex (M:F)	102:49	53:24	49:25	–
Underlying disease[b]				
None	16 (10.6)	10	6	–
Hepatic disease	33 (21.9)	17	16	–
Solid tumor	31 (20.5)	9	22	0.006
Pulmonary disease	22 (14.6)	16	6	0.03
Hematologic disease	22 (14.6)	9	13	–
Cardiovascular disease	16 (10.6)	11	5	–
Diabetes mellitus	16 (10.6)	6	10	–
Biliary disease	11 (7.3)	3	8	–
Urologic disease	7 (4.6)	5	2	–
Renal disease	5 (3.3)	4	1	–
Neurologic disease	4 (2.6)	4	0	–
Connective tissue disease	4 (2.6)	3	1	–
Underlying condition				
Antineoplastic chemotherapy	19 (12.6)	8	11	–
Invasive procedure	18 (11.9)	7	11	–
Central venous catheter	4 (2.6)	0	4	–
Indwelling urinary catheter	3 (2.0)	1	2	–
Biliary drainage catheter	14 (9.3)	3	11	0.03
Immunosuppressive therapy	9 (6.0)	7	2	–
Alcoholism	8 (5.3)	3	5	–
Leukopenia	35 (23.2)	15	20	–
Recent bleeding	10 (6.6)	6	4	–
Nosocomial acquisition	45 (29.8)	20	25	–
Previous admission	48 (31.8)	26	22	–
Previous β-lactam therapy	6 (4.0)	0	6	0.01

PSSP, penicillin-susceptible *Streptococcus pneumoniae*; PRSP, penicillin-resistant *Streptococcus pneumoniae*

[a] Using either the chi-square test or Fisher's two-tailed exact test. Only statistically significant *P* values are shown

[b] Patients had one or more underlying medical disease and condition

mococcal bacteremia due to isolates resistant to TMP-SMX remained stable at 50% in 1996 and 42.4% in 2000, and the incidence due to multidrug-resistant isolates also remained stable. All the temporal trends of resistance to clindamycin, erythromycin, and multiple drugs did not significantly change over the study period.

Risk Factors for Penicillin Resistance

One or more underlying medical diseases were present in 135 cases (Table 2). Common underlying diseases were hepatic diseases, including cirrhosis with or without hepatoma of variable causes in 33 cases (21.9%) and solid tumors in 31 (20.5%). No patients with human immunodeficiency virus infection developed pneumococcal bacteremia. Patients received antineoplastic chemotherapy in 19 cases and immunosuppressive therapy in 9 cases. Invasive procedures were performed in 18 cases. Two cases occurred in ICU patients and one in a patient who was mechanically ventilated. Leukopenia was present before or at the onset of bacteremia in 35 cases. In 48 cases (31.8%), patients had been hospitalized within 6 months of the onset of bacteremia. Previous use of β-lactam antibiotics within the previous month was identified in six cases (4%).

Notably, in 10 cases, patients presented with recent bleeding at the onset of bacteremia or just before admis-

Table 3 Clinical features and outcomes in 151 cases of pneumococcal bacteremia

Characteristic	No. (%) of cases		
	Total (*n*=151)	PSSP (*n*=77)	PRSP (*n*=74)
Complication			
Septic shock	28 (18.5)	12	16
Respiratory failure	22 (14.6)	14	8
Adult respiratory distress syndrome	2 (1.3)	0	2
Deteriorated mental status	39 (25.8)	23	16
Acute renal failure	14 (9.3)	8	6
Disseminated intravascular coagulation	4 (2.6)	2	2
ICU admission	39 (25.8)	21	18
Seizure	4 (2.6)	1	3
Endophthalmitis	2 (1.3)	2	0
Polymicrobial bacteremia	14 (9.3)	5	9
Site of infection			
Pneumonia[a]	68 (45.0)	41	27
Primary bacteremia	34 (22.5)	15	19
Peritonitis	17 (11.3)	9	8
Biliary infection	12 (7.9)	3	9
Meningitis	11 (7.3)	4	7
Other[b]	9 (6.0)	5	4
Mortality[c]	35 (23.8)	17 (23.0)	18 (24.7)

