RESISTANCE TO PENICILLIN AND CEPHALOSPORIN AND MORTALITY FROM SEVERE PNEUMOCOCCAL PNEUMONIA IN BARCELONA, SPAIN

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Abstract *Background. Penicillin-resistant strains of Streptococcus pneumoniae are now found worldwide, and strains with resistance to cephalosporin are being reported. The appropriate antibiotic therapy for pneumococcal pneumonia due to resistant strains remains controversial.*

Methods. To examine the effect of resistance to penicillin and cephalosporin on mortality, we conducted a 10-year, prospective study in Barcelona of 504 adults with culture-proved pneumococcal pneumonia.

Results. Among the 504 patients, 145 (29 percent) had penicillin-resistant strains of S. pneumoniae (minimal inhibitory concentration [MIC] of penicillin G, 0.12 to 4.0 μg per milliliter), and 31 patients (6 percent) had cephalosporin-resistant strains (MIC of ceftriaxone or cefotaxime, 1.0 to 4.0 μg per milliliter). Mortality was 38 percent in patients with penicillin-resistant strains, as compared with 24 percent in patients with penicillin-sensitive strains (P = 0.001). However, after the exclusion of patients with polymicrobial pneumonia and adjustment for other predictors of mortality, the odds ratio for mortality in patients with penicillin-resistant strains was 1.0 (95 percent confidence interval, 0.5 to 1.9; P = 0.84). Among patients treated with penicillin G or ampicillin, the mortality was 25 percent in the 24 with penicillin-resistant strains and 19 percent in the 126 with penicillin-sensitive strains (P = 0.51). Among patients treated with ceftriaxone or cefotaxime, the mortality was 22 percent in the 59 with penicillin-resistant strains and 25 percent in the 127 with penicillin-sensitive strains (P = 0.64).

The frequency of resistance to cephalosporin increased from 2 percent in 1984–1988 to 9 percent in 1989–1993 (P = 0.002). Mortality was 26 percent in patients with cephalosporin-resistant S. pneumoniae and 28 percent in patients with susceptible organisms (P = 0.89). Among patients treated with ceftriaxone or cefotaxime, mortality was 22 percent in the 18 with cephalosporin-resistant strains and 24 percent in the 168 with cephalosporin-sensitive organisms (P = 0.64).

Conclusions. Current levels of resistance to penicillin and cephalosporin by S. pneumoniae are not associated with increased mortality in patients with pneumococcal pneumonia. Hence, these antibiotics remain the therapy of choice for this disease. (N Engl J Med 1995;333:474-80.)

SINCE the first descriptions two decades ago of strains of *Streptococcus pneumoniae* with a decreased susceptibility to penicillin (minimal inhibitory concentration [MIC] of penicillin G, or the lowest concentration that inhibits pneumococcal growth, ≥0.12 μg per milliliter),[1,2] there have been increasing reports of infections caused by pneumococcal strains with high levels of resistance to penicillin, to multiple antibiotics, and more recently to cephalosporin.[3-13] The prognostic factors have been studied,[14,15] but the effect of resistance to penicillin and cephalosporin on mortality due to pneumococcal pneumonia in adults is not known.

Despite the decreased susceptibility of pneumococci to penicillin G, it is probable that penicillin, the time-honored treatment for pneumococcal infection, should remain the antibiotic of choice for some such infections. However, it is not clear which types of pneumococcal infection may be treated successfully with penicillin, and up to what MIC.

On the basis of reports by us and others,[13,16] pneumococcal meningitis due to strains against which the MIC of penicillin is 0.12 μg per milliliter or higher should not be treated with that drug. Instead, either a third-generation cephalosporin or vancomycin is recommended.[13,16] Recently, cephalosporin therapy has been reported to have failed in patients with pneumococcal meningitis due to strains against which cefotaxime and ceftriaxone have high MICs.[17]

On the other hand, preliminary data suggest that in some cases pneumococcal pneumonia against which the MIC of penicillin is increased may respond to penicillin or related β-lactam antibiotics,[18-20] because the serum concentrations achieved with these drugs[21] are several times higher than the MICs. Nevertheless, the efficacy of penicillin is uncertain, and the role of extended-spectrum cephalosporins (ceftriaxone or cefotaxime) in treating resistant pneumococcal pneumonia is not well defined.

We sought to determine the factors influencing mortality in adults with severe pneumococcal pneumonia, as well as to assess the effect of resistance to penicillin and cephalosporin on mortality in such patients. In addition, we evaluated the response to therapy with penicillin or cephalosporin in relation to the degree of resistance of the infecting strain.

