



Published in final edited form as:

Expert Rev Anti Infect Ther. 2008 December ; 6(6): 805–824. doi:10.1586/14787210.6.6.805.

Cefepime: a reappraisal in an era of increasing antimicrobial resistance

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Abstract

Cefepime is a ‘fourth-generation’ cephalosporin with an *in vitro* extended-spectrum of activity against Gram-negative and Gram-positive pathogens. Cefepime is approved for the treatment of moderate-to-severe infections, such as pneumonia, uncomplicated and complicated urinary tract infections, skin and soft-tissue infections, intra-abdominal infections and febrile neutropenia. In this article, we provide a critical review of pharmacodynamics, clinical management, pharmacokinetics, metabolism, pharmacodynamic target analyses, clinical efficacy, safety and tolerability of cefepime after more than a decade of clinical use.

Keywords

cephalosporin; ESBL; extended-spectrum β -lactamase; susceptibility

Cefepime is a ‘fourth-generation’ cephalosporin with an *in vitro* extended-spectrum of activity against Gram-negative and Gram-positive pathogens. Cefepime was introduced into clinical practice in 1994 and is approved for the treatment of moderate-to-severe infections, such as pneumonia, uncomplicated and complicated urinary tract infections (UTIs), skin and soft-tissue infections, intra-abdominal infections and febrile neutropenia.

In the past 15 years, we have observed an increased occurrence of multidrug-resistant Enterobacteriaceae, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Staphylococcus aureus* in the community, long-term care and hospital settings, posing serious problems in the choice of an appropriate antibiotic treatment [1,2]. In this article, we provide a critical reappraisal of cefepime after more than a decade of clinical experience.

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Chemistry

The chemical structure of cefepime is represented in Figure 1. As shown, cefepime is a zwitterionic oxymino β -lactam with an amino-thiazole side chain.

Pharmacodynamics

Mechanism of action

Cefepime, similar to other β -lactams, inhibits bacterial cell wall biosynthesis by covalent attachment to penicillin-binding proteins (PBPs) and impedes the final transpeptidation step of peptidoglycan synthesis. Bacteria exposed to a concentration of cefepime above their MIC lyse due to the combined inhibition of PBPs and ongoing activity of cell wall autolytic enzymes (autolysis and murein hydrolases) [3].

Unlike other extended-spectrum cephalosporins, the methylpyrrolidinium group of cefepime confers a zwitterionic charge that enhances bactericidal activity by rapid penetration through the porin channels in the outer membrane of Gram-negative pathogens [4,5]. In addition, *in vitro* studies and clinical observations suggest that cefepime may select for resistance at a lower rate than other extended-spectrum cephalosporins [6,7]. For example, *in vitro* development of resistance to cefepime versus other β -lactams (i.e., ceftazidime, ceftaxime, piperacillin and imipenem) in *P. aeruginosa* was evaluated. Stepwise resistance was assessed by serial passage of colonies located nearest to the inhibition zone. The lowest frequencies of spontaneous resistance mutations were found with cefepime and imipenem. These drugs also resulted in the slowest appearance of resistance by spontaneous mutations: cefepime-selected isolates required a mean of 30 passages to reach resistance, whereas resistance occurred more rapidly in strains selected with other cephalosporins [8].

Mechanism of resistance in Gram-negative organisms

The most frequent mechanism of resistance expressed by Gram-negative organisms against cefepime is the production of β -lactamases that are able to hydrolyze the drug [9]. Enterobacteriaceae (e.g., *Escherichia coli* and *Klebsiella* spp.) demonstrate resistance to cefepime by producing class A extended-spectrum β -lactamases (ESBLs) or, more rarely, carbapenemases of class A (e.g., *Klebsiella pneumoniae* carbapenemases) or class B (e.g., VIM and IMP metallo- β -lactamases) [9-12].

Resistance to cefepime in *P. aeruginosa* is generally mediated by the combination of hyperproduction of class C chromosomal enzymes (i.e., AmpC) and/or upregulation of efflux pumps [13]. Among *P. aeruginosa*, there is basal production of chromosomal AmpC β -lactamases that generally does not result in full resistance to cefepime. However, some of these strains produce high levels of AmpC β -lactamases, due to induction or complete derepression, and become fully cefepime resistant [13]. This phenotype is usually observed in isolates from intensive care unit (ICU) patients and patients with cystic fibrosis (CF) who frequently receive multiple treatment courses of expanded-spectrum β -lactam antibiotics for prolonged periods [13,14]. A phenotype commonly observed among *P. aeruginosa* is resistance to cefepime and susceptibility to ceftazidime; this is due to over-expression of the MexXY-OprM efflux system [15]. In certain geographic regions, production of metallo- β -lactamases is also an important mechanism of resistance that may be found in *P. aeruginosa* [10,13,16].

Cefepime resistance is demonstrated in *A. baumannii* by a combination of hyperproduction of the chromosomal OXA-51/69-like carbapenemases, activation of efflux pumps (i.e., AdeABC) and probably porin changes [17,18]. The expression of OXA-type carbapenemases in the absence of the other mechanisms of resistance does not result in high-level cefepime resistance [19]. Similarly, expression of chromosomal *Acinetobacter*-derived cephalosporinase by *A.*

baumannii does not seem to confer resistance [20]. By contrast, production of certain acquired class D OXA-type carbapenemases and/or metallo- β -lactamases are important mechanisms of resistance against cefepime [10,13,16,17,21].

As shown in Table 1, Ambler class A ESBLs (e.g., TEM-, SHV- and CTX-M-type) show high affinity for cefepime, similar to that expressed against cefotaxime and ceftazidime. By contrast, cefepime has a much lower affinity for chromosomal or plasmid-mediated AmpC β -lactamases than cefotaxime or ceftazidime [9,22,23]. Cefepime is also hydrolyzed less than ceftazidime by carbapenemases of Ambler class A and class B [10,19,21,24].

Mechanism of resistance in Gram-positive organisms

The major mechanism conferring resistance to cefepime in Gram-positive bacteria is changes in the PBPs. Cefepime exhibits low affinity for PBP-2a in methicillin-resistant staphylococci and low affinity to PBP-4 and PBP-5 in *Enterococcus* spp. [25-27].

