Multivariate Analysis of Risk Factors for Infection Due to Penicillin-Resistant and Multidrug-Resistant *Streptococcus pneumoniae:* A Multicenter Study

Antonio Jesús Clavo-Sánchez, José Antonio Girón-González, Dolores López-Prieto, Jesús Canueto-Quintero, Antonio Sánchez-Porto, Antonio Vergara-Campos, Pilar Marín-Casanova, and Juan Antonio Córdoba-Doña

*From the Hospital Universitario Puerta del Mar, and the Hospital de la Línea de la Concepción, Cádiz; the Hospital Universitario Puerto Real, Puerto Real; the Hospital de Jerez, Jerez; and the Hospital Punta de Europa, Algeciras, Spain**

Pneumococcal disease was studied prospectively to determine the risk factors associated with resistance to penicillin and other antibiotics. One hundred twelve clinically significant pneumococcal isolates were recovered from 95 patients. Approximately one-half (49.47%) of the cases were due to penicillin-resistant strains. Multivariate analysis showed that previous use of β-lactam antibiotics (odds ratio [OR], 2.81; 95% confidence interval [CI], 0.95–8.27), alcoholism (OR, 5.22; 95% CI, 1.43–19.01), and noninvasive disease (OR, 4.53; 95% CI, 1.54–13.34) were associated with penicillin resistance, whereas intravenous drug use (OR, 0.14; 95% CI, 0.03–0.74) was not. Statistical analyses of the variables associated with resistance to multiple antibiotics detected age of younger than 5 years (OR, 16.79; 95% CI, 1.60–176.34) or of 65 years or older (OR, 4.33; 95% CI, 1.42–13.21) and previous use of β-lactam antibiotics by patients with noninvasive disease (OR, 7.92; 95% CI, 1.84–34.06) as parameters associated with increased risk. We conclude that multivariate analysis provides clues for empirical therapy for pneumococcal infection.

For many years, pneumococci were uniformly susceptible to penicillin. However, since the first isolate resistant to penicillin was reported from Australia in 1967 [1], the problem of penicillin resistance has spread throughout the world [2]. 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.

Although infections due to penicillin-resistant pneumococci may occur more often in patients with identifiable predisposing conditions, we are aware of only one previous prospective study that analyzed the independent effect of risk factors for patients with pneumococcal disease. In a population-based analysis of the predictive factors for meningitis, pneumonia, or sepsis, Nava et al. [3] considered age of 0–4 years, presence of immunosuppressive underlying disease, and previous use of β-lactam antibiotics as factors for invasive infection by resistant pneumococci.

The overall clinical spectrum of pneumococcal infection includes other entities aside from invasive disease [4, 5]. In a prospective study of pneumococcal disease, both invasive and noninvasive, in Cádiz, Spain, we determined the risk factors associated with resistance to penicillin and other antibiotics. Our findings facilitate the choice of initial empirical antibiotic therapy for pneumococcal infection.

Materials and Methods

We performed a population-based study in Cádiz (southern Spain) with the cooperation of the staffs of the infectious diseases and microbiology units at five hospitals; these personnel make up the Group for the Study of Infectious Diseases in Cádiz. The five hospitals (two university hospitals, one general hospital, and two acute care hospitals with specialized departments) serve a population of 1,100,000 people. From February 1993 to March 1994, all isolates of *Streptococcus pneumoniae* from hospitalized patients were subjected to uniform microbiological analysis and clinical study. Only those isolates of clinical significance were evaluated.

Clinical study. All patients from whom *S. pneumoniae* was isolated were followed up, and information about each patient was obtained by one of the authors. The following variables were analyzed: age, sex, underlying disease(s), clinical condition at the time of admission, risk factors for infection, and site of the infection. All patients were followed up until death or discharge.

The severity of the underlying diseases was classified according to the criteria of McCabe and Jackson [6] as rapidly fatal, ultimately fatal, or nonfatal. The patient's clinical condi-

Received 1 November 1995; revised 31 October 1996.

Grant support: This work was supported by the Junta de Andalucía (Andalusian Regional Autonomous Government; 83(1992).

* The personnel of the infectious diseases and microbiology units of these five hospitals make up the Group for the Study of Infectious Diseases in Cádiz, Spain.

Reprints or correspondence: Dr. José A. Girón-González, Unidad de Enfermedades Infecciosas, Hospital Universitario Puerta del Mar, Ana de Viya 21, Cádiz 11009, Spain.

