Efficacy of Cefepime in the Treatment of Infections Due to Multiply Resistant *Enterobacter* Species

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Cefepime is a new cephalosporin with an enhanced antibacterial potency and spectrum. More rapid penetration into many gram-negative bacilli, targeting of multiple penicillin-binding proteins, and resistance to inactivation by many β-lactamases account for its activity against organisms that have developed resistance to agents such as ceftazidime, cefotaxime, or ceftriaxone. This study identified 16 patients with 17 infections due to *Enterobacter* species organisms with reduced susceptibility or resistance to ceftazidime. Most isolates were multiply resistant to other β-lactam drugs as well, but all were susceptible to cefepime. All 17 infections, which included pneumonia, urinary tract infection, intraabdominal infection, and bacteremia, responded clinically to intravenous cefepime. In particular, cefepime was successfully used in the management of cases of chronic infection that had responded poorly to repeated therapy with imipenem, aminoglycosides, or ciprofloxacin. Eradication of *Enterobacter* species organisms occurred at 15 (88.2%) of the 17 sites of infection. No emergence of resistance to cefepime was noted.

Cefepime is a new aminothiazolylacetamido cephalosporin with a broader antimicrobial spectrum and greater potency than currently available cephalosporins [1, 2]. The unique features of cefepime result from three characteristics: (1) more rapid penetration into gram-negative bacteria, (2) targeting of multiple essential penicillin-binding proteins, and (3) resistance to inactivation by many β-lactamases because of the low affinity of these enzymes for the drug. The last characteristic is most striking in organisms with Bush group 1 β-lactamases, which when derepressed cause resistance to nearly all currently available penicillins and cephalosporins. Cefepime, however, retains activity against organisms (e.g., *Enterobacter* species) that have developed resistance to even the most recently marketed "broad-spectrum" cephalosporins as a result of stable derepression of the group 1 enzymes.

The enhanced antibacterial spectrum and potency of cefepime, in contrast to those of earlier cephalosporins such as cefotaxime, ceftriaxone, cefoperazone, and ceftazidime, have been demonstrated in a large number of in vitro studies and confirmed in experimental infections (especially those due to gram-negative bacilli) in animals [2]. In addition, cefepime appears less likely than earlier cephalosporins to select resistant mutants among organisms that characteristically produce the Bush group 1 β-lactamases [3]. In experimental murine infections due to *Enterobacter* and *Citrobacter* species, emergence of resistance was rare in cefepime-treated animals but occurred in a substantial percentage of animals treated with ceftazidime or ceftriaxone [4, 5].

For licensing purposes, it is required that comparative clinical trials include at least one presently marketed agent and that infecting organisms be susceptible to both the new and old drug or drugs. Hence, it may be difficult to demonstrate an advantage when the new agent is active against organisms resistant to the most-comparable older agents.

Cefepime is a case in point. Most early studies compared cefepime with ceftazidime, with the stipulation that infections due to organisms resistant to either cefepime or ceftazidime be excluded. However, in the course of a variety of clinical trials worldwide and in the "compassionate use" program, a number of infections were identified as being caused by multiply β-lactam-resistant, cefepime-susceptible organisms, especially of the genus *Enterobacter*.

To determine whether the apparent advantages of cefepime over other β-lactam antibiotics against *Enterobacter* species in vitro and in animal infections translate into successful therapy in the clinic, we reviewed all enterobacter infections treated with cefepime in the United States and Europe during a 3-year period. We focused on infections due to *Enterobacter* strains with reduced susceptibility to ceftazidime and analyzed in detail the clinical and bacteriologic responses of these patients.

Patients and Methods

Case reports regarding patients treated in the United States and Europe were available for review. Infections due to the various *Enterobacter* species were identified. Records of

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specific infections due to organisms with reduced susceptibility or resistance to cefepime or the comparative agent(s) (usually ceftazidime) were selected for further study. Reduced susceptibility to cefepime or ceftazidime or both was defined by (1) a zone size on disk-diffusion assay considered to be in the intermediate range (15–17 mm in the United States) or (2) an MIC of 8–16 μg/mL. Resistance was defined by (1) a zone size on disk-diffusion assay of ≤14 mm or (2) an MIC of ≥32 μg/mL.

For some European isolates, disk-diffusion assay results were reported only as susceptible, intermediate, or resistant. In these instances only, isolates from the last two categories were included in our analysis. Most of the isolates from patients in the United States were shipped to the research laboratories of Bristol-Myers Squibb (Wallingford, CT) for confirmation of the investigator's microbiological identification and susceptibility findings and for further testing as indicated. In the event of discrepancies between diffusion and dilution assay results, the dilution result was considered the standard. Other tests, primarily to confirm identity of sequential isolates, were performed at Creighton University (Omaha, NE).

