Clinical Outcomes of Meningitis Caused by Streptococcus pneumoniae in the Era of Antibiotic Resistance

Anthony E. Fiore,¹ John F. Moroney,¹ Monica M. Farley,¹ Lee H. Harrison,¹ Jan E. Patterson,¹ James H. Jorgensen,³ Martin Cetron,¹ Margarette S. Kolczak,² Robert F. Breiman,¹ and Anne Schuchat¹

Limited data are available on clinical outcomes of meningitis due to cefotaxime-nonsusceptible Streptococcus pneumoniae. We analyzed data from 109 cases of pneumococcal meningitis in Atlanta, Baltimore, and San Antonio, which were identified through population-based active surveillance from November 1994 to April 1996. Pneumococcal isolates from 9% of the cases were resistant to cefotaxime, and isolates from 11% had intermediate susceptibility. Children were more likely to have cephalosporin-nonsusceptible pneumococcal meningitis, but mortality was significantly higher among adults aged 18–64 years. Vancomycin was given upon admission to 29% of patients, and within 48 h of admission to 52%. Nonsusceptibility to cefotaxime was not associated with the following outcomes: increased mortality, prolonged length of hospital or intensive care unit (ICU) stay, requirement of intubation or oxygen, ICU care, discharge to another medical or long-term-care facility, or neurological deficit. Empirical use of vancomycin, current prevalence of drug-resistant S. pneumoniae, and degree of nonsusceptibility to cefotaxime may have influenced these findings.

Streptococcus pneumoniae is the most frequent cause of bacterial meningitis in the United States. Based on data from a population-based, multistate active surveillance system, the estimated annual incidence of pneumococcal meningitis in the United States is 1.1 cases per 100,000 population (or ~3000 cases), with an estimated case-fatality rate of 21% [1].

Until recently, patients with suspected pneumococcal meningitis were treated with penicillin or extended-spectrum cephalosporins. However, the prevalence of resistance to penicillin and cephalosporin among pneumococci (drug-resistant S. pneumoniae) isolated from sterile sites has risen dramatically during the past decade [2, 3]. In 1994, 27% of sterile-site isolates from children in Atlanta were nonsusceptible (i.e., resistant or intermediate) to penicillin, as defined by the National Committee for Clinical Laboratory Standards (NCCLS), and 13% were nonsusceptible to cefotaxime [4].

Meningitis-treatment failures attributed to cephalosporin resistance have been reported [5–13]. The American Academy of Pediatrics recommends vancomycin (an antibiotic to which all S. pneumoniae strains remain susceptible) in addition to an extended-spectrum cephalosporin for treatment of suspected pneumococcal meningitis [14], and this recommendation has also been proposed for the treatment of adult patients with suspected pneumococcal meningitis [15].

Despite these recommendations, there is scant evidence that vancomycin use improves clinical outcomes of invasive disease caused by drug-resistant S. pneumoniae. One study found no difference between outcomes for 5 children with meningitis caused by cefotaxime-nonsusceptible pneumococci versus those for 5 children with meningitis caused by cefotaxime-susceptible pneumococci [16]. Several studies have indicated that the clinical outcomes for persons with invasive pneumococcal infection due to drug-resistant S. pneumoniae are similar to those for persons with infections caused by susceptible pneumococci [17–19]. These studies included too few case patients to allow any conclusions about meningitis due to drug-resistant S. pneumoniae. A multicenter, retrospective study of the outcome of pneumococcal meningitis in children was recently reported, in which mortality and frequency of neurological sequelae were not influenced by the antibiotic susceptibility of the pneumococcal isolate [20].

¹From the ¹Respiratory Diseases Branch, ²Biostatistics and Information Management Branch, Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, and ³Atlanta Veterans Affairs Medical Center and Emory University School of Medicine, Atlanta, Georgia; ⁴Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland; and ⁵University of Texas Health Science Center at San Antonio, San Antonio, Texas.
We conducted a population-based study of persons with meningitis caused by drug-resistant *S. pneumoniae*. Our objectives were to characterize the clinical course and prognosis of meningitis due to *S. pneumoniae* and to determine whether meningitis due to cefotaxime-nonsusceptible *S. pneumoniae* (resistant or intermediately resistant to cefotaxime) results in clinical outcomes different from those of meningitis due to cefotaxime-susceptible *S. pneumoniae*.

