MAJOR ARTICLE

An International Prospective Study of Pneumococcal Bacteremia: Correlation with In Vitro Resistance, Antibiotics Administered, and Clinical Outcome

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We performed a prospective, international, observational study of 844 hospitalized patients with blood cultures positive for *Streptococcus pneumoniae*. Fifteen percent of isolates had in vitro intermediate susceptibility to penicillin (minimum inhibitory concentration [MIC], 0.12–1 μg/mL), and 9.6% of isolates were resistant (MIC, ≥2 μg/mL). Age, severity of illness, and underlying disease with immunosuppression were significantly associated with mortality; penicillin resistance was not a risk factor for mortality. The impact of concordant antibiotic therapy (i.e., receipt of a single antibiotic with in vitro activity against *S. pneumoniae*) versus discordant therapy (inactive in vitro) on mortality was assessed at 14 days. Discordant therapy with penicillins, cefotaxime, and ceftriaxone (but not cefuroxime) did not result in a higher mortality rate. Similarly, time required for defervescence and frequency of suppurative complications were not associated with concordance of β-lactam antibiotic therapy. β-Lactam antibiotics should still be useful for treatment of pneumococcal infections that do not involve cerebrospinal fluid, regardless of in vitro susceptibility, as determined by current NCCLS breakpoints.

The alarming increase in the prevalence of penicillin resistance among *Streptococcus pneumoniae* has been well publicized, and, as a result, shifts in the empirical antibiotic therapy administered for community-acquired pneumonia are occurring. Considerable surveillance data have been reported for the in vitro susceptibility of invasive and noninvasive *S. pneumoniae* isolates [1–5]. However, the clinical relevance is uncertain, because there is a paucity of data on the outcome of patients infected with penicillin-nonsusceptible pneumococci [6].

Some studies have suggested that antibiotic resistance in *S. pneumoniae* is not clinically relevant [7–19], whereas others have reported higher mortality rates among

Received 10 December 2002; accepted 12 June 2003; electronically published 7 July 2003.

Financial support: After the study protocol was approved and initiated by the investigators, unrestricted educational grant support was obtained for in vitro susceptibility testing and laboratory costs from Wyeth-Ayerst Laboratories, Glaxo Smith-Kline Beecham, Roche Labs, Pfizer Laboratories, and Abbott Laboratories.

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Clinical Infectious Diseases 2003; 37:230–7

1058-4838/2003/3702-0011$15.00

patients infected with penicillin-nonsusceptible *S. pneumoniae* [20–22]. However, limitations exist in all of these studies, including retrospective study design [12, 14, 17, 20, 22], lack of clinical data [20], small sample size [13, 14, 18], inclusion of nonbacteremic patients [11, 13, 14, 18, 19], and failure to stratify for severity of illness [21]. These limitations have precluded an evidence-based solution to this important clinical question.

Therefore, we conducted a prospective, international, large-scale, observational study involving patients with pneumococcal bacteremia. We evaluated risk factors for emergence of drug resistance, performed in vitro susceptibility testing for blood isolates, and, most importantly, recorded data on the antibiotics administered, including timing of antibiotic therapy in relation to the onset of symptoms, dose, duration of therapy, and route of administration. Our primary objective was to assess the clinical impact of emerging drug resistance for *S. pneumoniae* to clarify antibiotic recommendations for community-acquired pneumonia.

MATERIALS AND METHODS

Study design. From December 1998 through January 2001, 844 consecutive hospitalized adults with pneumococcal bacteremia were enrolled in 21 hospitals in 10 countries (South Africa, 29.6% of patients; United States, 13.6%; Sweden, 12.1%; Spain, 11.7%; New Zealand, 11.7%; Taiwan, 5.7%; Argentina, 5.2%; Brazil, 3.9%; Hong Kong, 3.9%; and France, 2.6%). The health care centers in the United States were located in Boston; Knoxville, Tennessee; Pittsburgh; and Washington, D.C.