Clinical Infectious Diseases 1997; 24:1052–9

1058–4838/97/2406–0003$02.00

tion at the time of the study was classified according to the criteria of Winston et al. [7] as stable, fair, poor, or critical. True infection was defined as isolation of *S. pneumoniae* from clinically significant material or isolation of *S. pneumoniae* from other samples and clinical evidence of infection not attributable to other microorganisms.

Sources of isolates and specimen collection. During the study period, 112 consecutive clinically significant pneumococcal isolates were recovered from 95 patients (74 males and 21 females) aged 1 to 81 years (mean age ± SD, 45.34 ± 20.69 years). The sources of the clinically significant isolates were blood (41 isolates), pleural fluid (8), sputum (30), bronchoalveolar lavage fluid (7), CSF (7), otic specimens (6), conjunctival specimens (3), ascitic fluid (4), and miscellaneous samples (6; protected brush catheter specimens obtained via a bronchoscope [2], skin biopsy specimens [2], deep bone biopsy specimen obtained during surgery for acute osteomyelitis [1], and bile obtained during surgery for acute noncalculous cholecystitis [1]).

To exclude contaminated specimens, sputum was collected after the patients rinsed out their mouths with water and coughed deeply. Only those samples with >25 neutrophils and <10 squamous epithelial cells per low-power field ($\times 100$) were cultured [8, 9].

Two cases of pneumococcal pneumonia were diagnosed on the basis of findings of examinations of protected brush catheter samples obtained via a fiberoptic bronchoscope. The patients did not have chronic bronchitis as an underlying structural disease and had not previously received antibiotic therapy. The presence of $>10^3$ bacteria was required for the diagnosis of pneumonia [10].

Examination of bronchoalveolar lavage fluid specimens revealed the etiologies of five cases of ventilator-associated pneumonia and two cases of community-acquired pneumonia. Less than 1% of the cells in these samples were squamous epithelial cells. In every case, quantitative cultures showed $>10^5$ cfu/mL [10, 11]. Cultures of sputum or specimens obtained by protected brush catheters or bronchoalveolar lavage were required only in cases with clinical and radiological signs of pneumonia.

Ear drainage fluid for bacterial cultures was obtained after cleaning the canal; fresh pus was sampled as it exuded from the tympanic membrane. A calcium alginate swab dipped in trypticase soy broth was used to obtain material from the conjunctival sacs; samples were obtained from both eyes. The specimens were transported to the laboratory within 30 minutes after collection. Cultures of blood, pleural fluid, CSF, ascitic fluid, bile, and deep bone or skin biopsy specimens were done as previously indicated [12].

Microbiological study. *S. pneumoniae* was identified on the basis of typical colonial morphology on Mueller-Hinton agar with 5% defibrinated horse blood, characteristic findings of gram staining, results of disk diffusion tests with optochin, bile solubility, and results of latex agglutination tests. Antibiotic susceptibility was tested by means of the disk-diffusion technique with Mueller-Hinton agar supplemented with 5% horse blood; a 1-μg oxacillin disk was used to reveal resistance to penicillin.

MICs were determined by the Etest [13, 14]. An isolate was defined as susceptible, intermediately resistant, and highly resistant to penicillin when the MICs were <0.1 μg/mL, 0.1–1.0 μg/mL, and >1.0 μg/mL, respectively [15].

Susceptibility to other antibiotics was determined by disk-diffusion testing [16]. The diameters of the zones of inhibition that were considered to reveal susceptibility were as follows: erythromycin, $\geq$23 mm; chloramphenicol, $\geq$18 mm; tetracycline, $\geq$19 mm; co-trimoxazole, $\geq$16 mm; clindamycin, $\geq$21 mm; vancomycin, $\geq$12 mm; and cefotaxime, $\geq$23 mm [17]. Pneumococci that were resistant to three or more antibiotics (including penicillin) were considered multidrug resistant [18].

Patients in all five centers were specifically questioned during their hospitalizations about the variables putatively associated with penicillin resistance and multidrug resistance: age, sex, use of β-lactam agents during the previous 3 months, alcoholism, liver cirrhosis, cancer, pneumonia in the last year, HIV infection, intravenous drug use (IVDU), hospitalization during the previous 6 months, diabetes mellitus, chronic obstructive pulmonary disease (COPD), and nosocomial infection (nosocomial infection was diagnosed when signs and symptoms of disease developed after 48 hours of hospitalization for an unrelated illness).

