

A Multicenter Comparative Study of Cefepime Versus Broad-Spectrum Antibacterial Therapy in Moderate and Severe Bacterial Infections

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The safety and efficacy of cefepime empiric monotherapy compared with standard broad-spectrum combination therapy for hospitalized adult patients with moderate to severe community-acquired bacterial infections were evaluated. In an open-label, multicenter study, 317 patients with an Acute Physiology and Chronic Health Evaluation (APACHE II) score ranging from >5 to $=19$ were enrolled with documented pneumonia ($n=196$), urinary tract infection ($n=65$), intra-abdominal infection ($n=38$), or sepsis ($n=18$). Patients were randomly assigned 1:1 to receive cefepime 1 to 2 g IV twice daily or three times a day or IV ampicillin, cephalothin, or ceftriaxone \pm aminoglycoside therapy for 3 to 21 days. For both treatment groups, metronidazole, vancomycin, or macrolide therapy was added as deemed necessary. The primary efficacy variable was clinical response at the end of therapy. Two hundred ninety-six (93%) patients met evaluation criteria and were included in the efficacy analysis. Diagnoses included the following: 180 pneumonias (90 cefepime, 90 comparator), 62 urinary tract infections (29 cefepime, 33 comparator), 37 intra-abdominal infections (19 cefepime, 18 comparator), and 17 sepsis (8 cefepime, 9 comparator). At the end of therapy, overall clinical success rates were 131/146 (90%) for patients treated with cefepime vs 125/150 (83%) for those treated with comparator (95% confidence interval [CI]: -2.6% to 16.3%). The clinical success rate for patients with community-acquired pneumonia, the most frequent infection, was 86% for both treatment groups. Among the patients clinically evaluated, 162 pathogens were isolated and identified before therapy. The most commonly isolated pathogens were *Escherichia coli* ($n=49$), *Streptococcus pneumoniae* ($n=29$), *Haemophilus influenzae* ($n=14$), and *Staphylococcus aureus* ($n=11$). Bacteriologic eradication/presumed eradication was 97% for cefepime vs 94% for comparator-treated patients. Drug-related adverse events were reported in 16% of cefepime patients and 19% of comparator patients. In conclusion, cefepime had higher cure rates compared with broad-spectrum combination therapy as an initial empiric treatment for hospitalized patients with moderate to severe community-acquired infections, including urinary tract infections, intra-abdominal infections, and sepsis. **Key Words:** Cefepime, ampicillin, cephalothin, ceftriaxone, aminoglycoside, urinary tract infections, intra-abdominal infections, sepsis.

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The initial selection of an empiric antimicrobial regimen for the treatment of hospitalized patients with serious community-acquired infections requires the use of broad-spectrum antibiotics. It has been common practice to treat presumed bacterial infections (e.g. pneumonia, urinary tract infection, sepsis) with combination antibiotic therapy, such as a β -lactam plus an aminoglycoside, in order to cover likely Gram-positive and Gram-negative organisms. In addition, combination therapy is prescribed to provide synergy against difficult-to-treat pathogens or ones that are likely to emerge resistant (e.g. *Staphylococcus aureus*,

Enterococcus spp, *Pseudomonas aeruginosa*) [1]. The past decade has witnessed the development of agents with broad spectrums of *in vitro* activity and has permitted the option of monotherapy in select patients [2-4]. The potential advantages of monotherapy include decreased risk for toxicity and drug interactions, reduced drug expenditures, and other pharmacoeconomic benefits [5-7].

Before an initial empiric antimicrobial regimen for the treatment of serious community-acquired infections is prescribed, local susceptibility patterns must be considered [1]. In Latin America, antimicrobial resistance has escalated against commonly isolated community-acquired pathogens from the respiratory tract [8, 9], urinary tract [10], and blood [11].

Cefepime is a potent, broad-spectrum, fourth-generation cephalosporin with enhanced activity against many Gram-positive and Gram-negative aerobic bacteria, including multiply resistant strains of Enterobacteriaceae [12-16]. In addition, cefepime has excellent *in vitro* activity against methicillin-susceptible *S. aureus* and *P. aeruginosa*. Cefepime's broad spectrum of *in vitro* activity is attributable to its low affinity for most β -lactamases (especially Bush group 1) [17], its high affinity for essential penicillin-binding proteins, and its zwitterionic structure [12-16]. Cefepime also appears to have a low propensity toward the development of resistance.

