Randomized, Double-Blind Comparison of Oral Cefpodoxime and Parenteral Ceftriaxone in Hospitalized Adults with Community-Acquired Pneumonia

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Introduction

Each year, approximately 12 of every 1000 adults in the United States contract pneumonia, amounting to nearly 4 million cases of pneumonia annually [1]. More than 600,000 of these patients require hospitalization at a treatment cost of $23 billion [1]. Immediate parenteral therapy with an antibiotic is the usual treatment regimen for hospitalized patients. Many physicians prescribe intravenous (IV) therapy for 7 to 10 days; some switch to oral drugs after the patient has been stabilized to complete the course [2]. The average length of stay for patients with pneumonia is 8.3 days [3].

Pressures to contain costs combined with the availability of newer, more potent oral agents has led to a growing interest in oral therapy for community-acquired pneumonia (CAP). Recently, the Infectious Diseases Society of America (IDSA) endorsed oral therapy for those patients who can tolerate it, noting that there are no studies showing superior outcomes of parenteral administration compared with the oral route [4]. In addition, oral medications are more easily administered, less costly, and may permit earlier discharge from the hospital.

Objective: To evaluate the efficacy and safety of oral cefpodoxime compared with parenteral ceftriaxone in the treatment of community-acquired pneumonia (CAP) requiring hospitalization.

Design: Prospective, randomized, double-blind, multicenter trial.

Patients and setting: Patients aged 18 years or older with acute signs and symptoms of CAP requiring hospitalization at 10 U.S. medical centers and private practices.

Interventions: Oral cefpodoxime 200 mg twice daily and placebo infusion of 0.9% sodium chloride or parenteral (intravenous or intramuscular) ceftriaxone 1 g daily and oral placebo for 7 to 14 days.

Main outcome measures: Bacteriologic and clinical response rates at end of therapy.

Results: Of the 85 patients enrolled in the trial, 44 received oral cefpodoxime and 41 received parenteral ceftriaxone. Bacterial eradication rates were 100% in both treatment groups. Fifty-nine of the 85 patients (69%) were considered clinically assessable. Of the 33 clinically assessable patients in the cefpodoxime group, 20 (60.6%) were clinically cured, 8 (24.2%) were improved, and 5 (15.2%) were failures. Of the 26 clinically assessable patients in the ceftriaxone group, 15 (57.7%) were clinically cured, 6 (23.1%) were improved, and 5 (19.2%) were failures. A total of 45.5% of patients in the cefpodoxime group and 46.3% of those in the ceftriaxone group reported adverse events, most of which were mild. Drug-related diarrhea occurred in 6 ceftriaxone patients but not in the cefpodoxime group. Three patients treated with cefpodoxime and 2 receiving ceftriaxone withdrew from the study because of adverse events.

Conclusion: Oral cefpodoxime is as safe and effective as parenteral ceftriaxone in the treatment of CAP requiring hospitalization.
Initial oral therapy may be a cost-effective alternative to parenterally administered antimicrobials [5–13].

The objective of our study was to evaluate the efficacy and safety of orally administered cefpodoxime proxetil (Vantin®, Pharmacia & Upjohn, Kalamazoo, MI) compared with parenterally administered ceftriaxone sodium (Rocephin®, Roche Laboratories, Nutley, NJ) in the treatment of patients with moderately severe CAP who require hospitalization. Ceftriaxone has been shown to be a cost-effective parenteral choice for the treatment of CAP requiring hospitalization [14,15]. Cefpodoxime offers an antimicrobial spectrum similar to that of ceftriaxone for common lower respiratory tract pathogens [16,17], and susceptibility results for ceftriaxone can be used to predict cefpodoxime susceptibility [18]. In a randomized, open-label, multicenter trial of 96 high-risk patients with acute CAP [19], oral cefpodoxime was as effective as intramuscular (IM) ceftriaxone in both clinical cure and bacterial eradication rates.