The collaborative study institutions and investigators were not selected at random. Investigators who had previously conducted clinical studies on pneumococcal pneumonia and investigators who were located at institutions in countries or cities reporting a notable prevalence of drug-nonsusceptible pneumococci were recruited. Furthermore, they had to be sufficiently motivated to participate in a large-scale clinical study without formal funding. Institutional review board approval was obtained in accordance with local requirements.

Patients were observed for ⩾14 days after the onset of bacteremia to assess clinical outcome, including mortality and complications of infection. The study was observational in that administration of antimicrobial agents and other therapies was managed by the patients' physicians and not by the investigators. The end point was mortality at 14 days after the first blood culture positive for *S. pneumoniae* was obtained.

In vitro susceptibility testing and serotyping. A total of 793 (94%) of 844 blood isolates were available for in vitro susceptibility testing and serotyping. All isolates were frozen at −70°C and then sent on Dorset egg medium to the Veterans Affairs Pittsburgh Special Pathogens Laboratory, where the identity of *S. pneumoniae* was confirmed for each isolate.

The susceptibility results for all antimicrobials administered for pneumococcal infections were determined using Etest (AB Biodisk), in accordance with the manufacturer's instructions, and on the basis of NCCLS breakpoints for pneumonia [23]. The term "nonsusceptible" was used when the MIC of penicillin for *S. pneumoniae* was intermediate (MIC, 0.12–1.0 μg/mL) or indicative of resistance (MIC, ⩾2 μg/mL). High-level penicillin resistance was defined as an MIC of ⩾3 μg/mL, as determined by Etest. Although Etest results are approved by the US Food and Drug Administration for susceptibility testing of *S. pneumoniae,* persons at 2 independent laboratories (M. Jacobs and R. N. Jones) retested all penicillin-nonsusceptible isolates in a blinded protocol using NCCLS broth microdilution methods. The concordance rates between Etest and broth microdilution were 100% in one laboratory and 81% in the other.

Definitions. "Underlying chronic disease" was defined as presence of heart disease, liver disease, renal disease, lung disease, or diabetes mellitus. "Underlying disease or risk factor associated with immunosuppression" was defined as HIV infection, receipt of a splenectomy, hematological malignancy, autoimmune disorder, receipt of a transplant, and receipt of cancer chemotherapy within 4 weeks before onset of bacteremia. "Prior antibiotic therapy" was defined as use of antibiotics for ⩾1 day within 3 months before the onset of bacteremia.

Antibiotic therapy. "Concordant therapy" was defined as receipt for the first 2 days after the blood was obtained for culture of a single antibiotic that had in vitro activity (i.e., neither intermediate nor resistant in vitro) against the *S. pneumoniae* isolated. "Discordant therapy" was defined as receipt for the first 2 days after the blood sample was obtained for culture of a single antibiotic that was inactive in vitro against the *S. pneumoniae* isolated.

Severity of illness was assessed using the Pitt bacteremia [24] and APACHE II scores at the time of the positive blood culture result. The Pitt bacteremia score was calculated within 1 day after hospital admission for all patients on the basis of vital signs and mental status. "Critical illness" was defined as a Pitt bacteremia score of >4 points; this score has been validated in 10 observational studies of bloodstream infection. The APACHE II score was applied only for patients admitted to the intensive care unit (ICU) at the time of the positive blood culture result. Nosocomial bacteremia was considered to have occurred if the first positive blood culture result was obtained >3 days after hospital admission.

Statistical analysis. Clinical and laboratory data for analysis were entered into a computerized database (Prophet Systems, National Institute of Health; Bethesda, MD). Categorical data were analyzed using the χ^2 or Fisher's exact test. Continuous variables were compared using the *t* test or the Mann-Whitney *U* test. A logistic regression model was used to examine the effects of multiple risk factors on penicillin resistance and

Table 1. Multivariate analysis of factors potentially associated with penicillin resistance in vitro.