**Methods**

Population-based active surveillance for invasive pneumococcal disease was established in 1994 by the Centers for Disease Control and Prevention (CDC) in collaboration with investigators in several geographic areas. Surveillance officers regularly contacted laboratories serving all acute care hospitals in each active surveillance area and completed a report form on each case of invasive pneumococcal disease. For the current study, data were obtained from the Atlanta, San Antonio, and Baltimore metropolitan areas. Surveillance was conducted in 17 hospitals in the San Antonio area (Bexar County), 14 hospitals in the Baltimore city and Baltimore County area, and 32 hospitals in the Atlanta metropolitan area (including Fulton, DeKalb, Cobb, Clayton, Rockdale, Douglas, Newton, and Gwinnett counties), representing a total population of ~5.4 million persons (according to 1995 census data).

The study period began on 1 November 1994 and ended on 30 April 1996. The case definition for pneumococcal meningitis was isolation of *S. pneumoniae* from the CSF or blood of a person with evidence of meningitis (CSF WBC count $>20/\text{mL}$ and an elevated CSF protein concentration). Only hospitalized residents of the surveillance area were included. Nosocomial pneumococcal meningitis, defined by development of clinical symptoms of meningitis and collection of the CSF specimen $>2$ days after the admission date, was excluded. No nosocomial pneumococcal meningitis was identified among persons initially treated for pneumococcal infection at other anatomic sites.

The surveillance was laboratory-based. Laboratory audits were performed at least every 6 months to evaluate reporting sensitivity and to identify unreported cases. Surveillance personnel collected data and submitted pneumococcal isolates to the CDC or the University of Texas Health Science Center at San Antonio. The isolates were sent on blood agar slants and were confirmed as pneumococci on the basis of ethylhydrocupreine susceptibility and bile solubility.

Antimicrobial susceptibility testing was performed by use of the NCCLS broth dilution method and standards for interpretation of results [21]. Isolates were classified as cefotaxime-susceptible if the MIC was $\leq 0.5 \mu g/\text{mL}$, cefotaxime-intermediate if the MIC was $1 \mu g/\text{mL}$, and cefotaxime-resistant if the MIC was $>2 \mu g/\text{mL}$. Here the nonsusceptible category comprises both resistant and intermediate isolates. Isolates nonsusceptible to cefotaxime are also considered nonsusceptible to ceftriaxone.

Case patients were evaluated by abstraction of clinical, demographic, and laboratory information from the hospital chart by use of a standardized data-extraction form. Ages were categorized according to the following groups: (1) children (aged $<18$ years), (2) adults (aged 18–64 years), and (3) older adults (aged $\geq 65$ years). Race was defined as either black or white/other (which included 2 Asians and 9 nonblack Hispanics). Conditions that were considered “underlying” for the analyses included congestive heart failure, chronic obstructive lung disease, HIV infection with a last recorded CD4 cell count $<100/\text{mL}$, malignancy not in remission, diabetes mellitus, asplenia, sickle cell disease, CSF leak, Down syndrome, presence of a transplanted organ, and long-term use of corticosteroids or other immunosuppressive medications. Previous antibiotic use was defined as the use of any antibiotic continuously during the 48 h before admission.

Previously validated scoring systems were used to adjust for severity of illness. Acute physiology and chronic health evaluation (APACHE II) scores were calculated for adults [22], and pediatric risk of mortality (PRISM) scores were calculated for children [23]. For multivariate analysis, the scores were classified into quartiles, with the referent being the first quartile (lowest scores). When a particular parameter was missing, the parameter was assumed to be within normal range for scoring purposes.

Data were collected on antimicrobial drug and corticosteroid use during the first 14 hospital days. Patients were considered to have received corticosteroids only if administration began on the date of admission; data on whether corticosteroid administration proceeded or followed antibiotic administration were not collected. Discordant antibiotic therapy was defined as nonreceipt during the first 2 days of hospitalization of any antibiotic to which the isolated *S. pneumoniae* was susceptible. The presence of neurological deficits resulting from meningitis (hearing loss or other sensory deficits, motor deficits, cognitive deficits, or anoxic encephalopathy) was determined by use of the discharge ICD-9 (International Classification of Diseases, 9th revision) codes.