In vitro activity

Data regarding the *in vitro* activity of cefepime compared with ceftazidime and imipenem against clinical isolates of Enterobacteriaceae, Gram-negative non-Enterobacteriaceae and Gram-positive bacteria are summarized in TABLES 2, 3 & 4. The majority of published antimicrobial susceptibility data are interpreted according to Clinical and Laboratory Standards Institute (CLSI) criteria, and this may underestimate resistance [28]. Notably, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) asserts that resistance breakpoints should be much lower than CLSI criteria [201]. A comparison of the two criteria is shown in Table 5.

Clinical isolates of Enterobacteriaceae are frequently susceptible to cefepime (Table 2). Cefepime's activity is similar to that of ceftazidime against organisms such as *Klebsiella* spp. and *Proteus mirabilis*, which do not possess AmpC chromosomally mediated β -lactamases. By contrast, Enterobacteriaceae that harbor inducible chromosomal AmpC β -lactamases, such as *Citrobacter* spp., *Enterobacter* spp., *Hafnia* spp., *Morganella morganii*, *Proteus vulgaris*, *Providencia* spp. and *Serratia marcescens* are typically resistant to other extended-spectrum cephalosporins, while cefepime maintains its activity (Table 2). Even in the case of high-level production of AmpC β -lactamases, ceftazidime-resistant Enterobacteriaceae may still be in the susceptible range for cefepime. For example, only 5% of clinical *Enterobacter* spp. strains show resistance (Table 2). Consequently, cefepime is an attractive clinical choice for the treatment of infections caused by these organisms, even in the presence of increased production of the AmpC β -lactamases [29]. As shown by EUCAST guidelines (Table 5), Enterobacteriaceae producing AmpC enzymes often have slightly elevated MICs for cefepime (e.g., between 2 and 8 mg/l). This phenomenon might affect the clinical outcome of patients with serious infections, such as bacteremia [30]. To date, clinical studies analyzing the outcome of patients treated with cefepime compared with other cephalosporins are very limited.

Recent data from Europe and America show that ESBL-producing *E. coli* and *K. pneumoniae* isolates tested susceptible to cefepime in 39.6 and 51.4% of cases, respectively (Table 2) [31]. In the Asia-Pacific region, among organisms expressing an ESBL phenotype, susceptibility to cefepime ranged from 33 to 93% for *E. coli*, from 25 to 100% for *K. pneumoniae*, from 33 to 100% for *E. cloacae* and from 0 to 57% for *P. mirabilis* [32,33]. In a European survey conducted in 2004, the susceptibility of cefepime against ESBL-producing *E. coli* and *Klebsiella* spp. isolates was 25.6 and 63.6%, respectively [34]. Although many *in vitro* studies have shown that ESBL-producing Enterobacteriaceae are susceptible to cefepime (i.e., MIC \leq 8 mg/l), it is important to note that these isolates must be reported by clinical laboratories as resistant to cefepime (e.g., all penicillins and cephalosporins), according to

CLSI criteria [28]. For ESBL-producing enterobacteria, the EUCAST criteria suggest reporting any susceptible results as intermediate and any intermediate results as resistant [202].

Approximately 10-35% of *P. aeruginosa* isolates are resistant to cefepime (Table 3). The activity of cefepime against other *Pseudomonas* spp. is variable: *P. putida*, *P. fluorescens* and *P. oryzae* show susceptibilities of 80-85%, whereas resistant *P. stutzeri* isolates are extremely rare [35].

As shown in Table 3, clinical isolates of *A. baumannii* are frequently resistant to cefepime (i.e., >45% of isolates). Interestingly, this may be largely dependent upon clones that are prevalent in certain geographic locations (e.g., 85% susceptible in North America). The majority of strains of *Stenotrophomonas maltophilia* and *Burkholderia cepacia* complex show MICs of greater than 8 mg/l (Table 3). Notably, EUCAST does not report susceptibility breakpoints for cefepime against *Acinetobacter* spp., *S. maltophilia* and *B. cepacia*, as most isolates have MICs of greater than 8 mg/l (Table 5).

Clinical isolates of *Haemophilus influenzae* appear fully susceptible to cefepime (Table 3). With regard to *Moraxella catarrhalis*, high values of MIC_{50/90} were recorded among clinical isolates (Table 3). Data regarding cefepime susceptibility in clinical strains of *Neisseria meningitidis* and *N. gonorrhoeae* are very limited (Table 3).

Although criteria of interpretation have not been established, the activity of cefepime appears poor against Gram-negative anaerobes such as *Bacteroides* spp., *Prevotella* spp. and *Fusobacterium* spp. [36-38].

Cefepime MIC values for clinical isolates of *Streptococcus pneumoniae* are comparable to those of ceftriaxone. In these strains, the MICs of cefepime are consistently lower than the MICs of penicillin G [39,40]. At least 95% of penicillin-intermediate and 80% of penicillin-resistant isolates remain susceptible to cefepime (Table 4) [41].

Oxacillin-susceptible *S. aureus* and coagulase-negative staphylococci, β -hemolytic streptococci and viridans group streptococci are susceptible to cefepime (Table 4). As is the case with other cephalosporins, methicillin-resistant staphylococci and *Enterococcus* spp. are resistant to cefepime [28].

Clinical management & dosage

Cefepime is usually administered by the intravenous or intramuscular routes in doses of 0.5, 1 and 2 g. Each intravenous dose is usually diluted in 50 or 100 ml of compatible intravenous fluid, which is then administered as a 30-min infusion.

According to data from clinical trials, the following dosing schedules are recommended:

- Moderately severe infections such as pneumonia due to *S. pneumoniae* and/or Gram-negative organisms: 1-2 g intravenously every 12 h for 10 days;
- Mild/moderate uncomplicated or complicated UTIs, including pyelonephritis, due to Enterobacteriaceae: 0.5-2 g intravenously every 12 h for 7-10 days;
- Moderate/severe skin and soft-tissue infections due to *S. aureus* or *Streptococcus pyogenes*: 2 g intravenously every 12 h for 10 days;
- Intra-abdominal infections: 2 g intravenously every 12 h for 7-10 days.

In neutropenic fever, the suggested dosing is 2 g intravenously every 8 h for at least 7 days. Notably, many clinicians use cefepime in suspected or confirmed Gram-negative infections of

the CNS. Although not approved for this, the 2 g intravenously every 8 h dosing regimen is followed [42]. The usual dosage in pediatric patients (2 months up to 16 years) is 50 mg/kg every 12 h (50 mg/kg every 8 h for febrile neutropenic patients).

Pharmacokinetics & metabolism

Serum levels

Pharmacokinetic parameters after intravenous and intramuscular administration of cefepime in healthy adults and patients with different levels of renal function are shown in Table 6.

