Sequential Therapy With Cefuroxime Followed by Cefuroxime Axetil in Community-Acquired Pneumonia*

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Study objectives: To compare the efficacy of two sequential therapy regimens of IV cefuroxime followed by oral cefuroxime axetil for the treatment of community-acquired pneumonia (CAP). Design: Prospective, multicenter, randomized, open-label, parallel-group study. Setting: Sixty-six centers in 11 countries (Belgium, Canada, Czech Republic, Germany, Hungary, Ireland, Israel, Poland, Portugal, South Africa, and the United Kingdom). Patients: Six hundred thirty-six adults with CAP requiring hospitalization and initial IV antibiotic treatment. Interventions: Cefuroxime, 1.5 g IV tid or bid for 48 to 72 h followed by oral cefuroxime axetil, 500 mg bid for 7 days. Measurements and results: For clinically evaluable patients, the clinical response rates were equivalent for cefuroxime tid and bid groups posttreatment (cure/improvement, 79% and 84%, respectively) and at follow-up (maintained cure, 87% and 82%, respectively). All signs and symptoms of pneumonia showed improvement at the time of switch from IV to oral therapy. A total of 111 pathogens were isolated, the most common being Streptococcus pneumoniae (23%), Haemophilus influenzae (18%), and Enterobacteriaceae (15%). Bacteriologic clearance was obtained posttreatment in 47 of 49 and 36 of 42 of bacteriologically evaluable patients in the cefuroxime tid and bid groups, respectively. Both regimens were well tolerated with a low incidence of drug-related adverse events, the most common being GI. Conclusions: Twice daily IV cefuroxime followed by oral cefuroxime axetil is a simple and effective sequential therapy regimen for the treatment of CAP. It offers potential cost savings and can replace the current tid regimen in this indication. (CHEST 1997; 112:406-15)

Key words: antibiotic treatment; cefuroxime; cefuroxime axetil; community-acquired pneumonia; sequential therapy

Abbreviations: CAP=community-acquired pneumonia; CI=confidence interval; MIC=minimum inhibitory concentration

Community-acquired pneumonia (CAP) is a common illness causing substantial morbidity and mortality, particularly among the elderly. In the United States, it is estimated that the annual incidence of CAP is 2 to 4 million adults, with more than 700,000 hospitalizations and about 60,000 deaths.

Although only 10 to 20% of patients with CAP require hospitalization, those who are admitted to hospital usually need IV antibiotic therapy. Initial treatment is commonly empiric, with a broad-spectrum antibiotic, because the pathogen(s) responsible for the infection is usually unknown at the moment of diagnosis. Parenteral therapy ensures that therapeutic concentrations of the antibiotic are achieved rapidly at the site of infection at the time when the bacterial load is highest. In patients who respond to the antibiotic therapy, symptoms frequently begin to resolve within 48 to 72 h. Nevertheless, IV therapy is usually continued for 10 days to ensure complete eradication of pathogens from the primary site of infection and to prevent recurrent infection.

IV therapy is costly and requires continued hospitalization. In recent years, efforts to reduce costs have led to the introduction of sequential therapy, in
which a relatively short course (2 to 3 days) of parenteral therapy is followed by a switch to oral treatment.\textsuperscript{5-11} This approach not only provides significant cost savings, but also decreases the risk of developing nosocomial infections and adverse events associated with IV therapy such as phlebitis. Furthermore, an early switch to oral therapy improves patient comfort and mobility, and may allow for an earlier discharge from hospital with attendant cost savings.\textsuperscript{12,13} Several studies have confirmed the cost-effectiveness of sequential therapy.\textsuperscript{4,10-12,14,15}

A number of antibiotics have been used in sequential therapy\textsuperscript{4,6,12} and ideally, oral and injectable forms of the same antibiotic should be used.\textsuperscript{13} Cefuroxime is a well-characterized second-generation cephalosporin and is currently the only β-lactamase stable cephalosporin available in both oral and parenteral formulations; it is active against the most common pathogens associated with CAP, including \textit{Streptococcus pneumoniae}, \textit{Haemophilus influenzae}, and \textit{Moraxella catarrhalis}.\textsuperscript{16,17}