Factor	OR (95% CI)	*P*
Underlying disease or risk factor associated with immunosuppression	2.1 (1.5–3.1)	.0001
Prior antibiotic therapy	1.9 (1.2–2.9)	.0091
Critical illness	1.6 (1.0–2.5)	.10 (NS)
Nosocomially acquired infection	1.9 (0.99–3.6)	.073 (NS)
Underlying chronic disease	1.4 (0.9–2.0)	.10 (NS)

NOTE. NS, not significant ($P > .20$, unless otherwise indicated).

mortality. The factors in the regression model included those found to be significant by univariate analysis and those previously hypothesized to affect penicillin resistance or mortality. Statistical significance was defined as $P < .05$. In this report, $P \geq .05$ was considered not significant (NS). If the *P* value was .05–.20, it was still considered NS, but the precise *P* value is given in parentheses (see tables 1–3).

RESULTS

Patient characteristics. Eight hundred forty-four consecutive patients with pneumococcal bacteremia were enrolled during the study period. The mean patient age was 52.1 years (median, 51 years; range, 15–97 years). A total of 48.2% of patients had ⩾1 chronic underlying disease, and 42.1% had an underlying disease or risk factor associated with immunosuppression; 32.4% of patients had >1 underlying disease. A total of 19.3% of patients were critically ill, as defined in Methods. A total of 20.2% of patients were admitted to ICU with a mean APACHE II score of 18.4 (range, 3–45). The Pitt bacteremia and APACHE II scores were highly correlated with each other ($P = .0001$); the predictive value for mortality was superior for the Pitt bacteremia score, compared with the APACHE II score (81.0 vs. 74.9).

Microbiology results. Seven hundred ninety-three pneumococcal isolates were available for in vitro susceptibility testing. Fifty-one (6%) of the isolates did not survive initial storage at −70°C. Of interest, all isolates survived handling and shipping to the central reference laboratory. To exclude the possibility of bias, the following clinical factors were compared for the patients infected with the 51 missing isolates versus the other patients: ICU admission, immunosuppression, community-acquired versus nosocomially acquired bacteremia, suppurative complications, and mortality; no significant differences were found. Moreover, the antibiotic susceptibility patterns of the 51 missing isolates, as initially determined at the original hospital, were not significantly different from the susceptibility patterns of the 793 isolates, as determined at the reference laboratory.

One hundred nineteen (15%) of the 793 pneumococcal isolates had intermediate susceptibility to penicillin, and 76 (9.6%) were resistant. Thirteen pneumococci had an MIC of penicillin of ⩾3 μg/mL and were considered to be highly resistant. The prevalence for penicillin-nonsusceptible pneumococci, by region, was as follows: Taiwan, 57.4% of isolates; Hong Kong, 53.1%; United States, 30.8%; France, 29.4%; Spain, 27.6%; South Africa, 24.0%; Brazil, 18.7%; New Zealand, 18.6%; Sweden, 6.9%; Argentina, 2.6%.

Prior antibiotics. A total of 20.3% of patients received ⩾1 antibiotic for 1–70 days (median duration, 8 days) ⩽3 months before this episode of pneumococcal bacteremia. A total of 10.6% received penicillins (i.e., penicillin, ampicillin, amoxicillin, amoxicillin-clavulanate, or ampicillin-sulbactam), 13.4% received cephalosporins, 2.1% received macrolides, 3.8% received quinolones, and 4.3% received other antibiotics (i.e., clindamycin, chloramphenicol, tetracycline, trimethoprim-sulfamethoxazole, rifampin, or vancomycin). Note that many patients received >1 antibiotic.

Antibiotic therapy. Three hundred eighty-nine patients received only 1 antibiotic for at least the first 2 days after blood samples were obtained for culture. Of the 389 episodes of pneumococcal bacteremia, 21 pneumococcal isolates were not available, and 8 involved patients who received antibiotics for which NCCLS breakpoints for pneumococci were not available. Thus, data for 360 patients were evaluable for adequacy of antibiotic therapy. Three hundred thirty-five (93.1%) of 360 patients received concordant therapy, and 25 (6.9%) received discordant therapy.