In pediatric patients, following single and multiple doses of 50 mg/kg every 8-12 h, the average peak serum level (C_{max}) ranged from 130 to 180 mg/l, whereas, for a dose of 30 mg/kg every 8-12 h, it was 114 mg/l. After 8 h from the first intravenous or intramuscular dose of 50 mg/kg, the serum concentration was approximately 5 mg/l in both cases. The mean elimination half-life was 1.3-1.9 h and the average steady state C_{max} of the 50-mg/kg intravenous regimen was 177 mg/l for every 12 h and 188 mg/l for every 8 h [43].

The pharmacokinetics of cefepime 2 g intravenously every 12 h was measured in critically ill patients with normal serum creatinine [44]. The mean plasma cefepime concentration after 12 h from the first dose was 3.2 mg/l and the mean half-life was 2.5 h. There was a large variation in plasma drug concentrations among patients, and a number of patients had very low plasma cefepime levels (median: 1.9 mg/l). Trough levels after multiple doses were low (median: 1.7-1.8 mg/l). The clinical consequences of these low levels may be important if they involve inadequate bacterial killing or the development of resistance. The large scatter in trough levels could be accounted for by the variability in creatinine clearance (ClCr) of patients who were critically ill and, therefore, probably had renal dysfunction [44].

In burn patients receiving intravenous cefepime 2 g every 12 h, the C_{max} after infusion ranged from 89 to 146 mg/l at day 1 and from 72 to 243 mg/l at day 3. The average cefepime concentrations 12 h after the beginning of infusion were 2.1 and 2.4 mg/l, respectively, at day 1 and 3. The mean half-life was 2.5 h on day 1 and 2.6 h on day 3 [45].

Distribution in body sites

The average steady-state volume of distribution of cefepime is 18.0 ± 2.0 l. The serum protein binding is approximately 20% [46]. As shown in Table 6, total body clearance (Cl_T) ranges from 122 to 136 ml/min within doses of 0.25-2 g. The mean renal clearance (Cl_R) of 105 ml/min is nearly the same as that of ClCr in normal adults [47].

In adult patients with external ventricular drains who received cefepime (2g intravenously every 12 h) for the treatment of pneumonia, penetration into the CNS was variable (4-34%), but appeared similar to that reported for other cephalosporins administered to treat meningitis. In the CNS, the C_{min} attained by most patients at the steady state was 2 mg/l [48]. In children, after the third dose (50 mg/kg intravenously every 8 h), concentrations in the cerebrospinal fluid (CSF) were 3.3 mg/l at 0.5 h and 5.7 mg/l at 8 h (9 and 67% of plasma concentration, respectively) [49].

In patients undergoing diagnostic bronchoscopy, after a single 2-g dose of cefepime, the mean bronchial mucosal concentration of the drug was 24 μ g per gram of tissue and the mean serum concentration was 40.4 mg/l [50]. The concentration of cefepime in the epithelial lining fluid of critically ill patients with bacterial pneumonia was determined at steady state after 48 h of therapy, using 2 g intravenously, followed by a continuous infusion of 4 g over 24 h. The mean epithelial lining fluid concentration was 14 mg/l [51]. Pharmacokinetic parameters were also studied at the steady state in patients subjected to lung surgery for lung cancer. Cefepime was

administered in a dose of 2 g every 12 h for 2 days with a final dose of drug administered 0.5-12 h before pulmonary artery clamping. The mean concentration into the lung was 120 µg/g at 0.5 h, 12 µg/g at 8 h and 9 µg/g at 12 h (94, 108 and 112% of plasma concentration, respectively) [52].

In patients undergoing vitreous surgery, a single 1- or 2-g intravenous dose of cefepime before the intervention resulted in a mean peak vitreous concentration of 1.9 and 2.9 mg/l, respectively. The level of cefepime in the vitreous at 12 h was 0.9 and 1.0 mg/l, respectively [53].

Cefepime concentration in the peritoneal fluid and bile was evaluated in patients undergoing elective cholecystectomy receiving 2 g intravenously every 12 h. After approximately 8.5 h the values for plasma, peritoneal fluid, bile and gall bladder tissue concentrations were 8, 6 and 16 mg/l and 5 mg/g, respectively. There was a correlation between plasma concentration and peritoneal fluid or gall bladder tissue concentrations. By contrast, a correlation was not found between bile and plasma concentrations [54]. In one study of patients with extra-hepatic biliary disease, cefepime concentrations in bile and gall bladder tissue were 20 and 48 mg/l (20 and 48% of serum level, respectively). Also in this case, a correlation between serum and bile concentrations of the drug was not observed. Notably, in patients with nonfunctioning gall bladder, very low tissue levels of cefepime (<0.2 mg/l) were measured [55].

After a 2-g intravenous dose, the concentration of cefepime in pancreatic pseudocyst fluid and pancreatic tissue was 27 mg/l (120-200 min after the end of infusion). Mean pancreatic cefepime concentration was 6 mg/l in pseudocyst and 11 mg/l in pancreatic tissue [56].

Bone tissue penetration of cefepime at a dose of 2 g intravenously was evaluated in patients undergoing total hip replacement. The mean plasma concentration of cefepime at the time of bone removal was 73 mg/l, whereas the mean concentrations in cancellous and cortical bone tissues were 74 and 68 mg/l, respectively [57].

Excretion & inactivation

Cefepime is primarily eliminated via the kidney as the unchanged active drug. Urinary recovery of intact cefepime is approximately 80% of the administered dose (Table 6) [47,58]. The urinary recovery of intact cefepime was consistent among the various dosages (0.25-2 g) every 8 h during the course of treatment. Differences in the percentage of cefepime excretion on day 9 among the dose groups were not found [46]. After administration of a low-dose of 0.25 g intravenously, cefepime concentrations in urine were 190 mg/l during the first 2 h and 90 mg/l at 8 h [47]. In pediatric patients, the renal excretion was 60% for treatments of 50 mg/kg every 8 h and 80% for regimens every 12 h [43]. Cefepime is excreted in human milk: an infant receiving 1 l/day of milk receives approximately 0.5 mg of the drug.

Approximately 10-20% of the administered dose of cefepime is metabolized to *N*-methylpyrrolidine (NMP) and rapidly converted to the *N*-oxide (NMP-*N*-oxide). Less than 1% of the administered dose is recovered from urine as NMP, approximately 7% is recovered as NMP-*N*-oxide and 2-3% is recovered as an epimer of cefepime [59].