The primary purpose of this trial was to evaluate the efficacy and safety of cefepime monotherapy compared with standard broad-spectrum antimicrobial combination regimens as initial empiric treatment of hospitalized adults with moderate to severe infections; these infections include community-acquired pneumonia (CAP), urinary tract infection (UTI), intra-abdominal infection, and sepsis. This study was conducted in the 4 Latin American countries of Argentina, Brazil, Mexico, and Peru.

Material and Methods

Study design and initial antimicrobial therapy

Inclusion criteria

This was a prospective, open-label, randomized, multicenter study conducted between June 1999 and

March 2000 at 34 centers in Mexico, Brazil, Argentina, and Peru. After satisfying enrollment criteria and providing informed consent, patients were randomly assigned 1:1 to receive cefepime 1 or 2 g IV twice daily or three times a day (moderate or severe infections, respectively) or a standard antimicrobial combination, according to the investigator's discretion or the center's usual regimen. Standard antimicrobial combinations included the following: 1) ampicillin 2 to 3g IV four times daily \pm gentamicin 80mg IV two times daily or three times a day or amikacin 500mg IV three times daily; 2) cephalothin 2 to 3g IV four times daily \pm gentamicin 80mg IV twice daily or three times a day or amikacin 500mg IV three times daily; or 3) ceftriaxone 1 to 2g IV twice daily \pm gentamicin 80mg IV twice daily or three times a day or amikacin 500mg IV three times daily. For both treatment groups, metronidazole was added if anaerobes were suspected, vancomycin was given if methicillin-resistant *S. aureus* was suspected or documented, and macrolides were added for patients with CAP, if deemed appropriate (Figure 1). In the event that a pretherapy culture revealed at least 1 pathogen resistant to study drug, the patient was allowed to continue to receive the assigned antimicrobial, unless the investigator deemed that an alternative antimicrobial was necessary.

Eligible patients were men and women who were at least 18 years of age with a clinical diagnosis of moderate to severe CAP, UTI, intra-abdominal infection, or sepsis. All participants required hospitalization for their infection for less than 3 days prior to study entry. Each patient had an Acute Physiology and Chronic Health Evaluation (APACHE) II [18] score ranging from more than 5 to 19 or less.

Enrollment criteria for patients entering the pneumonia arm of the study included a new infiltrate on chest x-ray plus at least 2 clinical signs/symptoms, such as fever ($>38^{\circ}\text{C}$ or $>100.4^{\circ}\text{F}$); leukocytosis ($>10,000$ white blood cells [WBCs]/ mm^3 or $>15\%$ bands); cough; purulent sputum (>25 polymorphonuclear leukocytes [PMNs] and <10 squamous epithelial cells per low power field); chest pain; auscultatory findings (e.g. rales or egophony); chills; headache; or malaise.

The diagnosis of UTI required the isolation of more than 10 WBCs/high power field (HPF) obtained from centrifuged urine, collected by clean-catch technique or by catheterization, and at least 2 of the following: fever ($>38^{\circ}\text{C}$ or $>100.4^{\circ}\text{F}$); leukocytosis ($>10,000$ WBCs/ mm^3 or $>15\%$ bands); or upper tract symptoms (flank or back pain or costovertebral angle tenderness).

Individuals entering the bacterial sepsis arm of the study had to have clinical evidence of infection, including fever ($>38^{\circ}\text{C}$ or $>100.4^{\circ}\text{F}$); tachycardia (≥ 90 beats per minute [bpm]); leukocytosis ($>10,000$ WBCs/ mm^3 or $>15\%$ bands); respiratory frequency of 20 or more; increased arterial carbon dioxide tension (PaCO_2) of less than 32 mm/Hg; and evidence or suspicion of infection in another site. In addition, each patient must have had evidence of at least 1 of the following: hypotension (reduced systolic and diastolic blood pressures of 20 mm/Hg and 10 mm/Hg, respectively, below the patient's baseline for at least 8 hours in the absence of an obvious cause other than sepsis); oliguria ($<15\text{mL/h}$ urine during 4 hours); or hyperventilation (respiratory rate >25 bpm, or an increase of 15 bpm above the patient's baseline over 4 hours, in the absence of an obvious cause other than sepsis).

The diagnosis of intra-abdominal infection required clinical evidence, such as abdominal tenderness or hypoactive bowel sounds, and at least 2 of the following: fever ($>38^{\circ}\text{C}$ or $>100.4^{\circ}\text{F}$); leukocytosis ($>10,000$ WBCs/ mm^3 or $>15\%$ bands); radiographic, computed tomographic, or ultrasonographic findings suggestive of perforation or abscess; or documentation of a perforation or abscess at the time of surgery.