PSSP, penicillin-susceptible *Streptococcus pneumoniae*; PRSP, penicillin-resistant *Streptococcus pneumoniae*

[a] P=0.04 using the chi-square test

[b] Includes empyema (3 cases), sinusitis (2 cases), skin and soft tissue infections (2 cases), endocarditis (1 case), and liver abscess (1 case)

[c] Outcomes were not available for 3 cases caused by PSSP and 1 case caused by PRSP

sion. All of these instances of recent bleeding occurred in patients with hepatic disease who had primary bacteremia or peritonitis. One of these 10 cases involved recurrent hepatoma rupture into peritoneal space; the patient underwent transcatheter arterial embolization to control the bleeding on hospital day 15. In the remaining nine cases of esophageal variceal origin, eight underwent esophageal variceal ligation or sclerotherapy. Bleeding stopped spontaneously in one case.

A univariate analysis of risk factors potentially associated with penicillin resistance revealed that solid tumor, placement of biliary drainage catheter, and previous β-lactam therapy were significantly associated with penicillin resistance (Table 2). However, none of these conditions was significantly associated with penicillin resistance in the multivariate analysis.

Clinical Features and Outcomes

Clinical features and outcomes are shown in Table 3. Fourteen cases (9.3%) were polymicrobial. Pneumonia was identified in 68 cases (45%), primary bacteremia in 34 (22.5%), peritonitis in 17 (11.3%), biliary infections in 12 (7.9%), meningitis in 11 (7.3%), and other infections in 9 (6%). Complications were documented in 68 cases. In 39 cases (25.8%), patients were admitted to the ICU. Deterioration of mental status was found in 39 cases (25.8%). Septic shock developed in 28 cases (18.5%) and respiratory failure in 22 (14.6%). There were two cases of endophthalmitis that occurred in patients with PSSP isolates. The mean length of hospital stay after the onset of bacteremia was 18.6 days (standard deviation=20 days; range, 0–116 days), which was similar for cases due to PSSP and those due to PRSP isolates (P=0.31).

Forty-five cases (29.8%) were nosocomial bacteremia. Community-acquired cases are compared with nosocomially acquired cases in Table 4. More patients received previous β-lactam therapy in nosocomially acquired cases than in community-acquired cases (5/45 vs. 1/106; P=0.009). Invasive procedure, biliary drainage catheter, indwelling urinary catheter, central venous catheter, and recent bleeding were more commonly associated with nosocomial pneumococcal bacteremia. Antibiotic resistance rates were higher in nosocomially acquired cases than in community-acquired cases, although the differences were not statistically significant. Mortality did not increase significantly in nosocomially acquired cases (25% vs. 23.3%; P=0.83). Community-acquired pneumococcal bacteremia was more frequently associated with primary bacteremia and biliary infection, while nosocomial pneumococcal bacteremia was more frequently associated with pneumonia. No factor was identified as an independent risk factor for penicillin resistance in the stepwise logistic regression, neither in community-acquired nor nosocomially acquired cases.

All but 10 cases were treated with antibiotics. In 77 (51%) cases, patients received a single antibiotic agent, while in 64 cases (41.4%), patients were treated with combination therapy. In 10 cases no antibiotic therapy was administered; of these, 9 were fatal within 24 h after hospital admission, before the initiation of antibiotic therapy. The tenth patient was transferred to another hospital and survived. When demographic and clinical characteristics in cases caused by isolates with intermediate penicillin resistance versus cases caused by high-level penicillin resistance were compared, no significant differences were observed (data not shown). Mortality rate among these groups was also similar (26.7% vs. 20%; P=0.53).