Special populations

Elderly patients

Due to the progressive decline of the glomerular filtration rate, the normal cefepime terminal half-life of 2 h observed in young volunteers is prolonged to approximately 3 h in the elderly (>65 years of age). However, the magnitude of age-related changes in the pharmacokinetics of cefepime is not significant enough to recommend dosage adjustment in elderly patients with normal kidney function [60].

Renal insufficiency

A dosage reduction is necessary in patients with renal failure. If there is renal impairment, but ClCr is still greater than 30 ml/min, a dose of 1 g every 12 h is recommended. If ClCr is 10-30 ml/min, the dosage is 0.5 g every 24 h, but if ClCr is less than 10 ml/min, the suggested dosage is 0.25 g every 24 h. If patients are treated with hemodialysis, a supplementary dose of 0.25 g is recommended after each hemodialysis session [61]. In patients undergoing continuous ambulatory peritoneal dialysis, an intravenous cefepime dose of 1 or 2 g every 48 h would maintain the antibiotic levels in plasma and peritoneal fluid above the MIC₉₀ values of common enteric bacteria responsible for intraperitoneal infections [46]. Pharmacokinetic models suggest that most automated peritoneal dialysis patients would achieve adequate serum cefepime concentrations if treated with standard doses of 1 g every 24 h administered intraperitoneally [62].

The pharmacokinetics of drug removal in critically ill patients receiving continuous renal replacement therapy is affected by multiple variables influencing clearance [63]. However, if the goal in critically ill patients is to maintain a therapeutic concentration of cefepime for the entire dosing interval, a normal, unadjusted dose may be used. In fact, a cefepime dosage of 1 g every 12 h is appropriate for most patients receiving continuous venovenous hemofiltration and a dosage of up to 2 g every 12 h is appropriate for patients receiving continuous venovenous hemo dialysis or receiving continuous venovenous hemodiafiltration [64,65].

Children

In neonates with severe nosocomial infection, the dose regimen should take in to consideration the ClCr and the body surface area. Cefepime therapy using 250 mg/m² every 12 h is adequate to achieve plasma concentrations of at least 8 mg/l during more than 60% of the dosing interval and is expected to be effective in the treatment of bloodstream infections caused by most Gram-negative organisms. A dose of 550 mg/m² would be required for the treatment of infections caused by *Pseudomonas* spp. [66].

Cystic fibrosis

The elimination half-life of cefepime in patients with CF is 11% shorter than in other patients, and the clearance is almost 40% higher. However, the difference in pharmacokinetics is minor and changes in dosage are not usually recommended. *P. aeruginosa* isolates with high MICs against cefepime are responsible for the majority of respiratory infections in CF patients; therefore, a dosage of 2 g every 6 h or 50 mg/kg every 8 h is recommended to maintain adequate serum levels [67,68].

Burn patients

After 12 h following a dose of 1 g, the cefepime concentrations measured in burned skin were 33 ± 41.6 µg/g [45]. In another study, a single 2-g dose of cefepime was evaluated in patients with thermal burn injury and infection. Simulated steady-state serum concentrations obtained by using the patients' pharmacokinetic parameters exceeded the susceptibility interpretive standard of cefepime for at least 60% of the dosing interval, with dosing regimens of 1 g every 8 h, 2 g every 8 h and 2 g every 12 h. It appeared that these dosing regimens were clinically adequate [69].

Pharmacodynamic target analyses

It is well documented that clinical success with cefepime correlates with the percentage of time (%T) that the concentration of the antibiotic in serum exceeds the MIC (%T > MIC) for the infecting organism [70]. In animal models of infection caused by Enterobacteriaceae and streptococci, maximal efficacy for cephalosporins is obtained when %T > MIC occurs during

60-70% of the dosing interval. For staphylococci, efficacy is demonstrated when %T > MIC occurs during 40-50% of the dosing interval. The recommended dose of cefepime is sufficient to attain these goals for susceptible organisms [71]. For example, cefepime intravenous dosing regimens of 1 g every 8 h, 2 g every 8 h and 2 g every 12 h have the greatest likelihood of achieving this pharmacodynamic target against isolates of fully susceptible (i.e., MICs < 1 mg/l) Enterobacteriaceae [72,73].

By contrast, there is concern that standard treatments of 2 g every 8-12 h are not able to attain such targets and eradicate serious infections due to ESBL-producing Enterobacteriaceae, *P. aeruginosa* and *A. baumannii* isolates. Furthermore, cefepime continuous monotherapy infusion (i.e., 4 g infused for a 24-h period) seems unable to achieve these targets against *P. aeruginosa* and *A. baumannii* [72,73]. Patients infected with ESBL-producing Enterobacteriaceae, *P. aeruginosa* and *A. baumannii* have a much lower %T > MIC than patients with fully susceptible organisms. This is due to the significantly greater MIC values of those organisms, even when still considered 'susceptible'. To illustrate, standard dosing recommendations resulted in a C_{min} that was greater than the MIC in more than 80% of the simulated *P. aeruginosa* strains with a maximum MIC of 2 mg/l. By contrast, the same regimens were suboptimal for less-susceptible *P. aeruginosa* isolates (e.g., those with MIC \geq 4 mg/l) [58].

It has been observed that, in order to achieve a probability of 80 and 90% 'microbiological success', it would be necessary for serum cefepime concentration to be above 4.3-times the MIC for 83% and 95% of the dosing interval, respectively [74]. The pharmacodynamic target (i.e., $4.3 \times$ MIC for 83% of the dosing interval) was adopted and involved in a simulation investigating *P. aeruginosa* isolates expressing different MIC values against cefepime [75]. The standard recommended dosage had less than 80% probability of attaining the pharmacodynamic target for all MICs when ClCr was 120 ml/min, but the probability was achievable for MIC values lower than 1 mg/l when ClCr was 90 ml/min and for MIC values of at least 2 mg/l when ClCr was 60 ml/min. Overall, the probability could be improved by increasing the dose to 2 g intravenously every 8 h, or by extending the infusion time to 6 h (2 g every 12 h). In this study, continuous infusion of 4 g over 24 h offered the most promising chance of attaining this target [75].