Exclusion criteria

Patients were excluded from the study if they had any of the following characteristics or conditions: APACHE II scores of 5 or lower or higher than 19; pregnancy and/or lactation; limited life expectancy (i.e. <3 days, or patients on "do not resuscitate" status); clinically significant hepatic disease (i.e. alanine aminotransferase and/or aspartate aminotransferase and/or total bilirubin ≥ 5 times the upper limit of normal);

chronic renal insufficiency (e.g. serum creatinine $=3.0\text{mg/dL}$ or requiring renal dialysis); and required intubation for daily respiratory support.

Clinical and bacteriologic evaluations: definitions of response

All patients receiving at least 1 dose of study drug were evaluated on an intent-to-treat basis. Antimicrobial effectiveness was evaluated on the bases of the clinical response of the patient and the bacteriologic response of the organism. Clinical and bacteriologic assessments were conducted during therapy (days 3-4), at the end of therapy, and at follow-up (7-10 days after treatment). Identification of causative organisms was performed using standard methods and susceptibility tests according to the E-test and standard procedures approved by the National Committee for Clinical Laboratory Standards (NCCLS).

To be considered evaluable for clinical response, patients must have satisfied the following requirements: 1) met all inclusion/exclusion criteria, 2) received at least 3 days of treatment with study drugs, and 3) completed an end-of-treatment or post-treatment assessment. The primary clinical response end point was success or failure at the end of initial therapy. Specific criteria for determining the clinical response of patients with pneumonia, UTI, sepsis, and intra-abdominal infections are outlined in Table 1. In general, success with initial therapy was defined as resolution of all acute signs and symptoms and improvement, but no deterioration, in radiographic and laboratory abnormalities. Failure with initial therapy was defined as persistence or progression of signs and symptoms relevant to the original infection after 3 to 4 days of therapy; development of new clinical findings consistent with active infection; progression of radiographic and/or laboratory abnormalities; or death due to the original infection. Clinical response was considered indeterminate under the following circumstances: modification of the initial therapy or administration of nonstudy antimicrobials before the 3- to 4-day on-treatment evaluation; early withdrawal from the study

Table 1. Criteria for response to treatment in patients with infection

Infection	Response criteria
Pneumonia	Improvement or normalization of respiratory status as measured by respiratory rate, oxygenation, severity of cough, and sputum production when compared with day 1, and at least 1 of the following: Normalization of body temperature Reduction or resolution of left shift of WBCs on differential Nonprogression or resolution of chest x-ray findings
UTI	Improvement or resolution of clinical signs and symptoms when compared with day 1, and at least 1 of the following: <10 WBCs/HPF and <10 ⁴ CFUs/mL in microscopic evaluation of spun urine Reduction or resolution of left shift of WBCs on differential Normalization of body temperature
Sepsis	Normalization or improvement of body temperature, heart rate, and respiratory rate; improvement of clinical signs and symptoms when compared with day 1; and at least 1 of the following: Reduction or resolution of left shift of WBCs on differential Return of appetite
Intra-abdominal infections (such as abdominal abscess and peritonitis)	Normalization or improvement of body temperature and improvement or resolution of clinical signs and symptoms, such as: Abdominal pain/discomfort Abdominal tenderness Normalization or peristalsis and peristaltic sounds

CFU: colony-forming unit; HPF: high power field; WBC: white blood cell.

before the 3- to 4-day on-treatment evaluation; or inability to complete the study because of drug-related adverse events.

To be evaluated for bacteriologic response and to represent the clinical response population, the patient must have met the evaluation criteria and must have had a positive pretreatment culture for a bacterial pathogen obtained immediately prior to receipt of the first dose of study antibiotic, or during the first 48 hours following randomization. Bacteriologic response was determined to be eradication/presumed eradication (causative organism absent or no material to culture in a patient who was clinically cured), persistence/presumed persistence (causative organism present or no material to culture in a patient whose clinical

response was failure), or indeterminate (e.g. patient received a nonstudy systemic antibiotic with activity against the initial pathogen, or pathogen was resistant to the study medication).

Safety evaluation

The safety of study drug therapy was monitored by clinical observation and by conventional laboratory tests from the first antibiotic dose up to 30 days after treatment. Adverse events were rated by the investigator according to their severity (mild, moderate, severe) and their relationship to the study drug (certainly, probably, possibly, or not likely related, or unrelated).

