MAJOR ARTICLE

Clinical Outcomes of Pneumococcal Pneumonia Caused by Antibiotic-Resistant Strains in Asian Countries: A Study by the Asian Network for Surveillance of Resistant Pathogens

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To evaluate the clinical outcomes of pneumococcal pneumonia caused by antibiotic-resistant strains in Asian countries, we performed a prospective observational study of 233 cases of adult pneumococcal pneumonia in 9 Asian countries from January 2000 to June 2001. Among 233 isolates, 128 (55%) were not susceptible to penicillin (25.3% were intermediately susceptible, and 29.6% were resistant). Clinical severity of pneumococcal pneumonia was not significantly different between antibiotic-resistant and antibiotic-susceptible groups. Mortality rates among patients with pneumococcal pneumonia caused by penicillin-, cephalosporin-, or macrolide-resistant strains were not higher than those with antibiotic-susceptible pneumococcal pneumonia. Bacteremia and mechanical ventilation were significant risk factors for death, but any kind of antibiotic resistance was not associated with increased mortality due to pneumococcal pneumonia. Outcome of pneumococcal pneumonia was not significantly affected by drug resistance, and current antimicrobial regimens are mostly effective in the treatment of pneumococcal pneumonia, despite the widespread emergence of in vitro resistance.

Streptococcus pneumoniae remains one of the most important bacterial pathogens causing community-acquired pneumonia, meningitis, otitis media, and septicemia. Since the 1980s, global emergence of in vitro antibiotic resistance among *S. pneumoniae* has become a serious clinical concern [1, 2]. Although the prevalence of resistance varied among antimicrobial agents and countries, rapid escalation of antimicrobial resistance to penicillin, other β-lactam agents, and macrolides has been reported from many parts of the world during the previous 2 decades [3–6]. In some Asian countries in particular, the reported prevalence of penicillin and macrolide resistance was the highest in the world [7–9]. With the increasing prevalence of in vitro resistance to multiple antibiotics among *S. pneumoniae,* questions and concerns about the clinical impact of resistance have been raised. Treatment failure associated with antibiotic-resistant pneumococci has been reported for patients with otitis media and meningitis,

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although the clinical significance of antimicrobial resistance for patients with pneumococcal pneumonia remains controversial [10]. Previous data indicated that low-level resistance to penicillin or cephalosporins did not affect the clinical outcome of pneumococcal pneumonia [11–13], whereas high-level resistance to these β-lactam agents could increase mortality due to pneumococcal pneumonia [14]. Failures of macrolide antibiotic treatment in cases of pneumonia [15] or bacteremia [16] due to erythromycin-resistant *S. pneumoniae* were also reported. Recent reports have documented the therapeutic failures of fluoroquinolone treatment in patients with pneumococcal pneumonia [17].

Because of the frequency and importance of *S. pneumoniae* in community-acquired pneumonia, the clinical relevance of the increasing prevalence of resistance among pneumococcal isolates in relation to the antimicrobials currently used to treat pneumonia should be clarified. To evaluate the clinical features and final outcomes of pneumococcal pneumonia caused by antibiotic-resistant strains, the Asian Network for Surveillance of Resistant Pathogens (ANSORP) conducted a prospective multinational study in Asia.

PATIENTS AND METHODS

Participating centers. The following 9 medical centers in the ANSORP Study Group participated in the study: Samsung Medical Center (Seoul, Korea), Princess Margaret Hospital (Hong Kong), Chulalongkorn University (Bangkok, Thailand), Chang Gung Memorial Hospital (Taipei, Taiwan), Christian Medical College (Vellore, India), University of Colombo (Colombo, Sri Lanka), National University of Singapore (Singapore), University Malaya (Kuala Lumpur, Malaysia), and Research Institute of Tropical Medicine (Manila, The Philippines) (table 1).

Patients with pneumococcal pneumonia. All consecutive cases of community-acquired pneumococcal pneumonia in adult patients (age, $\geq$18 years) diagnosed between January 2000 and June 2001 were prospectively enrolled at 9 study centers in Asia. Patients were enrolled only if all of the following findings were present: clinical symptoms and signs of pneumonia, such as fever, cough, and sputum; a distinct pulmonary infiltrate revealed on a chest radiograph; and isolation of *S. pneumoniae* from sterile specimens (blood or pleural fluid) and/or from lower respiratory tract specimens with compatible Gram stain findings. Investigators at each participating center evaluated the eligibility of the cases. Patients who did not receive a diagnosis of pneumonia within 48 h after hospital admission, who did not complete the follow-up schedule, or who had inadequate specimens as the only available source of isolates were excluded from the study.