The same strategies to achieve pharmacodynamic targets by using a higher dose of cefepime and extending the infusion time have been adopted for other bacterial species. Higher doses of 4-6 g administered as a continuous infusion or 2 g administered every 6-8 h with prolonged infusion are required to optimize therapy against ESBL-producing *Klebsiella* spp. or *E. coli*. Cefepime, however, fails to achieve bactericidal targets against *A. baumannii* isolates, even when administered at such high doses or with prolonged infusion [76-79].

An additional consideration in achieving targets of therapy is the limited penetration of antibiotic into certain body compartments, such as the CNS. The study of the pharmacodynamic profile of cefepime in the CSF of patients with ventricular drains revealed that neither cefepime doses of 2 g every 8-12 h nor cefepime in continuous infusion could achieve the set target (50 and 100% T > MIC for >90% patients for MICs \geq 1 mg/l and for >80% patients for MICs \geq 0.5 mg/l). The clinical implications of this finding are concerning, especially considering that CSF penetration was, on average, only 10% (reflecting noninflamed meninges) and that the precise pharmacodynamic target for CNS infections in humans is unknown [80].

Similar pharmacodynamic analyses were performed under the Optimizing Pharmacodynamic Target Attainment program, using Monte Carlo simulations based upon MICs for different susceptible Gram-negative organisms obtained from the Meropenem Yearly Susceptibility Test Information Collection database. Cefepime 2 g every 12 h demonstrated a higher

probability of attaining targets for bactericidal activity when used empirically for the treatment of bloodstream infections, nosocomial pneumonia (provided methicillin-resistant *S. aureus* prevalence was low) and secondary peritonitis (in combination with metronidazole) [81-83]. When the analysis was performed for specific nosocomial pathogens isolated from centers in North America, a standard regimen of cefepime had a high probability of attaining targets for Enterobacteriaceae, but not for *P. aeruginosa* and *A. baumannii* [84,85].

Expected probabilities of target attainment for cefepime (%T > MIC for 40% of dosing interval) were evaluated using a Monte Carlo simulation against a large collection of *Staphylococcus* spp. isolates detected during the SENTRY study in 1998-2004. Using the existing CLSI breakpoints, cefepime showed an advantage over ceftazidime (four- to eightfold) and superiority at the usual dosing over ceftriaxone for oxacillin-susceptible staphylococci. Probabilities of target attainment remained at a minimum of 90% to a breakpoint of 8 mg/l using 1 g every 8-12 h. It seems that, when used at doses of at least 3 g/day, cefepime assures maximal coverage of oxacillin-susceptible staphylococci [86]. The pharmacodynamics in the CSF of cefepime against *S. pneumoniae* ($MIC_{50} \leq 0.06$ mg/l) were compared with those of ceftriaxone. The probabilities of achieving targets of therapy (50 and 100% T > MIC) were superior for cefepime (91.8 and 82%, respectively) than for ceftriaxone (76 and 65%, respectively) [87].

The integration of pharmacokinetic and pharmacodynamic data to predict the efficacy of an antibiotic regimen provides tremendous insights. However, these analyses have limitations. They represent mathematical models that incorporate changing parameters (for instance, the exact %T > MIC that correlates with bactericidal vs bacteriostatic activity), which vary with location and time (MICs for different bacteria) and that may vary widely in different patient populations (pharmacokinetic data). Furthermore, these studies simplify by design and are unable to incorporate other clinical and host factors that have an impact on the course of an infection. Therefore, these studies complement but do not replace the systematic and experimental evaluation of clinical outcomes.

Clinical efficacy

Serious infections

In a retrospective analysis, cefepime treatment was analyzed in 13 ICU patients with different sites of infection due to ESBL-producing *K. pneumoniae*/*E. coli* isolates. Overall, 77% of cases were clinically cured. However, it is important to note that MICs for cefepime were no greater than 1 mg/l for ten cases, 2 mg/l for two cases and greater than 64 mg/l for the remaining one [88]. The efficacy of treatment with cefepime (2 g every 8 h) versus carbapenems (0.5 g every 6 h) was also retrospectively evaluated among ICU patients infected with a clonal TEM-24 ESBL-producing *E. aerogenes* isolate. Treatment failure was observed in 38% of patients treated with cefepime versus 30% of those receiving carbapenems [89]. In another retrospective study performed to analyze the outcome of cephalosporin treatment for serious infections due to Enterobacteriaceae-producing ESBLs, the overall failure of cefepime treatment was 83% [90]. In a retrospective study of nonurine ESBL-producing *Klebsiella* spp. or *E. coli* infections, patients receiving cefepime monotherapy (1 g every 12 h or 1 g every 24 h) were compared with cases receiving cefepime for infections due to non-ESBL producers. Patients receiving cefepime for an infection caused by ESBL producers were approximately ten-times as likely to have an unsuccessful clinical response compared with those with non-ESBL producers. In particular, among patients with infections due to ESBL producers, treatment failure was observed in 50% of cases when the MIC for cefepime was a maximum of 4 mg/l and in 75% of cases when the MIC was at least 16 mg/l [91].

In a recent analysis, clinical outcomes of 204 cases of bacteremia due to Gram-negative organisms have been retrospectively analyzed by Bhat *et al.* to establish whether current cepime breakpoints need to be revised [30]. Mortality at 28 days varied according to the cepime MIC of the pathogens: 23% for a MIC of up to 1 mg/l, 28% for a MIC of 2 mg/l, 27% for a MIC of 4 mg/l, 56% for a MIC of 8 mg/l and 53% for a MIC of at least 16 mg/l. Patients infected with organisms with a MIC of at least 8 mg/l had twice or greater mortality compared with those patients infected with bacteria with a cepime of MIC less than 8 mg/l (55 vs 24%, respectively; $p = 0.001$). Mortality was higher for *P. aeruginosa* cases treated with cepime when isolates had a MIC of at least 8 mg/l (59%) versus those with MIC values no higher than 4 mg/l (21%) [30].

In the cases of pneumonia due to *S. pneumoniae* and *H. influenzae*, satisfactory outcomes were obtained using intravenous cepime 1 g every 12 h [92,93]. In a study analyzing ICU patients affected by pneumonia due to *P. aeruginosa*, clinical success rates and microbiological eradication were 78 and 77%, respectively [94]. Severe nosocomial pneumonia in ICUs has been successfully treated with cepime 2 g intravenously every 12 h, plus amikacin 7.5 mg/kg every 12 h. The main pathogens in this analysis were *S. aureus*, *P. aeruginosa*, *Klebsiella* spp., *Enterobacter* spp. and *Serratia* spp. [95]. A randomized evaluator blind trial compared cepime (2 g every 8 h) with imipenem (0.5 g every 6 h) for the treatment of nosocomial pneumonia among ICU patients. Pneumonia therapy caused by ESBL producers failed in 31% of patients in the cepime group (the MIC values for these cases ranged from 2 to 4 mg/l), while all patients in the imipenem group were cured [96].