Methods
Study Design and Setting
The study was a prospective, randomized, double-blind, multicenter trial. The participating sites were 10 U.S. medical centers and private practices in 10 states.

Patients
Patients aged 18 years or older who were hospitalized with CAP were enrolled in the study. CAP was defined as evidence of lung infiltrates on chest films and purulent sputum (<10 squamous cells and >25 white blood cells per high-power field on Gram stain). Patients were excluded from the study if they were hypersensitive to cephalosporins, penicillins, or lidocaine or had leukopenia (white blood cell count <2000/mm³), neutropenia (neutrophil count <1000/mm³), renal impairment (creatinine >3.0 mg/dL), hepatic dysfunction (alanine aminotransferase [ALT] >200 IU/L or total bilirubin >3 mg/dL), acute respiratory distress syndrome, heart failure (New York Heart Association class IV), pulmonary infarction, or HIV infection. Patients also were excluded if they were receiving treatment for neoplastic disease; had received more than one dose of a systemic antibiotic within 48 hours of enrollment, or required concomitant systemic antimicrobial therapy. Patients in whom pneumonia was an expected terminal event, patients hospitalized during the 7 days preceding enrollment, and patients with a previous episode of pneumonia within 6 weeks of enrollment were excluded. Female patients who were pregnant, nursing, or not using an acceptable contraceptive method also were excluded.

Intervention and Assessment
Patients were randomly assigned to treatment with either (1) oral cefpodoxime 200 mg twice daily and placebo infusion of 0.9% sodium chloride, or (2) parenteral (IV or intramuscular) ceftriaxone 1 g daily and oral placebo twice daily. Treatment duration was 7 to 14 days. On discharge from the hospital, patients were given the remainder of their oral medication, and parenteral medication was continued with the use of follow-up home care.

Patient assessment took place at enrollment, twice during therapy, at the end of therapy (EOT), and at 2 to 4 weeks posttherapy. Infection-site samples (respiratory tract and blood) were cultured and organisms identified using standard techniques. Susceptibility of the organisms was determined using disk diffusion testing [20]. Assessable pathogens were those susceptible or moderately susceptible to both study drugs.

Primary Efficacy Variables
The primary efficacy variables were bacteriologic and clinical responses at EOT. When more than 1 pathogen was isolated from the same site, each pathogen was assessed separately.

Bacteriologic response. The bacteriologic response was classified as follows:
• Eradication—all assessable pathogens isolated at enrollment were eradicated during and after treatment. Included in this category were bacteriologic cures when an EOT culture was not obtainable (ie, no sputum) and the patient was clinically cured or improved.
• Not assessable—culture was negative at enrollment (ie, patient was entered for clinical response only) or patient did not return for an EOT visit.

Clinical response. The clinical response was classified as follows:
• Clinical cure—complete disappearance of all clinical signs and symptoms of CAP or a return to baseline levels in patients with chronic symptoms.
• Clinical improvement—clinical findings that subsided significantly at the completion of the medication period or a substantial return toward baseline levels in patients with chronic symptoms.
• Clinical failure—little or no improvement in clinical findings at the end of the study period.

Patients who could not be contacted for final follow-up were considered not assessable.

Adverse events were recorded at each assessment and classified as mild (does not interfere with the patient’s usual function), moderate (interferes to some extent with the patient’s usual function), or severe (interferes significantly with the patient’s usual function).
Statistical Analysis
Patients were eligible for efficacy analysis if they satisfied the inclusion and exclusion criteria, had a properly timed EOT visit and no resistant pathogens, took no concomitant antibiotics, were able to be adequately followed up (patient returned for final follow-up visit or responded by telephone interview), took 80% or more of the study-drug therapy, did not miss two consecutive doses, and were judged assessable by the investigator. Data from patients who did not have pathogens isolated on initial culture were analyzed separately for clinical response.