METHODS

Study Patients and Sources of Data

This 10-year, prospective study included patients with pneumonia and no other focal disease, such as meningitis, for whom cultures of blood, pleural fluid, or specimens from the lower respiratory tract were positive for *S. pneumoniae.* The study was carried out in the Hospital de Bellvitge "Princeps d'Espanya," a 1000-bed teaching institution in Barcelona, Spain, that serves an area with a population of more than 1 million and admits only adult patients.

From January 1984 through December 1993, a total of 494 isolates of *S. pneumoniae* were identified from blood samples in our microbiology laboratory; 412 of these strains were isolated from patients with pneumonia, whereas the remainder were from patients with meningitis (49 patients) or bacteremia (33 patients). In addition, 138 patients whose blood cultures were negative had *S. pneumoniae* isolated

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from cultures of pleural fluid (46 patients), cultures of specimens obtained by transthoracic needle aspiration (37 patients), or cultures of bronchoscopic specimens obtained by brushing that had more than 1000 colony-forming units (cfu) (55 patients). Thus, a total of 550 patients had diagnoses of culture-proved pneumococcal pneumonia. At our institution, selected patients with severe pneumonia whose initial diagnoses were unclear were included in a prospective protocol (approved by the ethics committee of the hospital) in recent years to study the efficacy of procedures to obtain bronchoscopic specimens by brushing and transthoracic needle aspiration.[22] Studies of susceptibility to antibiotics were conducted for all the strains obtained; several were included in previous reports.[18,23]

When pneumococci were isolated from blood or another specimen, the patient was evaluated by a staff member of the Infectious Disease Service or the Pulmonary Disease Service. Most patients were seen at outpatient clinics within one month after discharge. Data on mortality were obtained by following the patients during hospitalization and reviewing the clinical records of the outpatient clinic and records of deaths.

We decided to include both patients with bacteremia and those without bacteremia in the study, because no significant differences in mortality were found between the two groups (28 percent and 29 percent, respectively). This study design allowed us to enroll more patients with strains resistant to penicillin and cephalosporin, so that more accurate statistical comparisons could be made.

Among the 550 patients, 504 completed the study protocol; the remaining 46 were excluded from the univariate and multivariate analyses. The mortality rate among these 46 patients was 26 percent, similar to the rate of 28 percent among the patients who were included. The entire group of 550 patients was included in the studies of susceptibility to antibiotics (Table 1).

*Table 1. Susceptibility to Antibiotics in 550 Strains of Pneumococci Isolated from Patients with Pneumonia.**

Drug and MIC (μg/ml)	No. (%) of Strains		P Value†
	1984–1988 (N = 221)	1989–1993 (N = 329)	
Penicillin G			<0.001
≤0.06	178 (81)	214 (65)	
0.12–1.0	29 (13)	67 (20)	
2.0	11 (5)	35 (11)	
4.0	3 (1)	13 (4)	
Ceftriaxone or cefotaxime			0.002
≤0.5	216 (98)	299 (91)	
1.0–4.0	5 (2)	30 (9)	
Imipenem			<0.001
≤0.12	208 (94)	271 (82)	
0.25–1.0	13 (6)	58 (18)	
Erythromycin			0.03
≤0.5	206 (93)	287 (87)	
1.0–128.0	15 (7)	42 (13)	
Tetracycline			0.02
≤2.0	124 (56)	219 (67)	
4.0–128.0	97 (44)	110 (33)	
Trimethoprim–sulfamethoxazole			0.66
≤0.05	110 (50)	173 (53)	
1.0–2.0	20 (9)	33 (10)	
≥4.0	91 (41)	123 (37)	

*Of the 550 strains, 412 were isolated from blood cultures and 138 from cultures of specimens from the lower respiratory tract. The most frequent serotypes of penicillin-resistant pneumococci were serotypes 14 (in 19 percent of isolates), 6 (18 percent), 9 (17 percent), 23 (16 percent), 19 (15 percent), and 15 (7 percent); the most frequent serotypes of cephalosporin-resistant pneumococci were serotypes 23 (in 28 percent of isolates), 6 (28 percent), 14 (23 percent), 9 (10 percent), and 19 (5 percent). None of the strains were resistant to vancomycin at a minimal inhibitory concentration (MIC) greater than 1.0 μg per milliliter.

†P values are for the comparison of the two periods for all MICs of each drug; they were obtained by the chi-square test from two-by-k contingency tables, where k was the number of categories of MICs studied.