Risk factors for penicillin nonsusceptibility. Statistically significant risk factors for penicillin resistance on univariate analysis included liver disease, cancer, receipt of corticosteroid therapy, receipt of a transplant, chronic underlying disease,

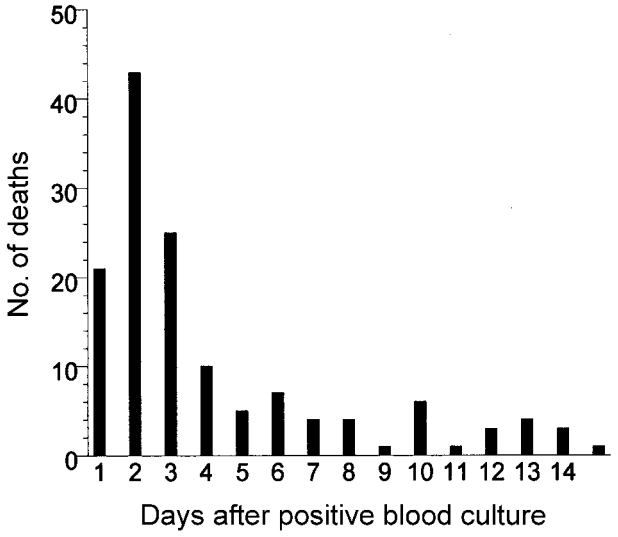

Figure 1. Distribution of deaths in relation to the time initial blood cultures were obtained. A total of 64.5% of deaths occurred within 3 days after a blood culture positive for *Streptococcus pneumoniae* was obtained.

Table 2. Multivariate analysis of factors potentially associated with mortality in 844 patients.

Factor	OR (95% CI)	*P*
Age of >65 years	2.9 (1.6–5.2)	.0004
Critical illness	21.1 (12.5–35.6)	.0001
Underlying disease or risk factor associated with immunosuppression	3.1 (1.8–5.3)	.0001
Nosocomially acquired infection	1.77 (0.8–4.0)	.16 (NS)
Underlying chronic disease	1.27 (0.7–2.2)	NS
Penicillin susceptibility in vitro	1.42 (0.8–2.4)	.19 (NS)

NOTE. Age of >65 years, critical illness (Pitt bacteremia score of >4), and underlying disease or risk factor associated with immunosuppression were associated with mortality on multivariate analysis, but in vitro penicillin susceptibility was not. NS, not significant ($P > .20$, unless otherwise indicated).

underlying disease or risk factor associated with immunosuppression, and nosocomially acquired bacteremia (data not shown). On multivariate analysis (table 1), only 2 factors were found to be statistically significant: underlying diseases or risk factors associated with immunosuppression ($P = .0001$) and prior receipt of antibiotics ($P = .009$).

Outcome. The mortality rate for patients with pneumococcal bacteremia was 16.9% (139 of 823 patients died). A total of 64.5% of the deaths occurred within the first 3 days after a blood sample was obtained for culture (figure 1). The following factors were significantly associated with mortality on univariate analyses: prior hospitalization, chronic underlying disease, underlying disease or risk factor associated with immunosuppression (especially HIV infection), bilateral infiltrates on chest radiograph obtained at hospital admission, meningitis, suppurative complications, and old age. Fever, rigors, and chest pain were each significantly associated with survival, as has been reported elsewhere [25]. Although in vitro penicillin nonsusceptibility was associated with mortality on univariate analysis, statistical significance disappeared on the multivariate analysis. Age of >65 years ($P = .0001$), severity of illness ($P = .0001$), and presence of an underlying disease or risk factor associated with immunosuppression ($P = .0001$) remained significant on multivariate analysis (table 2).