Cefuroxime axetil is an orally bioavailable prodrug, which undergoes de-esterification to cefuroxime in the intestinal mucosa.\textsuperscript{18} Randomized multicenter studies have shown that sequential therapy with IV cefuroxime followed by oral cefuroxime axetil is as effective as a full course of IV cefuroxime therapy in CAP,\textsuperscript{19} or amoxicillin plus clavulanic acid in the treatment of lower respiratory tract infection.\textsuperscript{20}

The rationale for this study, that bid and tid IV cefuroxime may be equivalent in terms of efficacy, is based on the pharmacodynamics of cefuroxime. The bactericidal activity of cefuroxime and other β-lactam antibiotics is dependent on the length of time that plasma levels exceed the minimum inhibitory concentrations (MICs) of likely pathogens, which, in CAP, are ≤2 mg/L.\textsuperscript{16,21} Furthermore, maximum bactericidal activity is obtained when this time period approaches 60 to 70% of the dosing interval, with a minimum period of 30 to 40% of the dosing interval necessary to produce a bacteriostatic effect.\textsuperscript{22} It was estimated that, in immunocompetent patients, dosing regimens that maintained plasma concentrations of cephalosporins above the MIC for about 35 to 40% of the dosing interval would provide therapeutic efficacy. Using pharmacokinetic data obtained from healthy subjects after administration of the current standard doses of cefuroxime, 1.5 g IV tid and bid, and cefuroxime axetil, 500 mg bid,\textsuperscript{23,24} it was calculated that the percentage of the dosing interval during which the serum levels of cefuroxime exceed the MIC value of 2 mg/L was 94%, 63%, and 35%, respectively.

Levels of cefuroxime in the serum, sputum, and bronchial tissues also exceed the MICs of most common respiratory pathogens for up to 8 h after dosing with either cefuroxime sodium or cefuroxime axetil.\textsuperscript{23,25-27} Therefore, both IV dosing regimens used in the present study are theoretically equally effective, and the bid oral dosing with cefuroxime axetil would provide sufficient cover to maintain the bacteriostatic effect while simplifying the sequential therapy regimen.

The aims of the present study were to compare the efficacy, safety, and tolerance of two cefuroxime sequential therapy regimens: cefuroxime, 1.5 g administered IV bid or tid followed by oral cefuroxime axetil, 500 mg bid, in the treatment of patients hospitalized with CAP.

\section*{Materials and Methods}

This was a prospective, multicenter, randomized, open-label, parallel-group study conducted at 66 centers in 11 countries (Belgium, Canada, Czech Republic, Germany, Hungary, Ireland, Israel, Poland, Portugal, South Africa, and the United Kingdom). Regulatory approval was obtained where required and the study was approved by local ethics committees in each country. The study was conducted in accordance with the Declaration of Helsinki (Hong Kong revision, 1989), and patients gave their written informed consent before participating in the study.

\subsection*{Patients}

Male or female patients aged 18 years or older with CAP requiring hospitalization and initial treatment with IV antibiotics were recruited. To be eligible to enter the study, patients had to have radiologic evidence of pneumonia, together with one of the following: fever (≥37.5°C); WBC count ≥12×10^3/L with immature forms; auscultatory findings consistent with pneumonia; and pleuritic pain. Patients were excluded if they had any of the following: acute exacerbations of chronic bronchitis or hospital-acquired pneumonia; if they were hypersensitive or allergic to cephalosporins or penicillins; if they had received systemic antimicrobial therapy in the previous 48 h, unless there was no clinical response; women who were pregnant or lactating; if they suffered from bronchial carcinoma, pulmonary tuberculosis or atypical pneumonia, or were immunocompromised (all based on the clinical judgment of the investigator); if they had marked renal impairment (creatinine clearance <20 mL/min), terminally ill, or required assisted ventilation; or had pathogens known to be resistant to cefuroxime. Patients were not allowed to receive other antibiotics during the study.

\subsection*{Treatment and Assessments}

Participants underwent a pretreatment clinical assessment within the 24 h before commencing study treatment, including a chest radiograph. The severity of the infection was classified by the investigator according to his clinical judgment. A sample of sputum was obtained if possible for bacteriologic culture and susceptibility testing to cefuroxime and ampicillin using the disk diffusion method. A Gram's stain confirmed the validity of each sputum sample, defined as containing <10 epithelial cells and >25 leukocytes per low-power field. Pathogens were also tested to identify β-lactamase-producing organisms.