All patients who received at least one dose of study medication constituted the intention-to-treat population and were included in the safety analysis. A statistical comparison of treatment groups was made with respect to adverse events overall and drug-related adverse events using the two-tailed Fisher’s exact test. Categorical patient characteristic variables were compared with the chi-square test, and continuous variables with one-way analysis of variance. For laboratory results, values more than 20% above or below the investigator’s normal range were considered abnormal for all tests except for the following, which were considered abnormal only if the values exceeded the normal range: bands, neutrophils, eosinophils, monocytes, basophils, alkaline phosphatase, total bilirubin, aspartate aminotransferase, alanine aminotransferase, and creatinine.

All statistical tests were two-sided. P values less than 0.05 were considered statistically significant.

Results
Patient Characteristics
We enrolled 85 patients between 11 December 1991 and 31 March 1994. Forty-four patients (84.1% males) received oral cefpodoxime and 41 (90.2% males) received parenteral ceftriaxone. The mean age of the study population was 59 years, and the median age was 66 years. Statistically significant differences between the two groups were absent with respect to age, gender, race, medical history, height, weight, and physical examination findings.

Patients were classified using a modification of the scheme described by Fine et al [21] for stratifying patients with CAP according to risk of death within 30 days. Fine’s prediction rule assigns points based on host factors, physical findings, and laboratory values. Because we did not routinely measure blood urea nitrogen (BUN) and arterial partial pressure of oxygen, we substituted an elevated creatinine level (> 2.0 mg/dL) for the Fine BUN criterion and regarded patients with no oxygen measurements as having measurement in the normal range. In addition, we did not routinely record nursing home status or serum sodium level and therefore could not assign points based on these factors. Our calculations placed most patients in risk classes 3 and 4 (Figure 1).

Efficacy Analysis
Thirty-three of the 44 patients (75%) in the cefpodoxime group and 26 of the 41 patients (63.4%) in the ceftriaxone group were assessable for efficacy. Patients were excluded from the efficacy analysis because of resistant pathogens (4 patients in the cefpodoxime group and 9 patients in the ceftriaxone group), failure to meet entry criteria (2 patients in each group), use of additional antibiotic therapy (2 patients in the cefpodoxime group and 1 patient in the ceftriaxone group), dosage noncompliance (1 patient in the cefpodoxime group and 2 patients in the ceftriaxone group), protocol violation (1 patient in each group), and no follow-up (1 patient in the cefpodoxime group). Patients with a negative pretreatment culture (3 patients in the cefpodoxime group and 5 patients in the ceftriaxone group), although not assessable for bacteriologic analysis, were included in the clinical analysis.

In general, compliance was good, with 28 of 44 patients (63.6%) in the cefpodoxime group and 27 of 41 patients (65.9%) in the ceftriaxone group completing treatment as required. Most patients (cefepodoxime group, 72.1%; ceftriaxone group, 82.5%) received medication for at least 7 days.

The most common reason for study discontinuation was lack of efficacy, leading to withdrawal of 5 of 44 patients (11.4%) in the cefpodoxime group and 3 of 41 patients (7.3%) in the ceftriaxone group. Several patients became ineligible after treatment was started (2 of 44 [4.5%] in the cefpodoxime group and 5 of 41 [12.2%] in the ceftriaxone group). Three patients in the cefpodoxime group and 2 in the ceftriaxone group withdrew from the study because of adverse events.
Bacteriologic Response Rate

Pathogens were eradicated in all assessable patients who had an initial pathogen (Table 1). Of the 39 intention-to-treat patients in the cefpodoxime group and the 31 intention-to-treat patients in the ceftriaxone group with assessable EOT microbiologic response, all had complete eradication of pathogens.