Data collection. We recorded the following data on a standardized case report form: baseline information, including sociodemographic characteristics, underlying conditions, history of antibiotic use within the 3 months before presentation to the hospital, clinical manifestations, laboratory results, chest radiographic findings at presentation, antimicrobial therapy, clinical course, and death; underlying conditions, such as bronchopulmonary diseases, smoking, cerebrovascular disease, malignancy, diabetes mellitus, chronic renal disease, chronic liver disease, corticosteroid use, asplenia, and transplantation; and clinical and laboratory features, including vital signs at presentation, alteration in mental status, hypoxemia (arterial O_2 pressure, <60 mm Hg), WBC count, hematocrit, blood urea nitrogen level, serum creatinine level, blood glucose level, pH of arterial blood, and results of blood cultures at initial presentation to the hospital were recorded for all patients. On the basis of these parameters, clinical severity of pneumococcal pneumonia was assessed by means of the Pneumonia Severity Index (PSI), as proposed by Fine et al. [18]. Patients were classified into risk classes of 1–5 on the basis of the PSI score.

Table 1. Number of enrolled patients with pneumococcal pneumonia, by location and participating center.

Location	Center	No. of assessable patients
Hong Kong, China	Princess Margaret Hospital	80
Bangkok, Thailand	Chulalongkorn University	30
Taipei, Taiwan	Chang Gung Memorial Hospital	23
Colombo, Sri Lanka	University of Colombo	23
Seoul, Korea	Samsung Medical Center	21
Singapore	National University of Singapore	20
Vellore, India	Christian Medical College	18
Kuala Lampur, Malaysia	University Malaya	15
Manila, The Philippines	Research Institute of Tropical Medicine	3
Total	…	233

Mortality was defined to include all deaths within 30 days after the diagnosis of pneumonia.

Antimicrobial susceptibility testing of 233 isolates was performed using the broth microdilution test at a central laboratory (Samsung Medical Center, Korea), according to NCCLS guidelines [19]. The following 14 antimicrobial agents were tested: penicillin, amoxicillin-clavulanate, cefuroxime, ceftriaxone, erythromycin, azithromycin, clarithromycin, clindamycin, ciprofloxacin, levofloxacin, moxifloxacin, gatifloxacin, doxycycline, and trimethoprim-sulfamethoxazole. *S. pneumoniae* ATCC 49619 was used as a control. We used susceptibility interpretive criteria found in NCCLS approved standard M100-S13 [20]. The NCCLS M100-S13 guidelines include new interpretive susceptibility criteria for nonmeningeal isolates of *S. pneumoniae,* with MICs of ceftriaxone ≤1 mg/L (susceptible), 2 mg/L (intermediately susceptible), and ≥4 mg/L (resistant). For the purpose of the present study, ciprofloxacin MICs of ≥4 mg/L were used to define the resistance category.

Data analysis. Statistical analysis was performed using SPSS, version 9.0 for Windows NT (SPSS). Clinical manifestations and disease severity were compared between antibiotic-susceptible and antibiotic-resistant strains with regard to penicillin, cefuroxime, erythromycin, and levofloxacin using Student's *t* test, Fisher's exact test, or χ^2 analysis. Crude mortality rates within 30 days after diagnosis were obtained for all patients and for patients with severe pneumonia (PSI class 4/5). ORs and 95% CIs of mortality associated with pneumococcal pneumonia were calculated by unconditional logistic regression models. Multivariate odds ratios (mORs) to analyze the risk factors were adjusted for antibiotic resistance, comorbidities, and disease severity.

To evaluate the direct impact of antimicrobial resistance on medical outcomes, the concordance of antimicrobial therapy administered within the first 48 h of treatment was assessed for patients with antibiotic-nonsusceptible pneumococcal pneumonia. Antimicrobial regimens were classified as concordant therapy when the patient received ≥1 antibiotic during the first 48 h of treatment to which a pneumococcal isolate was fully susceptible. Antimicrobial regimens were classified as discordant therapy when the patient did not receive any single antibiotic during the first 48 h of treatment to which the pneumococcal isolate was susceptible or intermediately susceptible, regardless of the modification of the antibiotic regimen after 48 h. $P < .05$ was considered to be statistically significant.

