

# Prospective Randomized Comparison of Cefepime and Cefotaxime for Treatment of Bacterial Meningitis in Infants and Children

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**Ninety infants and children were prospectively randomized to receive cefepime ( $n = 43$ ) or cefotaxime ( $n = 47$ ) for therapy of bacterial meningitis. The two treatment groups were comparable in terms of age, duration of illness before enrollment, history of seizures, clinical status on admission, and etiology. Six (7%) patients died—two treated with cefepime and four treated with cefotaxime. Clinical response, cerebrospinal fluid sterilization, development of complications, antibiotic toxicity, and hospital stay were similar for the two treatment regimens. Concentrations of cefepime in cerebrospinal fluid varied from 55 to 95 times greater than the maximal MIC required by the causative pathogens. Audiologic and/or neurologic sequelae were found in 16% of the cefepime-treated patients and 15% of the cefotaxime-treated patients examined 2 to 6 months after discharge. We conclude that cefepime is safe and therapeutically equivalent to cefotaxime for management of bacterial meningitis in infants and children.**

Currently, most centers in developed countries are using broad-spectrum cephalosporins as the initial empiric treatment of bacterial meningitis in infants and children (3, 6). The justifications for this approach include ease of administration, extraordinary activity against the usual meningeal pathogens, excellent safety profiles, rapidity of cerebrospinal fluid (CSF) sterilization, and efficacies comparable or superior to those of ampicillin and chloramphenicol, the regimen used previously as standard therapy.

Cefepime is a new broad-spectrum parenteral cephalosporin with in vitro activity similar to that of cefotaxime or ceftriaxone against the common meningeal pathogens *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis* and greater activity against *Enterobacter* species and *Pseudomonas aeruginosa* (10). Experience in adult patients indicates that cefepime is well tolerated and safe after intravenous administration.

The aim of the present study was to compare the safety and efficacy of cefepime with those of cefotaxime and to determine the pharmacokinetics of cefepime in CSF and plasma in infants and children with bacterial meningitis.

## MATERIALS AND METHODS

**Patients.** All infants and children (2 months to 15 years of age) with strongly suspected (i.e., clinical signs plus grossly abnormal CSF findings) or bacteriologically proven bacterial meningitis admitted to Hospital del Niño of Panama City, Panama, were eligible for the study. The study protocol was approved by the Review Board in Clinical Research of Hospital del Niño and by the Institutional Review Board of the University of Texas Southwestern Medical School at Dallas. An arbitrary sample size of approximately 100 patients was used.

After written informed consent was provided by the parents or legal guardians, the patients were allocated according to a list of randomized therapy assignments to receive either cefepime or cefotaxime. Patients with a history of allergy to beta-lactams, infection with a cephalosporin-resistant strain, renal or hepatic disease, or preexisting abnormalities of the central nervous system were excluded from this study.

**Drug administration.** Cefepime and cefotaxime were given intravenously in a dosage of 50 mg/kg of body weight every 8 and 6 h, respectively, for 7 to 10 days. Both antibiotics were infused in 15 to 20 min. In addition, all patients received

12 to 16 doses of 0.15 mg of dexamethasone per kg of body weight. The first dexamethasone dose was given 15 to 20 min before the first antibiotic dose.

**Bacteriologic studies.** Blood and CSF cultures were obtained from all patients on admission to the hospital and approximately 24 h later. All positive 24-h samplings were repeated daily until the samples became negative. The identification of bacterial isolates and Kirby-Bauer susceptibility testing were performed in Panama with standard validated techniques. Specimens were immediately sent to Bristol-Myers Squibb's microbiology laboratory to determine the MICs of cefepime and cefotaxime.

**Pharmacokinetics.** Blood and CSF samples were sent to Bristol-Myers Squibb's pharmacokinetics department to determine cefepime concentrations by means of a high-performance liquid chromatography-UV method. Various groups of five to seven patients each were chosen for pharmacokinetic studies at one of the following time intervals after cefepime administration: 30 min or 1, 2, 4, or 8 h.

**Efficacy evaluation.** The efficacies of the treatment regimens were evaluated by comparing sequelae and case-fatality rates, numbers of days of fever and meningeal signs, and numbers of days of positive cultures. The outcome of surviving patients was assessed by neurologic examinations during hospitalization, at discharge, and, if abnormal, at 2- to 6-month follow-up visits. Additionally, brain stem auditory responses and tympanometries were used to evaluate audiologic outcome and performed at discharge and, if abnormal, 2 to 6 months later. The degree of hearing loss was interpreted by an experienced audiologist (M.P.) as follows. An absence of response at less than 50 dB was considered a mild loss, an absence of response at 50 to 60 dB was considered a moderate loss, an absence of response at 70 to 90 dB was considered a severe loss, and an absence of response at >90 dB was considered a profound loss.