Pathogens (≥5 isolates in either treatment group) isolated in the study were Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Klebsiella pneumoniae, and Haemophilus parainfluenzae. All but one isolate of H. influenzae, H. parainfluenzae, and K. pneumoniae were susceptible to both study drugs by in vitro disk testing. The remaining isolates for these pathogens had unknown susceptibility. For S. aureus, 2 of 6 isolates were susceptible to cefpodoxime, while the remaining 4 isolates had moderate susceptibility to cefpodoxime. All isolates of this pathogen were susceptible to ceftriaxone. For S. pneumoniae, 25 of 27 isolates were susceptible to cefpodoxime by in vitro disk testing, 24 of 27 isolates were susceptible to ceftriaxone, and 1 isolate was moderately susceptible to cefpodoxime; the susceptibility of 3 isolates to either drug was unknown.

The two most common pathogens isolated in this study were S. pneumoniae and H. influenzae. Both drugs eradicated 100% of these pathogens (Table 2). Nine patients had an initial resistant S. pneumoniae among the isolates. These pathogens were not assessable at EOT. No pathogens developed resistance during the study.

Clinical Response Rate

Most patients in each group were clinically cured (Table 1). There were no statistically significant differences between treatment groups in clinical response rate; the 95% confidence limits for the difference in the success rates (cured or improved versus failure) were –18.8% and 27.0%.

Eight patients with no initial pathogen were clinically assessable only (3 in the cefpodoxime group, 5 in the ceftriaxone group). One of the 3 assessable patients in the cefpodoxime group was clinically cured at EOT, 1 patient was clinically improved, and 1 patient did not respond to treatment. Of the 5 patients in the ceftriaxone group, 1 was clinically cured and 2 each were either clinically improved or clinical failures.

In the intention-to-treat population, clinical response rates were similar in the two treatment groups but lower than those in the assessable patients. This was expected because the intention-to-treat patients had negative pretreatment cultures, had bacterial pathogens resistant to study drug at admission, or did not comply with the medication regimen. Some had no clinical assessment at completion of therapy. Forty of the 44 intention-to-treat patients in the cefpodoxime group were assessable at EOT. Of these, 22 (55.0%) were cured, 12 (30.0%) were improved, and 6 (15.0%) failed. Thirty-nine of the 41 intention-to-treat patients (95.1%) in the ceftriaxone group were assessable at EOT. Of these, 19 (48.7%) were cured, 14 (35.9%) were improved, and 6 (15.4%) failed.

### Table 1. Bacteriologic and Clinical Response Rates

<table>
<thead>
<tr>
<th></th>
<th>Cefpodoxime</th>
<th>Ceftriaxone</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n = 44</td>
<td>n = 41</td>
<td>n = 85</td>
</tr>
<tr>
<td><strong>Bacteriologic evaluation</strong></td>
<td></td>
<td></td>
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<tr>
<td>Assessable patients with initial pathogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eradication</td>
<td>30 (100%)</td>
<td>21 (100%)</td>
<td>51 (100%)</td>
</tr>
<tr>
<td>Intention-to-treat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eradication</td>
<td>39 (88.6%)</td>
<td>31 (75.6%)</td>
<td>70 (82.4%)</td>
</tr>
<tr>
<td>Not assessable</td>
<td>5 (11.4%)</td>
<td>10 (24.4%)</td>
<td>15 (17.6%)</td>
</tr>
<tr>
<td>Assessable patients with single pathogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eradication</td>
<td>17 (100%)</td>
<td>15 (100%)</td>
<td>32 (100%)</td>
</tr>
<tr>
<td>Assessable patients, multiple pathogens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eradication</td>
<td>13 (100%)</td>
<td>6 (100%)</td>
<td>19 (100%)</td>
</tr>
<tr>
<td><strong>Clinical evaluation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cured</td>
<td>20 (60.6%)</td>
<td>15 (57.7%)</td>
<td>35 (59.3%)</td>
</tr>
<tr>
<td>Improved</td>
<td>8 (24.2%)</td>
<td>6 (23.1%)</td>
<td>14 (23.7%)</td>
</tr>
<tr>
<td>Failed</td>
<td>5 (15.2%)</td>
<td>5 (19.2%)</td>
<td>10 (16.9%)</td>
</tr>
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</table>
Patients in the cefpodoxime group who had multiple pathogens had a similar percentage of clinical failure compared to patients in this group with a single pathogen; 2 of 13 patients (15.4%) with multiple pathogens were clinical failures versus 2 of 17 patients (11.8%) with a single pathogen. Among the 15 patients in the ceftriaxone group with a single pathogen, 3 (20%) were clinical failures. There were no clinical failures among patients in this group with multiple pathogens. Among patients with a single pathogen, the clinical response rates for cure and improvement were higher in the cefpodoxime group than in the ceftriaxone group; this difference was not tested statistically.