RESULTS

Patient characteristics. A total of 233 adults with pneumococcal pneumonia were evaluated between January 2000 and June 2001. The number of assessable cases varied by center because of differing periods of enrollment (table 1). The mean age of the patients was 60.8 ± 17.5 years (range, 18–89 years); 70.4% were men. Of these 233 patients, 163 (70%) had underlying conditions, such as pulmonary diseases (22.7%), smoking (25.8%), cerebrovascular accident (17.6%), diabetes mellitus (14.2%), malignancy (11.2%), asplenia (6%), chronic renal disease (5.1%), corticosteroid use (3.9%), chronic liver diseases (1.7%), or transplantation (0.8%). On the basis of the PSI, assessable cases belonged to class 1 (8.2%), 2 (31.3%), 3 (21%), 4 (27.5%), and 5 (12%). Bacteremia was documented in 72 patients (30.9%). Mean duration of fever (±SD) after the initiation of antimicrobial treatment was 4.8 ± 6.2 days. The initial antibiotic regimen provided to the patients varied by country, with the most commonly administered antibiotics being penicillin (India and Sri Lanka), amoxicillin-clavulanate (Hong Kong), second-generation cephalosporins (Malaysia), third-generation cephalosporins (Taiwan and Singapore), and second-generation cephalosporins plus macrolides (Korea).

In vitro susceptibility of infecting pathogens. Of the 233 isolates of *S. pneumoniae,* 128 (55%) were not susceptible to penicillin (25.3% were intermediately susceptible and 29.6% were resistant) (table 2). MICs of penicillin were 0.008–4 mg/L, and the MIC_{90} was 2 mg/L. On the basis of the nonmeningeal breakpoint for resistance to ceftriaxone (MIC, ≥4 mg/L), only 1 isolate was fully resistant to ceftriaxone. Multivariate analysis did not identify any significant risk factors for acquiring penicillin resistance. More than one-half of the isolates were not susceptible to erythromycin (1.3% were intermediately susceptible, and 52.4% were resistant), with very high-level resistance. $MICs_{90}$ of erythromycin, azithromycin, and clarithromycin were >32 mg/L. Age ≥50 years (mOR, 2.8; 95% CI, 1.1–7.1) and cefuroxime resistance (mOR, 7.9; 95% CI, 2.4–26.1) were independent risk factors for erythromycin resistance. Rate of resistance to ciprofloxacin (MIC, ≥4 mg/L) was relatively high (9.6%), especially among isolates from Hong Kong, whereas resistance to levofloxacin (4.3% of isolates), moxifloxacin (0.4%), and gatifloxacin (0.4%) were low at the time of the study. Resistance to doxycycline and trimethoprim-sulfamethoxazole was also high (50.2% and 47.8% of isolates, respectively).

Impact of resistance on clinical features and severity. Mean age (±SD) was significantly higher among patients with penicillin-nonsusceptible strains (64.5 ± 16.4 years) and patients with penicillin-resistant strains (66.6 ± 15.5 years) than among those with penicillin-susceptible strains (56.3 ± 17.7 years) ($P < .01$). In general, vital signs and abnormal laboratory findings at the time of presentation in patients infected with penicillin-nonsusceptible strains (i.e., intermediately susceptible and resistant strains with MICs ≥1 mg/L) or penicillin-resistant strains (MIC, ≥2 mg/L) were not significantly different from those in patients infected with penicillin-susceptible strains (table 3). However, pleural effusion ($P = .008$) and bacteremia ($P < .001$) were significantly more frequent among pa-

Table 2. In vitro susceptibility of infecting pathogens from patients with pneumococcal pneumonia in Asian countries.

Antimicrobial agent	No. isolates tested	Antimicrobial susceptibility, no. (%) of isolates			MIC, mg/L	MIC_{90}, mg/L
		Susceptible	Intermediate	Resistant		
Penicillin	233	105 (45.0)	59 (25.3)	69 (29.6)	<0.008–4	2
Amoxicillin-clavulanate[a]	232	222 (95.7)	6 (2.6)	4 (1.7)	<0.015–16	2
Cefuroxime	232	131 (56.5)	8 (3.4)	93 (40.0)	<0.03–16	8
Ceftriaxone	228	223 (97.8)	4 (1.8)	1 (0.4)	<0.015–4	1
Erythromycin	233	108 (46.4)	3 (1.3)	122 (52.4)	<0.015 to >128	64
Azithromycin	228	106 (46.5)	6 (2.6)	116 (50.9)	<0.03 to >32	>32
Clarithromycin	228	112 (49.1)	5 (2.2)	111 (48.7)	<0.015 to >32	>32
Ciprofloxacin[b]	230	208 (90.4)	…	22 (9.6)	0.008–32	2
Gatifloxacin	227	226 (99.6)	…	1 (0.4)	<0.03 to >16	0.5
Levofloxacin	233	222 (95.3)	1 (0.4)	10 (4.3)	0.008–16	1
Moxifloxacin	233	223 (95.7)	9 (3.9)	1 (0.4)	0.015–16	0.25
Doxycycline	227	82 (36.1)	31 (13.7)	114 (50.2)	<0.03–16	8
TMP-SMZ[c]	228	89 (39.0)	30 (13.2)	109 (47.8)	<0.12 to >4	>4

NOTE. TMP-SMZ, trimethoprim-sulfamethoxazole.