Information on some variables (mechanical ventilation and invasive disease) was obtained from the chart while the patient was hospitalized. Invasive disease was diagnosed when a culture-positive specimen was obtained from a normally sterile site (pleural fluid, CSF, pericardial fluid, ascitic fluid, or blood). Because pneumococcal bile cyst and bone infections imply previous bacteremia, cholecystitis (one case) and osteomyelitis (one case) were also classified as invasive diseases. Thus, invasive disease was diagnosed in cases of pneumonia with bacteremia, empyema, meningitis, peritonitis, pericarditis, cholecystitis, osteomyelitis, and bacteremia from an unidentified focus.

Statistical analysis. The statistical significance of qualitative variables was analyzed with either the χ^2 test or Fisher's exact test. The relation of covariates with resistance was initially assessed by univariate analysis, and then odds ratios were determined. Multivariate analyses were performed via stepwise logistic regression; penicillin resistance or multidrug resistance was the dependent variable. Variables associated with resistance in the univariate analysis and other potentially related factors were considered independent variables in the models. The analysis included testing for the existence of an interaction between the different variables. Goodness of fit of the final models was assessed with the $\hat{C}$ statistic reported by Hosmer and Lemeshow [19].

Results

Risk factors for pneumococcal infection. Of the 95 patients studied, 15 (15.79%) had been hospitalized previously and 11

Table 1. Main clinical and epidemiological characteristics of 95 patients with pneumococcal infection and susceptibility of the isolates to penicillin.

Characteristic	No. (%) of patients from whom isolates were recovered		
	Penicillin-susceptible (n = 48)	Penicillin-resistant (n = 47)	Total (n = 95)
Underlying disease	39 (81.25)	39 (82.98)	78 (82.11)
Severity of underlying disease			
Nonfatal	12 (30.77)	14 (35.90)	26 (33.33)
Ultimately fatal	18 (46.15)	18 (46.15)	36 (46.15)
Rapidly fatal	9 (23.08)	7 (17.95)	16 (20.51)
Mode of acquisition			
Nosocomial	3 (6.25)	8 (17.02)	11 (11.58)
Community	45 (93.75)	39 (82.98)	84 (88.42)
Invasive disease	33 (68.75)	23 (48.94)	56 (58.95)
Bacteremia	24 (50.00)	17 (36.17)	41 (43.16)
Clinical outcome			
Cure	41 (85.42)	41 (87.23)	82 (86.32)
Death	7 (14.58)	6 (12.76)	13 (13.68)
Pneumococcal infection related	4 (8.33)	4 (8.51)	8 (8.42)
Pneumococcal infection unrelated	3 (6.25)	2 (4.26)	5 (5.26)

(11.58%) had nosocomial infections. Previous use of β-lactam antibiotics during the last 3 months was reported by 25 patients (26.32%). Underlying diseases that might have contributed to pneumococcal infection were present in 78 patients (82.11%). These underlying conditions were HIV infection (26.31%), alcoholism (23.15%), COPD (21.05%), diabetes (12.63%), neoplasia (11.57%), and liver cirrhosis (7.36%). Some patients (19 cases) had more than one underlying disease. There were no significant differences in terms of age, sex, underlying disease, or site of the infection between the patient populations from the five hospitals participating in this study.

Clinical characteristics. The most frequent diagnoses were pneumonia (66.31%), empyema (8.42%), meningitis (7.36%), otitis (6.31%), peritonitis (4.21%), pneumococcal bacteremia from an unidentified focus (4.21%), and conjunctivitis (3.15%). The pneumococcal infection was invasive in 56 patients (58.95%). Pneumococcal bacteremia (41 cases) was generally secondary to pneumonia (29 cases [70.73%]), meningitis (4 [9.76%]), or empyema, peritonitis, otitis, or endocarditis (1 each [2.44%]).

The clinical conditions of the patients at the time of the study were considered stable in 11 cases (11.58%), fair in 34 cases (35.80%), poor in 26 cases (27.36%), and critical in 24 cases (25.26%). Thirteen patients (13.68%) died in the hospital. Death was directly attributable to pneumococcal infection in eight (8.42%) of these patients.