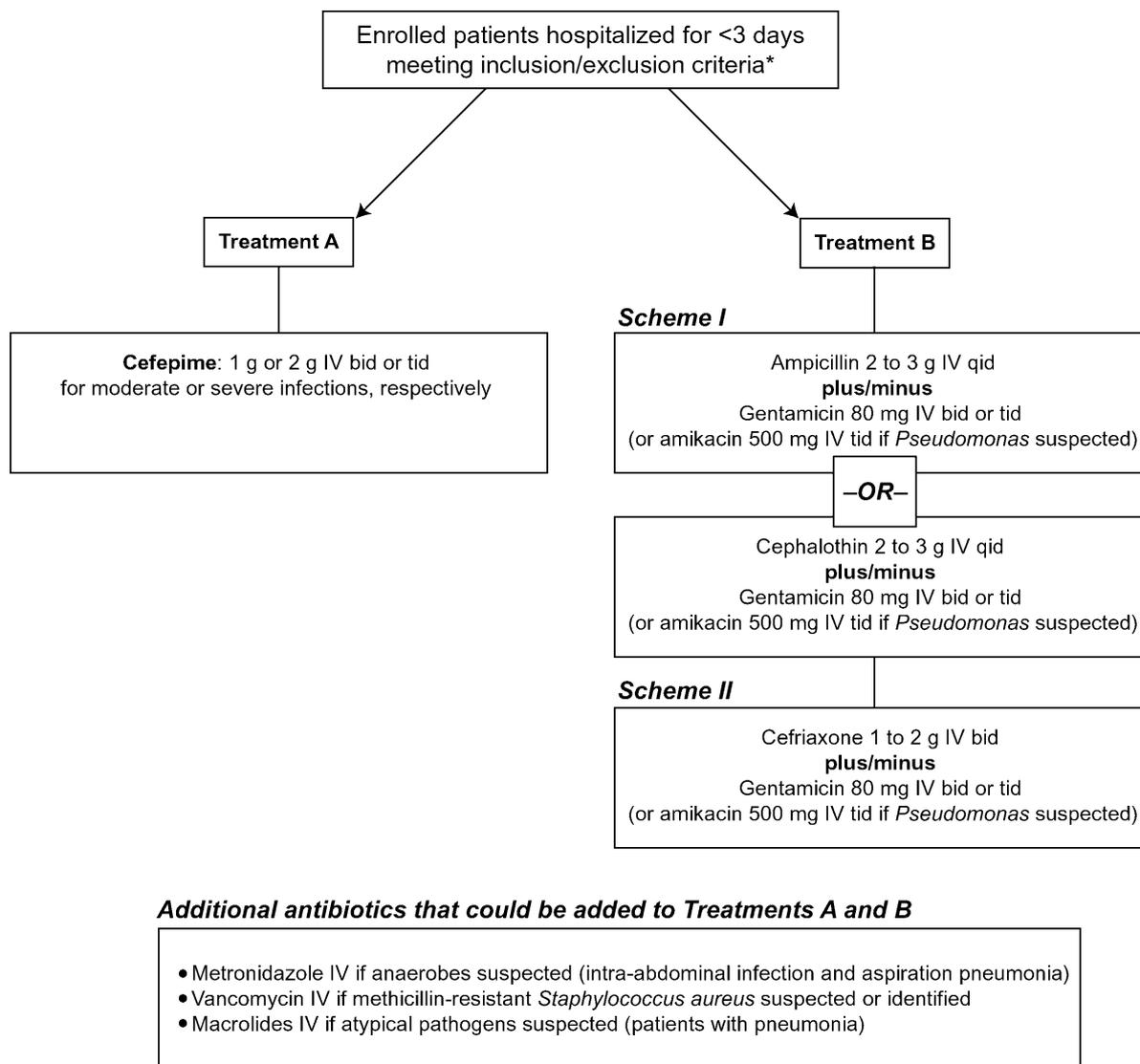
Table 2. Baseline demographics and medical characteristics of intent-to-treat population

	Cefepime (N=159)	Comparator (N=158)
Women, No. (%)	77 (48)	84 (53)
Race, No. (%)		
White	64 (40)	47 (30)
Hispanic	75 (47)	91 (58)
Black	17 (11)	16 (10)
Other	3 (2)	4 (3)
Age, median (range) years	57 (18–91)	47 (16–97)
Received antibacterial pretherapy, No. (%)	18 (11)	21 (13)
Clinical diagnosis, No. (%)		
CAP	101 (64)	95 (60)
UTI	30 (19)	35 (22)
Intra-abdominal infection	20 (13)	18 (11)
Sepsis	8 (5)	10 (6)
APACHE II scores*, No. (%)		
Mild (5)	3 (2)	2 (1)
Moderate (5–12)	115 (72)	116 (73)
Severe (≥ 13)	37 (23)	39 (25)

*Missing responses excluded from calculations. APACHE II: Acute Physiology and Chronic Health Evaluation II; CAP: community-acquired pneumonia; UTI: urinary tract infection.