Definitions

A diagnosis of pneumococcal pneumonia was made if a patient was found to have infection of the lower respiratory tract in the clinical history and on physical examination, as well as a pulmonary infiltrate on chest radiography, and if *S. pneumoniae* was isolated from cultures of one or more of the following types of specimens: blood, pleural fluid, or specimens obtained by transthoracic needle aspiration or bronchoscopic-specimen brushing. Patients who had only sputum cultures positive for pneumococci were not included.

Mortality in the hospital was defined to include deaths within one month after the diagnosis of pneumonia. Serious underlying disease was considered to be present if the patient had a confirmed diagnosis of one of the following: cancer, systemic vasculitis, or cirrhosis of the liver; diabetes, if that disease had been diagnosed and the patient was receiving hypoglycemic drugs; chronic renal failure, if the patient was undergoing dialysis; human immunodeficiency virus (HIV) infection, if the patient had a positive enzyme-linked immunosorbent assay and Western blot assay for HIV type 1 or type 2; heart failure, if the patient had a history of congestive heart failure, evidence of heart failure, or both at the time of admission; and chronic pulmonary disease, if the patient had had chronic respiratory symptoms for more than three months during the preceding two years. Nosocomially acquired pneumonia was defined by the presence of signs and symptoms of lower respiratory tract infection that developed after three days of hospitalization for an unrelated illness. Shock was defined as systolic blood pressure below 90 mm Hg together with hypoperfusion of the peripheral tissues. Multilobar involvement and pleural effusion were considered to be present when more than one pulmonary lobe was involved and when there was evidence of pleural fluid on a chest film, respectively. Leukopenia was diagnosed if the initial white-cell count was below 5000 per cubic millimeter. Polymicrobial pneumonia was considered to be present when *S. pneumoniae* and another microorganism were isolated from cultures of blood or specimens obtained from the lower respiratory tract; monomicrobial pneumonia was considered to be present when *S. pneumoniae* was the only microorganism isolated.

Antibiotic therapy was initially prescribed by the attending physician. When the results of the in vitro susceptibility testing were known, the patient was evaluated by an infectious-disease specialist, and most patients continued to receive the drugs initially prescribed, because their conditions were clearly improving. For the analysis, patients were divided into three groups: the penicillin group (those treated with penicillin G or ampicillin); the cephalosporin group (those treated with ceftriaxone or cefotaxime); and the group treated with other antibiotics. In order to include more patients with penicillin-resistant disease in each group, those treated with penicillin G and ampicillin were grouped together, as were those treated with ceftriaxone and cefotaxime, because the drugs in each pair have almost identical MICs and produce similar clinical responses. Antibiotic therapy usually lasted from 7 to 14 days. The usual total intravenous dose of penicillin G was 2 million U every 4 hours; of ampicillin, 2 g every 6 hours; of ceftriaxone, 1 to 2 g every 24 hours; and of cefotaxime, 1 to 2 g every 6 hours. The other antibiotics were administered according to standard criteria.[21]

Microbiologic Studies

Strains of *S. pneumoniae* were identified by standard methods. All strains were initially screened for susceptibility to antimicrobial agents by the disk-diffusion method, with Mueller–Hinton blood agar plates.[24] A 1-μg oxacillin disk was used to detect all strains that had decreased sensitivity to penicillin. The MICs of the oxacillin-resistant strains were determined by the microdilution method in cation-supplemented Mueller–Hinton broth with 5 percent whole defibrinated horse blood, at the appropriate concentration of antibiotic. The wells of the microdilution plates were inoculated to a volume of 100 μl with an inoculum containing 1 million cfu per milliliter. All pneumococcal strains were stored frozen at −40°C in skim milk until their MICs were determined by the agar-dilution method. Two strains of *S. pneumoniae* were used as controls: American Type Culture Collection (ATCC) 49619 (serotype 19) and ATCC 6303 (serotype 3). The MIC was defined as the lowest concentration of antibiotic that prevented growth visible without the microscope after an overnight incubation of plates at 35°C. The MICs of the antibiotics shown in Table 1 and elsewhere in this article were determined by the agar-dilution method. Resistance to antimicrobial agents was defined according to the criteria of the National Committee for Clinical Laboratory Standards.[25] Strains were serotyped at the Spanish Pneumococcal Reference Laboratory (Majadahonda, Madrid) with standard antiserum

*Table 2. Univariate Analysis of Factors Influencing Mortality in 504 Adult Patients with Pneumococcal Pneumonia.**