Patients were randomly assigned to treatment with either cefuroxime sodium, 1.5 g IV tid for 48 to 72 h (six to nine doses)
treatment group and their resolution laboratory evaluation of or therapy), during organism date of events (elimination or therapy), superinfection producing signs and collection of the date of the posttreatment assessment of the patients. Patients with clinical failure or failure to respond to treatment were classified as maintained cure, relapse (recurrence of clinical signs and symptoms of initial infection), or unevaluable. Patients who were clinical failures or unevaluable posttreatment had their response carried forward at follow-up. Patients’ signs and symptoms of pneumonia present pretreatment and their resolution at the interim and posttreatment assessments were compared for the two treatment groups.

Bacteriologic response was rated as clearance (absence of the original pathogen[s] in the posttreatment specimen), partial clearance (elimination of at least one of multiple pathogens), failure (persistence of the original pathogen[s]), colonization (isolation of a new organism during up to 2 days posttreatment, not requiring further therapy), superinfection (isolation of a new organism during up to 2 days posttreatment, requiring further therapy), or unevaluable. Bacteriologic clearance also included the absence of posttreatment sputum sample due to clinical cure.

Safety and tolerability were assessed by monitoring all adverse events reported during the study. For each adverse event, the date of onset, severity, outcome, action taken, and the investigator’s opinion of the possible relationship to study medication was recorded. Blood samples were collected before treatment and at the end of treatment (if pretreatment values abnormal) for laboratory evaluation of hemoglobin, WBC, and differential cell counts and, where possible, any evidence of immature forms.

**Statistical Analysis**

Using the assumption that a clinical cure/improvement rate of 80% would be achieved by both treatment regimens, it was estimated that a sample size of 254 evaluable patients in each treatment group would be required to demonstrate that the treatment difference was ≤10%, with a significance level of 10% and 80% power. A treatment difference of ≤10% was not considered to be clinically relevant. To allow for 15% unevaluable, a total of 592 patients were required to enter the study (296 in each treatment group).

All patients randomized to treatment who received at least one dose of study medication were included in the safety analysis (intent-to-treat population). Patients were clinically evaluable if they met the entry criteria and did not have a major protocol violation. The bacteriologically evaluable population consisted of those patients who were clinically evaluable, had a pretreatment pathogen isolated that was not resistant to cefuroxime, and a posttreatment sputum sample (unless specimen collection was impossible due to clinical cure). Clinical response was analyzed for the intent-to-treat population and the clinically evaluable population, and the results of the clinically evaluable population are presented in this article.

The two treatment regimens were considered clinically equivalent if the 90% confidence interval (CI) for the difference in the proportion cured/improved posttreatment (or the proportion maintained cure/improvement at follow-up) lay within ±10%. The CI was calculated using the normal approximation to the binomial distribution, and homogeneity of response across countries was assessed using the Breslow-Day test.

The proportion of patients who withdrew from the study were compared between treatments using the Mantel-Haenszel χ² test without continuity correction, and stratified by country to ensure that withdrawal from the study was independent of treatment.

**RESULTS**

**Patient Demographic and Baseline Characteristics**

A total of 636 patients entered this study and were randomized to treatment: 310 in the cefuroxime tid group and 326 in the cefuroxime bid group. The two treatment groups were demographically well matched as summarized in Table 1. The mean age of the patients was 59.9 years (range, 18 to 102 years) and 54% were smokers or ex-smokers. Mean duration of infection before entry into the study was 6.5 days and most patients had a moderate (72%) or severe (27%) infection: only 1% presented with a mild infection. A total of 143 patients (22%) had received antibiotic therapy in the 48 h before entering the study; the three most common antibiotics used were amoxicillin (4%), amoxicillin plus clavulanic acid (4%), and erythromycin (3%). Most patients (81%) were taking concurrent medications for concomitant illnesses; cardiovascular and respiratory conditions were most prevalent.

Before treatment, patients had a mean body temperature of 38.2°C, 598 of 636 (94%) had cough present, 366 of 636 (55%) had purulent or mucopurulent sputum, 603 of 636 (94%) had wheeze and/or crepitations, and 296 of 636 (47%) had pleuritic pain. Most patients presented with bronchopneumonia (338/636, 53%) or lobar pneumonia (257/636, 40%) as diagnosed using chest radiograph. There were nine cases of pleuropneumonia and six patients had a normal chest radiographic that excluded them from the clinically evaluable population.