[a] Ratio of concentration of amoxicillin and clavulanate is 2:1, and data reflect the amoxicillin component.

[b] Resistance to ciprofloxacin was defined as MIC $\geq$ 4 mg/L.

[c] Ratio of concentration of TMP and SMZ is 1:19, and data reflect the TMP component.

tients infected with penicillin-susceptible strains, whereas low arterial blood pH was more common in patients with penicillin-resistant strains than in patients with penicillin-susceptible strains ($P = .01$). Duration of fever was not different in any groups. Mean pneumonia severity-of-illness scores ($\pm$SD) based on PSI calculations at the time of enrollment were higher among patients with penicillin-nonsusceptible strains (90.9 $\pm$ 30.9; $P = .03$) and patients with penicillin-resistant strains (98.2 $\pm$ 31.6; $P = .002$) than among those with penicillin-susceptible strains (81.1 $\pm$ 36.1). The proportion of patients in the 2 highest severity-of-illness categories (PSI risk classes, 4/5) in the penicillin-nonsusceptible group (57 of 128 patients) was not significantly different from that in the penicillin-susceptible group (35 of 105 patients) ($P = .08$). However, patients infected with penicillin-resistant strains (MIC of penicillin, $\geq$2 mg/L) were more frequently associated with PSI risk classes 4/5 than were those with penicillin-susceptible strains (OR, 2.6; 95% CI, 1.3–5.1; $P < .01$).

Comparison between erythromycin-susceptible and -resistant groups revealed that metabolic acidosis (arterial blood pH <7.35) was more frequent in the resistant group (OR, 3.14; 95% CI, 1.55–6.41; $P < .001$), whereas bacteremia (OR, 0.5; 95% CI, 0.3–0.9; $P = .01$) and pleural effusion (OR, 0.4; 95% CI, 0.2–0.9; $P = .02$) were more frequent in patients with erythromycin-susceptible pneumonia (table 4). Patients with erythromycin-resistant strains were significantly older than patients with erythromycin-susceptible strains ($P < .01$). The erythromycin-resistant group had higher a mean PSI score ($\pm$SD) and number of patients with class 4/5 pneumonia (97.4 $\pm$ 30.5 and 60 of 122 patients, respectively) than did the erythromycin-susceptible group (81.2 $\pm$ 30.9 and 31 of 108 patients, respectively; $P < .001$ for both).

Impact of resistance on mortality. Of the 233 patients with pneumococcal pneumonia, 202 patients (86.7%) showed clinical improvement; 31 patients (13.3%) died within 30 days after they received a diagnosis of pneumonia. Mortality was significantly higher among patients with bacteremic pneumococcal pneumonia (23 [31.9%] of 72 patients) than among patients without bacteremia (8 [5.0%] of 161 patients) (OR, 8.9; 95% CI, 3.5–23.4; $P < .01$). Microbiological eradication was documented in 92 patients (39.5%), but 6 (2.6%) exhibited persistent growth of bacteria despite antibiotic treatment. However, 135 patients (57.9%) were not evaluated with regard to the microbiological outcome, as a result of lack of or inability to perform follow-up cultures.

Of the 233 patients with pneumococcal pneumonia, mortality among patients infected with penicillin-susceptible strains (12.4%) was not different from that among patients with penicillin-nonsusceptible strains (14.1%), penicillin-resistant strains (15.9%; MIC, $\geq$2 mg/L), or high-level resistant strains (13.6%; MIC, 4 mg/L). Of the 74 patients who had more-severe illness (PSI class 4/5), mortality was similar among those with penicillin-susceptible strains (20%) and those with penicillin-nonsusceptible strains (28.2%) (OR, 1.5; 95% CI, 0.4–5.3; $P = .4$). Pneumonia caused by cefuroxime-resistant strains (16.1% of cases) resulted in mortality similar to that associated

Table 3. Clinical characteristics of 233 patients with pneumococcal pneumonia, according to penicillin susceptibility.