Table 3. Drug-related adverse events occurring in $\geq 2\%$ of patients, N (%)

Adverse event	Cefepime (N=159)	Comparator (N=158)
Any event	25 (16)	30 (19)
Phlebitis	5 (3)	6 (4)
Reaction at IV site	3 (2)	—
Fever	2 (1)	4 (3)
Diarrhea	4 (3)	1 (<1)
Nausea	1 (<1)	4 (3)
Abdominal pain	3 (2)	4 (3)
Rash	1 (<1)	5 (3)
Tachycardia	—	6 (4)

Figure 1. Treatment administration

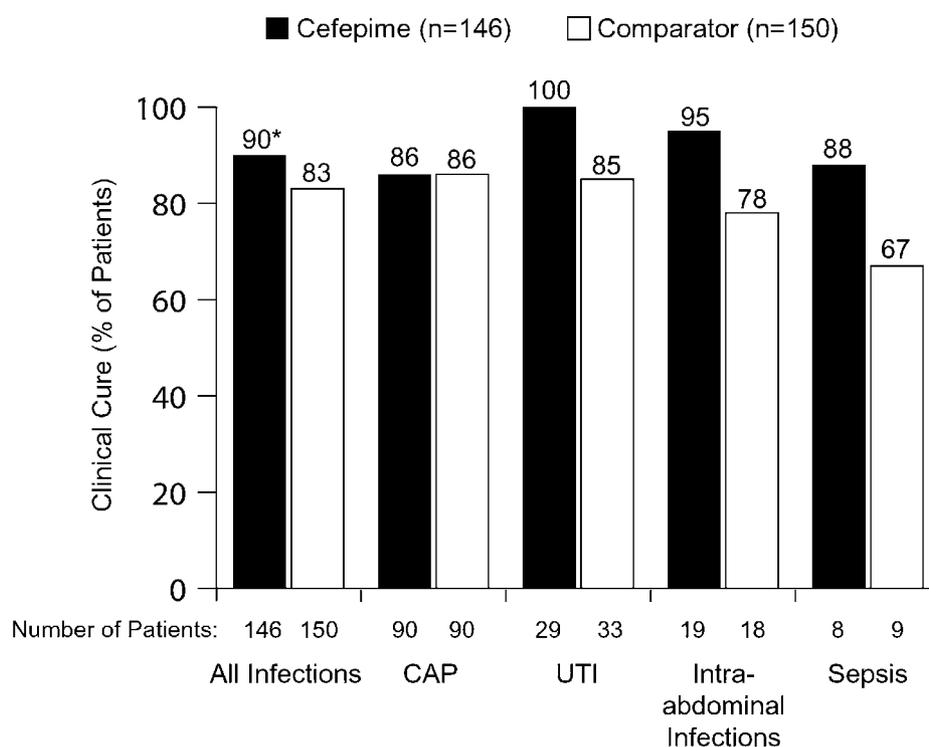
*See text for inclusion/exclusion criteria.

Ethical issues

Each patient provided written informed consent following approval of the protocol by each institution's internal review board and in accordance with the Declaration of Helsinki.

Statistical analysis

The primary measure of efficacy was the overall proportion of patients in each treatment group with clinical success vs failure at the end of initial antibiotic therapy. Secondary efficacy analysis included both

Figure 2. Clinical cure at end of treatment: clinically evaluable population

*95% CI for the difference in cure rates: -2.6% to 16.3%.

CAP = community-acquired pneumonia; UTI = urinary tract infection.

bacteriologic eradication rates for those with a pretreatment pathogen and clinical cure rates by infection type.

For the end-of-therapy clinical and bacteriologic responses, 95% 2-sided confidence intervals (95% CIs) were calculated for the mean differences between resolutions or eradication rates. Each of the 2 treatment comparisons was declared equivalent at the 2.5% significance level if the lower boundary was $\geq 15\%$ CI. These analyses were performed for both the efficacy-evaluable and intent-to-treat populations.

For demographic and baseline medical characteristics, descriptive statistics were performed

for the frequencies and percentages of categorical variables, numbers of patients, means, standard deviations, and minimum and maximum values for continuous variables. The incidence rates of adverse events and reasons for premature discontinuation were tabulated by both treatment group and body system.