Susceptibility of S. pneumoniae isolates to penicillin and other antibiotics. Of the 95 cases of pneumococcal infection studied, 48 (50.53%) were due to penicillin-susceptible strains. The remaining 47 cases (49.47%) were due to penicillin-resistant strains; of all 95 cases, 23 (24.21%) were due to intermediately penicillin-resistant pneumococci, and 24 (25.26%) were due to highly penicillin-resistant strains. All pneumococcal isolates were susceptible to cefotaxime and vancomycin.

The main clinical and epidemiological characteristics of the 95 patients with *S. pneumoniae* infection are shown in table 1; the characteristics are classified according to the susceptibility of isolates to penicillin. Of the 95 strains studied, 30 (31.6%) were multidrug resistant. Susceptibility testing revealed that 4.17% of penicillin-susceptible pneumococci, 47.83% of intermediately penicillin-resistant pneumococci, and 70.83% of highly penicillin-resistant pneumococci were resistant to multiple antibiotics (table 2). There were no significant differences in the frequency of resistant pneumococci isolated from the patient populations at the different hospitals participating in this study (data not shown). The different patterns of multidrug resistance are summarized in table 3. All multidrug-resistant isolates were resistant to co-trimoxazole.

Statistical analysis of factors implicated in penicillin resistance and multidrug resistance. No significant differences were observed between clinical characteristics (age, sex, use of β-lactam agents during the previous 3 months, alcoholism, liver cirrhosis, cancer, pneumonia in the last year, HIV infection, IVDU, hospitalization during the previous 6 months, mechanical ventilation, diabetes mellitus, COPD, nosocomial infection, and invasive disease) of patients infected with pneumococci with intermediate- and high-level penicillin resistance (table 4). Thus, univariate and multivariate analyses of risk factors associated with penicillin resistance and multidrug resistance were done with use of penicillin resistance as a single variable.

The distribution of different variables in relation to penicillin resistance (MIC, >0.1 μg/mL) is shown in table 5. The univari-

Table 2. Susceptibility of 95 pneumococcal isolates to antibiotics other than penicillin according to the MIC of penicillin.

Antibiotic(s)	No. (%) of isolates: Penicillin-susceptible (n = 48)	Intermediately resistant to penicillin (n = 23)	Highly resistant to penicillin (n = 24)
Erythromycin	4 (8.33)	9 (39.13)	8 (33.33)
Chloramphenicol	1 (2.08)	1 (4.35)	7 (29.17)
Tetracycline	8 (16.67)	14 (60.87)	20 (83.33)
Co-trimoxazole	13 (27.08)	19 (82.61)	22 (91.67)
Clindamycin	6 (12.50)	6 (26.09)	9 (37.50)
Multiple agents	2 (4.17)	11 (47.83)	17 (70.83)

NOTE. All strains were susceptible to cefotaxime and vancomycin.

ate analysis revealed that previous use of β-lactam antibiotics was significantly associated with penicillin resistance. IVDU was not associated with penicillin resistance. The lack of association between invasive disease and penicillin resistance approached statistical significance (P = .0508).

Multivariate analysis of risk factors potentially associated with penicillin resistance showed that previous use of β-lactam antibiotics, alcoholism, and noninvasive disease were associated with resistance, whereas IVDU was not (table 6). Therefore, we studied those risk factors suspected of being associated with multidrug resistance. Univariate analysis of these putative risk factors (table 7) showed that previous use of β-lactam antibiotics (OR, 2.67; 95% CI, 0.92–7.76; P = .0707) was associated with resistance to multiple antibiotics (although not in a statistically significant manner). Multivariate analysis showed that noninvasive disease, previous use of β-lactam antibiotics, and age of younger than 5 years or 65 years or older were significantly associated with increased risk.

We observed an interaction between the first two variables. Noninvasive disease was associated with multidrug resistance only in those cases in which β-lactam agents were previously used. Inversely, a greater risk of multidrug resistance was detected for patients who used β-lactam antibiotics previously and had noninvasive disease (table 8).

Table 3. Patterns of multidrug resistance in 30 pneumococcal isolates.