Clinical and microbiological outcomes were recorded for patients who received >48 hours' treatment. The authors relied almost exclusively upon the individual investigator's final assessment of clinical outcome: failure, improvement, or cure (resolution). In the infrequent absence of such an overall clinical conclusion, a composite of the investigator's assessments of outcomes of specific signs and symptoms was used to reach a final conclusion. Microbiological outcome (failure or eradication) was assessed from the results of cultures performed during or after treatment or both. In instances in which complete recovery occurred and no further cultures were performed, the infecting organism was considered to have been eradicated.

Results

A total of 2,487 patients from whom pretreatment bacterial isolates were recovered were enrolled for study of cefepime in the United States and Europe. The isolates from 135 (5.4%) were of the genus *Enterobacter*. Twenty (14.8%) of these 135 patients were found to harbor an organism that was susceptible to cefepime but resistant or with reduced susceptibility to ceftazidime. No isolates with the reverse pattern of susceptibility were identified.

Four of the 20 patients either could not be evaluated or did not fit the selection criteria established before examination of the database. Administration of cefepime to two of these four was discontinued after just a few doses because susceptibility test results indicated that the *Enterobacter* strain was resistant to the comparative drug (ceftazidime); thus, the patients were ineligible for the study. The clinical condition of both patients was stable when cefepime was withdrawn. The other two patients, both of whom were receiving respiratory support and in whom respiratory tract infections developed, did not meet the selection criteria because their pretreatment isolates were susceptible to both agents. However, isolates susceptible to cefepime but resistant to ceftazidime were recovered during or at the end of therapy.

Following cefepime treatment of the remaining 115 infections (due to cefepime-susceptible, ceftazidime-susceptible isolates), *Enterobacter* species organisms were again isolated from 10 patients. Such organisms were also isolated from three additional infections shortly before cefepime therapy was discontinued because the infection was not controlled. None of these 13 *Enterobacter* isolates were resistant to cefepime.

A total of 16 patients met the study inclusion criteria (table 1). There were 4 patients with pneumonia, 4 with urinary tract infections, 3 with wound infections, 2 with bone and joint infections, and 2 with intraabdominal infections (1 with concomitant bacteremia). One patient had bacteremia without a local source. Six of the 16 isolates were *Enterobacter cloacae*, and 10 were *Enterobacter aerogenes*. Depending upon the susceptibility test method employed and laboratory site, 71%–78% of the isolates were resistant, and the balance were of reduced susceptibility to ceftazidime. All were susceptible to cefepime. Ten of the 16 isolates were tested for susceptibility to other cephalosporins, such as cefotaxime, ceftriaxone, and cefoperazone; 9 (80%) were multiply resistant to these agents, while 2 (20%) had reduced susceptibility.

Clinical and bacteriologic responses to cefepime therapy are recorded in table 1. Clinical cure or significant improvement occurred in each (100%) of the 16 patients and 17 sites of infection. Infecting organisms were considered to have been eradicated from 15 (88.2%) of the 17 sites. An *Enterobacter* species organism was isolated from the synovial fluid of a patient nearly 1 year post-treatment, when a previously infected joint (clinically without symptoms for ~1 year) became inflamed. *Enterobacter* species persistently colonized the sputum of another patient after a satisfactory clinical response to treatment of pneumonia.

Of the 15 instances of bacteriologic eradication, 10 were documented by culture and the other 5 were presumed on the basis of clinical criteria (see table 1). Three patients were given a second antimicrobial agent, in a regimen overlapping at least a portion of the cefepime regimen. Two received an agent with no activity against *Enterobacter* species (oral vancomycin for 3 days or metronidazole). One patient was given concurrent therapy with tobramycin, which had previously failed in combination with ceftriaxone (three courses) and ciprofloxacin (one course).

Summaries of the 16 cases follow. We have attempted to provide sufficient detail for readers to validate conclusions regarding outcome.

Patient 1. A 73-year-old man was admitted because of a cerebrovascular accident. He had recently undergone surgery for carcinoma of the colon, was fed by gastrostomy, and required mechanical ventilation. He survived an episode of catheter-related bacteremia due to *Staphylococcus aureus*, but

Table 1. Summary of data regarding patients treated with cefepime for resistant* *Enterobacter* infections: results of cultures and susceptibility tests, as related to clinical and microbiological outcomes.