A recent meta-analysis evaluating the safety and efficacy of cepime versus other β -lactams [97] (see later) included a subgroup analysis of patients with community-acquired and hospital-acquired pneumonia. The difference in mortality in these subgroups did not reach statistical significance (Table 7). Rather, it was observed that the overall increased mortality among patients treated with cepime was driven by the subgroup of patients with febrile neutropenia (relative risk [RR] = 1.42; $p = 0.009$).

Empirical treatment of febrile neutropenia

Despite its potent antimicrobial efficacy, there is ongoing concern regarding the increased mortality among patients with febrile neutropenia who are empirically treated with cepime compared with other β -lactams. In a meta-analysis performed by Paul *et al.*, cepime was assessed in 17 trials, of which it was compared with ceftazidime in eight trials, imipenem in four, piperacillin/tazobactam in three and meropenem in two [98]. This analysis showed that all-cause mortality was significantly higher with cepime compared with other β -lactams (RR = 1.44; 95% confidence interval [CI]: 1.06-1.94; $p = 0.02$). Four studies recruited only children and mortality was higher with cepime when compared with ceftazidime (RR = 2.28; 95% CI: 0.53-9.79; $p = 0.02$) and equal compared with meropenem. The 'effect estimate' was higher among studies that used less than the recommended dose for cepime in febrile neutropenia, but did not reach statistical significance (RR = 2.01; 95% CI: 0.87-5.08). Significant differences were not detected between cepime and comparators with regard to all secondary efficacy outcomes (i.e., treatment failure, microbiological failure, infection-related mortality, any antibiotic modification, glycopeptide addition, antifungal drug addition, any superinfection, bacterial superinfection and any adverse event) [98]. Similar findings were reported in a more recent meta-analysis by Yahav *et al.* involving a total of 19 studies (Table 7) [97].

It should be noted that, although it is the point of meta-analyses to combine results of trials so that significance can be achieved, only two out of 19 trials demonstrated statistically significant higher mortality with the use of cepime [99,100]. One of the trials is a prospective, double-blind, randomized trial of cepime versus ceftazidime for the treatment of 276 neutropenic cancer patients with fever [100]. Treatment success, clearance of bacteremia and adverse

effects were similar in both groups. There was a higher overall mortality within 30 days of discontinuation of the drugs in the cefepime group (15% [22 out of 143] vs 8% [10 out of 133]). However, the deaths were not attributed to administration of the drug. Mortality rates within 2 weeks of stopping the drug were equivalent (8 vs 6%) and only three deaths in each group were due to progression of the initial infection; the rest were deemed to be superinfections.

Overall, we would also emphasize that the authors included studies in which another antibiotic in addition to cefepime was part of the therapy (e.g., glycopeptides and aminoglycosides) and a third of the trials were performed more than 10 years ago, when the spread of multidrug-resistant organisms (e.g., ESBL producers) was still limited and our ability to collect clinical and epidemiological information was less sophisticated.

Meningitis

In patients with community-acquired *K. pneumoniae* meningitis who were treated with cefepime, there was a lower mortality rate when compared with ceftazidime [101]. Cefepime (2 g every 8 h) plus ciprofloxacin (400 mg every 8 h) was able to eradicate a postoperative meningitis due to *E. cloacae* [102]. A 6-week course of intravenous cefepime (2 g every 8 h) plus gentamicin (200 mg every 8 h) was able to cure a 56-year-old woman affected by endocarditis and meningitis due to *P. aeruginosa* [103]. A total of 90 pediatric patients were prospectively randomized to receive cefepime (n = 43) or cefotaxime (n = 47) for therapy of bacterial meningitis. Overall, the following pathogens were detected: *H. influenzae* type b (61%), *N. meningitidis* (18%) and *S. pneumoniae* (13%). Notably, MIC values for cefepime and cefotaxime were constantly no higher than 0.06 mg/l for all bacteria isolated from CSF. In total, six (7%) patients died (two treated with cefepime and four treated with cefotaxime). Clinical response and hospital stay were similar for the two treatment regimens. Concentrations of cefepime in CSF 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 and 15% of the cefotaxime-treated patients [49].

Urinary tract & gynecological infections

Results comparable to those obtained with ceftazidime are observed with the use of cefepime in complicated UTI [92,104]. A total of 300 episodes of pyelonephritis were observed in pediatric patients enrolled in a randomized, open label, multicenter trial where cefepime was compared with ceftazidime (both administered parenterally at 50 mg/kg every 8 h). Bacteriologic eradication was achieved in 96 and 94% of cefepime and ceftazidime patients and was maintained after 4-6 weeks in 86 and in 83% of cases, respectively. A satisfactory clinical response occurred in 98 and 96% of cefepime and ceftazidime patients, respectively. Cefepime and ceftazidime were equally safe [105].

Patients with acute gynecological infections were randomized to receive cefepime (2 g every 12 h) or cefotaxime (2 g every 8 h), both intramuscularly or by a 30-min intravenous administration for approximately 4-5 days. Clinical response was satisfactory in 85% of cefepime recipients and 83% of cefotaxime recipients. All pathogens were eradicated in 81% of cefepime-treated and in 86% of cefotaxime-treated patients [106].

Abdominal infections

In a clinical trial, cefepime (2 g every 12 h intravenously) plus metronidazole (500 mg every 6 h) was compared with imipenem-cilastatin (500 mg every 6 h) for the treatment of complicated intra-abdominal infections. Patients treated with cefepime plus metronidazole were cured (88%) more frequently than those receiving imipenem-cilastatin (76%). Pathogens were eradicated in significantly more patients treated with combined cefepime and metronidazole (89%) than with imipenem-cilastatin (76%) (p = 0.01) [107].

A double-blind, randomized study compared cefepime plus metronidazole (2 g intravenously every 12 h and 500 mg intravenously every 8 h) with gentamicin plus clindamycin (1.5 mg/kg intravenously and 0.9 g intravenously every 8 h), administered in surgically treated patients with appendicitis. The efficacy of cefepime plus metronidazole was equivalent to that of clindamycin plus gentamicin [108]. An open, prospective, randomized trial compared cefepime (2 g every 12 h) with gentamicin plus mezlocillin (1.5 mg/kg every 8 h and 3 g every 4 h) in patients affected by acute cholecystitis/cholangitis. All patients treated with gentamicin plus mezlocillin were cured, as were 97.5% of the patients treated with cefepime [109].