Multidrug pattern	No. (%) of resistant isolates
Co-trimoxazole, penicillin, tetracycline	11 (36.67)
Co-trimoxazole, penicillin, erythromycin	5 (16.67)
Co-trimoxazole, penicillin, clindamycin, erythromycin, tetracycline	4 (13.33)
Co-trimoxazole, penicillin, erythromycin, tetracycline	4 (13.33)
Co-trimoxazole, penicillin, clindamycin, erythromycin	3 (10.00)
Co-trimoxazole, penicillin, clindamycin	1 (3.33)
Co-trimoxazole, penicillin, chloramphenicol	1 (3.33)
Co-trimoxazole, erythromycin, tetracycline	1 (3.33)

Discussion

Recent studies have reported an increase in the rate of resistance to various antimicrobial agents (particularly penicillin)

Table 4. Risk factors associated with intermediate and high resistance to penicillin for 47 patients with pneumococcal infection.

Risk factor	No. (%) of patients with indicated characteristic according to strain type: Intermediate resistance (n = 23)	High resistance (n = 24)	Total (n = 47)	P value
Age (y)				
5 or younger	3	0	3 (6.38)	
6 to 44	6	13	19 (40.43)	
45 to 64	8	4	12 (25.53)	
65 or older	6	7	13 (27.66)	.3524
Sex				
Male	17	19	36 (76.60)	
Female	6	5	11 (23.40)	.9356
Use of β-lactam agents in previous 3 mo	9	8	17 (36.17)	.9125
Alcoholism	8	6	14 (29.79)	.6788
Liver cirrhosis	2	1	3 (6.38)	.4836
Cancer	2	3	5 (10.64)	.9598
Pneumonia in the last year	2	3	5 (10.64)	.9598
HIV infection	3	7	10 (21.28)	.1604
Intravenous drug use	0	3	3 (6.38)	.1248
Hospitalization in previous 6 mo	3	7	10 (21.28)	.1604
Mechanical ventilation	3	5	8 (17.02)	.3753
Diabetes mellitus	3	4	7 (14.89)	.9513
Chronic obstructive pulmonary disease	6	5	11 (23.40)	.9357
Nosocomial infection	3	5	8 (17.02)	.3753
Invasive disease	13	10	23 (48.94)	.4675

Table 5. Risk factors for infection due to penicillin-resistant *Streptococcus pneumoniae* and results of univariate analysis.

Risk factor	No. (%) of patients with indicated characteristic according to strain type			Result of univariate analysis		
	Penicillin-susceptible (n = 48)	Penicillin-resistant (n = 47)	Total (n = 95)	OR	95% CI	P value
Age (y)						
Younger than 5	2	3	5 (5.26)	1.82	0.19–23.55	.4375
5 to 44	24	19	43 (45.26)	1.00		
45 to 64	13	12	25 (26.32)	1.12	0.37–3.39	.9728
65 or older	9	13	22 (23.16)	1.75	0.55–5.68	.4297
Alcoholism	8	14	22 (23.16)	2.12	0.71–6.43	.1316
Use of β-lactam agents in previous 3 mo	8	17	25 (26.32)	2.83	0.97–8.42	.0308
Cancer	6	5	11 (11.58)	0.83	0.20–3.45	.7779
Chronic obstructive pulmonary disease	9	11	20 (21.05)	1.32	0.44–4.02	.5799
Diabetes mellitus	5	7	12 (12.63)	1.50	0.38–6.10	.5135
Hospitalization in previous 6 mo	5	10	15 (15.79)	2.32	0.64–8.79	.1488
Invasive disease	33	23	56 (58.95)	0.44	0.17–1.10	.0508
Liver cirrhosis	4	3	7 (7.37)	0.75	0.12–4.35	.5118
Mechanical ventilation	3	8	11 (11.58)	3.08	0.67–16.07	.1027
Nosocomial infection	3	8	11 (11.58)	3.08	0.67–16.07	.1027
Pneumonia in previous year	4	5	9 (9.47)	1.31	0.28–6.40	.7028
Intravenous drug use	12	3	15 (15.79)	0.20	0.04–0.88	.0133
Sex						
Male	38	36	74 (77.89)	1.00		
Female	10	11	21 (22.11)	1.16	0.39–3.44	.7639
HIV infection	15	10	25 (26.32)	0.59	0.21–1.66	.2722

in pneumococci in certain geographic areas [2, 18]. Our prospective study confirms the rates reported by other investigators in Spain [4, 20–22].