Patient no./ diagnosis: causative organism	Culture		Results of susceptibility testing (zone [mm] of inhibition/MIC [μg/mL]) by:				Resistance to other cephalosporins‡	Response: clinical/ microbiological	Dosage and duration of treatment with cefepime	Comment(s)
			Investigator		Manufacturer					
	Type or source of specimen	Performed on Rx day†	Fep	Czid	Fep	Czid				
1/Pneumonia: *Enterobacter aerogenes*	Sputum	1	28/. . .	14/. . .				Cure/presumed eradication	2 g q12h × 8 d	The patient received 1 w of treatment with cefotaxime that ended 5 d before cefepime therapy started. No sputum was produced after therapy.
	Sputum	5	28/. . .	12/. . .						
	Sputum	8	22/. . .	12/. . .						
2/Pneumonia: *Enterobacter cloacae*	Sputum	−2	24/. . .	10/. . .	29/0.125	11/32.0	Y	Cure/eradication	2 g q12h × 15 d	Prior therapy with cefazolin.
	Sputum	−1	26/. . .	12/. . .	33/0.03	27/0.25	Y			
	Sputum	4	24/. . .	10/. . .	27/0.125	12/32.0	Y			
	Sputum	8	24/. . .	10/. . .						
	Sputum	11	Neg cult							
	Sputum	15	Neg cult							
3/Pneumonia: *E. aerogenes*	TA	−1	24/. . .	10/. . .	29/0.5	12/64.0	Y	Cure/eradication	2 g q12h × 13 d	The patient received ceftazidime (1 g) 1 w before onset. No sputum produced after day 7 of therapy.
	TA	4	26/. . .	10/. . .	27/0.125	13/32.0	Y			
	Sputum	7	Neg cult							
4/Pneumonia: *E. aerogenes*	Sputum	−1	26/. . .	9/. . .	24/0.25	10/64.0	Y	Cure/persistent colonization	1 g q12h × 11 d	Pretreatment and day 9 isolates had identical plasmid profiles.
	Sputum	3	26/. . .	0/. . .						
	Sputum	4	26/. . .	0/. . .						
	Sputum	9	16/. . .	0/. . .	18/16.0	6/>128	Y			
	Sputum	+1	19/. . .	0/. . .						
	Sputum	+2	15/. . .	0/. . .						
5/UTI: *E. aerogenes*	Urine	−1	27/0.25	13/>32.0				Cure/eradication	0.5 g q12h × 5 d	
	Urine	5	Neg cult							
6/UTI: *E. cloacae*	Urine	−2	S/. . .	R/. . .				Cure/eradication	2 g q12h × 7 d	
	Urine	5, 8, +6, +11	Neg cult							
7/UTI: *E. aerogenes*	Urine	1	35/. . .	23/. . .	35/0.06	25/8.0	Y	Cure/eradication	0.5 g q12h × 15 d	
	Urine	4	Neg cult							
	Urine	+8	Neg cult							
8/UTI: *E. aerogenes*	Urine	1	27/. . .		26/0.25	13/32.0	Y	Cure/eradication	2 g q12h × 8 d	Concurrent infection with *P. mirabilis* responded well.
	Urine	3	Neg cult							
	Urine	+6	Neg cult							
9/Wound infection: *E. cloacae*	Wound	1	15/. . .	6/. . .	18/4.0	6/128	Y	Cure/presumed eradication	1 g q12h × 4 d	Wound healed; no additional cultures done.
10/Wound infection: *E. cloacae*	Wound	−2	29/. . .		31/0.125	17/8.0	Y	Improvement/ eradication	2 g q12h × 14 d	
	Wound	3	Neg cult							
	Wound	4	Neg cult							
	Wound	+1	Neg cult							
11/Wound infection: *E. aerogenes*	Wound	1	24/. . .		25/1.0	15/8.0	Y	Cure/eradication	1 g q12h × 10 d	Group A streptococcus and *S. aureus* also eradicated.
	Wound	5	28/. . .		29/0.03	29/0.25	N			
	Wound	+1	Neg cult							
12/Biliary sepsis, bacteremia: *E. cloacae*	Bile Drainage	−1	S/1.0	R/32.0				Cure/eradication	2 g q12h × 12.5 d	Biliary infection and bloodstream infection cleared promptly.
	Bile Drainage	7, +3 +11	Neg cult							
	Blood	1	S/. . .					Cure/presumed eradication		
13/Bacteremia: *E. cloacae*	Blood	−2	S/1.0	S/16.0				Cure/presumed eradication	2 g q12h × 10 d	
	Blood	−1	S/1.0	S/16.0						
	Blood	−1	S/1.0	S/16.0						

Table 1. (*Continued*)