The 8 outcome variables of interest were as follows: death, admission to an intensive care unit (ICU), need for supplemental oxygen, need for mechanical ventilation; length of stay in the ICU, length of stay in the hospital, presence of neurological deficit upon discharge, and discharge to an extended care facility. We analyzed the data using Statistical Analysis System (SAS) software, version 6.12 (SAS Institute, Cary, NC); we used the $x^2$ test and Fisher’s exact test to compare proportions; we considered $P < .05$ significant.

We employed unconditional logistic regression and the Cox proportional hazards procedure to adjust for multiple potential confounders. Initial models included age group, severity of illness quartile, receipt of antibiotics before admission, metropolitan area, receipt of vancomycin or corticosteroids, presence of underlying conditions as previously defined, and race/ethnicity. Clinical laboratory parameters such as WBC count were frequently not available and were not included in the multivariate analysis. Final models were chosen by use of a backward-selection procedure and included only statistically significant ($P < .05$) variables.

**Results**

Pneumococcal meningitis in 101 persons was identified by the surveillance system during the study period. After review of medical records for persons with other invasive pneumococcal infections, an additional 15 persons who met the case definition for meningitis were enrolled. For 7 of these 116 case patients there was no isolate available for susceptibility testing; thus, 109 case patients were in the final cohort.

The annual incidence rate for pneumococcal meningitis in
Within each age category, the annual incidence of pneumococcal meningitis among blacks comprised 64% and blacks comprised 48% of the cohort. The surveillance area was 1.35 cases per 100,000 persons. Males were 0.96 cases per 100,000 (P <.001) and tracked the proportion of isolates nonsusceptible to cefotaxime within each age category.

The mortality rate was highest in the adult age group (11 deaths; Fisher’s exact test for 3 × 2 table, P = .03), compared with that in the other 2 age groups. Patients in this age group who died had a variety of underlying conditions, including HIV infection (3 patients), alcoholism (1), systemic lupus erythematosus (1), and cardiovascular disease (2); 4 patients had either hypertension or no underlying condition. Risk of death was not associated in univariate analysis with race/ethnicity, gender, presence of underlying condition(s), HIV infection, alcohol-related illness, state of residence, or use of antibiotics before hospitalization (data not shown). Five of the 15 deaths occurred on the day of or the day after admission. Vancomycin or corticosteroid use did not significantly affect mortality (data not shown).

Systemic corticosteroids were administered on the day of admission to 22% of the cohort: 33% of children received corticosteroids, compared with 13% of adults and 21% of older adults (Fisher’s exact test for 3 × 2 table, P = .07). Fifty-two percent received at least 1 dose of vancomycin within the first 48 h of their hospital admission, and 29% received vancomycin on the date of admission. Significant differences in nonsusceptibility to cefotaxime were noted among age groups (P <.01; figure 1) and by metropolitan area (P = .05; figure 2). Age groups (figure 1) and metropolitan areas (figure 2) with a higher prevalence of pneumococci that were nonsusceptible to cefotaxime and penicillin also had a higher prevalence of empirical use of vancomycin (administration of the antibiotic before availability of culture results).

The susceptibility to cefotaxime and penicillin of pneumococcal isolates causing meningitis varied by geographic region (table 1). The overall prevalence of nonsusceptibility among pneumococcal isolates causing meningitis was 20% against cefotaxime (10 resistant and 12 intermediate isolates) and 35% against penicillin (21 resistant and 17 intermediate isolates). Both deaths associated with pneumococci that were not susceptible to cefotaxime occurred among adults aged 18–64 years.

Most persons (87%) received at least 1 antibiotic on the day of admission to which their isolate was susceptible. Eight of 109 (7%) received discordant antibiotic therapy; of these 8, none died, and the isolates of only 2 were fully resistant to cefotaxime. Two deaths occurred among patients whose isolates were cefotaxime-nonsusceptible; both isolates showed intermediate susceptibility to cefotaxime. One of these 2 patients received vancomycin at admission, and the other received clindamycin (to which the isolate was susceptible) and ceftriaxone during the first 2 days of hospitalization and vancomycin thereafter.

A comparison of demographic and prehospitalization characteristics is presented in table 2. Receiving antibiotics continuously during the 48 h before hospitalization was associated with infection due to a nonsusceptible strain (P <.02).