Bacteriologic assessment was not a primary end point for the study. In both treatment groups, positive pretreatment sputum or blood samples were obtained from <20% of patients reflecting the common experience in pneumonia patients. A total of 111 pathogens were isolated from 91 patients (16 patients had more than one pathogen, 12 patients
Table 1—Demographic and Baseline Characteristics of Patients in the Cefuroxime tid and Cefuroxime bid Group (Intent-to-Treat Population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cefuroxime tid Group (n=310)</th>
<th>Cefuroxime bid Group (n=326)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F, %</td>
<td>59/41</td>
<td>57/43</td>
</tr>
<tr>
<td>Age, yr, mean±SD (range)</td>
<td>59.6±19.9 (18-102)</td>
<td>60.3±18.4 (18-101)</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>Black</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Smoking history, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>42</td>
<td>50</td>
</tr>
<tr>
<td>Current/ex-smoker</td>
<td>58</td>
<td>50</td>
</tr>
<tr>
<td>Chest radiograph, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar pneumonia</td>
<td>42</td>
<td>39</td>
</tr>
<tr>
<td>Bronchopneumonia</td>
<td>53</td>
<td>54</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Duration of infection, d, mean±SD</td>
<td>6.4±5.8</td>
<td>6.5±6.4</td>
</tr>
<tr>
<td>Severity of infection, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Moderate</td>
<td>70</td>
<td>74</td>
</tr>
<tr>
<td>Severe</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>Antibiotic therapy in the past</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>48 h, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concurrent medication, %</td>
<td>81</td>
<td>81</td>
</tr>
</tbody>
</table>

had two pathogens, and four patients had three pathogens). The most common pathogens were *S pneumoniae* (23%), *H influenzae* (18%, of which 20% were β-lactamase producers), *Enterobacteriaceae* (15%), other *Streptococcus* species (14%), *Staphylococcus* species (5%), and *M catarrhalis* (5%, of which 100% were β-lactamase producers). The distribution of pretreatment pathogens is shown in Figure 1. There was a similar distribution of pathogens in the two treatment groups. Of the isolates tested, 16 (11%) were resistant to cefuroxime.

A total of 93 of 310 (30%) patients in the cefuroxime tid group and 92 of 326 (28%) patients in the cefuroxime bid group withdrew from the study (p=0.538) for similar reasons in each treatment group. The main reason (15%) for withdrawal from the study was that the patient required IV treatment for more than the allowed 72 h, which was considered a failure of the treatment regimen.

Most patients in the clinically evaluable population received IV therapy for 72 h; 78% patients in the cefuroxime tid group and 82% patients in the cefuroxime bid group. Twelve percent of patients in the cefuroxime tid group and 11% patients in the cefuroxime bid group received IV therapy for 48 h. A total of 21% and 22% patients in the cefuroxime tid and bid groups, respectively, were discharged from hospital to complete their oral treatment at home.

**Clinical Response**

The clinical responses at posttreatment and at follow-up for the clinically evaluable population in both treatment groups are given in Table 2 and Figure 2. The number of patients cured or improved posttreatment was 204 (79%) in the cefuroxime tid group and 222 (84%) in the cefuroxime bid group. The 90% CIs for the difference in clinical response between the two treatment groups (−11%, 0%) were just outside the limits set for equivalence. The difference was in favor of cefuroxime bid which can, therefore, be regarded as being as effective as the cefuroxime tid regimen. At the follow-up assessment 14 to 28 days after completion of oral therapy, cure was maintained in 178 of 204 (87%) patients in the cefuroxime tid group and 183 of 222 (82%) in the cefuroxime bid group.

Of the 377 patients who remained cured at follow-up and who had a chest radiograph performed, 81% (150 and 155 patients in the cefuroxime tid and bid groups, respectively) of patients demonstrated clearance of the radiologic evidence of their pneumonia. Of the 26 patients who had a clinical relapse at follow-up, 5 patients in the cefuroxime tid group and 9 patients in the cefuroxime bid group retained evidence of pneumonia on radiograph.