Clinical characteristic	Patient group, by penicillin susceptibility						
	Susceptible (n = 105)	Nonsusceptible (n = 128)[a]			Resistant (n = 69)[b]		
		Value	OR (95% CI)	P	Value	OR (95% CI)	P
Age, years	56.3 ± 17.7	64.5 ± 16.4	…	<.01[c]	66.6 ± 15.5	…	<.01[c]
Sex, M/F	69/36	95/33	1.50 (0.82–2.75)	.15	56/13	2.25 (1.03–4.96)	.02
Altered mental status	10 (9.5)	9 (7.0)	0.72 (0.26–2.01)	.49	7 (10.1)	1.07 (0.35–3.27)	.89
Body temperature <35 to >40°C	3 (2.9)	2 (1.6)	0.54 (0.06–4.06)	.66	1 (1.4)	0.50 (0.05–5.55)	1.00[d]
RR ⩾30 breaths/min	7 (6.7)	13 (10.2)	1.58 (0.56–4.59)	.35	6 (8.7)	2.44 (0.38–4.68)	.62
Systolic blood pressure <90 mm Hg	3 (2.9)	5 (3.9)	1.38 (0.28–7.50)	.73	3 (4.3)	1.55 (0.24–9.95)	.68[d]
WBC count <5000 cells/mm^3	7 (6.7)	11 (8.6)	1.32 (0.45–3.93)	.58	7 (10.1)	1.58 (0.47–5.32)	.41
Blood urea nitrogen level >30 mg/dL	10 (9.5)	7 (5.5)	0.55 (0.18–1.64)	.24	6 (8.7)	0.90 (0.28–2.88)	.85
Na level <130 mEq/L	5 (4.8)	10 (7.8)	1.69 (0.51–5.91)	.35	7 (10.1)	2.26 (0.61–8.64)	.22[d]
Arterial blood pH <7.35	20 (19)	37 (28.9)	1.73 (0.89–3.37)	.08	26 (37.7)	2.57 (1.22–5.43)	.01
PaO_2 <60 mm Hg	20 (19)	15 (11.7)	0.56 (0.26–1.23)	.12	11 (15.9)	0.81 (0.33–1.93)	.60
Multilobar or bilateral involvement	13 (12.4)	14 (10.9)	0.87 (0.36–2.08)	.73	8 (11.6)	1.01 (0.35–2.84)	.87
Pleural effusion	24 (22.9)	13 (10.2)	0.38 (0.17–0.84)	.008	5 (7.2)	0.26 (0.08–0.78)	<.01
Bacteremia	48 (45.7)	24 (18.8)	0.27 (0.15–0.51)	<.001	15 (21.7)	0.33 (0.16–0.69)	<.01
Mechanical ventilation	17 (16.2)	18 (14.1)	0.85 (0.39–1.84)	.65	11 (15.9)	0.98 (0.40–2.41)	.96
Defervescence, days	4.60 ± 5.08	4.96 ± 6.92	…	.68[c]	5.09 ± 8.67	…	.68[c]
PSI							
Score	81.1 ± 36.1	90.9 ± 30.9	…	.027[c]	98.2 ± 31.6	…	<.01[c]
Risk class 4/5	35 (33.3)	57 (44.5)	1.48 (0.84–2.60)	.08	39 (56.5)	2.60 (1.33–5.11)	<.01

NOTE. Data are no. (%) of patients or mean values ± SD. Statistical analyses were performed using the susceptible group as a comparison. PaO_2, arterial O_2 pressure; PSI, Pneumonia Severity Index; RR, respiratory rate.

[a] Includes patients with intermediately susceptible isolates and patients with resistant isolates.
[b] MIC of penicillin, ⩾2 mg/L.
[c] By Student's t test.
[d] By Fisher's exact test.

with cefuroxime-susceptible strains (11.5% of cases) (OR, 1.4; 95% CI, 0.6–3.4; $P = .3$) (table 5).

Mortality among patients with erythromycin-resistant pneumonia (16.1%) was not statistically different than that among patients with erythromycin-susceptible pneumonia (12%) (OR, 1.4; 95% CI, 0.5–3.3; $P = .6$) (table 5). Pneumococcal pneumonia caused by a stain with high-level erythromycin resistance (MIC, ⩾64 mg/L) also resulted in similar mortality among patients with erythromycin-susceptible pneumonia (data not shown). Mortality was comparable between patients in the erythromycin-susceptible and erythromycin-resistant groups with PSI class 4/5 pneumonia (OR, 1.0; 95% CI, 0.3–3.5; $P = .9$).

Of the 233 patients with pneumococcal pneumonia, 127 were infected by multidrug-resistant strains (i.e., strains with resistance to agents from ⩾3 antibiotic classes), and 32 patients were infected with strains that were susceptible to all antimicrobial agents tested. Comparison of mortality between these 2 groups showed that multidrug resistance did not affect mortality due to pneumococcal pneumonia (mortality, 14.9% in the multidrug-resistant group vs. 15.6% in the "all-susceptible" groups; OR, 0.9; 95% CI, 0.3–3.2; $P = 1.0$)