A comparison of clinical characteristics of persons infected with susceptible and nonsusceptible pneumococci is presented in table 3. Persons infected with a cefotaxime-susceptible pneumococcus had a significantly higher level of CSF protein; otherwise, the 2 groups were similar in the treatment and clinical characteristics measured. Univariate analysis of outcome variables for persons with susceptible versus nonsusceptible pneumococcal infections is shown in table 4. No association between cefotaxime susceptibility and these outcomes was noted.
Among the 8 who received discordant therapy, with antibiotic susceptibility of the causative pneumococci. No timicrobial therapy for individual patients was rarely discordant eral factors. Empirical vancomycin was given to a majority of facility admission are similar among persons with susceptible oxyg, mechanical ventilation, ICU care, or extended-care-frequency of neurological sequelae, and need for supplemental study suggest that mortality, length of hospital or ICU stay, identi®cation techniques become available. The results from this treatment until more rapid susceptibility testing and pathogen-susceptibility to antibiotics is crucial for making the most ra-erately increased risk effect was seen (OR, 4.79; 95% CI, 1.09±21.17 [data not shown]). Patients who received vanco-mycin were less likely to be discharged to a long-term-care facility (OR, 0.07; 95% CI, 0.01±0.71). However, patients who received vancomycin were more likely to have neurological def-sible, <0.06 µg/mL; intermediately susceptible, 0.12-1 µg/mL; resistant, ≥2 µg/mL. b MICs: susceptible, <0.5 µg/mL; intermediately susceptible, 1 µg/mL; resistant, ≥2 µg/mL.

Multivariate modeling for 3 of the outcome variables is presented in table 5. For length of hospital stay (a continuous variable), the OR is interpreted as the risk of discharge; for example, persons with higher severity-of-illness scores were significantly less likely to be discharged on any given day. Cefotaxime susceptibility of the pneumococcal isolate was not associated with any of the 5 additional measured outcomes in the multivariate analysis (data not shown). Corticosteroid use on admission was not a signi®cant risk factor for any outcome except requirement of mechanical ventilation, for which a moderately increased risk effect was seen (OR, 4.79; 95% CI, 1.09±21.17 [data not shown]). Patients who received vancomycin were less likely to be discharged to a long-term-care facility (OR, 0.07; 95% CI, 0.01–0.71). However, patients who received vancomycin were more likely to have neurological deficits (OR, 6.20; 95% CI, 1.69–22.79).

Discussion

Pneumococcal meningitis is the most common form of bacterial meningitis in the United States [1]. Information on the outcomes of infection with pneumococci that exhibit decreased susceptibility to antibiotics is crucial for making the most rational treatment choices. Empirical antibiotic therapy for suspected bacterial meningitis will remain the cornerstone of treatment until more rapid susceptibility testing and pathogen-identification techniques become available. The results from this study suggest that mortality, length of hospital or ICU stay, frequency of neurological sequelae, and need for supplemental oxygen, mechanical ventilation, ICU care, or extended-care-facility admission are similar among persons with susceptible and nonsusceptible pneumococcal meningitis.

However, interpretation of our results is complicated by several factors. Empirical vancomycin was given to a majority of patients during the first 48 h of hospitalization; therefore, antimicrobial therapy for individual patients was rarely discordant with antibiotic susceptibility of the causative pneumococci. No deaths occurred among the 8 who received discordant therapy, but the small number of subjects in this subset limits the generalizability of these findings. Moreover, very-high-level cefotaxime resistance (MIC, ≥4 µg/mL) was seen in isolates from only 5 patients.

The lack of association between cefotaxime susceptibility and death or increased length of hospital stay may also be due to an underestimation of the antimicrobial concentrations achievable in human CSF. Cefotaxime concentrations in CSF may exceed MICs for nonsusceptible strains, especially when the susceptibility level is intermediate (MIC, 1 µg/mL) [24]; and in our study, the isolates from 55% of patients with cefotaxime-nonsusceptible infections were intermediately susceptible. Others have suggested that current MIC breakpoints are too conservative and that meningitis due to organisms that exhibit intermediate susceptibility to cefotaxime can be successfully treated with cefotaxime alone [16]. However, in this study we did not directly address these issues. We had too few patients with fully cefotaxime-resistant pneumococcal infection to assess with multivariate analysis whether those persons were at higher risk of poor outcomes than those with cefotaxime-intermediate and -susceptible pneumococcal meningitis.