![Figure 1. The distribution of pretreatment pathogens.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21749/ on 06/26/2017)
Table 2—Clinical Response Posttreatment and at Follow-up in the Cefuroxime tid Group and the Cefuroxime bid Group (Clinically Evaluable Population)

<table>
<thead>
<tr>
<th>Clinical Response</th>
<th>Cefuroxime tid</th>
<th>Cefuroxime bid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posttreatment</td>
<td>(n=259)</td>
<td>(n=264)</td>
</tr>
<tr>
<td>Cure</td>
<td>144 (56%)</td>
<td>147 (56%)</td>
</tr>
<tr>
<td>Improvement</td>
<td>60 (23%)</td>
<td>75 (28%)</td>
</tr>
<tr>
<td>Failure</td>
<td>55 (21%)</td>
<td>42 (16%)</td>
</tr>
<tr>
<td>Follow-up*</td>
<td>(n=204)</td>
<td>(n=222)</td>
</tr>
<tr>
<td>Maintained cure</td>
<td>178 (87%)</td>
<td>183 (82%)</td>
</tr>
<tr>
<td>Relapse</td>
<td>9 (4%)</td>
<td>16 (7%)</td>
</tr>
<tr>
<td>Unevaluable</td>
<td>17 (8%)</td>
<td>23 (10%)</td>
</tr>
</tbody>
</table>

*Clinical response at follow-up for patients cured/improved at posttreatment.

When clinical response was analyzed by the severity of infection pretreatment, all seven patients with mild infection were cured/improved posttreatment. In the cefuroxime tid group, 151 of 179 (84%) patients with moderate infection and 50 of 77 (65%) patients with severe infection were cured/improved posttreatment. In the cefuroxime bid group, 171 of 196 (87%) patients with moderate infection and 47 of 64 (73%) patients with severe infection were cured/improved posttreatment.

Resolution of Signs and Symptoms

Resolution of the signs and symptoms of pneumonia for the clinically evaluable population, as shown in Figure 3, was similar in both treatment groups.

Compared with pretreatment values, the proportion of patients with the signs and symptoms of pneumonia (cough, dyspnea, auscultatory findings, pleuritic pain, purulent or mucopurulent sputum, and fever) had decreased at the time of switch from IV to oral therapy (interim assessment) and were decreased even further at the end of oral treatment.

For patients who had pretreatment and posttreatment samples taken, pretreatment WBC levels were high in 131 of 184 (71%) patients in the cefuroxime tid group and 141 of 202 (70%) patients in the cefuroxime bid group. Posttreatment, the proportion of patients with high WBC levels had decreased to 53 of 184 (29%) and 52 of 202 (26%) in the cefuroxime tid and bid groups, respectively (Fig 3).

Bacteriologic Response

The posttreatment bacteriologic response for the bacteriologically evaluable population of patients in both treatment groups is shown in Figure 4. Infections in 47 of 49 (96%) patients in the cefuroxime tid group and 36 of 42 (86%) patients in the cefuroxime bid group were resolved posttreatment. The difference in the proportion cleared between the two treatment groups was 10% (90% CI=0%, 20%), but the analysis lacked sufficient power to demonstrate bacteriologic equivalence.

In the cefuroxime tid group, two patients had pathogens present posttreatment; one patient had colonization with H influenzae and one patient had bacteriologic failure. In the cefuroxime bid group, six patients had pathogens present posttreatment, two patients had colonization (one with Enterobacter cloacae and the other with Escherichia coli and Klebsiella pneumoniae), one patient had partial clearance, and three patients had bacteriologic failure.

Of the 59 pretreatment pathogens isolated in the cefuroxime tid group, 35 (59%) were eradicated, 1 Enterobacteriaceae (2%) persisted, and 23 (39%) were unevaluable posttreatment. In the cefuroxime bid group, 38 of 52 (73%) pathogens were eradicated, 4 of 52 (8%) persisted (of which 4% were H influenzae, 2% H parainfluenzae, and 2% K pneumoniae), and 10 of 52 (19%) were unevaluable posttreatment. All patients with persistent pathogens posttreatment were clinically cured/improved.