Impact of discordant antimicrobial therapy on mortality. A total of 207 patients were evaluated for mortality with respect to the concordance of their antimicrobial therapy. One hundred seventy patients (82.1%) received a concordant regimen, whereas 37 (17.9%) did not receive any antimicrobial agent to which an infecting pathogen was susceptible in vitro. Mortality among patients who received discordant therapy was less than that among patients who received concordant therapy (5 [13.5%] of 37 vs. 24 [14.1%] of 170 patients) (OR, 0.9; 95% CI, 0.3–2.6; $P = .9$). Discordant therapy in terms of resistance to specific antimicrobial agents also did not result in increased mortality. Mortality associated with penicillin discordance (6 [25%] of 24 patients) was less than that associated with penicillin concordance (6 [28.6%] of 21 patients) (OR, 0.8; 95% CI, 0.2–3.1; $P = .78$). Also, discordant therapy involving cefuroxime and erythromycin did not result in increased mortality (table 5). Discordant antimicrobial therapy did not result in increased mortality among 72 patients with bacteremic pneumococcal pneumonia (data not shown).

Risk factors for mortality associated with pneumococcal pneumonia. Univariate analysis of risk factors showed that

Table 4. Clinical characteristics of 230 patients with pneumococcal pneumonia, according to erythromycin susceptibility.

Clinical characteristic	Patient group, by erythromycin susceptibility: Susceptible (n = 108)	Resistant (n = 122)[a]	OR (95% CI)	P
Age, years	56.22 ± 18.40	64.95 ± 15.84	…	<.01
Sex, M/F	71/37	90/32	1.47 (0.80–2.69)	.18
Altered mental status	7 (6.5)	11 (9.0)	1.43 (0.49–4.27)	.47
Body temperature <35 to >40°C	4 (3.7)	1 (0.8)	0.21 (0.01–2.08)	.18[b]
RR ⩾30 breaths/min	14 (13.0)	6 (4.9)	0.30 (0.11–1.02)	.05
Systolic blood pressure <90 mm Hg	5 (4.6)	3 (2.5)	0.52 (0.10–2.57)	.47[b]
WBC count <5000 cells/mm^3	4 (3.7)	12 (9.8)	2.84 (0.81–1.80)	.06
Blood urea nitrogen level >30 mg/dL	6 (5.6)	11 (9.0)	1.68 (0.55–5.34)	.31
Na level <130 mEq/L	6 (5.6)	8 (6.6)	1.19 (0.36–4.03)	.75
Arterial blood pH <7.35	15 (13.9)	41 (33.6)	3.10 (1.53–6.35)	<.01
PaO_2 <60 mm Hg	17 (15.7)	17 (13.9)	0.87 (0.39–1.91)	.70
Multilobar or bilateral enhancement	13 (12.0)	13 (10.7)	0.87 (0.36–2.12)	.74
Pleural effusion	23 (21.3)	13 (10.7)	0.44 (0.20–.97)	.02
Bacteremia	42 (38.9)	29 (23.8)	0.49 (0.27–.90)	.01
Mechanical ventilation	16 (14.8)	18 (14.8)	1.00 (0.45–2.19)	.99
Defervescence, days	5.65 ± 5.93	4.11 ± 6.40	…	.09
PSI				
Score	77.3 ± 32.4	94.1 ± 31.9	…	<.01
Risk class 4/5	31 (28.7)	60 (49.2)	2.74 (1.53–4.93)	<.01

NOTE. Data are presented as no. (%) of patients or mean values ± SD. Data from 3 patients with erythromycin–intermediately susceptible strains were not included. PaO_2, arterial O_2 pressure; PSI, Pneumonia Severity Index; RR, respiratory rate.

[a] MIC of erythromycin, ⩾1.

[b] By Fisher's exact test.

underlying lung diseases, malignancy, chronic renal disease, altered mental status at presentation, hypotension, leukopenia, anemia, uremia, bacteremia, and mechanical ventilation were significant risk factors for death among patients with pneumococcal pneumonia (data not shown). However, when multivariate analysis was used to compare the relative contribution of the factors associated with mortality, only bacteremia (OR, 10.5; 95% CI, 2.9–37.8; $P < .01$) and mechanical ventilation (OR, 12.5; 95% CI, 3.6–42.9; $P < .01$) were significant risk factors for death among patients with pneumococcal pneumonia (table 6). Antimicrobial resistance of any kind among the infecting pathogens was not associated with increased mortality among patients with pneumococcal pneumonia.

DISCUSSION

Lower respiratory tract infections remain the leading cause of death in developing countries and the fourth leading cause of death in developed countries [21]. Because *S. pneumoniae* is obviously the most common pathogen associated with community-acquired pneumonia, clinical implications of antimicrobial resistance in *S. pneumoniae* are critical in clinical practice.