In a recent multicenter, open-labeled, randomized study, the prophylactic efficacy of cefepime and ceftriaxone was compared in patients undergoing biliary tract surgery. A total of 209 patients were randomized to receive a preoperative infusion of 2 g of cefepime or ceftriaxone, both in a single intravenous administration. Antimicrobial prophylaxis was successful in 98.9% of patients in the cefepime group and 97.7% in the ceftriaxone group [110].

Osteomyelitis

In one clinical study, 23 patients with osteomyelitis, mainly due to *S. aureus*, were treated with cefepime 2 g intravenously every 12 h. Of these, 20 were cured, but treatment failed in three [111]. In a prospective, randomized, open-label trial, the efficacy of cefepime in the treatment of osteomyelitis caused by Gram-negative bacilli was evaluated. Cefepime was administered intravenously or intramuscularly (2 g every 8 h or 12 h). Overall, 73.3% of patients were cured [112].

Safety & tolerability

The results of a meta-analysis published in early 2007 indicated a potential increased mortality of 26% in patients treated with cefepime compared with patients treated with other β -lactam drugs [97]. The US FDA requested additional data from the manufacturer and, at this point, has not reached a definitive conclusion as to whether the observed increased mortality is due to cefepime. In the interim, the continued use of cefepime is conditioned by information from that meta-analysis but also from the previously published body of clinical experience with the use of cefepime.

The meta-analysis by Yahav *et al.* reviewed the efficacy and safety of cefepime in 57 clinical trials [97]. The trials assessed different sites of infection treated with different β -lactam antimicrobials (Table 7). The 30-day all-cause mortality was higher with cefepime than other β -lactams. All antibiotic comparators were associated with lower all-cause mortality, with significance shown for piperacillin-tazobactam. Exclusion of studies that compared cefepime with carbapenems did not eliminate the disadvantages observed for cefepime. All-cause mortality was higher for cefepime in all types of infection, with the exception of UTIs. However, as previously discussed, the difference in all-cause mortality was significant only for febrile neutropenia (Table 7) [97]. Overall, significant differences between groups in treatment failure, superinfection and adverse events were not found. Therefore, a clear explanation for the findings, especially given the previous safety record of cefepime is not available (see later).

In general, toxic effects of cefepime appear to be infrequent and similar to those observed with other cephalosporins, such as ceftazidime. In clinical trials using multiple doses of cefepime, patients were treated with the recommended dosages of cefepime (0.5-2 g intravenously every 12 h). Deaths or permanent disabilities related to drug toxicity were not found. The percentage of cefepime-treated patients who discontinued the study drug was very similar at daily doses of 0.5, 1 and 2 g every 12 h (0.8, 1.1 and 2.0%, respectively). The following adverse events were related to cefepime: local reactions (3%), including phlebitis (1.3%), pain or inflammation

(0.6%) and rash (1.1%). Colitis (including pseudomembranous colitis), diarrhea, fever, headache, nausea, oral moniliasis, pruritus, urticaria, vaginitis and vomiting were observed in less than 1% of patients. At the higher dose of 2 g every 6-8 h, the incidence of probably related adverse events was higher: rash (4%), diarrhea (3%), nausea (2%), vomiting (1%), pruritus (1%), fever (1%) and headache (1%) [47,60,92,93,113-115].

Neurotoxicity of cefepime has been reported [116-119]. The spectrum of manifestations has been broad, including confusion, hallucinations, agitation, convulsions, tremor, delirium and coma. Convulsions have been reported in 0.2% of patients. The period between the start of cefepime treatment and neurologic manifestations varied between 1 and 10 days, and the majority of neurological symptoms regressed within 2-7 days after stopping the antibiotic infusion. Almost all patients affected have had renal failure and the dose of cefepime was relatively high for the level of renal failure [116-119].

During cefepime administration, there was a decrease in *E. coli* and bifidobacteria in feces, whereas *Bacteroides* spp. and *Clostridium* spp. showed a slight increase. The numbers of fecal bacteria returned to normal 20-48 days after the study was completed [120]. Cephalosporins have long been implicated as an important predisposing cause of *C. difficile*-associated disease (CDAD). In particular, the extensive use of the extended-spectrum cephalosporins has been well recognized as an important risk factor for CDAD [121-123]. However, clinical data regarding the possible role of cefepime in CDAD are limited. A matched univariate analysis of case and control patients showed a significant difference between the two groups of cases in the use of cefepime during the 4 weeks prior to the detection of *C. difficile* toxin in the stool (24.1 vs 13.8%, respectively) [124]. This contrasts with data from animal studies. The subcutaneous administration of cefepime to mice did not facilitate *in vitro* growth and toxin production by *C. difficile* in cecal contents, unlike antibiotics that probably disrupt the anaerobic microflora (e.g., clindamycin) [125]. Similarly, cefepime may possess a low potential for promoting rectal colonization with resistant Gram-negative rods among pediatric ICU patients [126]. By contrast, the acquisition of rectal colonization of vancomycin-resistant *Enterococcus* (VRE) among ICU patients revealed that the administration of cefepime may be associated with the frequent acquisition of VRE [127].

The following adverse laboratory changes have been reported: positive Coombs' test (16.2%), decreased phosphorous (2.8%), increased serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase (~2.5%), eosinophils (1.7%) and abnormal PT and PTT (~1.5%). Whereas, increased alkaline phosphatase, blood urea nitrogen, calcium, creatinine, potassium and total bilirubin or decreased calcium, hematocrit, neutrophils, platelets and white blood cells were recorded in fewer than 1% of patients [47,60,92,93,113-115]. Notably, neutropenia resulted in 62% of patients receiving long-term cefepime therapy (17-30 days) for osteomyelitis. Blood counts returned to normal within 1 week of cefepime discontinuation [128].

Conclusion & expert commentary

Cefepime possess higher *in vitro* activity than other extended-spectrum cephalosporins against common Gram-negative and Gram-positive pathogens. However, cefepime is ineffective against ESBL-producing Enterobacteriaceae, *A. baumannii* and highly derepressed AmpC-producing *P. aeruginosa* isolates. The re-evaluation of the existent CLSI Gram-negative susceptibility breakpoints for cefepime is necessary. The EUCAST susceptibility criteria (e.g., MIC for Enterobacteriaceae ≤ 1 mg/l) seem to better integrate *in vitro*, pharmacodynamic and clinical data.