Patients with resistant pretreatment pathogens or pathogens with unknown susceptibility were excluded from the bacteriologically evaluable population. Of the 14 patients with resistant pathogens, 9 (64%) were clinically cured/improved posttreatment, as were 26 of 31 (84%) patients with pathogens of unknown susceptibility.
Figure 3. Resolution of the signs and symptoms of CAP (cough, dyspnea, auscultatory findings, sputum, pleuritic pain, and WBC count).
Adverse Events

Both treatment regimens were well tolerated by patients with only 45 of the 636 (7%) patients in the intent-to-treat population reporting adverse events considered to be drug-related (39 events during treatment and 6 events posttreatment). During the treatment period, drug-related events were predominantly GI (26/39), which included abdominal discomfort, nausea and vomiting, dyspepsia, or diarrhea, which are all commonly associated with antibiotic treatment. The posttreatment drug-related events were again mainly GI (three events), but also abnormal WBC or platelet counts (two events) and one event of vaginal inflammation.

Twenty-four patients withdrew from the study due to an adverse event. There was no commonly reported event leading to withdrawal and events were evenly distributed between the two treatment groups. Serious adverse events reported were as expected with such an elderly population and were mostly cardiovascular or respiratory in nature, and eight patients were diagnosed as having a carcinoma. Two of the serious adverse events were considered by the investigator to be drug-related; these were an allergic reaction and an episode of hematemesis. Fourteen (2%) patients died during the study, but none of the deaths were considered related to the study medication. Causality was believed to be related to the underlying cardiovascular or cardiorespiratory failures/disorders (13 patients) and to the severity of the infection in one elderly patient.

Discussion

The efficacy of sequential cefuroxime therapy has been established in several randomized comparative studies. Sequential therapy with IV cefuroxime tid followed by oral cefuroxime axetil has equivalent efficacy to a full IV course of cefuroxime,10 IV cefotaxime,9 cefotiam,31 or amoxicillin plus clavulanic acid20 in patients with lower respiratory tract infections. Two noncomparative studies have indicated that sequential therapy with cefuroxime administered IM twice daily followed by oral cefuroxime axetil may be effective in community-acquired lower respiratory tract infections.32,33

One of the major advantages of cefuroxime over other cephalosporins is that it is available in IV and oral preparations; therefore, clinicians can change the route of drug administration without altering the spectrum of antibacterial activity. This study has shown that the IV treatment phase can be reduced from tid to bid dosing without loss of efficacy. A bid regimen is simple and more convenient, and patients are more compliant with less frequent dosing regimens.13 Some oral cephalosporins or penicillins have a poor bioavailability, a short plasma half-life, and are, consequently, unsuitable for serious infections.6 Cefuroxime has an absolute bioavailability of 50 to 60% when taken with food,26 reaches peak serum concentrations of approximately 10 mg/L which remain above 1 mg/L for 8 h with cefuroxime axetil, 500 mg bid, in elderly patients with lower respiratory tract infections.26 Cefuroxime also penetrates well into sputum and the bronchial mucosa.12-27 and clearance is slower from the sputum than from the circulation. Cefuroxime thus achieves effective concentrations at the site of infection, which are maintained for sufficient periods to permit bid dosing.

Signs and symptoms of pneumonia often start to resolve within 48 to 72 h of commencing parenteral antibiotic therapy,3,4 and those patients who are responding can be switched to oral treatment without compromising their recovery. In the present study, >90% of patients were able to switch from IV to oral therapy within the 48 to 72 h time frame. Patients requiring continuation of the IV treatment after 72 h were removed from the study, as the treatment regimen was considered to have failed. Diagnosis of CAP requires specific and sensitive clinical markers that also allow the clinical condition of the patient to be easily assessed to determine the time to change from IV to oral treatment. A previous study in children with pneumonia suggested that resolution of fever and a reduction in WBC count were useful clinical markers in the decision-making process.34 Bartlett and Mundy1 recommend that parenteral therapy with second- or third-generation
cephalosporins should be continued until the patient has been afebrile for >24 h. In the present study, mean body temperature had normalized at the time of switch to oral therapy, and the proportion of patients with a high WBC count was greatly reduced posttreatment. In addition, the other clinical signs and symptoms of pneumonia were improved at the interim assessment. Other lower respiratory tract infections such as acute exacerbations of bronchitis, clear improvements in peak expiratory flow rate, dyspnea, and cough are apparent at the point of change to oral therapy and thus may serve as useful clinical markers for determining when to change to oral therapy.\(^\text{35}\)

Although chest radiographs are necessary to confirm a diagnosis of pneumonia and are important for evaluating severity of illness,\(^\text{1}\) they are not sensitive enough to be used as a determinant of when to change from IV to oral therapy.\(^\text{34}\) Moreover, radiographic changes occur more slowly than clinical responses.\(^\text{1}\) Radiologic response obtained in the present study was consistent with the clinical response.