Concordant and discordant antibiotic therapy. To assess the impact of antimicrobial susceptibility on patient outcome, we examined the concordance of antimicrobial therapy within the first 2 days after the blood sample was obtained for culture. This analysis was confined to the 360 patients receiving monotherapy. Receipt of discordant therapy did not result in a statistically significantly higher mortality rate. The mortality rate was high for critically ill patients in both concordant and discordant therapy groups. Patients who were infected with pneumococci that were not susceptible to cefuroxime (median MIC by Etest, 3 μg/mL; median MIC by broth microdilution assay, 8 μg/mL) but who were treated with cefuroxime experienced a significantly higher mortality rate (4 [5.8%] of 53 patients died) with cefuroxime concordance, compared with cefuroxime discordance (4 [36.4%] of 11; $P = .02$). On the other hand, discordant therapy involving penicillins, cefotaxime, and ceftriaxone did not result in a significantly higher mortality rate, regardless of severity of illness (table 3). We also examined the effect of therapy concordance on mortality for the total sample, with the following exclusions: (1) patients with meningitis were excluded, and (2) patients who died $\leq$3 days after blood cultures were performed were excluded. The above 2 groups were also stratified by severity of illness. The results for these subgroups were similar to the results for all patients; only discordant therapy involving cefuroxime was significantly associated with a higher mortality rate ($P = .01$; data not shown; none of the patients had meningitis). This association was most pronounced in patients who were not critically ill.

Clinical response. Time to defervescence was compared for 3 patient groups: (1) patients infected with penicillin-susceptible pneumococci versus those infected with penicillin-nonsusceptible pneumococci (figure 2*A*), (2) patients receiving concordant therapy versus those receiving discordant therapy (figure 2*B*), and (3) patients receiving concordant therapy involving cefuroxime only versus those receiving discordant therapy involving cefuroxime only (figure 2*C*). Clinical response, as measured by time to defervescence in days, was also unaffected by the in vitro susceptibility of the infecting pneumococci: 19.2% of patients infected with in vitro nonsusceptible pneumococci had defervescence on day 5, compared with 12.5% of patients infected with susceptible pneumococci ($P =$ NS; figure 2*A*). Time to defervescence also did not significantly differ on the basis of concordant versus discordant therapy: 15% of recipients of concordant therapy had defervescence by day 5, and 24% in the discordant therapy group had defervescence by day 5 ($P =$ NS; figure 2*B*). Of interest, discordant therapy involving cefuroxime showed a trend for slower defervescence, although statistical significance was not attained ($P = .09$; figure 2*C*).

Table 3. Factors evaluated for mortality in 360 patients receiving antibiotic monotherapy on multivariate analyses.

Factor	*P*
Critical illness[a]	.0001
Discordant therapy	
Cefuroxime	.0175
Penicillin	NS
Ceftriaxone/cefotaxime	NS

NOTE. On multivariate analysis, severity of illness and cefuroxime-associated discordant therapy were significantly associated with higher mortality rate, but discordant therapy involving penicillin or ceftriaxone/cefotaxime was not. NS, not significant ($P > .20$, unless otherwise indicated).

[a] Defined as a Pitt bacteremia score of >4.