FACTOR	MORTALITY		UNADJUSTED ODDS RATIO (95% CI)	P VALUE
	NO. OF DEATHS/ NO. OF PATIENTS	PERCENT		
Demographics and history				
Age (yr)				
19–39	19/114	17	1.0	—
40–69	71/252	28	1.9 (1.1–3.4)	0.02
≥70	50/138	36	2.8 (1.5–5.1)	<0.001
Sex				
Male	100/376	27	1.0	—
Female	40/128	31	1.2 (0.8–1.9)	0.31
Serious underlying disease†				
No	80/370	22	1.0	—
Yes	60/134	45	2.9 (1.9–4.4)	<0.001
Diabetes				
No	124/449	28	1.0	—
Yes	16/55	29	1.0 (0.8–3.8)	0.82
Chronic renal failure				
No	135/488	28	1.0	—
Yes	5/16	31	1.1 (0.4–3.4)	0.75
HIV infection				
No	134/462	29	1.0	—
Yes	6/42	14	0.4 (0.1–0.9)	0.05
Heart failure				
No	117/453	26	1.0	—
Yes	23/51	45	2.3 (1.3–4.2)	0.004
Chronic pulmonary disease				
No	109/385	28	1.0	—
Yes	31/119	26	0.8 (0.5–1.4)	0.63
Findings at presentation				
Shock				
No	85/429	20	1.0	—
Yes	55/75	73	11.1 (6.3–19.5)	<0.001
Multilobar involvement				
No	67/364	18	1.0	—
Yes	73/140	52	4.8 (3.1–7.3)	<0.001
Leukopenia (<5000 cells/mm^3)				
No	98/436	22	1.0	—
Yes	42/68	62	5.5 (3.2–9.5)	<0.001
Polymicrobial pneumonia‡				
No	115/464	25	1.0	—
Yes	25/40	62	5.0 (2.5–9.9)	<0.001
Place pneumonia acquired				
Community	91/396	23	1.0	—
Hospital	49/108	45	2.7 (1.7–4.3)	<0.001
Penicillin resistance§				
No	85/359	24	1.0	—
Yes	55/145	38	1.9 (1.3–2.9)	0.001
Cephalosporin resistance¶				
No	132/473	28	1.0	—
Yes	8/31	26	0.9 (0.4–2.1)	0.89
Antibiotic therapy‖				
Penicillin G or ampicillin	31/152	20	1.0	—
Ceftriaxone or cefotaxime	52/199	26	1.3 (0.8–2.2)	0.21
Other	47/143	33	1.9 (1.1–3.2)	0.02
None**	10/10	—	—	—

*Pneumococcal pneumonia was diagnosed on the basis of blood cultures in 407 patients and cultures of specimens from the lower respiratory tract in 97. CI denotes confidence interval, and HIV human immunodeficiency virus.

†Serious underlying disease was considered to be present when the patient had one or more of the following: cancer (39 deaths among 91 patients), liver cirrhosis (23 deaths among 40 patients), systemic vasculitis (1 death among 8 patients), or splenectomy (2 deaths among 2 patients).

‡In addition to *S. pneumoniae,* other microorganisms isolated in the patients with polymicrobial pneumonia were *Haemophilus influenzae* (in 14 patients), *Staphylococcus aureus* (12), *Salmonella enteritidis* (2), *Pseudomonas aeruginosa* (4), *Escherichia coli* (4), acinetobacter species (4), klebsiella species (1), and enterobacter species (1).

§Resistance to penicillin G was defined by an MIC of penicillin G ≥0.12 μg per milliliter. The distribution of deaths according to the MIC of penicillin G was as follows: 0.12 μg per milliliter, 5 deaths among 14 patients; 0.25 μg per milliliter, 10 deaths among 22 patients; 0.5 μg per milliliter, 6 deaths among 15 patients; 1.0 μg per milliliter, 14 deaths among 38 patients; 2.0 μg per milliliter, 16 deaths among 43 patients; and 4.0 μg per milliliter, 4 deaths among 13 patients.

¶Resistance to cephalosporin was defined by an MIC of ceftriaxone or cefotaxime ≥1.0 μg per milliliter. The distribution of deaths according to the MIC of ceftriaxone or cefotaxime was as follows: 1.0 μg per milliliter, 5 deaths among 25 patients; 2.0 μg per milliliter, 3 deaths among 5 patients; and 4.0 μg per milliliter, 1 patient, who survived.

‖Antibiotic therapy was given as follows: penicillin G to 115 patients, ampicillin to 37, ceftriaxone to 161, cefotaxime to 38, erythromycin to 34, erythromycin plus cephalosporin to 26, clindamycin to 9, vancomycin to 5, imipenem to 9, and other antimicrobial agents to 60.