Despite the relatively large size of this cohort, this study had limited power to detect a difference in severe outcomes on the basis of susceptibility to cefotaxime. While planning the study, we had hypothesized that there might be a relatively high rate of mortality among persons with meningitis caused by cefotaxime-nonsusceptible pneumococcal strains, and especially

Table 1. Percentage of pneumococcal isolates susceptible, interme-
diate, and resistant to penicillin and cefotaxime per study site of hos-
pitalization for pneumococcal meningitis.

<table>
<thead>
<tr>
<th>Antibiotic susceptibility</th>
<th>Atlanta (n = 53)</th>
<th>Baltimore (n = 29)</th>
<th>San Antonio (n = 27)</th>
<th>Total (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>56</td>
<td>79</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td>Intermediate</td>
<td>19</td>
<td>14</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Resistant</td>
<td>25</td>
<td>7</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Cefotaxime&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Susceptible</td>
<td>76</td>
<td>93</td>
<td>74</td>
<td>80</td>
</tr>
<tr>
<td>Intermediate</td>
<td>13</td>
<td>0</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>Resistant</td>
<td>11</td>
<td>7</td>
<td>7</td>
<td>9</td>
</tr>
</tbody>
</table>

<sup>a</sup> MICs: susceptible, <0.06 µg/mL; intermediately susceptible, 0.12-1 µg/mL; resistant, ≥2 µg/mL.

Table 2. Demographic and clinical characteristics of persons hos-
pitalized with culture-confirmed pneumococcal meningitis in the San Antonio, Baltimore, and Atlanta areas during the study period, as related to cefotaxime-nonsusceptibility of isolates.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Isolates nonsusceptible&lt;sup&gt;a&lt;/sup&gt; to cefotaxime, no./total no. (%)</th>
<th>RR (95% CI)</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-17</td>
<td>12/43 (28)</td>
<td>.82</td>
<td>.10</td>
</tr>
<tr>
<td>18-64</td>
<td>5/47 (11)</td>
<td>.05</td>
<td>.02</td>
</tr>
<tr>
<td>≥65</td>
<td>5/19 (26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>.03</td>
</tr>
<tr>
<td>Black</td>
<td>9/52 (17)</td>
<td>0.83 (0.48–1.43)</td>
<td>.30</td>
</tr>
<tr>
<td>Other</td>
<td>13/57 (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>.08</td>
</tr>
<tr>
<td>Male</td>
<td>15/70 (21)</td>
<td>1.08 (0.77–1.52)</td>
<td>.04</td>
</tr>
<tr>
<td>Female</td>
<td>7/39 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>State of residence</td>
<td></td>
<td></td>
<td>.10</td>
</tr>
<tr>
<td>Georgia</td>
<td>13/52 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maryland</td>
<td>2/29 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Texas</td>
<td>7/27 (26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underlying condition</td>
<td></td>
<td></td>
<td>.42</td>
</tr>
<tr>
<td>≥1</td>
<td>14/53 (26)</td>
<td>1.42 (0.92–2.20)</td>
<td>.01</td>
</tr>
<tr>
<td>None</td>
<td>8/56 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous antibiotics&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>.24</td>
</tr>
<tr>
<td>Any</td>
<td>9/23 (39)</td>
<td>2.54 (1.24–5.23)</td>
<td>.02</td>
</tr>
<tr>
<td>None</td>
<td>13/86 (15)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes 10 resistant and 12 intermediately resistant isolates. MICs: susceptible, <0.5 µg/mL; nonsusceptible, ≥1 µg/mL.

<sup>b</sup> Fisher’s exact test for 2 x 3 table.

<sup>c</sup> Antibiotic(s) taken continuously for the 48 h before admission.
among those with cefotaxime-resistant strains. Antibiotic levels are lower in CSF than in serum, and differences in outcome should be easier to detect in cases of meningitis than in cases of bacteremic pneumonia. However, because resistance was seen more often among children (among whom mortality is lower), the power of our study was further lowered.

A larger study might have detected a difference; however, such studies would be difficult to perform because empirical use of vancomycin for suspected bacterial meningitis has become the standard care for all patients [14, 15, 25–27]. In observational studies such as this one, treatment decisions are influenced by the clinician’s assessment of the patient’s clinical status. Thus patients who are clinically unstable or face a poor prognosis are probably over represented in the patient group that receives vancomycin (and therefore does not receive discordant antimicrobial therapy) or receives corticosteroids.