A number of predisposing conditions (such as young age [4, 23], previous hospitalization [25], severity of the underlying disease [4, 24], previous antibiotic therapy [4, 24], immunosuppression [4, 18], nosocomial pneumonia or previous episodes of pneumonia [24], and isolation of certain serotypes [4]) have been identified as risk factors for pneumococcal infections caused by penicillin-resistant strains in case-control studies [4]. However, conflicting results have been found in large case series, even in reports from similar geographic areas [25, 26]. The coincidence of several risk factors in the same patients [4, 27], the retrospective nature of most studies [5, 24, 27], and the lack of multivariate analyses make interpretation of these results difficult.

Table 6. Results of multivariate analysis of risk factors associated with penicillin resistance in isolates from 95 patients with pneumococcal infection.

Risk factor	OR	95% CI
Use of β-lactam antibiotics in previous 3 mo	2.81	0.95–8.27
Alcoholism	5.22	1.43–19.01
Intravenous drug use	0.14	0.03–0.74
Noninvasive disease	4.53	1.54–13.34
Age (y)		
Younger than 5	4.15	0.43–40.10
5 to 44	3.40	0.88–13.20
65 or older	3.78	0.94–15.18

To our knowledge, only one study has assessed the independent contribution of possible risk factors for infection due to penicillin-resistant pneumococci. Nava et al. [3] studied 374 episodes of invasive pneumococcal disease (pneumonia, meningitis, or bacteremia) in the province of Barcelona, Spain, and found that 88 were caused by penicillin-resistant strains. Multivariate analysis showed that the variables associated with penicillin resistance were age of younger than 5 years, immunosuppressive underlying disease (including HIV infection, liver cirrhosis, and neoplasms), and prior use of β-lactam antibiotics.

The results of our multivariate analysis showed that noninvasive disease, previous use of β-lactam antibiotics, and alcoholism are risk factors for infection with penicillin-resistant pneumococci. IVDU was not associated with penicillin resistance.

Our study confirms that previous use of β-lactam antibiotics is a risk factor associated with penicillin resistance [3]. Baquero et al. [28] argued that the repetitive use of β-lactam agents exerts a selection effect on the pneumococcal strains in carriers, thus leading to the emergence of resistant strains.

Because alcoholism may be related to immune deficiency [29, 30], it is another risk factor for infection due to penicillin-resistant pneumococci. Other studies have shown an increased risk of infection due to penicillin-resistant pneumococci in pa-

Table 7. Risk factors for infection due to multidrug-resistant pneumococci and results of univariate analysis.

Risk factor	No. (%) of patients with indicated characteristic according to strain type			Result of univariate analysis		
	Non-multidrug-resistant isolates (n = 65)	Multidrug-resistant isolates (n = 30)	Total (n = 95)	OR	95% CI	P value
Age (y)						
5 or younger	1	4	5 (5.26)	2.75	0.80–9.56	.1209
6 to 44	33	10	43 (45.26)	1.00		
45 to 64	19	6	25 (26.32)	1.04	0.28–3.81	.8206
65 or older	12	10	22 (23.16)	13.20	1.07–668.97	.0210
Alcoholism	15	7	22 (23.16)	1.01	0.32–3.17	.8149
Use of β-lactam agents in previous 3 mo	13	12	25 (26.32)	2.67	0.92–7.76	.0707
Cancer	7	4	11 (11.58)	1.27	0.28–5.53	.4792
Chronic obstructive pulmonary disease	14	6	20 (21.05)	0.91	0.27–2.99	.9205
Diabetes mellitus	8	4	12 (12.63)	1.10	0.25–4.60	.5635
Hospitalization in previous 6 mo	11	4	15 (15.79)	0.76	0.18–2.96	.4535
Invasive disease	42	14	56 (58.95)	0.48	0.18–1.27	.1530
Liver cirrhosis	6	1	7 (7.37)	0.34	0.01–3.09	.2872
Mechanical ventilation	7	4	11 (11.58)	1.27	0.28–5.53	.4792
Nosocomial infection	8	3	11 (11.58)	0.79	0.15–3.72	.5207
Pneumonia in previous year	6	3	9 (9.47)	1.09	0.20–5.54	.5861
Intravenous drug use	13	2	15 (15.79)	0.29	0.04–1.50	.0831
Sex						
Male	51	23	74 (77.89)	1.00		
Female	14	7	21 (22.11)	1.11	0.34–3.50	.9442
HIV infection	18	7	25 (26.32)	0.79	0.25–2.42	.8431

tients with liver cirrhosis [18, 31]. It would be interesting to know the cause of the liver disease and the influence of alcoholism in these patients.