**Evaluation of safety.** In all patients, hematologic and renal and hepatic function tests were performed on admission, 4 to 5 days later, and at discontinuation of antimicrobial therapy. Patients were closely observed for the development of seizures after the first antibiotic dose, rash, phlebitis, diarrhea, fever, or *Candida* superinfection.

**Statistical analysis.** Results are expressed as means  $\pm$  standard deviations. Analysis of the data for statistically significant differences among the two treatment groups was performed with two-tailed chi-square and Fisher's exact tests for nominal measurements and by unpaired *t* or Mann-Whitney tests for parametric or nonparametric continuous variables, respectively. A difference was considered significant when  $P$  was  $\leq 0.05$ .

## RESULTS

From November 1991 through October 1993, 103 infants and children with bacterial meningitis were enrolled. Of these patients, 13 were excluded from the final analysis because a bacterial etiology was unlikely (11 patients) or a cephalosporin-resistant pathogen was isolated (i.e., two infants had *Listeria monocytogenes* isolated from CSF). Overall, 90 patients were evaluated, of whom 43 received cefepime and 47 received

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TABLE 1. Clinical and bacteriologic characteristics of patients on admission

Characteristic <sup>a</sup>	Result with:	
	Cefepime (n = 43)	Cefotaxime (n = 47)
Mean age (± SD [mo])	29.8 ± 34.7	22.8 ± 25.3
Median age	12	9
Mean no. of days (± SD) ill before admission	3.2 ± 3.0	3.7 ± 3.3
No. (%) of patients with convulsions before enrollment	13 (30)	12 (26)
No. (%) of patients with meningeal signs	33 (77)	27 (64)
Mean Todd score (± SD) for <i>H. influenzae</i> type b meningitis	3.0 ± 1.8	2.6 ± 1.7
No. (%) of patients with coma or stupor	4 (9)	5 (11)
No. (%) of patients with bacteremia	19 (44)	22 (47)
No. of patients infected with <sup>b</sup> :	35 (81)	41 (87)
<i>H. influenzae</i> (type b)	18	28
<i>N. meningitidis</i>	9	5
<i>S. pneumoniae</i>	7	3
<i>E. coli</i>	0	1
<i>Streptococcus agalactiae</i>	0	2
<i>Salmonella</i> sp.	0	1
<i>S. aureus</i>	1	0
<i>S. pyogenes</i>	0	1

<sup>a</sup> No significant differences between treatment groups were detected.

<sup>b</sup> All isolates were susceptible to both antibiotics. No penicillin-resistant pneumococci were identified.

cefotaxime. The two treatment groups were comparable regarding sex, age, duration of symptoms and/or presence of seizures before enrollment, and clinical condition on admission (Table 1). Forty-four (49%) patients (20 cefepime-treated patients and 24 cefotaxime recipients) had a history of previous antimicrobial therapy (mostly intramuscular penicillin or oral erythromycin).

**Bacteriology.** A bacterial pathogen was recovered from CSF in 76 (84%) of 90 patients. All patients with negative CSF cultures also had negative blood cultures. Simultaneous microbial recovery from blood cultures occurred in 41 (54%) of those 76 patients (23 of the 35 culture-negative patients had received prior antimicrobial therapy). All 14 children without a pathogen isolated had CSF findings strongly suggestive of a bacterial etiology (i.e., more than 3,000 leukocytes per mm<sup>3</sup>; protein, >150 mg/dl; glucose, <20 mg/dl).

*H. influenzae* type b was identified in 46 (61%) of 76 isolates, *N. meningitidis* was identified in 14 (18%) isolates, *S. pneumoniae* was identified in 10 (13%) isolates, and other bacteria were identified in 6 (8%) isolates. Pathogens were distributed

similarly in both treatment groups (Table 1). All bacteria were susceptible to both antibiotics; no penicillin-resistant pneumococci were identified in this study. MICs of cefepime and cefotaxime for *H. influenzae* were below or equal to 0.06 and 0.015 µg/ml, respectively; those for *N. meningitidis* were ≤0.007 µg/ml for both antibiotics, and those for *S. pneumoniae* were ≤0.015 µg/ml for both antibiotics.

**Laboratory results.** The leukocyte count, protein concentration, and glucose content in CSF samples obtained on admission and 24 to 30 h later were similar for both treatment groups (Table 2). Positive Gram-stained smears were obtained for 69 (77%) and 10 (11%) patients on admission and on the second CSF sampling (CSF 2), respectively. Initial CSF cultures were positive for 76 (84%) patients, whereas none was positive on repeat cultures at 24 to 30 h. Culture results were similar for both treatment groups (Table 2).