Patient no./ diagnosis: causative organism	Culture: Type or source of specimen	Culture: Performed on Rx day†	Results of susceptibility testing (zone [mm] of inhibition/MIC [μg/mL]) by: Investigator: Fep	Investigator: Czid	Manufacturer: Fep	Manufacturer: Czid	Resistance to other cephalosporins‡	Response: clinical/ microbiological	Dosage and duration of treatment with cefepime	Comment(s)
14/Intraabdominal infection: *E. aerogenes*	Biliary tissue	2	26/. . .		27/0.5	9/>128		Cure/eradication	2 g q12h × 5 d	
15/Osteomyelitis, soft-tissue infection: *E. aerogenes*	Bone	−26	19/. . .				Y	Cure/presumed eradication	2 g q8h × 53 d	No clinical or radiographic evidence of bone infection 2 mo posttreatment.
	Bone	−22, −19, −15								
	Bone	−10								
	Wound	−10								
	Bone	−7	18/. . .		24/1.0	12/64.0				
16/Septic arthritis, soft-tissue infection: *E. aerogenes*	Wound	−28	. . ./2.0		22/2.0	6/128	Y	Improvement/ persistence	2 g q8h × 48 d	The patient had no symptoms for 1 y posttreatment. Joint symptoms flared up at this time; cefepime-susceptible *Enterobacter* was isolated.
	Wound	−3	22/2.0		22/2.0	6/128	Y			

NOTE. Czid = ceftazidime; Fep = cefepime; N = no; Neg cult = negative culture; R = resistant; S = susceptible; TA = tracheal aspirate or transtracheal aspirate; UTI = urinary tract infection; Y = yes.

* See text for definitions.

† Rx day = treatment day (− = days before therapy; digit alone = day of therapy; + = days after therapy).

‡ Cefotaxime, ceftriaxone, or cefoperazone.

pneumonia developed shortly thereafter. *E. aerogenes* that was susceptible to a variety of β-lactam drugs was isolated from sputum. The patient was given cefotaxime for 7 days. Signs and symptoms of respiratory infection persisted, and the *Enterobacter* strain developed resistance to a multiplicity of β-lactam agents. The organism was susceptible to cefepime and resistant to ceftazidime by disk-diffusion assay. The patient was treated for 8 days with cefepime. Signs and symptoms of infection promptly resolved. Bilateral pulmonary infiltrates diminished. Sputum cleared, and then its production ceased during therapy. His neurological deficits improved and no pulmonary symptoms recurred.

Patient 2. A 70-year-old woman was admitted for mitral valve replacement. Postoperatively, severe respiratory failure developed, necessitating tracheotomy and mechanical ventilation. Cefazolin was given intermittently during the ensuing week. Severe, multilobe pneumonia then developed. Culture of sputum and bronchial aspirates yielded normal oral flora and *E. cloacae*. The *Enterobacter* strain was resistant to ceftazidime and other β-lactam antibiotics but susceptible to cefepime by disk-diffusion and agar-dilution assays (table 1). The patient was treated with cefepime for 2 weeks.

Signs and symptoms diminished during the first week. The patient was gradually removed from ventilatory support. Pulmonary infiltrates diminished by day 6 of treatment. *Pseudomonas aeruginosa* (susceptible to both cefepime and ceftazidime) transiently appeared in sputum cultures (days 4, 8, and 11 of therapy); it was considered to be a colonizer and was absent from subsequent cultures as the patient's condition improved. The patient was discharged, free of respiratory symptoms, 1 week following completion of therapy. She was well at a follow-up 2 weeks later.

Patient 3. A 77-year-old man was admitted for resection of a thoracoabdominal aneurysm. Ceftazidime was given for 2 days before surgery. Postoperatively, acute respiratory insufficiency developed, necessitating tracheostomy and ventilatory support; gastrointestinal bleeding and pseudomembranous enterocolitis also occurred. These problems resolved promptly with appropriate therapy, and the patient was removed from the intensive care unit.

Shortly thereafter, severe gastrointestinal bleeding occurred. Laparotomy was required to oversew a duodenal ulcer and to perform a vagotomy and pyloroplasty. The patient transiently did well and was weaned from the ventilator. However, acute respiratory failure developed and was associated with signs and symptoms of pneumonia. Left-lower-lobe consolidation and scattered small left-upper-lobe infiltrates were noted. Sputum became grossly purulent.

E. aerogenes and *Proteus mirabilis* were isolated. The *Proteus* strain was susceptible to a variety of antimicrobial agents, while the *Enterobacter* strain was resistant to ceftazidime and other β-lactam agents but susceptible to cefepime by disk-diffusion and agar-dilution assays (table 1).

The patient was given cefepime. Cough, dyspnea, and pulmonary findings markedly improved over the first few days of therapy. The patient was weaned from the ventilator on the sixth day. Sputum cultures performed on the fourth and seventh day of therapy yielded *P. aeruginosa* that was susceptible to both cefepime and ceftazidime. Chest radiographic findings on the sixth day appeared slightly worse, but the patient's symptoms were nearly all resolved. Consequently, therapy was not changed.