With regard to the severity of pneumonia, our data showed that infection with penicillin-resistant or erythromycin-resistant *S. pneumoniae* strains did not result in more-severe illness than that associated with infection due to strains susceptible to either antibiotic, although higher mean PSI score and higher numbers of patients with PSI class 4/5 pneumonia were observed in the antimicrobial-resistant groups. The main reason for the higher mean PSI score and the higher number of patients with class 4/5 illness in the antibiotic-resistant group was the significantly higher age of patients in this group. Previous reports also suggest that the clinical severity of pneumonia is not affected by antibiotic resistance [11–13], although one recent report documented more-severe illness and more-frequent suppurative complications in patients with bacteremic pneumococcal pneumonia caused by penicillin-nonsusceptible strains [22].

The 30-day crude mortality of 13.3% among all patients with pneumococcal pneumonia in this study was comparable with that in other reports [11, 14, 18]. It is believed that bacteremia is documented in ~20% of patients hospitalized for pneu-

Table 5. Mortality rates of pneumococcal pneumonia with regard to antimicrobial resistance of infecting pathogens.

	Mortality, by Pneumonia Severity Index class								Mortality, by therapy type			
	1–5				4/5							
Antimicrobial	Susceptible	Resistant	OR (95% CI)	*P*	Susceptible	Resistant	OR (95% CI)	*P*	Concordant	Discordant	OR (95% CI)	*P*
Penicillin	13/105 (12.4)	11/69 (15.9)	1.3 (0.5–3.4)	.5	7/35 (20.0)	11/39 (28.2)	1.5 (0.4–5.3)	.4	6/21 (28.6)	6/24 (25)	0.83 (0.2–3.1)	.78
Cefuroxime	15/131 (11.5)	15/93 (16.1)	1.4 (0.6–3.4)	.3	7/42 (16.7)	11/45 (24.4)	1.6 (0.5–5.3)	.3	1/7 (14.3)	1/7 (14.3)	1 (0.05–19.9)	1
Erythromycin	13/108 (12)	15/93 (16.1)	1.4 (0.5–3.3)	.6	6/31 (19.4)	12/60 (20.0)	1.0 (0.3–3.5)	.9	1/13 (7.7)	2/11 (18.2)	2.6 (0.2–34.2)	.43
Levofloxacin	28/222 (12.6)	3/10 (30.0)	2.9 (0.5–13.8)	.1[a]	16/85 (19.0)	3/8 (37.5)	2.5 (0.4–14.2)	.3[a]	…	…	…	…

NOTE. Data are no. of patient deaths/no. of patients treated (%). Resistant strains did not include intermediately susceptible strains.

[a] By Fisher's exact test.

mococcal pneumonia [23]. However, in our study, 30% of patients with pneumococcal pneumonia had blood cultures positive for *S. pneumoniae.* Also, the proportion of patients with severe pneumonia (PSI class 4/5) was 40%, which was much higher than in other reports [18]. Because all participating centers in our study were tertiary care hospitals in urban areas, patients with pneumococcal pneumonia could have had more-severe illness than those in the general population. In our study, the case fatality rate for bacteremic pneumococcal pneumonia was 31.9%, which is comparable with rates of 7%–35% reported elsewhere [24–26].

Data from our study suggest that the 30-day crude mortality associated with pneumococcal pneumonia was not affected by penicillin resistance, regardless of severity of illness or level of resistance. The mean PSI score and the proportion of patients with PSI class 4/5 illness, which were significantly higher among patients infected with penicillin-resistant strains, did not have direct association with increased overall mortality. When we mutually adjusted risk factors for mortality, only the presence of bacteremia and the use of mechanical ventilation sustained a significant association with mortality. Although PSI class 4/5 illness was significantly associated with death in univariate analysis, it was not significant in multivariate analysis, probably because of the lack of power. Mortality among 69 patients infected with strains that were highly resistant to penicillin (MIC, $\geq$2 mg/L, including MICs of 4 mg/L for 22 strains) was also not different from that in the group with penicillin-susceptible strains, regardless of the clinical severity of illness.

Previous reports suggest that the current level of resistance to penicillin and cephalosporins among *S. pneumoniae* strains is not associated with increased mortality among patients with pneumococcal pneumonia [11–13]. In contrast, Feikin et al. [14] have reported that mortality was significantly associated with MICs of penicillin and cefotaxime of $\geq$4 and $\geq$2 mg/L, respectively, when deaths during the first 4 hospital days were excluded. However, this study did not include data on antimicrobial therapy, and, therefore, the impact of discordant therapy on mortality could not be assessed. A recent report showed that discordant therapy for patients with pneumococcal bacteremia caused by cefuroxime-resistant strains resulted in increased mortality [27]. Our data show that discordant therapy with penicillin or cefuroxime did not result in increased mortality among patients with pneumococcal pneumonia, regardless of the presence of bacteremia. These data are consistent with those in previous reports [12, 22].