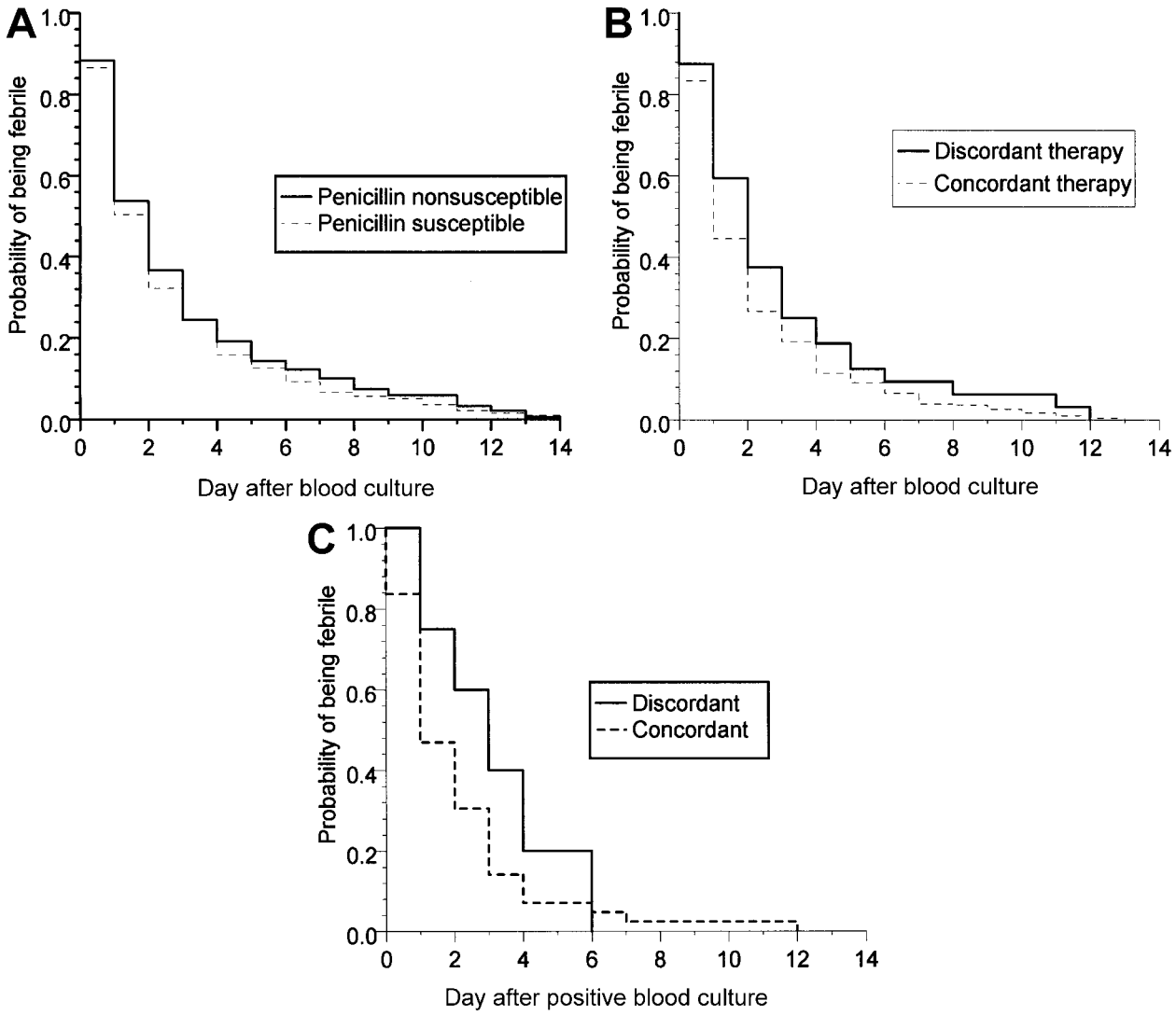

Figure 2. Clinical response (time to defervescence) among patients with pneumococcal bacteremia. *A,* Penicillin-susceptible vs. -nonsusceptible pneumococci. No statistically significant difference in clinical response (duration of fever) was seen among patients infected with penicillin-susceptible vs. -nonsusceptible pneumococci (P = NS, by Mantel-Cox test). *B,* Concordant vs. discordant therapy. No significant difference in the duration of fever was seen in patients receiving concordant vs. discordant therapy. (P = NS, by Mantel-Cox test). *C,* Discordant therapy with cefuroxime. Discordant therapy with cefuroxime resulted in prolongation of fever, but statistical significance was not achieved (P = .09 [NS], by Mantel-Cox text). NS, not significant.

Suppurative complications of meningitis (6.9%), empyema (3.3%), endocarditis (0.6%), lung abscess (0.5%), and pericarditis (0.4%) did not occur significantly more frequently in patients infected with penicillin-nonsusceptible pneumococci, compared with those infected with penicillin-susceptible pneumococci (13% vs. 10.5%, respectively; P = NS). The frequency of suppurative complications was somewhat higher among patients receiving discordant therapy than among patients receiving concordant therapy, but statistical significance was not attained (17% vs 8.9%; P = .13).