The patient's symptoms completely resolved over the next 24 hours, and no further sputum was produced. Therapy with cefepime was continued for a second week, as the chest radiograph showed signs of improvement. The patient was discharged shortly thereafter and had no recurrence of pulmonary symptoms at follow-up.

Patient 4. A 48-year-old man was admitted because of abdominal pain, which had increased in severity during 1 week. A subphrenic abscess was identified and drained surgically. Splenectomy was also performed. On the eighth postoperative day, fever, pleuritic chest pain, and shortness of breath developed. Ventilatory assistance was required. A chest radiograph suggested pneumonia in the left upper and lower lobes; left-lower-lobe inflammation was confirmed by a CT scan.

A sputum gram stain demonstrated ~20 WBCs and <5 epithelial cells per low-power field, with moderate numbers of gram-negative bacilli. Culture of sputum yielded *E. aerogenes* that was resistant to multiple β-lactam drugs, including ceftazidime, but susceptible to cefepime (table 1). The patient received cefepime, responded symptomatically, and was extubated 3 days later.

On the fifth day of therapy the patient's condition acutely deteriorated, with diminished breath sounds at the bases. A left pleural effusion was identified. The patient's respiratory status improved dramatically following thoracentesis; however, sputum cultures continued to yield *E. aerogenes.* Therapy was discontinued after 11 days. Bronchoscopic findings 2 days later were normal, although respiratory secretions contained *E. aerogenes.*

The organism was still susceptible to cefepime, although disk-zone diameters were smaller (reduced from 26 to 15 mm) and the MIC had risen to the intermediate range (0.25–16 μg/mL)]. It was resistant to multiple other β-lactam drugs. The change in degree of susceptibility to cefepime appeared to have resulted from an alteration in outer membrane (porin) proteins.

The patient's condition continued to improve, and he was discharged 4 days following completion of antimicrobial therapy. The plasmid profiles and pulsed-field gel electrophoresis patterns of pretreatment and posttreatment isolates were identical. It was concluded that the patient's pneumonia due to *E. aerogenes* was cured but that the etiologic agent persistently colonized respiratory secretions until sputum production ceased.

Patient 5. A 44-year-old man was admitted for treatment of severe congestive heart failure. After a few days in the hospital, dysuria and pyuria developed. Urinalysis revealed 15–19 WBCs and 3–4 RBCs per high-power field, as well as innumerable gram-negative bacilli. Culture of urine yielded $\geq$100,000 colonies of *E. aerogenes* per mL. The organism was susceptible to cefepime and resistant to ceftazidime by disk-diffusion and broth-dilution assays (table 1). The patient was given cefepime. Symptoms resolved promptly. Urine obtained after 5 days of therapy was sterile and microscopically normal.

Patient 6. A 69-year-old woman was admitted for surgery and radiotherapy of a glioblastoma. While she was in the hospital, signs and symptoms of an acute urinary tract infection developed. The patient became febrile and had a peripheral WBC count of 13,700/mm^3. Blood culture yielded *E. cloacae,* which was found to be susceptible to cefepime and resistant to ceftazidime by disk-diffusion test. She was given cefepime for 7 days. Local and systemic signs and symptoms of infection were resolved by day 4 of therapy. Subsequent WBC counts were normal. Follow-up urine cultures during weeks 1 and 2 after therapy were negative.

Patient 7. A 57-year-old man was admitted for transurethral resection of the prostate. He had previously had no other major medical problems. Postoperatively, fever, chills, and suprapubic and back pain developed, with pain and tenderness in the left scrotum, testicle, and lower quadrant of the abdomen. Leukocytosis with a left shift in differential count was noted on analysis of the peripheral blood.

Ultrasonography revealed fluid around the left testicle, which was thought to be inflammatory but without an abscess. Urine contained WBCs and numerous bacteria. Urine culture yielded $\geq$100,000 colonies of *E. aerogenes* per mL. Although this organism appeared to be susceptible to cefepime, ceftazidime, cefotaxime, ceftriaxone, and cefoperazone by disk susceptibility tests, it was highly susceptible to cefepime but had reduced susceptibility to the other cephalosporins when tested by agar-dilution assay (table 1).

The patient was treated with cefepime for 2 weeks. He was also given analgesics, ice packs, and scrotal support. Systemic signs and symptoms diminished significantly or resolved within 4 days. However, scrotal and testicular pain and swelling persisted into the second week of therapy and then slowly resolved. Urine cultures performed on the fourth day of therapy and in the second week after treatment were sterile.