Age was a significant risk factor for death in this study; however, the age group with the highest mortality differed from that in other published reports. In contrast with our findings, earlier studies found that age >65 years was associated with the highest rate of deaths due to pneumococcal meningitis [28, 29]. The reasons for higher mortality (23%) among the adults aged 18–64 years in this study are uncertain, but this finding was not attributable to a single underlying condition. Mortality for the oldest age group ranged from 20% to 53% [1, 28, 29]. Analysis of differences in outcome on the basis of susceptibility to cefotaxime among more restricted age cohorts (for example, those aged <6 years or >75 years) was also limited by the relatively few case patients in these age categories.

In multivariate modeling, vancomycin use was not associated with 6 of the 8 measured clinical outcomes. The results of multivariate modeling for the other 2 outcomes appear somewhat contradictory, with vancomycin use presenting a greater risk of neurological sequelae but less risk of discharge to a long-term-care facility. Although severity-of-illness scores were considered in the multivariate analysis, vancomycin use may have indicated a higher degree of clinical concern for patients who appeared more ill. Further study is needed to determine the impact of vancomycin use on outcomes of pneumococcal meningitis.

The benefit of corticosteroids in the treatment of meningitis was first demonstrated in a cohort that consisted primarily of children with *Haemophilus influenzae* type b (Hib) meningitis [30], a disease rarely seen in the United States since the introduction of Hib vaccines. Others have extended these findings to advocate the use of corticosteroids against all forms of meningitis in children [31]. A meta-analysis of studies involving children with pneumococcal meningitis suggested that dexamethasone provided some protection against neurological sequelae [32], although a recent observational study could not detect a benefit [20].

The use of corticosteroids in the treatment of meningitis in adults has been more controversial [33]. In our study, corticosteroid use on admission did not appear to influence outcomes, except for mechanical ventilation. However, on the basis of this study we cannot assess whether mechanical ventilation was provided because of concern about intracranial pressure, which is also an indication for corticosteroid use. In addition, corticosteroids may need to be given before or shortly after antibiotics in order to be effective, and we collected only the date of administration. Our study was not designed to assess among those with cefotaxime-resistant strains. Antibiotic levels are lower in CSF than in serum, and differences in outcome should be easier to detect in cases of meningitis than in cases of bacteremic pneumonia. However, because resistance was seen more often among children (among whom mortality is lower), the power of our study was further lowered.

A larger study might have detected a difference; however, such studies would be difficult to perform because empirical use of vancomycin for suspected bacterial meningitis has become the standard care for all patients [14, 15, 25–27]. In observational studies such as this one, treatment decisions are influenced by the clinician’s assessment of the patient’s clinical status. Thus patients who are clinically unstable or face a poor prognosis are probably over represented in the patient group that receives vancomycin (and therefore does not receive discordant antimicrobial therapy) or receives corticosteroids.

Age was a significant risk factor for death in this study; however, the age group with the highest mortality differed from that in other published reports. In contrast with our findings, earlier studies found that age >65 years was associated with the highest rate of deaths due to pneumococcal meningitis [28, 29]. The reasons for higher mortality (23%) among the adults aged 18–64 years in this study are uncertain, but this finding was not attributable to a single underlying condition. Mortality for the oldest age group in this study (11%) was less than that reported for similar age groups in other studies, in which mortality for the oldest age group ranged from 20% to 53% [1, 28, 29]. Analysis of differences in outcome on the basis of susceptibility to cefotaxime among more restricted age cohorts (for example, those aged <6 years or >75 years) was also limited by the relatively few case patients in these age categories.

In multivariate modeling, vancomycin use was not associated with 6 of the 8 measured clinical outcomes. The results of multivariate modeling for the other 2 outcomes appear somewhat contradictory, with vancomycin use presenting a greater risk of neurological sequelae but less risk of discharge to a long-term-care facility. Although severity-of-illness scores were considered in the multivariate analysis, vancomycin use may have indicated a higher degree of clinical concern for patients who appeared more ill. Further study is needed to determine the impact of vancomycin use on outcomes of pneumococcal meningitis.