Although HIV infection has been considered a risk factor for pneumococcal infection [4, 32, 33], there are conflicting results with respect to its effect on penicillin susceptibility [34, 35]. We did not detect any effect of HIV infection on penicillin resistance in pneumococci. However, to our knowledge, the effect of risky behaviors for HIV infection (IVDU, homosexuality, etc.) on penicillin susceptibility in pneumococci has not previously been analyzed. In our geographic area, 84% of HIV-infected patients are intravenous drug users [36]. Our data show that patients with a history of IVDU have a lower risk of infection by penicillin-resistant pneumococci. This finding could mask the effect of immunosuppression.

Table 8. Results of multivariate analysis of risk factors associated with multidrug resistance in isolates from 95 patients with pneumococcal infection.

Primary risk factor, secondary risk factor	OR	95% CI
Use of β-lactam agents in previous 3 mo		
Invasive disease	1.02	0.22–4.66
Noninvasive disease	7.92	1.84–34.06
Noninvasive disease		
No use of β-lactam agents in previous 3 mo	1.27	0.39–4.13
Use of β-lactam agents in previous 3 mo	9.87	1.49–65.04
Noninvasive disease and use of β-lactam agents in previous 3 mo		
Invasive disease and no use of β-lactam agents in previous 3 mo	10.07	2.56–39.57
Age of younger than 5 years	16.79	1.60–176.34
Age of 65 years or older	4.33	1.42–13.21

The rate of treatment compliance among intravenous drug users is lower than that among other patient groups [37, 38]. β-Lactam agents may be used less frequently by patients with a history of IVDU, thus making the emergence of resistant strains less likely. In fact, only two of 15 patients with a history of IVDU in our study had received prior antibiotic therapy. These data establish the need for analyzing the effect of risky behaviors for HIV infection on the likelihood of infection due to penicillin-resistant pneumococci.

This study included the analysis of invasive and noninvasive forms of pneumococcal infection; strict criteria for excluding contaminated specimens were used. Invasive disease was associated with a lower risk of infection by penicillin-resistant pneumococci in our study. Other studies have also found a higher rate of penicillin-susceptible pneumococci among the causal agents of pneumococcal bacteremia [4, 21]. However, to our knowledge, the lack of association between invasive disease and penicillin resistance in pneumococci has not been noted previously. This finding should be interpreted with caution. Although the rate of penicillin-resistant strains isolated from patients with invasive disease was low, these resistant

isolates represented 41.1% (intermediate resistance, 23.2%; high resistance, 17.9%) of the total number of isolates from patients with invasive disease.

It has been reported that invasive pneumococcal isolates resistant to penicillin and multiple drugs belong to one of six serotypes [39, 40]. Determination of the *S. pneumoniae* serotype was not possible in all five hospitals participating in this study. Nonetheless, we believe that this handicap did not limit the utility of our results, which are rapidly applicable to the clinical management of pneumococcal infection.

We have shown that the rate of multidrug resistance is higher among strains that are highly resistant to penicillin, thus complicating the selection of therapeutic agents. Therefore, two potentially useful antibiotics for the treatment of pneumococcal infection—co-trimoxazole and erythromycin—are not suitable in our area because of widespread resistance (table 3). Resistance to erythromycin has also been stressed in recent reports [22, 41].

Multivariate analysis of the risk factors associated with multidrug resistance identified factors similar to those associated with penicillin resistance: noninvasive disease and previous use of β-lactam antibiotics. Moreover, age of younger than 5 years or 65 years or older was associated with a higher rate of infection due to multidrug-resistant pneumococci.

Close attention should be given to the treatment of patients with pneumococcal infection who have one or several of the following: noninvasive disease, prior use of β-lactam antibiotics, alcoholism, and age of younger than 5 years or 65 years or older. Treatment will depend on antibiotic resistance profiles in each geographic area. Available experience suggests that extrameningeal infections due to intermediately susceptible strains can be managed by increasing the dose of penicillin. In our area, meningeal infections caused by pneumococci highly resistant to penicillin could be treated with cefotaxime [42]. Fortunately, the penicillin susceptibility in pneumococci infecting intravenous drug users is adequate, thus facilitating therapy for these individuals.

Acknowledgment

We thank Karen Shashok for grammatical assistance.

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