DISCUSSION

Although emerging antibiotic resistance among pneumococci is a well-publicized concern, the impact of penicillin resistance on the outcome of pneumococcal pneumonia has been controversial. In contrast to previous studies that have assessed this issue, our study was prospective, and specific details were recorded for the antibiotics administered, including dose, route of administration, and duration of therapy, as well as the clinical response to these antibiotics. Bacteremia was required for en-

rollment because it is an impeccable "gold standard"; the sputum isolates reported in large-scale surveillance studies without accompanying clinical data may not be pathogenic. Furthermore, patients can be colonized with >1 strain of pneumococcus in the upper respiratory tract, which could result in difficulties in correctly identifying the infecting strain, particularly for patients who have received antibiotics [26]. Bacteremia is also an established risk factor for death due to pneumonia, and, therefore, it involves the subgroup of patients most likely to die. This would maximize the clinical relevance of our study with respect to patient treatment.

One hundred ninety-five (24.6%) of the 793 pneumococcal isolates were not susceptible to penicillin (MIC for intermediate resistance, 0.12–1 μg/mL; MIC for resistance, $\geqslant$2 μg/mL), as determined by NCCLS criteria [23]. In our study, numerous factors were significantly associated with nonsusceptibility on univariate analysis (see Results), but only underlying disease or risk factors associated with immunosuppression and prior antibiotic use were significantly associated with penicillin nonsusceptibility on multivariate analyses (table 1). Prior antibiotic use as a risk factor for penicillin nonsusceptibility has been documented in numerous studies [9, 22, 27–29].

The mortality rate at 14 days was 16.9%, which is similar to the rate reported in other studies of pneumococcal bacteremia [18, 30]. Age >65 years, severity of illness, and underlying disease or risk factors involving immunosuppression were significantly associated with mortality on multivariate analysis (table 2).

It is difficult to assess the effect of antibiotics when multiple antibiotics are given with initial therapy [11, 31]. In our large-scale study, 389 patients received monotherapy, and data for 360 of these patients were evaluable. Within this subgroup, patients who received discordant therapy did not have a higher mortality rate than did patients who received concordant therapy, for all patients and for the subgroup of patients receiving penicillins (penicillin, ampicillin, and amoxicillin-clavulanate) and third-generation cephalosporins. However, patients who were treated with cefuroxime, a second-generation cephalosporin, and who were infected with pneumococci with in vitro nonsusceptibility to cefuroxime experienced significantly higher mortality rates on both univariate and multivariate analyses (table 3). Of note, after we stratified groups by severity of illness, the effect of discordant therapy with cefuroxime became even more pronounced in patients who were not critically ill ($P = .01$). On the other hand, discordant therapy involving cefotaxime or ceftriaxone, 2 third-generation cephalosporins with higher intrinsic activity, did not result in higher mortality rates, regardless of severity of illness (table 3).

The severity of illness was consistently the most important determinant of impending death in all analyses. The mortality rate was high among critically ill patients, irrespective of the antibiotics administered or receipt of concordant and discordant therapy. This may be explained by the 1964 study by Austrian and Gold [32] in which mortality associated with pneumococcal bacteremia occurred mainly $\leqslant$3 days after positive blood cultures were obtained, as is also shown in figure 1 of our study. In this early phase, excessive and dysregulated release of cytokines, nitric oxide, and hypotensive molecules, such as kinins, leads to septic shock. Antibiotics appear to have little effect in minimizing mortality. Critical illness simply overwhelmed the salutary effects of active in vitro antibiotic therapy such that the issue of concordant versus discordant therapy became irrelevant.

By excluding patients who died during the first 4 days of hospitalization (as in the study by Austrian and Gold [32]), investigators from the Centers for Disease Control and Prevention found that patients infected with pneumococci that had high-level penicillin resistance experienced significantly higher mortality rates [19]. Similarly, when we excluded patients who were critically ill, the association between mortality and the use of discordant therapy with cefuroxime became statistically significant; on the other hand, discordant therapy involving penicillins, cefotaxime, or ceftriaxone had no correlation with mortality in this subgroup.