**These patients died before antibiotic therapy was started.

(Statens Serumsinstitut, Copenhagen, Denmark). A more detailed description of the microbiologic methods used is given elsewhere.[18,23]

Statistical Analysis

To study trends in pneumococcal pneumonia and to avoid a selection bias, we included only patients with bacteremic pneumonia in the analysis, since blood cultures were performed routinely, whereas the other diagnostic methods were used selectively. We calculated the rates of infection acquired in the hospital by subtracting three days from each hospital stay and summing the residual durations of hospitalization.

The correlation of MICs for penicillin with those for cephalosporin was determined by the Pearson correlation coefficient. The chi-square test was used to compare the proportions in samples with use of two-by-k contingency tables, where k was the number of categories of MICs studied.

The relation of covariates with mortality was initially assessed by univariate analysis, and odds ratios were then determined with a logistic-regression model. An adjusted analysis was performed with models constructed by multiple logistic-regression analysis.[26] In this adjusted analysis, binary variables were coded as 0 (absent) or 1 (present), and polychotomous variables were coded with indicator variables. All variables that were significant in any of the models were included. Independent variables were checked for collinearity.

Age was subdivided into three groups: 19 to 39 years, 40 to 69 years, and 70 years or older. The categories of cancer, cirrhosis, systemic vasculitis, and disease necessitating splenectomy were combined as serious underlying diseases, because they were all associated with increased mortality, as shown in Table 2.

We considered the possibility that if drug-resistant organisms are more virulent than susceptible ones, then some variables related to the severity of infection might be intermediate variables, rather than predisposing factors requiring statistical control. When we compared the patients with penicillin-resistant strains and those with susceptible strains, however, there were no statistically significant differences in variables such as shock at admission (18 percent and 14 percent, respectively; $P=0.13$) and multilobar involvement (26 percent and 29 percent, $P=0.47$), suggesting that resistant strains were not more virulent than susceptible strains, as has been reported.[13,16]

We included the entire cohort of 504 subjects for whom data were complete in the univariate and multivariate analyses (Tables 2 and 3). Other models that involved only patients with monomicrobial pneumonia (those in which *S. pneumoniae* was the only microorganism isolated from cultures) and included the same covariates are also shown (Table 3). To measure the effect of drug resistance on mortality while adjusting for other terms, we fitted the variable of resistance to penicillin into the models, whether it was significant or not.

In assessing responses to antibiotic thera-

*Table 3. Multivariate Analysis of Factors Influencing Mortality in the Entire Cohort of 504 Patients with Pneumococcal Pneumonia and among All Patients with Monomicrobial Pneumonia and Only Those with Bacteremia.**

Variable	Entire Cohort (N = 504)		Patients with Monomicrobial Pneumonia			
			all (N = 464)		with bacteremia (N = 392)	
	Adjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Penicillin resistance†	1.3 (0.7–2.2)	0.32	1.0 (0.5–1.9)	0.84	0.9 (0.4–1.9)	0.84
Age (yr)						
19–39	1.0		1.0		1.0	
40–69	1.0 (0.9–4.1)	0.85	1.2 (0.5–2.7)	0.64	0.9 (0.3–2.3)	0.86
≥70	2.4 (1.2–5.2)	0.03	2.7 (1.2–6.5)	0.02	2.4 (0.9–6.3)	0.06
Serious underlying disease‡	1.9 (1.2–3.5)	0.02	1.8 (1.1–3.4)	0.05	2.2 (1.1–4.5)	0.02
Heart failure	2.0 (1.1–4.4)	0.05	2.2 (1.1–4.8)	0.04	1.8 (0.7–4.6)	0.17
Shock	7.5 (3.8–14.6)	<0.001	9.0 (4.4–18.3)	<0.001	13.4 (5.9–30.3)	<0.001
Multilobar involvement	4.4 (2.6–7.5)	<0.001	3.8 (2.2–6.7)	<0.001	3.7 (2.0–7.0)	<0.001
Leukopenia (<5000 cells/mm^3)	3.3 (1.6–6.9)	0.001	3.2 (1.5–6.9)	0.002	3.0 (1.2–7.0)	0.01
Nosocomial pneumonia	2.0 (1.1–3.8)	0.02	2.9 (1.5–5.7)	0.001	4.6 (2.0–10.7)	<0.001
Polymicrobial pneumonia	5.6 (2.3–13.6)	<0.001	—	—	—	—

*Patients with monomicrobial pneumonia were those in whom *S. pneumoniae* was the only microorganism isolated from blood cultures or cultures of specimens from the lower respiratory tract. OR denotes odds ratio, and CI confidence interval.

†Defined as an MIC of penicillin G ≥0.12 μg per milliliter.