In the entire intention-to-treat population, clinical failure was not associated with severity of illness. Overall, there were 12 cases with failure and 73 cases with cure, improvement, or inability to assess. Twenty-one of the 73 non-failures were sicker patients (Fine class 4 or 5), but only one of the 12 failures was in either of these classes. The lack of a link between clinical failure and more severe illness also was seen in both the cefpodoxime and ceftriaxone subgroups. Among the cefpodoxime patients, 1 of 6 failures and 9 of 38 non-failures were in class 4 or 5. Among the ceftriaxone patients, none of the 6 failures and 12 of the 35 non-failures were in class 4 or 5.

Clinical Failures
No single explanation emerged to account for the 12 clinical failures among the 85 patients in the intention-to-treat group. The question of reduced susceptibility of pneumococcus to β-lactams arose in two patients. One was a ceftriaxone patient with a sputum pneumococcus moderately susceptible to that drug who initially did well. Fever, chills, and malaise on days 6 and 7 prompted discontinuation of study drug, but the role of resistant pneumococcus is suspect considering that the EOT cultures of sputum and blood were negative. Another ceftriaxone patient had resistant pneumococcal bacteremia. After 3 days of increasing tachypnea and dyspnea with persistent fever, he was removed from study therapy; however, the negative EOT blood cultures (sputum cultures were not obtained) make it questionable to assign the failure to resistant pneumococcus. In addition, two patients had susceptible pneumococci in pretherapy sputum but did not improve clinically. Again, the role of pneumococcus in explaining the failure is uncertain since both patients had negative EOT blood cultures. One patient, given ceftriaxone, had a negative sputum culture at the end of therapy; the other, given cefpodoxime, did not have an EOT sputum culture. Resistance may help explain the failure of a cefpodoxime patient with sputum Pseudomonas aeruginosa who had a lung abscess.

In two patients, one from each treatment group, clinical failure occurred in the absence of an identified pretherapy sputum or blood pathogen. EOT cultures also failed to identify pathogens, raising the question of an atypical pathogen.

Three other cefpodoxime patients had susceptible organisms in pretherapy sputum specimens but failed to improve. One had K. pneumoniae, one had H. influenzae and Enterobacter cloacae, and the third had three organisms: H. influenzae, S. pneumoniae, and Streptococcus equisimilis. In none of these cases, however, was a pretherapy pathogen isolated on EOT cultures.

Diarrhea played a role in failure of two ceftriaxone patients. A patient from whom a susceptible Haemophilus haemolyticus was isolated from pretherapy sputum had a good response of pneumonia, requiring no additional antibiotic therapy after 6 days, but was classified as a side effect failure because diarrhea dictated the decision to stop the study drug. Another, with no initial pathogen, failed to improve after 10 days’ therapy, but EOT sputum culture was negative and EOT blood culture was not obtained.

Clinical Observation Changes
Cough, dyspnea, and sputum production decreased in most patients regardless of therapy. Patients were not required to have a final chest radiograph if infiltrates were clear on a previous chest radiograph. Of the 30 patients who had a chest radiograph at the final follow-up visit, the presence of pulmonary infiltrates resolved in 9 patients in the cefpodoxime group and 8 patients in the ceftriaxone group. Five patients in each treatment group showed improvement. Three patients in the cefpodoxime group had no change in pulmonary infiltrates.