Patient 8. A 50-year-old woman was admitted because of a posttraumatic frontoparietal hematoma and malnutrition. She was severely dehydrated and protein depleted. Massive fluid replacement was required. The hematoma resolved without evacuation. Shortly after admission pneumococcal pneumonia and a urinary tract infection developed, and both were treated effectively with ampicillin. Ventilatory support was required for the acute illness and throughout most of her subsequent hospitalization.

She survived an episode of acute respiratory distress syndrome and was treated for 2 weeks with ticarcillin, gentamicin, and vancomycin for suspected bacterial sepsis. Nine days later,

fever, leukocytosis, and pyuria were noted. A urine culture yielded significant numbers of *P. mirabilis* organisms that were susceptible to a variety of agents and *E. aerogenes* that was susceptible to cefepime but resistant to other cephalosporins (table 1).

The patient was given cefepime (2 g intravenously every 12 hours) for 8 days. There was prompt resolution of fever and of hematologic and urinary abnormalities. Urine cultures were sterile on the third day and 1 week following therapy. She was seen at follow-up 6 and 10 weeks later and had no symptoms referable to the urinary tract.

Patient 9. A 69-year-old man was admitted because of bowel obstruction. Adhesions were lysed successfully, but an abdominal wound infection developed 4 days postoperatively. Cefoxitin and gentamicin were administered for 5 days but produced no response. The patient continued to experience tenderness, warmth, erythema, and induration, with purulent drainage and peripheral leukocytosis. Informed consent was obtained and the patient was randomized to receive cefepime.

Culture of wound drainage fluid revealed *E. cloacae* and four other organisms, including both aerobic and anaerobic species. The *Enterobacter* isolate was susceptible to cefepime but highly resistant to ceftazidime (table 1). The patient received treatment with cefepime and local wound care for 4 days. The antimicrobial regimen was then terminated (as required by protocol) because of the isolation of other organisms that were resistant to a study drug.

Of interest was the patient's response during the brief course of cefepime. By the end of the fourth day, all signs and symptoms of the wound infection had resolved. The WBC count had returned to normal and drainage had ceased. The patient continued to do well when switched to "conventional" therapy.

Patient 10. A 70-year-old man was admitted because of abdominal pain, nausea, and vomiting. His medical history included pancreatic disease and other diseases involving multiple organ systems, as well as recent abdominal surgery (appendectomy and cholecystectomy). Diagnostic studies revealed a soft-tissue mass suggestive of pancreatic abscess or phlegmon. The patient started receiving cefoxitin. Percutaneous aspiration yielded *Enterococcus faecalis,* and the patient was switched to therapy with sulbactam/ampicillin. Subsequent abdominal cultures yielded *Escherichia coli* and occasionally *Candida albicans.*

The patient then suffered acute gastrointestinal bleeding that required surgery. A large gastric ulcer penetrating into the head of the pancreas was identified. There was also a large pancreatic mass that appeared to have eroded into the stomach. The patient required hemodynamic support postoperatively and did well for a few days, until the abdominal wound dehisced. A fistulous tract from the abdominal wound to the stomach and pancreas was identified.

The surgical wound was cultured and yielded *E. cloacae, P. aeruginosa,* an *Enterococcus* species, and *C. albicans.* The latter two organisms were thought to be superficial contaminants. The *Pseudomonas* isolate was susceptible to both cefepime and ceftazidime, while the *Enterobacter* isolate was susceptible to cefepime and marginally susceptible or resistant to other cephalosporins (table 1).

The patient started receiving cefepime. The surgical wound site improved promptly and the *Enterobacter* and *Pseudomonas* species organisms were eradicated. However, the patient's general condition deteriorated, with advancing renal failure and mental confusion. As required by protocol, cefepime was withdrawn after 14 days because of diminished creatinine clearance and the probable need for dialysis.

Patient 11. A 48-year-old woman was admitted because of postoperative wound dehiscence and infection. Two weeks earlier she had undergone a total abdominal hysterectomy. Symptoms on admission included fever, chills, vomiting, wound pain, and purulent drainage.

The wound culture contained group A streptococci, *S. aureus,* and *E. aerogenes.* All three organisms were susceptible to cefepime. The *Enterobacter* isolate was marginally susceptible to ceftazidime (table 1) and was of similar to intermediate susceptibility to other cephalosporins, including cefotaxime. The patient was treated with cefepime for 10 days, povidone-iodine baths twice daily, and local wound care. Signs and symptoms of infection resolved promptly. Cultures of the wound at the end of therapy yielded no pathogens. The clean wound was surgically closed and the patient did well.

Patient 12. A 64-year-old man was admitted for further treatment of known cholangiocarcinoma. While in the hospital the patient had rigors and fever associated with infection of a biliary fistula. This occurred despite administration of gentamicin, mezlocillin, and metronidazole for several days during the preceding week. Hypotension and right-upper-quadrant pain developed.