Results

Three hundred twenty hospitalized patients with severe infections were enrolled at 34 clinical sites; 3 patients were not eligible for efficacy or safety analysis because no study drug was received. Therefore, 317

patients constituted the intent-to-treat population (196 pneumonia, 65 UTI, 38 intra-abdominal infection, 18 sepsis). A total of 21 additional patients were excluded from evaluation of efficacy (13 cefepime, 8 comparator). Patients were ineligible for efficacy analysis on the basis of 1) pretreatment with antimicrobials (6 cefepime, 1 comparator) or 2) no test-of-cure evaluation (7 cefepime, 7 comparator). Accordingly, a total of 296 (93%) patients were considered evaluable for the efficacy analysis (146 cefepime, 150 comparator). Five patients (3 cefepime, 2 comparator) were included in the efficacy population despite failure to meet entry criteria (i.e. baseline APACHE II scores =5). Four patients (2 with UTI and 2 with sepsis) had an APACHE II score equal to 5, and 1 patient with a UTI had an APACHE II score of 4.

Forty-three patients (26 cefepime, 17 comparator) were prematurely discontinued from the study. The most common reasons for premature discontinuation of study drug were death (13 cefepime, 6 comparator), an adverse event (4 cefepime, 4 comparator), patient noncompliance (3 cefepime, 3 comparator), treatment failure (3 cefepime, 3 comparator), protocol violation (2 cefepime, 1 comparator), and laboratory abnormality (1 cefepime).

Baseline demographics and medical characteristics of the intent-to-treat population are outlined in Table 2. The median age of the intent-to-treat group was 57 years. Overall, approximately 51% of patients were women and 52% were Hispanic; more Hispanic patients were randomly assigned to comparator therapy (58%) compared with cefepime therapy (47%). A total of 12% of patients (11% cefepime, 13% comparator) received previous antibacterial therapy. A majority of patients had a clinical diagnosis of CAP (64% cefepime, 60% comparator), followed by UTI (19% cefepime, 22% comparator), intra-abdominal infection (13% cefepime, 11% comparator), and sepsis (5% cefepime, 6% comparator). Based on APACHE II scores, both groups had similar numbers of patients with moderate (72% cefepime, 73% comparator) and severe (23% cefepime, 25% comparator) infection. The population of clinically evaluable patients had similar

baseline demographics and medical characteristics compared with the intent-to-treat population; there were no differences across treatment groups for any infection site.

Clinical efficacy

The mean duration of antimicrobial therapy for both treatment groups was 10 days (9 cefepime, 10 comparator), with a range from 1 to 69 days. Compared with the comparator group, a greater number of patients from the cefepime group received treatment for ≥ 10 days (66% cefepime, 55% comparator). Clinical responses stratified by treatment and country were very similar, with the exception of Mexico, where clinical cure was 90% for cefepime-treated patients compared with 78% for patients receiving a comparator regimen. Clinical cure rates for the intent-to-treat population were 82% for cefepime and 80% for the comparator group.

Clinical response at the end of treatment by infection type is shown in Figure 2 for the clinically evaluable population. Regardless of infection type, clinical cure rates were higher among cefepime-treated patients (90%) compared with those given a comparator regimen (83%) (95% CI: -2.6% to 16.3%). For patients with CAP, both treatments provided an 86% clinical cure rate. Cefepime provided higher clinical cure rates compared with comparator regimens for patients diagnosed with UTI (100% vs 85%), intra-abdominal infection (95% vs 78%), and sepsis (88% vs 67%).

Bacteriologic efficacy

One hundred sixty-two pathogens (76 cefepime, 86 comparator) were isolated from clinically evaluable patients. The most common pathogens isolated were *Escherichia coli* (n=49), *Streptococcus pneumoniae* (n=29), *Haemophilus influenzae* (n=14), *Klebsiella pneumoniae* (n=6), and *S. aureus* (n=11), accounting for 64% of all isolated pathogens. None of the *E. coli* produced extended β -lactamases (ESBLs). In contrast, 2 isolates of *K. pneumoniae* were ESBL producers, 1 of which had intermediate susceptibility

to cefepime, and the other full resistance to cefepime. All but 1 isolate of *S. pneumoniae* were fully susceptible to penicillin.