Long-Term Follow-up
Fifty-nine patients returned for a long-term follow-up visit 2 to 4 weeks after cessation of therapy; 3 of 33 patients in the

<p>| Table 2. Pathogen Distribution and Eradication Rates, Most Common Pathogens |</p>
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Cefpodoxime</th>
<th>Ceftriaxone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td>18/18 100</td>
<td>9/9 100</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>10/10 100</td>
<td>6/6 100</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>4/4 100</td>
<td>2/2 100</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>3/3 100</td>
<td>2/2 100</td>
</tr>
<tr>
<td>Haemophilus parainfluenzae</td>
<td>3/3 100</td>
<td>2/2 100</td>
</tr>
</tbody>
</table>
Cefpodoxime group and 1 of 26 patients in the ceftriaxone group had nonassessable long-term follow-up data. Of the assessable pathogens (41 in the cefpodoxime group and 26 in the ceftriaxone group), there was no recurrence between EOT and long-term follow-up.

Recurrence of clinical symptoms of infection at the long-term follow-up for assessable patients with assessable response was similar in the two treatment groups, although this result was not tested statistically. In the cefpodoxime group, 1 of 17 patients (5.9%) had a recurrence of clinical symptoms, while none of the patients in the ceftriaxone group had recurrence of clinical symptoms. There were no superinfecting organisms in either treatment group.

**Safety**

Data from all 85 treated patients were evaluated for safety. Twenty of the 44 patients (45.5%) in the cefpodoxime group and 19 of the 41 patients (46.3%) in the ceftriaxone group experienced adverse events. In the cefpodoxime group, 31 (79.5%) events were classified as mild, 5 (12.8%) as moderate, and 3 (7.7%) as severe. In the ceftriaxone group, 23 (59.0%) events were classified as mild, 13 (33.3%) as moderate, and 3 (7.7%) as severe. There were no statistically significant differences between treatment groups with respect to the number of patients reporting at least one digestive event.

In 5 of 44 patients (11.4%) in the cefpodoxime group and 9 of 41 patients (22.0%) in the ceftriaxone group, adverse events were considered drug related. The most common drug-related adverse event was diarrhea, which was reported only in the ceftriaxone group (6 patients) and was a statistically significant finding \((P = 0.0262)\). Four patients in the cefpodoxime group reported serious adverse events; 3 were judged to be unrelated to the study medication. A case of severe colitis 3 days after cefpodoxime was discontinued was considered related to the study medication; the patient recovered without residual effects. Three patients in the ceftriaxone group experienced at least 1 serious adverse event; all were judged to be unrelated to the study medication. Two patients from each treatment group died (1 each on days 4, 5, 13, and 31 after treatment discontinuation). None of the deaths were considered related to the study medication.

Adverse events leading to discontinuation in the cefpodoxime group were moderate abscess (unrelated to study drug), moderate pruritus (drug related), and mild pleural effusion (unrelated to study drug). Adverse events leading to discontinuation in the ceftriaxone group were mild diarrhea (drug related) and severe acute respiratory distress syndrome (unrelated to study drug).

**Discussion**

We found that oral cefpodoxime 200 mg twice daily is as effective as parenteral ceftriaxone 1 g once daily in eradicating bacterial pathogens in carefully selected patients with CAP and in achieving favorable clinical outcomes in these patients. Adverse events were mild and consistent with those of other third-generation cephalosporins [22,23]. Of note is the significantly lower frequency of diarrhea seen in the cefpodoxime group. The lower incidence of diarrhea with cefpodoxime may be related to its primarily renal route of elimination, compared with that of ceftriaxone, which is substantially biliary. The percentage of ceftriaxone recovered in the bile during constant infusion varies from 11% to 65% [23].