Culture of biliary drainage and blood yielded *E. cloacae.* The bile isolate was found to be susceptible to cefepime and resistant to ceftazidime by disk-diffusion and dilution assays (table 1). The blood isolate appeared to be susceptible to both drugs; unfortunately, a dilution assay was not performed. The patient started treatment with a regimen of cefepime and metronidazole (not active against *Enterobacter* species). Defervescence occurred rapidly, and other signs of infection disappeared. Transient improvement in tests of hepatic function was also noted.

Administration of cefepime was continued for 12.5 days, with no recurrence of signs or symptoms of infection. *E. cloacae* was absent from each of four subsequent cultures of biliary drainage, including cultures performed at 3 and 11 days post-therapy. Other enteric organisms were intermittently isolated, but in the absence of signs of infection they were considered to be colonizers. Shortly thereafter, renal failure and inanition progressed rapidly, and the patient died. Death was thought to be unrelated to the infection or to previous antimicrobial therapy.

Patient 13. A 58-year-old man was admitted because of fever and signs and symptoms of a urinary tract infection. Urine culture yielded *E. coli* that was susceptible to a variety of antimicrobials, including cefepime. Blood cultures performed on 2 consecutive days yielded *E. cloacae.* Each of three blood isolates appeared to be susceptible to cefepime and ceftazidime by disk-diffusion tests but susceptible to cefepime and of reduced susceptibility to ceftazidime when tested by a dilution procedure (table 1).

The patient was treated with cefepime for 10 days. Signs and symptoms of infection resolved within 4 days. Urine cultures became negative after 24 hours. The patient was discharged 1 day after treatment. Follow-up cultures were not performed.

Patient 14. A 69-year-old woman was admitted because of colicky, right-upper-quadrant abdominal pain; the clinical diagnosis was acute cholecystitis. The patient started therapy with cefepime and underwent surgery. The gallbladder was found to be enlarged and gangrenous, with multiple stones. There was a small amount of pericholecystic fluid. Cholecystectomy was performed.

Infected surgical tissue contained *P. aeruginosa* (susceptible to cefepime and other antipseudomonal β-lactam drugs), *E. faecalis* (marginally resistant to cefepime and highly resistant to ceftazidime and cefotaxime), and *E. aerogenes* (susceptible to cefepime and highly resistant to ceftazidime). The patient did well postoperatively, and all signs and symptoms of infection resolved. Biliary drainage was sterile on the second day of antimicrobial therapy. After 5 days of drug therapy, the patient was discharged. The patient was doing well at follow-up 1 month later.

Patient 15. A previously well 56-year-old woman was admitted because of osteomyelitis and soft-tissue infection after internal fixation of an open, comminuted fracture of her right tibial plateau. The severe fracture had occurred when the patient fell while vacationing, and the open reduction and internal fixation had been performed immediately.

Three weeks later, the osteomyelitis was diagnosed. A course of oral antibiotics (nature unknown) was unsuccessful. Culture of infected tissue revealed *E. aerogenes* that was reportedly multiply resistant but susceptible to imipenem and gentamicin. Therapy with these two agents was begun and continued for 2.5 months. Response was poor, and the infecting organism developed resistance to both imipenem and gentamicin.

The patient was admitted and five surgical procedures were performed, including removal of implanted hardware, multiple debridements, and myocutaneous grafting. Unfortunately, culture specimens obtained during the last procedure yielded *E. aerogenes* that was resistant to all β-lactam antibiotics, all aminoglycosides, and imipenem. Draining sinuses persisted. Compassionate use of cefepime was requested, and informed consent was obtained.

The multiply resistant *Enterobacter* was susceptible to cefepime (table 1), and it was administered to the patient. She was discharged 4 days later and continued treatment with this regimen at home. Pain and drainage resolved within 1 month, while other symptoms of infection diminished. Healing and new bone formation were demonstrated radiographically. Therapy was continued.

Toward the end of the second month of treatment, a nonpruritic rash developed that worsened during administration of an antihistamine. Given the satisfactory clinical response of the infection and the possibility of a drug-related cutaneous reaction, cefepime therapy was discontinued after 53 days. The patient's condition continued to improve without further antimicrobial therapy. Follow-up over the next 2 months revealed new bone deposition on radiographic examination and no clinical evidence of recurrence of infection.

Patient 16. A 15-year-old girl with recently diagnosed acute nonlymphocytic leukemia was admitted for treatment of septic arthritis of the left elbow and right knee due to *E. cloacae.* She had undergone a bone marrow transplantation, which was followed by the development of severe graft-versus-host disease. She was initially treated with ceftriaxone and tobramycin but relapsed a few weeks later. The organism remained susceptible to these agents. Both the 5- and 6-week courses of the combination were followed by relapse of infection in the right knee. After the third relapse, *E. cloacae* was found to be resistant to all available cephalosporins but susceptible to imipenem, quinolones, and aminoglycosides.