The benefit of corticosteroids in the treatment of meningitis was first demonstrated in a cohort that consisted primarily of children with *Haemophilus influenzae* type b (Hib) meningitis [30], a disease rarely seen in the United States since the introduction of Hib vaccines. Others have extended these findings to advocate the use of corticosteroids against all forms of meningitis in children [31]. A meta-analysis of studies involving children with pneumococcal meningitis suggested that dexamethasone provided some protection against neurological sequelae [32], although a recent observational study could not detect a benefit [20].

The use of corticosteroids in the treatment of meningitis in adults has been more controversial [33]. In our study, corticosteroid use on admission did not appear to influence outcomes, except for mechanical ventilation. However, on the basis of this study we cannot assess whether mechanical ventilation was provided because of concern about intracranial pressure, which is also an indication for corticosteroid use. In addition, corticosteroids may need to be given before or shortly after antibiotics in order to be effective, and we collected only the date of administration. Our study was not designed to assess among those with cefotaxime-resistant strains. Antibiotic levels are lower in CSF than in serum, and differences in outcome should be easier to detect in cases of meningitis than in cases of bacteremic pneumonia. However, because resistance was seen more often among children (among whom mortality is lower), the power of our study was further lowered.

A larger study might have detected a difference; however, such studies would be difficult to perform because empirical use of vancomycin for suspected bacterial meningitis has become the standard care for all patients [14, 15, 25–27]. In observational studies such as this one, treatment decisions are influenced by the clinician’s assessment of the patient’s clinical status. Thus patients who are clinically unstable or face a poor prognosis are probably over represented in the patient group that receives vancomycin (and therefore does not receive discordant antimicrobial therapy) or receives corticosteroids.

Age was a significant risk factor for death in this study; however, the age group with the highest mortality differed from that in other published reports. In contrast with our findings, earlier studies found that age >65 years was associated with the highest rate of deaths due to pneumococcal meningitis [28, 29]. The reasons for higher mortality (23%) among the adults aged 18–64 years in this study are uncertain, but this finding was not attributable to a single underlying condition. Mortality for the oldest age group in this study (11%) was less than that reported for similar age groups in other studies, in which mortality for the oldest age group ranged from 20% to 53% [1, 28, 29]. Analysis of differences in outcome on the basis of susceptibility to cefotaxime among more restricted age cohorts (for example, those aged <6 years or >75 years) was also limited by the relatively few case patients in these age categories.

In multivariate modeling, vancomycin use was not associated with 6 of the 8 measured clinical outcomes. The results of multivariate modeling for the other 2 outcomes appear somewhat contradictory, with vancomycin use presenting a greater risk of neurological sequelae but less risk of discharge to a long-term-care facility. Although severity-of-illness scores were considered in the multivariate analysis, vancomycin use may have indicated a higher degree of clinical concern for patients who appeared more ill. Further study is needed to determine the impact of vancomycin use on outcomes of pneumococcal meningitis.

The benefit of corticosteroids in the treatment of meningitis was first demonstrated in a cohort that consisted primarily of children with *Haemophilus influenzae* type b (Hib) meningitis [30], a disease rarely seen in the United States since the introduction of Hib vaccines. Others have extended these findings to advocate the use of corticosteroids against all forms of meningitis in children [31]. A meta-analysis of studies involving children with pneumococcal meningitis suggested that dexamethasone provided some protection against neurological sequelae [32], although a recent observational study could not detect a benefit [20].

The use of corticosteroids in the treatment of meningitis in adults has been more controversial [33]. In our study, corticosteroid use on admission did not appear to influence outcomes, except for mechanical ventilation. However, on the basis of this study we cannot assess whether mechanical ventilation was provided because of concern about intracranial pressure, which is also an indication for corticosteroid use. In addition, corticosteroids may need to be given before or shortly after antibiotics in order to be effective, and we collected only the date of administration. Our study was not designed to assess among those with cefotaxime-resistant strains. Antibiotic levels are lower in CSF than in serum, and differences in outcome should be easier to detect in cases of meningitis than in cases of bacteremic pneumonia. However, because resistance was seen more often among children (among whom mortality is lower), the power of our study was further lowered.