Prognostic Factors for Outcome

Outcomes were not determined in four cases because patients were transferred to another hospital or were lost

Table 4 Clinical characteristics of patients with community-acquired versus nosocomial pneumococcal bacteremia

Characteristic	Community-acquired (*n*=106)	Nosocomial (*n*=45)	*P* value[a]
Underlying disease[b]			
None	16	0	0.003
Hepatic disease	23	10	–
Solid tumor	22	9	–
Pulmonary disease	13	9	–
Hematologic disease	14	8	–
Cardiovascular disease	10	6	–
Diabetes mellitus	12	4	–
Biliary disease	6	5	–
Underlying condition			
Antineoplastic chemotherapy	10	9	–
Invasive procedure	1	17	<0.001
Biliary drainage catheter	4	10	0.001
Leukopenia	27	8	–
Immunosuppressive therapy	5	4	–
Indwelling urinary catheter	0	3	0.03
Central venous catheter	0	4	0.007
Recent bleeding	3	7	0.008
Previous admission	39	9	0.04
Previous β-lactam therapy	1	5	0.009
Rate of antibiotic resistance			
Penicillin	46.2%	55.6%	–
Ceftriaxone	18.9%	28.6%	–
Clindamycin	48.6%	55.6%	–
Erythromycin	58.1%	71.1%	–
TMP-SMX	39.6%	55.6%	–
Multidrug	44.3%	55.6%	–
Site of infection			
Primary bacteremia	15	19	<0.001
Pneumonia	56	12	0.003
Peritonitis	13	4	–
Biliary infection	5	7	0.02
Meningitis	9	2	–

[a] Using either the chi-square test or Fisher's two-tailed exact test. Only statistically significant *P* values are shown

[b] Patients had one or more underlying medical disease and condition

Table 5 Univariate analysis of risk factors for mortality in 147 cases of pneumococcal bacteremia

Factors	No. of deaths/ no. of cases (%)	*P* value[a]
Age ≥65 years	18/50 (36.0)	0.01
Neurologic disease	3/4 (75.0)	0.04
Underlying condition		
Antineoplastic chemotherapy	9/18 (50.0)	0.01
Indwelling urinary catheter	3/3 (100.0)	0.01
Bedridden state	3/3 (100.0)	0.01
Leukopenia	16/33 (48.5)	<0.001
Polymicrobial bacteremia	9/14 (64.3)	0.001
Complication		
Septic shock	19/27 (70.4)	<0.001
Respiratory failure	14/19 (73.7)	<0.001
Deteriorated mental status	18/37 (48.6)	<0.001
Acute renal failure	11/13 (84.6)	<0.001
Disseminated intravascular coagulation	3/4 (75.0)	0.04
ICU admission	14/37 (37.8)	0.02
Seizure	3/4 (75.0)	0.04

[a] Using either the chi-square test or Fisher's two-tailed exact test. Only statistically significant risk factors are shown

to follow-up. Mortality directly attributable to pneumococcal bacteremia was 23.8%. The mean time from the onset of bacteremia to death was 4.4 days (range, 0–28 days), and 21 (60%) deaths occurred within 48 h. Mortality rates in cases with PSSP and in cases with PRSP were 23% and 24.7%, respectively (*P*=0.81) (Table 3). Mortality was not significantly influenced even by high-level resistance (24.4% vs. 20%; *P*=0.64). Table 5 demonstrates the effect of different variables on survival. Mortality for cases with pneumonia was higher than for the rest of the group, but this was not statistically significant (*P*=0.08). Multivariate analysis revealed that antineoplastic chemotherapy (odds ratio [OR], 11.2; 95%CI, 2.6–52.3; *P*=0.001), respiratory failure (OR, 17.7; 95%CI, 2.9–144.4; *P*=0.003), and acute renal failure (OR, 21.6; 95%CI, 3.7–180.7; *P*=0.001) were inde-

pendent prognostic factors for mortality. The mortality rate was 25% in 1996, 35.7% in 1997, 28.6% in 1998, 22.2% in 1999, and 9.7% in 2000. The temporal trend of decrease in the mortality rate was not significant (P=0.06 by Cochran-Mantel-Haenszel trend test).