‡Serious underlying disease was considered to be present when the patient had one or more of the following: cancer, liver cirrhosis, systemic vasculitis, and splenectomy.

py, we studied only patients with monomicrobial pneumococcal pneumonia, comparing the mortality of patients with resistant strains with that of patients with susceptible strains with regard to each antimicrobial agent (or group of agents) (Table 4). Because the study was not a randomized clinical trial, comparisons between groups of antibiotics were avoided. P values of less than 0.05 were considered to indicate statistical significance, and all reported P values are two-tailed.

Results

Of the 504 adults with severe pneumococcal pneumonia, 145 (29 percent) had penicillin-resistant strains and 31 (6 percent) had cephalosporin-resistant strains. During the study period, we observed a significant increase in resistance to penicillin, cephalosporin, imipenem, and erythromycin (Table 1). The distribution of serotypes is shown in the first footnote to Table 1.

Trends in Bacteremic Pneumococcal Pneumonia

The incidence of community-acquired bacteremic pneumococcal pneumonia increased during the study period (Fig. 1). This increase was due mainly to the inclusion of the patients with HIV (who accounted for 4 episodes of pneumonia in 1984–1988 and 34 episodes in 1989–1993). The incidence of bacteremic pneumococcal pneumonia acquired in the hospital did not increase significantly (in 1984–1988 there were 0.019 and in 1989–1993 0.030 episodes per 1000 patient-days).

Analysis of Mortality

Overall mortality was 28 percent (140 of 504), and most deaths occurred within seven days after diagnosis (Fig. 2). The factors influencing mortality in the univariate analysis are shown in Table 2. Patients with HIV had lower mortality than those without HIV, but after we controlled for age (the patients with HIV being younger than those without HIV) the risk of death did not differ significantly (adjusted odds ratio for the patients with HIV, 0.7; 95 percent confidence interval, 0.2 to 1.9; P = 0.51).

In the multivariate analysis, the independent prognostic factors for mortality were age of 70 years or above, serious underlying disease, heart failure, shock, multilobar involvement, leukopenia (<5000 cells per cubic millimeter), nosocomially acquired pneumonia, and polymicrobial pneumonia (Table 3). The types of microorganisms recovered in the patients with polymicrobial pneumonia are shown in the third footnote to Table 2.

Overall, the mortality rate among the patients with penicillin-resistant strains was 38 percent, and among those with susceptible strains it was 24 percent (P = 0.001) (Table 2), but after we controlled for other predictors of mortality the odds ratios for those with resistant strains were 1.3 (95 percent confidence interval, 0.7 to 2.2; P = 0.32) in the entire cohort and 1.0 (95 percent confidence interval, 0.5 to 1.9; P = 0.84) among the patients with monomicrobial pneumococcal pneumonia. Similar results were obtained for the patients with bacteremia (Table 3).

When conditions that resulted from the infection, such as shock at the time of admission and multilobar involvement, were not included in the model for the en-

*Table 4. Mortality among 456 Patients with Monomicrobial Pneumococcal Pneumonia, According to Type of Antibiotic Therapy and Degree of Resistance of the Infecting Strain.**

Antibiotic and Response of Strain	Antibiotic Administered		
	penicillin G or ampicillin	ceftriaxone or cefotaxime	other†
	no. of patients who died/no. in group (%)		
Penicillin G			
Susceptible (MIC, ≤0.06 μg/ml)	24/126 (19)	32/127 (25)	18/87 (21)
Resistant (MIC, in μg/ml)			
0.12 to 1.0	4/14	5/33	11/22
2.0	1/9	7/18	2/8
4.0	1/1	1/8	1/3
All	6/24 (25)	13/59 (22)	14/33 (42)
Ceftriaxone or cefotaxime			
Susceptible (MIC, ≤0.5 μg/ml)	41/168 (24)	29/145 (20)	30/114 (26)
Resistant (MIC, in μg/ml)			
1.0	3/16	1/4	1/5
2.0	1/2	—	1/1
4.0	—	0/1	—
All	4/18 (22)	1/5 (20)	2/6 (33)

*The 48 patients who had polymicrobial pneumonia or who did not receive antibiotic therapy (or both) were excluded from this analysis. Eleven patients infected with penicillin-resistant strains and included here were also included in a previous report.[18]

†The other antibiotics administered included erythromycin, erythromycin plus cephalosporin, clindamycin, vancomycin, and imipenem.

tire cohort, and after we adjusted that analysis for the other terms shown in Table 3, resistance to penicillin was still not significantly associated with mortality (adjusted odds ratio, 1.1; 95 percent confidence interval, 0.6 to 1.8; P = 0.62). Similar results were obtained when the same covariates were studied in the model for the patients with monomicrobial pneumonia (data not shown).