A total of 97% (74/76) of pathogens isolated from cefepime-treated patients were eradicated compared with 96% (81/84) in the comparator group. In the cefepime group, 2 pathogens persisted. One patient with CAP had presumed persistent β -lactamase-negative *H. influenzae*; this patient was a clinical failure. A second patient with UTI had presumed persistent *K. pneumoniae* and was also a clinical failure. Two patients treated with a comparator regimen had 3 persistent/presumed persistent pathogens at the end of treatment. One patient with CAP had presumed persistent β -lactamase-negative *H. influenzae* and *Moraxella catarrhalis* and was a clinical failure. The second patient had persistent β -lactamase *H. influenzae* but was considered clinically cured. Bacteriologic response was indeterminate for 2 pathogens in the comparator group.

Safety and tolerance

Three hundred seventeen patients (159 cefepime, 158 comparator) were eligible for the safety analysis. Eighty-four (53%) cefepime- and 81 (51%) comparator-treated patients reported at least 1 treatment-emergent event. Twenty-five (16%) cefepime and 30 (19%) comparator recipients had at least 1 adverse event considered to be drug-related (Table 3). For cefepime, injection site reactions, phlebitis, diarrhea, and abdominal pain were the most common drug-related adverse events reported. For the comparator regimens, phlebitis, fever, nausea, rash, and tachycardia represented the most frequently reported drug-related adverse events. Most adverse events were mild to moderate in severity (25 cefepime, 28 comparator) and improved or resolved without intervention.

Four cefepime- and 4 comparator-treated patients were prematurely discontinued owing to occurrence of 1 or more adverse events. Three events (1 cefepime, 2 comparator) were considered to be probably or definitely related to the study drug. The cefepime-treated patient was discontinued early owing to a

urinary yeast infection. The 2 comparator-treated patients had premature discontinuation of therapy secondary to "loss of sensitivity" in the infusion arm or development of rash of moderate intensity.

A total of 27 (9%) patients died during the course of the study (17 cefepime, 10 comparator). The majority of deaths (86%) occurred in patients diagnosed with CAP before treatment began. Deaths were not considered treatment related, but were due to underlying disease and comorbidity.

Discussion

The main finding of this multicenter study was that empiric monotherapy with cefepime was at least as effective as conventional broad-spectrum antimicrobial combinations for treatment of moderate to severe community-acquired infections. For all infections combined, the clinical cure rate at the end of therapy was higher for those given cefepime alone (90%) compared with those receiving comparator combination regimens (83%). Furthermore, patients treated with cefepime who had a diagnosis of UTI, intra-abdominal infection, or sepsis had higher rates of clinical cure compared with comparator recipients. Approximately half of the clinically evaluable population had an isolated pathogen that was identified before treatment began. Cefepime eradicated 97% of all pathogens, similar to comparator therapy (94%). Accordingly, this study extends the findings of previously published clinical studies, which found cefepime to be effective for the treatment of moderate to serious infections of the lower respiratory tract [19-23] and the urinary tract [24], as well as intra-abdominal infections [25] and bacteremia [26].

This study also demonstrated that cefepime has an excellent safety and tolerability profile with adverse events primarily limited to injection site reactions (e.g. phlebitis) and effects on the gastrointestinal tract (e.g. diarrhea, abdominal pain). Importantly, most cefepime-related adverse events were of mild (76%) or moderate (24%) intensity. Only 1 cefepime-treated patient, a 38-year-old black female, discontinued the drug prematurely owing to "loss of sensitivity" in the arm receiving the drug infusion.

CAP was the most frequent diagnosis in this study, accounting for approximately two thirds of the 317 moderate to severe infections. The cefepime and comparator regimens were similarly effective, demonstrating an 86% clinical cure rate at the end of therapy. The most up-to-date guidelines published by the Infectious Diseases Society of America and the American Thoracic Society recommend a third-generation cephalosporin (e.g. ceftriaxone) plus a macrolide as 1 option for treatment of hospitalized patients with CAP [27, 28]. Among nearly 1,800 bacterial isolates obtained from patients with community-acquired respiratory tract infections in several Latin American countries, the average rate of penicillin-resistant *S. pneumoniae* was 39% [9]. Notably, the highest susceptibility rates were found in Argentina (77%) and Brazil (72%), and the lowest rate of penicillin susceptibility was detected in Mexico (33%). In the same surveillance study, rates of β -lactamase-positive *H. influenzae* and *M. catarrhalis* were approximately 13% and 92%, respectively. The administration of an advanced-generation cephalosporin with the addition of a macrolide as empiric therapy covers the most likely causes of lower respiratory tract infection, including *S. pneumoniae*, *H. influenzae*, and atypical pathogens. In clinical practice, many physicians omit the macrolide if infection with an atypical pathogen is deemed unlikely. Accordingly, cefepime monotherapy is a reasonable choice for hospitalized patients with CAP of moderate to severe intensity who are not considered to be at risk for infections with atypical respiratory pathogens.