**Pharmacokinetics of cefepime.** Table 3 shows the mean plasma and CSF drug concentrations at 30 min and 1, 2, 4, and 8 h after the third dose of cefepime. There were five to seven patients with nonbloody CSF samples included for each time point. CSF concentrations of cefepime were from 9 to 67% of corresponding peak and trough plasma drug concentrations, with mean values ranging from 3.3 to 5.7 µg/ml during the dosing interval.

**Clinical course.** Table 4 describes the clinical courses of all patients enrolled in the study. The case-fatality rate was 7% for the entire population, 8.5% (95% confidence interval, 2.4 to 20.4) in the cefotaxime group, and 4.7% (95% confidence intervals 0.6 to 15.8) in cefepime recipients. One patient each with *H. influenzae* and *S. pneumoniae* meningitis treated with cefepime died. Four cefotaxime-treated patients died: one with meningococcal disseminated disease, one with pneumococcal meningitis, one with group B streptococcal infection, and one with meningitis caused by an alpha-hemolyticum *Streptococcus* strain. Three patients died less than 48 h after admission; the other three died within the first 10 days of hospital stay.

The numbers of days with fever, meningeal signs, antibiotic therapy, and hospital stay were similar for both groups of patients. Twelve children (6 in each group) had seizures during the first 3 days of antimicrobial therapy. Secondary fever (i.e., resurgence of fever after a 24-h nonfebrile period) developed in 37 (41%) study patients. This secondary temperature rise was considered to be the result of a rebound phenomenon following discontinuation of dexamethasone treatment. In some instances, however, a nosocomial respiratory viral infection was judged to be the cause of this febrile event.

Three (3%) patients developed reactive arthritis between the fifth and 10th days of hospitalization. The syndrome of inappropriate secretion of antidiuretic hormone was docu-

TABLE 2. Results of examinations of CSF

Sample <sup>a</sup>	Mean no. of leukocytes/mm <sup>3</sup> (±SD)	Meant amt (mg/dl [±SD]) of:		No. (%) of patients with positive result	
		Protein	Glucose	Smear	Culture
Cefepime treated (n = 43)					
CSF 1	5,211 ± 4,385	247 ± 132	24 ± 26	32 (74)	35 (81)
CSF 2 <sup>b</sup>	4,035 ± 6,237	121 ± 74	59 ± 22	6 (14)	0
Cefotaxime treated (n = 47)					
CSF 1	6,391 ± 5,410	221 ± 187	28 ± 30	37 (79)	41 (87)
CSF 2 <sup>b</sup>	2,923 ± 3,142	108 ± 56	64 ± 29	4 (9)	0

<sup>a</sup> No significant differences between treatment groups were detected.

<sup>b</sup> CSF 2 was obtained 19 to 36 h after the initial sample.

TABLE 3. Plasma and CSF cefepime concentrations

Time after dosing (h)	Cefepime concn ( $\mu\text{g/ml}$ ) <sup>a</sup>		CSF/plasma ratio
	Plasma	CSF	
0.5	67.1 $\pm$ 57.2	5.7 $\pm$ 7.3	0.09
1.0	44.1 $\pm$ 7.8	4.3 $\pm$ 1.5	0.10
2.0	23.9 $\pm$ 12.9	3.6 $\pm$ 2.0	0.15
4.0	11.7 $\pm$ 15.7	4.2 $\pm$ 1.1	0.36
8.0	4.9 $\pm$ 5.9	3.3 $\pm$ 2.8	0.67

<sup>a</sup> Values are means  $\pm$  standard deviations for five to seven patients at each time point.

mented (i.e., hyponatremia of less than 125 meq/liter, urine/serum osmolality greater than 2, and oliguria of less than 6 ml/kg of body weight per day) for only three (3%) patients (Table 4).

**Sequelae.** At discharge, neurologic and/or audiologic abnormalities were detected in 20 (24%) surviving patients (25% in the cefepime group and 23% in the cefotaxime group). These children were monitored for 2 to 6 months; four (5%) patients (two in each group) did not return for follow-up. Persisting neurologic and/or moderate or greater audiologic sequelae occurred in six (16%) cefepime-treated patients and six (15%) cefotaxime recipients (Table 5).

**Antimicrobial toxicity.** Adverse events attributable to antibiotic treatment occurred in 7 (18%) cefepime-treated patients and 10 (23%) children receiving cefotaxime. These reactions consisted of diarrhea (five and nine patients, respectively) and macular rashes (two patients and one patient, respectively). These events abated while patients were receiving therapy or a few days after discontinuation of antibiotics. *Candida* mucosal superinfection (i.e., thrush) developed in one (3%) cefepime-treated patient and three (7%) cefotaxime recipients. Eosinophilia was detected in three (8%) patients and one (2%) patient, respectively.