Response to Antibiotic Therapy

As Table 4 shows, among the patients with monomicrobial pneumococcal pneumonia who were treated with penicillin G or ampicillin, the mortality rates among the 24 patients with penicillin-resistant strains and the 126 patients with susceptible strains were 25 percent and 19 percent, respectively (odds ratio, 1.4; 95 percent confidence interval, 0.5 to 3.9; P = 0.51). After adjustment, the odds ratio was 0.9 (95 percent confidence interval, 0.3 to 2.8; P = 0.90). It is important to note that eight of the nine patients with MICs of 2 μg per milliliter recovered and that the only patient with an MIC of 4 μg per milliliter (a patient with severe underlying disease) died.

Among the patients treated with ceftriaxone or cefotaxime, the mortality rates among the 59 patients with penicillin-resistant strains and the 127 patients with susceptible strains were 22 percent and 25 percent, respectively (odds ratio, 0.8; 95 percent confidence interval, 0.4 to 1.7; P = 0.64). After adjustment, the odds ratio was 0.4 (95 percent confidence interval, 0.2 to 1.1; P = 0.10).

Among the patients treated with other antibiotics, the mortality rates among the 33 with penicillin-resistant strains and the 87 with susceptible strains were 42 percent and 21 percent, respectively (odds ratio, 2.8; 95 percent confidence interval, 1.2 to 6.6; P = 0.02), but this difference was not significant after adjustment (adjusted odds ratio, 1.4; 95 percent confidence interval, 0.4 to 4.1; P = 0.54).

Emergence of Resistance to Cephalosporins

Strains with decreased susceptibility to cephalosporin (MIC of ceftriaxone or cefotaxime, ≥1.0 μg per milliliter) were found in 2 percent of patients in 1984–1988 and in 9 percent in 1989–1993 (P = 0.002) (Table 1). There was a close correlation between the MICs of the cephalosporins and that of penicillin (r = 0.85, P<0.001).

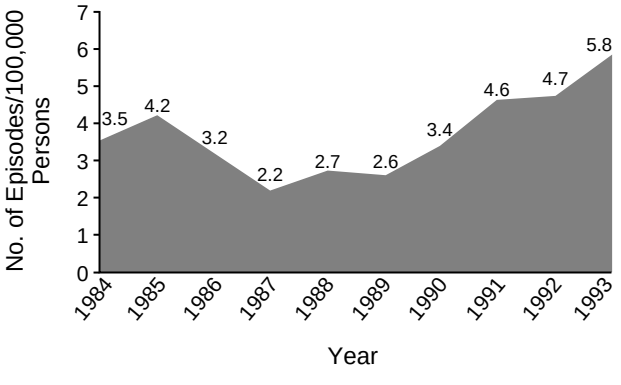

Figure 1. Trends in Community-Acquired Bacteremic Pneumococcal Pneumonia.

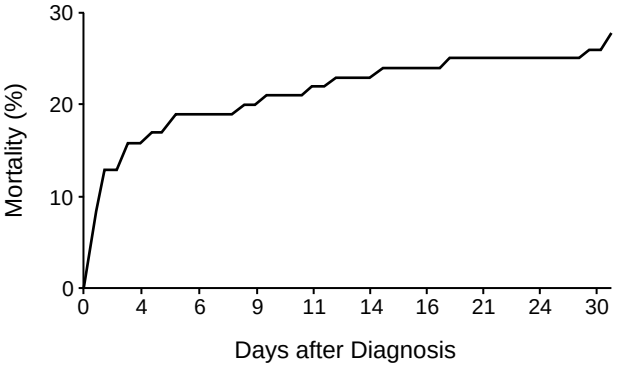

Figure 2. Cumulative Mortality among 504 Patients with Severe Pneumococcal Pneumonia.

During the first years of the study, the MICs of ceftriaxone and cefotaxime were usually two to four times smaller than that of penicillin G, but in the more recent years they were usually one to two times smaller. Moreover, we observed five instances of resistance in which the MICs of the cephalosporins were equal to that of penicillin G, and one instance in which the MIC of ceftriaxone or cefotaxime was 4 μg per milliliter and that of penicillin G was 0.5 μg per milliliter (the patient recovered with penicillin therapy).

Overall, the mortality rate among the patients with cephalosporin-resistant pneumococcal strains was similar to that among the patients with cephalosporin-susceptible strains (26 percent vs. 28 percent; odds ratio, 0.9; 95 percent confidence interval, 0.4 to 2.1; P = 0.89) (Table 2). Among the patients treated with ceftriaxone or cefotaxime, the mortality rates among the 18 with cephalosporin-resistant strains and the 168 with susceptible strains were 22 percent and 24 percent, respectively (odds ratio, 0.8; 95 percent confidence interval, 0.4 to 1.7; P = 0.64) (Table 4).