One of the most remarkable findings from our study was the very high prevalence and level of resistance to macrolides, such as erythromycin, azithromycin, and clarithromycin, in *S. pneumoniae* from Asian countries. Because most previous studies have focused on the impact that penicillin resistance has on pneumococcal pneumonia, relevant data on the impact that macrolide resistance has on pneumococcal pneumonia are lacking. Recently, clinical failures of macrolide therapy have been reported in patients with pneumococcal pneumonia or bacteremia caused by macrolide-resistant strains [15, 16]. These data suggested that in vitro macrolide resistance—either low-level resistance due to the efflux mechanism or high-level resistance due to the methylase mechanism—is clinically relevant. However, our data show that mortality among patients with erythromycin-resistant strains was not significantly different from that among patients with erythromycin-susceptible strains. Although there was no difference in mortality, in vitro susceptibility data for macrolide-resistant strains recovered from patients with pneumococcal pneumonia in Asian countries should be an important consideration for selecting an empirical therapeutic option for treatment of community-acquired pneumonia. In many Asian countries, the *ermB* gene is found in >50% of pneumococcal isolates, either alone or in combination with the *mefA* gene, and the level of erythromycin resistance is very high, with $MICs_{90}$ >128 mg/L [28].

There are some limitations to our study. First, mortality may be a relatively insensitive measurement of the impact of drug resistance in community-acquired pneumonia [10]. Furthermore, because data on attributable mortality or early death within 7–14 days after the onset of pneumococcal pneumonia was not available from the data, we could not evaluate the direct impact of resistance on early clinical outcome. Second, all patients in this study were enrolled at tertiary care centers in urban areas, and the number of patients from each participating center was relatively small. Therefore, current data do

Table 6. Risk factors revealed by multivariate analysis to have contributed to the death of patients with pneumococcal pneumonia.

Risk factor	Multivariate OR[a] (95% CI)	*P*
Bronchopulmonary disease	0.74 (0.12–4.33)	.74
Previous antibiotics	0.19 (0.02–2.24)	.18
Malignancy	2.78 (0.64–11.97)	.16
Chronic renal disease	1.35 (0.15–11.89)	.78
Immunosuppression	0.63 (0.01–28.48)	.81
Altered mentality	4.49 (0.93–21.65)	.06
Systolic blood pressure <90 mm Hg	0.84 (0.09–7.46)	.87
Bacteremia	11.4 (3.17–41.3)	<.01
Mechanical ventilation	12.1 (3.56–41.2)	<.01
PSI class 4/5	0.9[b] (0.27–3.15)	.90
Penicillin resistance	1.42 (0.36–5.58)	.61
Multidrug resistance	2.82 (0.70–11.38)	.14

NOTE. PSI, Pneumonia Severity Index.

[a] Mutually adjusted for bronchopulmonary diseases, previous antibiotics, malignancy, chronic renal disease, immunosuppression, altered mentality, systolic blood pressure <90 mm Hg, bacteremia, mechanical ventilation, penicillin resistance, and multiple drug resistance.

[b] Adjusted for bronchopulmonary disease, previous antibiotics, immunosuppression, bacteremia, mechanical ventilation, penicillin resistance, multiple drug resistance, and PSI class 4/5.

not represent the overall status of the clinical characteristics or the final outcome associated with pneumococcal pneumonia in each country. Because the main purpose of this study was to evaluate the clinical impact of antimicrobial resistance in pneumococcal pneumonia, all cases of pneumococcal pneumonia in different geographic regions were collectively analyzed. However, differences in the disease severity and the quality of clinical care in different centers could have affected the final outcome of pneumonia. Third, although our data showed that discordant therapy did not result in increased mortality among patients with pneumococcal pneumonia regardless of the type of antimicrobial resistance among infecting isolates, the number of patients with discordant therapy (particularly patients with bacteremic pneumococcal pneumonia) was relatively small. Because recent data on macrolide discordance documented increased mortality associated with invasive pneumococcal diseases, further studies involving more patients who received discordant therapy are warranted.

In summary, data from the first multicenter, prospective, observational study of pneumococcal pneumonia in Asian countries suggest that penicillin, cephalosporin, or macrolide resistance in *S. pneumoniae* may not affect mortality associated with pneumococcal pneumonia. Data suggest that current antimicrobial regimens are still effective in the treatment of pneumococcal pneumonia, despite the widespread emergence of in vitro resistance in *S. pneumoniae*. Because of the continuous increase in the level of resistance to penicillin, other β-lactam agents, and macrolides among pneumococcal isolates in many parts of the world, further clinical studies involving increased numbers of patients with highly resistant strains are warranted to evaluate the clinical impact of in vitro resistance.

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