Discussion

The emergence of penicillin resistance and multidrug resistance among pneumococcal strains has been a global concern. The incidence of PRSP strains has increased substantially worldwide, and it is extremely high in some parts of Europe and Asia. For example, in the 1990s, rates of 49% in Spain, 71% in Taiwan, 55.8% in Hong Kong, 58% in Hungary, 50% in Japan, 57.9% in Thailand, and 60.8% in Vietnam were reported [2, 3, 4, 5, 6, 7]. In Korea, PRSP strains were not reported until 1986, when 3 of 172 (1.7%) clinical isolates of pneumococci were found to be penicillin resistant [9]. Penicillin resistance was reported at 29% in 1988 [23]. Thereafter, the frequency of penicillin resistance has increased from 29% in 1988 to 67% in 1991–1993 and, most recently, to 78% in 1998 [8, 23]. The increasing problem of pneumococcal penicillin resistance in Asian countries has been suggested as possibly being due to the introduction and spread of international epidemic clones into these countries [7].

The proportion of PRSP strains varies, depending on the source of the pneumococci [2, 7, 24, 25, 26]. Blood and CSF isolates are not as likely to be penicillin resistant as respiratory tract isolates [2, 7, 24, 25, 26]. However, it is generally assumed that PRSP strains are no more or less virulent than PSSP strains [10]. In contrast, some investigators have argued that PRSP strains may be less virulent (cause less pulmonary infection) and/or less invasive (cause fewer bloodstream infections) than PSSP strains [24]. It is noted that the rate of penicillin resistance among blood isolates was lower compared with that among respiratory tract isolates [2, 7, 9, 24, 26]. For example, the rate of penicillin resistance among blood isolates was 64%, while that among lower respiratory tract isolates was 80% in the previous study from Korea [9]. Similar results were also observed in a recent report from Spain [2]. In a study that included Korean adults and children with pneumococcal bacteremia, the rate of penicillin resistance among blood isolates was reported at 68.3% in the early 1990s [27]. The difference in the rate of penicillin resistance in the latter study and ours might reflect the fact that the resistance rate among blood isolates from children was higher than that from adults. Our data showed that the rate of penicillin resistance among blood isolates in Korea has remained stable but higher than in any other country during the late 1990s.

Exposure to antibiotics is believed to provide the selective pressure that contributes to the emergence of PRSP strains. Previous use of β-lactam antibiotics has been shown to be a risk factor for penicillin-resistant pneumococcal carriage and diseases [15, 16, 24, 25, 28, 29, 30, 31, 32]. In our study, we failed to reveal an association between previous β-lactam therapy and penicillin resistance. Only six patients (4%) were identified to have a history of β-lactam antibiotic use. This might be due in part to the retrospective nature of the study, although a great effort was made to obtain detailed data regarding previous use of β-lactam antibiotics. In our study, a history of previous antibiotic use was obtained only for the previous month, while a history of use within the previous 3 or 6 months was obtained in other investigations [15, 16, 17, 20, 24, 25, 28, 29, 30, 31, 32]. This may have led to an underestimation of antibiotic use in our study patients.

PRSP strains are often resistant to multiple antibiotics, including ceftriaxone/cefotaxime, erythromycin, tetracycline, and TMP-SMX [2, 3, 4, 5, 6, 7, 8, 9]. Our study confirms that pneumococci can no longer be considered a pathogen with uniform, predictable susceptibility to ceftriaxone, macrolides, and other antibiotics in Korea. There is evidence from several countries that rates of antibiotic use correlate directly with the prevalence of PRSP strains [33, 34]. High rates of penicillin and multidrug resistance in Korea might be explained in part by injudicious use of antibiotics, because antibiotic consumption has not been properly restricted. Antibiotics were sold over-the-counter in Korea before the implementation of a medical reform plan. Under the new medical system, effective since August 2000, only physicians are allowed to prescribe drugs, including antibiotics, which can then be sold by pharmacists on prescription only. How this new system will affect the rate of antibiotic resistance among pneumococci as well as other bacterial pathogens merits further investigation. Previous studies have demonstrated that interventions to implement judicious antibiotic use can result in a reduction in antibiotic prescriptions and can also lead to a decrease in pneumococcal resistance [35].