## DISCUSSION

In this comparative therapeutic trial, cefepime was equivalent to cefotaxime for the treatment of bacterial meningitis in infants and children. The hospital course, CSF bacterial eradication, CSF analysis, antibiotic toxicity, incidence and severity of sequelae, and case-fatality rates for meningitis for the two therapeutic regimens were clinically and statistically comparable. With the small differences in case-fatality and long-term

TABLE 4. Clinical response and outcome of meningitis

Characteristic <sup>a</sup>	Result with:	
	Cefepime (n = 43)	Cefotaxime (n = 47)
Mean no. of days ( $\pm$ SD) of fever	1.5 $\pm$ 0.7	1.8 $\pm$ 0.8
Mean no. of days ( $\pm$ SD) of meningeal signs	4.1 $\pm$ 1.6	3.7 $\pm$ 2.0
No. (%) of patients with convulsions after enrollment	6 (14)	6 (13)
No. (%) of patients with secondary fever	16 (37)	21 (45)
No. (%) of patients with reactive arthritis	2 (5)	1 (2)
No. (%) of patients with SIADH <sup>b</sup>	1 (2)	2 (4)
Mean no. of days ( $\pm$ SD) of antibiotic therapy	9.5 $\pm$ 2.4	9.6 $\pm$ 3.2
Mean no. of days ( $\pm$ SD) of hospitalization	10.8 $\pm$ 4.6	12.3 $\pm$ 6.6
No. (%) of cases resulting in mortality	2 (5)	4 (9)

<sup>a</sup> No significant differences between treatment groups were detected.

<sup>b</sup> SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

TABLE 5. Sequelae at 2- to 6-month follow-up evaluations<sup>a</sup>

Sequelae <sup>b</sup>	Result with:	
	Cefepime (n = 38)	Cefotaxime (n = 41)
No. (%) of patients with neurologic sequelae <sup>c</sup>	3 (8)	4 (10)
No. (%) of patients with audiologic sequelae	5 (13)	4 (10)
Moderate (>50 dB)	4	3
Severe (>80 dB)	1	1
No. (%) of patients with any sequelae	6 (16)	6 (15)

<sup>a</sup> Four patients (two in each group) were lost to follow-up.

<sup>b</sup> There were not statistically significant differences between treatment groups.

<sup>c</sup> Including cerebral palsy, epilepsy, hemiplegia, and hydrocephalus.

morbidity rates between the two treatment groups and assuming a  $\beta$  of 0.70, it would have been necessary to enroll 551 and >16,000 patients, respectively, in each group to have achieved statistical significance.

The efficacy of cefepime for the treatment of bacterial meningitis had been previously demonstrated in experimental animal models with group B streptococci, *S. pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, and *P. aeruginosa* as meningeal pathogens (4, 5, 7, 11–13). In these investigations, concentrations of cefepime in CSF in relation to corresponding values in serum varied from 15 to 36% in neonatal rats and from 11 to 23% in rabbits. In our study, concentrations of cefepime in CSF ranged from 5.7  $\mu\text{g/ml}$  30 min after the dose to 3.3  $\mu\text{g/ml}$  8 h after the dose. These values represented 9 and 67% of concentrations in serum, respectively, and exceeded the MICs of the patients' meningeal pathogens manyfold. It is important to note, however, that no penicillin-resistant pneumococci were identified in this study; therefore, the usefulness of cefepime for the treatment of pneumococcal meningitis caused by these strains is presently unknown.

Transient and persistent neurologic and audiologic abnormalities were comparable in the two treatment groups but were much lower than previously experienced in this hospital with ampicillin and chloramphenicol. (The outcomes of the first 37 patients enrolled in this study were previously contrasted with those obtained after treatment with conventional antimicrobial agents [2].) Current use of dexamethasone, given 15 min before the first parenteral antimicrobial dose to all patients with presumed bacterial meningitis, could be one plausible explanation for these low morbidity figures (8, 9). The case-fatality rate of 6.7% in this study is similar to that reported from developed countries. As expected (1), the mortality rate was higher for pneumococcal meningitis (2 of 10 patients [20%]) than for *H. influenzae* (1 of 46 patients [2%]); such a difference had a *P* value of 0.08 (Fisher's exact test).

In summary, cefepime appeared to be safe and therapeutically equivalent to cefotaxime for the management of bacterial meningitis caused by susceptible meningeal pathogens and can be considered a suitable alternative agent for treatment of infants and children with this disease.

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