A larger study might have detected a difference; however, such studies would be difficult to perform because empirical use of vancomycin for suspected bacterial meningitis has become the standard care for all patients [14, 15, 25–27]. In observational studies such as this one, treatment decisions are influenced by the clinician’s assessment of the patient’s clinical status. Thus patients who are clinically unstable or face a poor prognosis are probably over represented in the patient group that receives vancomycin (and therefore does not receive discordant antimicrobial therapy) or receives corticosteroids.

Age was a significant risk factor for death in this study; however, the age group with the highest mortality differed from that in other published reports. In contrast with our findings, earlier studies found that age >65 years was associated with the highest rate of deaths due to pneumococcal meningitis [28, 29]. The reasons for higher mortality (23%) among the adults aged 18–64 years in this study are uncertain, but this finding was not attributable to a single underlying condition. Mortality for the oldest age group in this study (11%) was less than that reported for similar age groups in other studies, in which mortalit...
the benefits of corticosteroid use; however, it suggests that the issue needs to be clarified.

The results presented here do not challenge recommendations for the treatment of suspected bacterial meningitis. Rather, they serve to reassure clinicians that, at the current prevalence of drug-resistant \textit{S. pneumoniae} and use of vancomycin, clinical outcomes for those with meningitis caused by cefotaxime-non-susceptible pneumococci appear to be quite similar to those for patients with susceptible pneumococcal meningitis. Other investigators have noted a lack of association between poor clinical outcomes and invasive disease caused by nonsusceptible pneumococci, even for patients given discordant therapy [16–20]. Our study is the first large investigation of the clinical outcomes of meningococcal infection with drug-resistant \textit{S. pneumoniae} among all age groups, and it is the first to analyze data from a population-based surveillance system in an era in which combination therapy with a \beta-lactam and vancomycin has become standard for suspected pneumococcal meningitis.

The evolution of pneumococcal resistance to antibiotics suggests that as a result of the gradual increase in pneumococcal MICs, more pneumococci will become fully resistant to cefotaxime. As this occurs, an adverse clinical impact of antibiotic resistance among pneumococci may become apparent. Given this likely scenario, the combination of vancomycin and cefotaxime or ceftriaxone should remain the preferred therapy for the treatment of suspected bacterial meningitis. Rather, they serve to reassure clinicians that, at the current prevalence of drug-resistant \textit{S. pneumoniae} and use of vancomycin, clinical outcomes for those with meningitis caused by cefotaxime-non-susceptible pneumococci appear to be quite similar to those for patients with susceptible pneumococcal meningitis. Other investigators have noted a lack of association between poor clinical outcomes and invasive disease caused by nonsusceptible pneumococci, even for patients given discordant therapy [16–20]. Our study is the first large investigation of the clinical outcomes of meningococcal infection with drug-resistant \textit{S. pneumoniae} among all age groups, and it is the first to analyze data from a population-based surveillance system in an era in which combination therapy with a \beta-lactam and vancomycin has become standard for suspected pneumococcal meningitis.

The evolution of pneumococcal resistance to antibiotics suggests that as a result of the gradual increase in pneumococcal MICs, more pneumococci will become fully resistant to cefotaxime. As this occurs, an adverse clinical impact of antibiotic resistance among pneumococci may become apparent. Given this likely scenario, the combination of vancomycin and cefotaxime or ceftriaxone should remain the preferred therapy for suspected pneumococcal meningitis. Continued surveillance for resistance characteristics among pneumococci, linked with data on clinical outcomes for patients, is necessary. Prevention of antimicrobial-resistant infections by promotion of the judicious use of antimicrobials and the currently available polysaccharide vaccine [14, 34] (and, eventually, by the introduction of better pneumococcal vaccines [35]) should provide long-term solutions.

### Acknowledgments

We acknowledge the assistance of John Elliott, Ph.D., and Richard R. Facklam, Ph.D., for antimicrobial susceptibility testing; Katherine Robinson, M.P.H., Wendy Baughman, M.S.P.H., Lillian Billmann, R.N., M.P.H., Carolyn Wright, and Ariane Kraus, M.P.H., for assistance with surveillance; Kim Holmes, R.N., Denise Miller Hicks, M.P.H., Swarna Meyyazhagan, M.D., and Deborah Peabody, M.D., for performing medical chart abstraction; and the infection control practitioners, clinical microbiologists, and hospitals in the surveillance areas for their help in identifying cases.

### References