The patient was treated with ciprofloxacin and tobramycin intravenously for 2 weeks. Since cultures of specimens from the infected site had become negative, the patient was switched to therapy with high-dose oral ciprofloxacin and intravenous tobramycin. Three weeks later symptoms of infection recurred. Aspirates yielded *E. cloacae,* now resistant to all quinolones tested as well as to all available β-lactam agents. The organism was susceptible to cotrimoxazole, but the patient was allergic to this combination.

MRI revealed an extensive abscess in the right thigh. The patient, who was believed to be seizure-prone, was given imipenem in gradually increasing doses, and the abscess was drained surgically. There was no clinical response, and the *Enterobacter* species continued to be recovered from the knee and soft tissues of the thigh. This multiply resistant organism was found to be susceptible to cefepime (table 1). The patient was given cefepime plus tobramycin for 48 days.

Two additional debridement procedures were performed on the thigh during the first week of this regimen. Several cultures of knee and thigh specimens were sterile after 72 hours of treatment. The thigh wound gradually healed, and drainage ceased. Joint aspirates obtained 2 and 3 days after therapy were sterile. The patient did well without administration of antimicrobials and no recurrence was noted when she was seen at follow-up 6 months later. Nearly 1 year after the original operation, inflammation developed around the patient's knee, and an *Enterobacter* species organism—still susceptible to cefepime—was recovered from a synovial aspirate.

Cefepime was administered in combination with tobramycin. On the basis of the joint condition, an above-the-knee amputa-

tion was performed 1 week after therapy was initiated. Therapy was continued 2 weeks postoperatively, and when the patient was sent home the stump was healing.

Discussion and Conclusions

The clinical and microbiological data from trials and instances of compassionate use of cefepime confirm predictions based upon studies in vitro and in experimental animals. Strains of *Enterobacter* resistant to ceftazidime and its congeners are often susceptible to cefepime, and the drug is clinically effective in patients infected with these organisms. In this study, all isolates with reduced susceptibility or resistance to ceftazidime were susceptible to cefepime. Since all strains tested were also multiply resistant to other β-lactam drugs, the most likely mechanism of resistance would be stable derepression of the Bush group 1 β-lactamase [6].

In an in vitro study, 100% of strains of *Enterobacter* with proven stable derepression were susceptible to cefepime [7]. Furthermore, as cephalosporin-susceptible strains become derepressed by mutation (stable) or induction (reversible), multiple resistance develops to drugs such as ceftazidime [6]. MIC values for cefepime may rise during these processes, but they remain within the susceptible range, accounting for the efficacy of this agent in experimental and human infections.

Emergence of resistance among organisms with group 1 β-lactamases appears less likely with cefepime than with other cephalosporins in vitro [3] and in murine infections [4, 5]. In none of the patients reported herein did resistance to cefepime emerge. One isolate (from patient 4) that persistently colonized sputum was of intermediate susceptibility (16 μg/mL). Reported rates of emergence of resistance to other cephalosporins have varied from 19% to 80%, depending upon the location of the infection and the status of host defense mechanisms [8]. Hence, had one of these other cephalosporins been given to the patients reported herein, 3–13 instances of emergence of resistance would have been predicted.

On the basis of studies with previous agents, the high success rate of cefepime among these patients, most of whom were acutely ill with severe underlying diseases, was somewhat unexpected [9–12]. It is possible that the greater intrinsic potency of cefepime and the lower rate of emergence of resistance account for the observed differences in efficacy. Clearly, larger numbers of patients should be treated to confirm this observation and to provide an explanation if it is verified.

As exemplified by this study, the majority of patients in whom enterobacter infections develop have one or more major underlying diseases that compromise host defenses. Those infected with multiply resistant organisms have usually received a broad-spectrum cephalosporin in preceding weeks [12]. Soft-tissue and intraabdominal infections often require surgery for an optimal outcome. The investigators who cared for these patients clearly paid meticulous attention to detail and recognized the need for a multiplicity of therapeutic modalities in addition to use of cefepime to ensure success.

In the future, additional patients with multiple β-lactam resistance should be studied. Attention should be devoted especially to other genera with group 1 β-lactamases, such as *Citrobacter, Serratia,* and *Pseudomonas* species. At present, too few patients infected with multiply resistant strains of these other genera have been treated in order to permit meaningful assessments of outcome. However, because of similarities between their mechanisms of resistance and those of *Enterobacter* species, cefepime may have efficacy against these pathogens also.

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