In a second surveillance study conducted in Latin America, less than half of *E. coli* isolates obtained from hospitalized patients with UTIs were susceptible to broad-spectrum penicillins; *in vitro* resistance rates were also high against both old and new fluoroquinolones [10]. Cefepime monotherapy was also found to be clinically and bacteriologically effective in the management of hospitalized patients with moderate to severe UTIs. Clinical cure was 100% following cefepime vs 85% for the comparator regimen. A recent surveillance study, conducted in Latin America among hospitalized patients with UTI, found that

cefepime had excellent *in vitro* susceptibility against many antibiotic-resistant urinary *E. coli* isolates (91.7%). Because antimicrobial resistance among uropathogens causing community-acquired UTIs (e.g. *E. coli*) is increasing [29], especially against ampicillin and trimethoprim-sulfamethoxazole (TMP-SMX), new antibiotic options are needed to treat these infections [30, 31]. The data from our trial are promising; it appears that cefepime monotherapy is an effective empiric agent for the treatment of potentially antibiotic-resistant uropathogens and serious UTIs.

Treatment of intra-abdominal infection requires early diagnosis, timely and properly performed surgical procedures, and appropriately selected antibacterial agents to reduce the incidence of peritonitis, abscess, or local wound infection [32]. In this multicenter study, 37 clinically evaluable patients had intra-abdominal infections. Notably, cefepime-treated patients had a higher clinical cure rate (95%) compared with those who received combination antibiotic therapy (78%). Because of the small number of patients enrolled and evaluable in this trial, firm conclusions cannot be reached regarding the efficacy of cefepime (plus agents with anaerobic coverage) for treatment of serious intra-abdominal infections. However, our findings appear to confirm an earlier report by Barie, et al. in which cefepime plus metronidazole was associated with high cure rates (88%) in patients with severe intra-abdominal infections [25].

Patients with sepsis must be diagnosed early and treated promptly if death is to be prevented [33]. The antimicrobial regimen empirically selected typically has been of broad spectrum and includes activity against *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. Although combination β -lactam/aminoglycoside regimens have been given frequently, new monotherapy options with excellent pseudomonal coverage are now more often prescribed, especially when renal toxicity is a concern [3, 7]. A third Latin American surveillance study found that bloodstream infection isolates (e.g. *E. coli*) were uniformly more resistant to all classes of tested antimicrobial agents compared with similar isolates recovered from North American patients [11]. In this study, only 17 patients with sepsis (8 cefepime, 9

comparator) were evaluable for clinical efficacy. At the end of therapy, clinical cure was 88% for cefepime compared with 67% for comparator regimens. Despite the inadequate numbers of evaluable patients, cefepime's excellent *in vitro* activity against the organisms commonly associated with sepsis makes it a reasonable empiric treatment option.

Few clinical studies describe the "real-world" approach to treatment of serious infections with empiric antimicrobial therapy. Limitations of this study included the nonblinded design, the large number of centers, the variety of comparator agents studied, and the low number of patients in several of the infection subgroups. Although these limitations necessitate careful interpretation, evaluation of clinical success at the end of therapy reflects "real-world" clinical practice and is noteworthy.

In summary, the relatively recent availability of potent broad-spectrum antimicrobial agents has decreased the need for combination antimicrobial therapy for the treatment of hospitalized patients with serious infections. This study enrolled "real-world" hospitalized patients with moderate to severe community-acquired infections, who were treated with either cefepime monotherapy or a β -lactam \pm aminoglycoside therapy. Empiric use of cefepime monotherapy resulted in high rates of clinical success and bacteriologic eradication and was at least as effective as standard combination regimens for treatment of patients with CAP. For the subgroups of evaluable patients with UTI, intra-abdominal infection, and sepsis, cefepime monotherapy appeared to provide higher clinical cure rates compared with the comparator combination antimicrobial regimens. Overall, cefepime given alone was effective and well tolerated in the treatment of hospitalized adult patients with moderate to severe community-acquired infections.

If they are to prescribe appropriate empiric therapy, physicians must be knowledgeable about geographic differences in the causes and susceptibility patterns of organisms associated with serious community-acquired infections. Use of inappropriate empiric antimicrobial therapy may lead to increased rates of mortality and morbidity. As with

any serious infection, antimicrobial therapy should be tailored when culture and susceptibility data become available.

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