Our study population resembled other pneumonia populations. The median age of our study population was 66 years, which is consistent with the age of most patients with CAP [24]. The most common pathogens isolated in our study were *S. pneumoniae* and *H. influenzae*, reflecting the typical bacterial pathogens encountered in CAP [1,24]. *S. pneumoniae* is the most common pathogen in nearly all studies of hospitalized adults with CAP [1].

The most important limitation of our study was its small sample size (85 patients). This limited its power to detect differences between the 2 treatment groups. However, our study is the first double-blind comparison of oral and parenteral antibiotic therapy in hospitalized patients with CAP who had to meet strict sputum quality criteria for admission to the study. Thus, it complements studies with less rigorous designs that support a role for initial oral therapy in the treatment of CAP requiring hospitalization.

In an era of changing criteria for hospitalization, some may question whether our patients, although hospitalized, were very sick. We excluded seriously ill patients, including those with respiratory failure, and included mostly patients in Fine risk classes 3 and 4. Fine recognized, however, that the decision to hospitalize must be made on an individual basis, citing examples of patients with low risk scores for whom hospitalization is appropriate.

Our use of the Fine classification system was retrospective and is limited by the modifications we made: we substituted creatinine abnormalities for BUN abnormalities, regarded patients with no oxygen measurements as having measurements in the normal range, and were unable to assign points for nursing home status or serum sodium level. However, these factors constitute only a small number of the measurements used to calculate risk, and our modifications would have tended to lower the risk scores of our patients. Thus, our modified risk classification system was useful in determining the severity of illness in our study population and can allow other physicians to compare their patients with those enrolled in the study.

An additional limitation of our study is the increase in pathogen resistance that has developed in the United States since we enrolled our first patient in 1991. Indeed, the most common reason for exclusion from efficacy analysis in our
study was resistant pathogens. It is possible that our treat-
ment regimens will not be effective against the more resis-
tant set of pathogens emerging at the dawn of the new mil-
leennium. In some areas of the United States, more than 25% 
of *S. pneumoniae* isolates are penicillin-resistant [1]. Resis-
tance to trimethoprim/sulfamethoxazole, macrolides, and 
cephalosporins also is increasing. However, laboratory 
reports of in vitro resistance may, in fact, be irrelevant to the 
treatment of pneumonia. The authors of the IDSA guidelines 
were unaware of even 1 clinical failure of penicillin treat-
ment for pneumococcal pneumonia that had been ascribed 
to penicillin resistance and were skeptical of the clinical rele-
ance of in vitro pneumococcal resistance patterns [4]. Con-
sequently, β-lactams, such as cefpodoxime and ceftriaxone, 
may retain their usefulness in treating pneumonia despite 
laboratory reports of nonsusceptibility.

Many clinicians prefer giving empiric antimicrobials 
effective against atypical pathogens [4]. Because this study 
used only cephalosporins and because cephalosporins do 
not provide this coverage, the relevance of this study may 
seem limited. However, among the 85 patients, we encoun-
tered only 2 in whom a clinical failure occurred in a context 
that suggested a role for an atypical pathogen.

Our work outlines several directions for further explo-
ration. Initial oral therapy deserves consideration in part 
because of cost considerations. Studies of early conversion 
from parenteral to oral therapy have demonstrated cost sav-
ings [2,18,25,26]. We suggest that oral therapy be considered 
for initial treatment, not just as step-down therapy after initial 
parenteral therapy. Also, morbidity and mortality studies and 
cost-effectiveness analyses might prove of interest when an 
exclusively oral antimicrobial regimen is considered.

It would be valuable to repeat our study in a larger popu-
lation focusing on patient-selection criteria, such as those 
described by Fine et al [21], to determine which subpopula-
tions of patients requiring hospitalization for CAP are the best 
candidates for initial oral therapy. Proven patient-selection 
criteria would help clinicians in choosing oral versus par-
enteral antimicrobial therapy.

The relevance of resistance remains of interest. Future stud-
ies might monitor resistance to any oral antimicrobial chosen.

**References**

18. Hendrickson JR, North DS. Pharmacoeconomic benefit of