In the present study, the high response rate and the very low relapse rate at follow-up suggest that there was sustained eradication of pathogens. A similarly low rate of relapse (3%) was reported in pneumonia patients in the cefuroxime sequential therapy study of Brambilla et al.\(^\text{20}\)

The number of sputum and blood samples that yielded isolates was too small to demonstrate bacteriologic equivalence between the two treatment regimens, but such a low number of pathogens isolated is typical of pneumonia studies. Nevertheless, almost all of the pathogens isolated were cleared posttreatment, and this is consistent with the results obtained in previous studies with cefuroxime.\(^\text{19,20}\)

A wide range of antibiotics is available for treatment of CAP, including penicillins, tetracyclines, cephalosporins, and fluoroquinolones.\(^\text{4,6,12}\) Since the causative pathogen is rarely known, initial therapy is empiric and is known to vary widely between different countries.\(^\text{1}\) Cefuroxime has a broad spectrum of antibacterial activity and is one of the more active cephalosporins against intermediate-resistant strains,\(^\text{16}\) such as \textit{S. pneumoniae}, for which there is a worldwide increase in the rates of resistance to penicillin and other commonly prescribed antibiotics.\(^\text{36}\) \textit{S. pneumoniae} accounted for almost one quarter of the pathogens isolated pretreatment in the present study and none of the isolates tested was resistant to cefuroxime.

In the present study, there was evidence of \(\beta\)-lactamase-producing isolates of \textit{H. influenzae} and \textit{M. catarrhalis}, the incidence of which is also increasing in many countries.\(^\text{37}\) Cefuroxime is highly active against these \(\beta\)-lactamase-producing strains that are resistant to ampicillin.\(^\text{38}\)

Therapy in patients with severe infections is initially given IV to rapidly achieve effective antibiotic concentrations in patients who may be febrile and unable to take oral therapy. Simpler treatment regimens and measures, which permit a reduction in the number of IV injections without loss of efficacy, may not only improve patient compliance but result in substantial cost savings in terms of drug costs, time spent dispensing, preparing, and administering IV therapy, and fewer days spent in hospital.\(^\text{12,13}\)

Recent estimates from the United States indicate that the average length of stay in hospital for patients with CAP is 7 days.\(^\text{2}\) One study from Israel found that sequential therapy with IV cefuroxime followed by oral cefuroxime axetil significantly reduced the average length of hospital stay from 7.3 to 4.6 days in patients with lower respiratory tract infections, compared with a historical control of a full course of IV therapy.\(^\text{30}\) This reduced length of hospital stay led to considerable cost savings, and it has been demonstrated that shorter duration of hospitalization is the major cost-saving factor in sequential therapy.\(^\text{10}\) Although economic issues were not addressed in this study, more than one in five patients were discharged from hospital to complete their oral therapy at home. This clearly represents potential cost savings.

Incidence studies have shown that more than half of the patients with CAP are elderly.\(^\text{2}\) This study included only adult patients, and the mean age of 60 years showed that many of the patients were elderly. Most patients also had other medical conditions requiring concomitant medications. Age and coexisting diseases are known to be poor prognostic factors for patients hospitalized with CAP, and mortality rates of 10 to 25% have been reported.\(^\text{1}\) Populations of elderly patients are growing worldwide and simpler, cost-effective dosing regimens are likely to become increasingly important.

In conclusion, the results of this study support the use of bid IV cefuroxime in sequential therapy for the treatment of patients hospitalized with CAP, thereby replacing the tid dosing regimen. This simple bid regimen of cefuroxime IV bid followed by a switch to oral cefuroxime axetil bid is simple, well tolerated, effective, and more convenient, can reduce the duration of hospitalization, and should provide further cost savings for hospitals.

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