The pharmacodynamic features of individual antibiotics may explain, in part, our observations. The effectiveness of β-lactam antibiotics has been correlated with the duration of serum or tissue antibiotic concentrations above the MIC for the infecting organisms [33]. Eleven patients received monotherapy with cefuroxime for at least the first 48 h of therapy. Four of 11 patients infected with cefuroxime-resistant pneumococci died. Eight of the 11 patients and all 4 patients who died received the standard dose of cefuroxime (750 mg iv q8h). Pharmacodynamic studies suggest that cephalosporin concentrations should exceed the MIC for $\geqslant$50% of the dosing interval to ensure bacterial eradication and clinical cure in respiratory tract infections [26]. An analysis of the pharmacodynamics of cefuroxime at 750 mg 3 times per day reveals that the drug concentration exceeds 2 μg/mL for 50% of the dosing interval. Coverage of an MIC of 4 μg/mL for 50% of the dosing interval requires dosing at 1500 mg intravenously every 8 h [33–35]. Thus, our data are consistent with the concept that the higher dose should be recommended where cefuroxime-resistant pneumococci are likely to be encountered. In contrast, standard parenteral doses of ampicillin, penicillins, cefotaxime, and ceftriaxone achieve concentrations greater than the MIC for 75%–100% of the dosing interval for both susceptible and nonsusceptible pneumococci. It is noteworthy that bacteriological failure of first-generation cephalosporins and cefuroxime in patients with pneumococcal infection has been reported elsewhere [36–38].

One limitation of our study is that it could be argued that the low incidence of penicillin nonsusceptibility seen in this

study may not be representative of the overall population. However, study hospitals in countries reporting high-level resistance (France, Spain, Hong Kong, and Taiwan) were specifically recruited for participation. Tennessee also has a notably higher frequency of penicillin-nonsusceptible pneumococci than do other states in the United States and was thus represented in this study [4, 39]. If there is a bias of study hospitals toward in vitro susceptibility of pneumococci, it probably is toward a greater prevalence of resistance.

A second limitation is that this was an observational study, and the type of antibiotic administered could not be controlled. However, no controlled interventional trial has even been performed to assess the clinical significance of in vitro pneumococcal resistance.

A third limitation is that the macrolides and quinolones were not widely used as monotherapy. Thus, we could not assess the impact of in vitro resistance on mortality for these 2 classes of antibiotics. Of interest, both macrolides (33%) and quinolones (10%) were commonly used as components of combination antibiotic therapy.

In summary, with the exception of cefuroxime, the current NCCLS breakpoints for *S. pneumoniae* were not predictive of clinical outcome. Although in vitro resistance is increasing among pneumococci, it appears that this increase has not yet become clinically relevant for treatment of pneumococcal pneumonia.

S. pneumoniae is not only the most common cause of community-acquired pneumonia but the one that most frequently causes death. Its widely publicized increasing in vitro drug resistance has led to shifts in antibiotic prescription by physicians for community-acquired pneumonia [40–42]. Indeed, a premature shift to classes of antibiotics with increased potency against drug-resistant *S. pneumoniae,* such as quinolones, may render these valuable antibiotics less useful in the future. Quinolone-resistant pneumococci have already been reported as use of these antibiotics has increased [1, 43, 44]. Our study confirms that β-lactam agents, including penicillin, are still effective for the treatment of penicillin-nonsusceptible pneumococcal pneumonia. In our study, penicillin was found to still be in wide use in Sweden, South Africa, and New Zealand. It may be argued that penicillin should be more widely used in the United States and elsewhere.

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Acknowledgments

We thank Michael Jacobs and Ronald Jones for reconfirmation of Etest results by microtiter broth dilution. We thank Michael Jacobs and Ronald Dagen for their extensive and perceptive analyses. The following individuals also provided valuable critiques: Lionel Mandell, Michael Niederman, Sheldon Kaplan, Donald Low, James T. Jorgensen, Joshua Metlay, and Ian Friedland.

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