Discussion

Over the past two decades, pneumococci have become increasingly resistant to penicillin and other antibiotics.[8-10,27,28] The more recent identification of cephalosporin-resistant strains is a cause for additional concern.[13,29] At our institution, we have seen an increase in the frequency of infections due to pneumococci resistant to penicillin, cephalosporin, and erythromycin, the antibiotics used most commonly to treat pneumonia (Table 1).

During the study period, we found an increasing trend toward community-acquired bacteremic pneumococcal pneumonia (Fig. 1). This was at least partly due to the greater numbers of HIV-infected patients, who are at higher risk for pneumococcal infections.[30,31] The incidence of bacteremic pneumococcal pneumonia acquired in the hospital did not increase significantly. Al-

though outbreaks of pneumococcal pneumonia have been reported in hospitals and prisons,[18,32] no outbreaks were detected in the present study.

The overall mortality reported in patients with pneumococcal bacteremia (and usually with pneumonia) has remained unchanged at about 25 percent over the past four decades[14,15,33-37] and is close to the 28 percent mortality in our study. The factors associated with increased mortality in this study (Table 3) are clinically consistent and similar to those reported previously.[14,15] The increased mortality from nosocomially acquired infection[38] probably reflects the greater severity of underlying disease in these patients. There was also higher mortality among our patients with polymicrobial pneumonia, who had other serious pathogens in addition to pneumococci. On the other hand, the HIV-infected patients had lower mortality, probably because of their relative youth. In other reports HIV infection was not found to affect mortality from pneumococcal pneumonia significantly.[30,31]

In our study, the patients with penicillin-resistant pneumococcal strains had higher mortality than those with penicillin-susceptible strains in the univariate analysis. However, after adjustment for other variables, resistance to penicillin was not associated with increased mortality. The patients with penicillin-resistant strains had more serious underlying conditions than the patients with penicillin-susceptible strains.[18] Similarly, the case fatality rate of South African children with penicillin-resistant pneumococcal infections did not differ significantly from that of children with penicillin-susceptible infections.[6] In our study, resistance to cephalosporin was also not associated with increased mortality.

Our study was not designed to compare the efficacy of various antibiotics, and it was not a randomized clinical trial. Therefore, the response to antibiotic therapy was analyzed by comparing mortality in patients with resistant strains and patients with susceptible strains with regard to each antimicrobial agent (or group of agents) (Table 4).

Our data suggest that high-dose intravenous penicillin G (150,000 to 200,000 U per kilogram of body weight per day) may be effective in patients with pneumococcal pneumonia due to strains for which the MIC of penicillin ranges from 0.12 to 2 μg per milliliter. Ceftriaxone or cefotaxime may be a good alternative when the MIC of penicillin is higher and those of ceftriaxone and cefotaxime are 2 μg per milliliter or less. It is not known whether pneumonia due to strains for which the MIC of penicillin was 4 μg per milliliter or higher would respond to penicillin therapy, or whether infections for which the MICs of ceftriaxone and cefotaxime were 4 μg per milliliter or higher would respond to cephalosporin therapy.

Careful selection of an effective antibiotic for the initial empirical therapy requires an awareness of patterns of susceptibility in the patient's geographic area. We think that identifying patients at greater risk of dying (Table 3) or of having a resistant strain[18,39] may help in choosing the appropriate therapy. For example, patients with a low probability of death and no risk factors for penicillin-resistant strains could be given initial empirical treatment with high-dose intravenous penicillin G, ampicillin, or amoxicillin. In patients with a higher risk of death or with risk factors for pneumococci with a high level of resistance to penicillin, it would be prudent to start empirical treatment with an alternative antibiotic. In these cases, ceftriaxone or cefotaxime may be given, together with erythromycin when the presence of legionella or another atypical pathogen cannot reasonably be ruled out. Other alternatives, such as imipenem or vancomycin, ought to be considered in regions where a high level of resistance to cephalosporins has become prevalent.

In summary, our study suggests that the current levels of resistance to penicillin and cephalosporin do not appear to increase mortality in patients with pneumococcal pneumonia. High-dose intravenous penicillin may be effective for infections in which the MIC of penicillin is up to 2 μg per milliliter, and ceftriaxone or cefotaxime may be effective when the MIC of penicillin is higher. However, the emergence of high levels of resistance to cephalosporin is an alarming problem. It is to be hoped that administering the existing pneumococcal vaccine to adults at an earlier age as well as developing a new vaccine suitable for children will help to prevent these difficult-to-treat infections in the future.[40]

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