In our study, a substantial number of patients had hepatic or biliary disease, which affected the underlying conditions and the clinical presentations of pneumococcal bacteremia. A relatively high proportion of patients in our study had undergone invasive procedures involving the upper gastrointestinal or biliary tract, and relatively more patients had peritonitis and biliary infection. Recent bleeding has never been documented before in other studies as an underlying condition for pneumococcal bacteremia. All cases except one were of esophageal variceal origin in patients with hepatic disease. Patients with recent bleeding had an invasive pneumococcal disease such as primary bacteremia or peritonitis. It can be suggested that pneumococci previously colonizing the nasopharynx spread into the bloodstream during the bleeding, causing bacteremia.

Increasing pneumococcal resistance to penicillin in the community is paralleled by resistance appearing in nosocomial isolates: PRSP strains are now increasingly associated with pneumococcal infections in the hospital setting [36, 37]. Nosocomially acquired pneumococcal

strains are more resistant to penicillin than community-acquired strains [9, 16, 20, 25]. In our study, nosocomial acquisition was identified in 29.8% of the cases. Although nosocomial acquisition was not significantly associated with resistance of pneumococcal isolates to penicillin, rates of resistance to penicillin and other antibiotics were higher among nosocomially acquired isolates. A greater chance of exposure to antibiotics in hospitalized patients might contribute to the selection of pneumococcal isolates with high-level resistance. It has been shown that nosocomial acquisition of pneumococcal infection is a risk factor significantly associated with higher mortality [15, 38, 39]. However, nosocomial acquisition was not an independent risk factor for mortality in our study, although the mean length of hospital stay after the onset of pneumococcal bacteremia was longer in nosocomially acquired cases than in community-acquired cases.

Mortality attributable to pneumococcal bacteremia (23.8%) in our study was similar to that reported by others (17–36%) [11, 12, 13, 15, 40, 41], and there was no significant difference in mortality between cases caused by PSSP and those caused by PRSP. Penicillin-resistant isolates in patients with pneumococcal bacteremia was significantly associated with higher mortality in some studies [11], but not in others [12, 13, 15, 17]. In a study of neutropenic cancer patients with bacteremia, investigators did not find any difference in mortality between patients with PSSP isolates and those with PRSP isolates[42]. Recent studies have not found penicillin resistance to be significantly related to mortality in patients with pneumococcal pneumonia and meningitis [14, 18, 19]. In contrast, the overall mortality rate was significantly higher in patients with bacteremic pneumonia due to PRSP strains than in those with PSSP strains in a former study [16]. A recent retrospective study of Korean children with invasive pneumococcal disease showed no difference in mortality between patients with PSSP and those with PRSP strains [20], a finding that was consistent with ours.

Turett et al. [11] argued that high-level resistance to penicillin is an independent predictor of mortality in pneumococcal bacteremia. In that study, in which one-half of the patients had human immunodeficiency virus infection, the mortality rate among patients infected by isolates with versus without high-level resistance to penicillin was 42% versus 16% ($P<0.01$). However, we did not observe any significant difference in mortality between patients infected by isolates with versus without high-level resistance to penicillin (24.4% vs. 20%; $P=0.64$). We also did not observe any significant difference in mortality between patients infected by isolates with intermediate resistance versus high-level resistance to penicillin (26.7% vs. 20%; $P=0.53$).

To our knowledge, this is the first report from Asia to analyze cases of pneumococcal bacteremia in adults. However, this study has several limitations. First, we were not able to completely document outpatient antibiotic exposure and inpatient antibiotic exposure at other hospitals, because our study design depended on chart review data obtained retrospectively. Second, there was possible underdetection of pneumococcal bacteremia as a result of incomplete sampling. Third, mortality was not evaluated for each treatment regimen because diverse antibiotics and their combinations were administered.

In summary, rates of penicillin and multidrug resistance among pneumococcal blood isolates in Korea have been high, reaching alarming rates during the period 1996–2000. Mortality did not change during the study period. Penicillin resistance, even high-level penicillin resistance, was not significantly associated with increased mortality in adult patients with pneumococcal bacteremia. Continuous surveillance of the susceptibility of pneumococcal isolates, together with judicious use of antibiotics, is necessary to prevent future problems associated with drug resistance.

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