Pharmacokinetic studies show that cefepime reaches concentrations in the serum and body capable of inhibiting organisms possessing MICs lower than 2 mg/l. By contrast, retrospective analysis and statistical simulations showed that the standard scheduled dosages are not able to achieve satisfactory probabilities of microbiological eradication for Gram-negative organisms showing MICs for cefepime of at least 2 mg/l. Therefore, we recommend that cefepime should not be used to treat infections due to ESBL-producing Enterobacteriaceae and *A. baumannii*. For *P. aeruginosa*, the probability of achieving the pharmacodynamic target for isolates with MIC values of 2-8 mg/l could be improved by increasing the dose of cefepime and/or extending the infusion time. Unless this can be achieved, it is our opinion that the use of cefepime monotherapy to treat serious infection due to *P. aeruginosa* is not an advisable choice.

Since meta-analyses showed a higher mortality among patients receiving cefepime than other β -lactams, we believe that the use of cefepime as monotherapy should be tempered by a careful consideration of risks and benefits (at least in the case of febrile neutropenia). An extensive review of the previous trials involving cefepime is in progress and, in the near future, the FDA will release a final recommendation.

Five-year view

Questions regarding cefepime that remain to be answered in the next few years include the following:

- What susceptibility breakpoint for cefepime leads to the best outcome for infections due to Gram-negative organisms?
- Is cefepime able to ensure a better treatment outcome than other extended-spectrum cephalosporins during infections caused by AmpC producers (e.g., *Enterobacter* spp.)?
- What dosing regimens of cefepime offer the best clinical outcomes?
- Is cefepime treatment in patients with febrile neutropenia really related to a higher mortality rate than other extended-spectrum β -lactams?
- Should cefepime be combined with β -lactamase inhibitors to be used against Enterobacteriaceae-coproducing AmpC and ESBL enzymes?

Key issues

- Cefepime Clinical and Laboratory Standards Institute breakpoints of susceptibility against Gram-negative bacteria should be revised.
- Cefepime should not be used to treat infections due to extended-spectrum β -lactamase-producing organisms and *Acinetobacter baumannii*.
- Conventional doses of cefepime should not be used to treat infections caused by *Pseudomonas aeruginosa*.
- According to large international studies, the MIC_{50/90} for cefepime are lower than those of ceftazidime.
- Cefepime remains an option against methicillin-susceptible staphylococci and *Streptococcus pneumoniae* infections.

Acknowledgements

Financial & competing interests disclosure

RA Bonomo has received grants from AstraZeneca, Merck, Elan and Basilea Pharmaceutica, Inc. RA Bonomo serves as a consultant to Wyeth Pharmaceuticals, Pfizer and Basilea Pharmaceutica, Ltd. This work was supported in part by AstraZeneca (to A Endimiani and RA Bonomo), the National Institutes of Health (grant RO1-AI063517 to RA Bonomo), the Veterans Affairs Merit Review Program (RA Bonomo), and Geriatric Research Education and Clinical Center (RA Bonomo). F Perez is supported by the Wyeth Fellowship in Antimicrobial Resistance. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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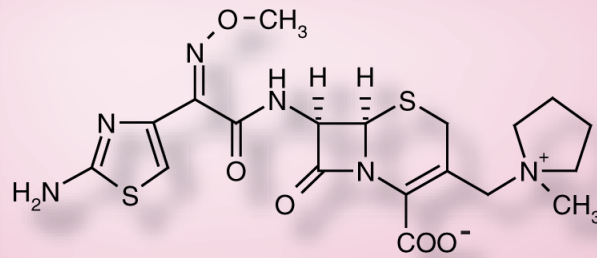


Figure 1. Cefepime

Table 1
Affinity (K_m or K_i) of different class of β -lactamase enzymes for cefepime and other cephalosporins

Enzyme class	K_m or K_i (μM)			Ref.
	Cefazidime	Cefotaxime	Cefepime	
<i>β-lactamase</i>				
TEM-1	200	NR	650	[129]
SHV-1	500	NR	81	[129]
<i>Extended-spectrum β-lactamases</i>				
TEM-3	100	26	190	[130]
TEM-12	130	94	130	[131]
TEM-24	180	25	90	[132]
TEM-26	10	13	105	[130]
TEM-121	150	430	40	[132]
SHV-5	9.2	5.0	100	[130]
SHV-18	47	8.7	81	[130]
CTX-M-3	>3000	113	170	[133]
CTX-M-10	NR	40	110	[130]
CTX-M-15	1760	54	1075	[133]
OXA-10	NR	NR	230	[129]
<i>Carbapenemases</i>				
VIM-2	98	32	184	[134]
IMP-2	111	NR	7	[135]
KPC-2	230	NR	540	[129]
<i>Ambler class C enzymes</i>				
AmpC <i>Pseudomonas aeruginosa</i>	8	NR	370	[129]
AmpC <i>Morganella morganii</i>	14	NR	690	[129]
AmpC <i>Providencia stuartii</i>	26	NR	780	[129]
AmpC <i>Serratia marcescens</i>	570	NR	>800	[129]
ADC-7	11.6	0.10	594	[20]
CMY-9	560	0.28	950	[136]
CMY-19	3.7	31	630	[136]
P99	15	NR	100	[137]

Enzyme class	K_m or K_i (μM)	Ref.
<i>Ceftazidime</i>	<i>Cefotaxime</i>	<i>Cefepime</i>

ADC: *Acinetobacter*-derived cephalosporinase; KPC: *Klebsiella pneumoniae* carbapenemases; NR: Not reported.

Table 2 MICs (mg/l) of, and susceptibility to, cefepime, ceftazidime and imipenem among clinical populations of Gram-negative Enterobacteriaceae

Organism	Region	Site of infection	Year(s) of collection	Cefepime			Ceftazidime*			Imipenem			Ref.
				MIC ₅₀	MIC ₉₀	S (%)	MIC ₅₀	MIC ₉₀	S (%)	MIC ₅₀	MIC ₉₀	S (%)	
				MIC (mg/l)			MIC (mg/l)			MIC (mg/l)			
<i>Escherichia coli</i>	North America	Mixture	2007	≤0.12	0.25	95.9	0.25	1	96.6	0.12	0.25	100	[138]
		BSI, RT	1998-2004	≤0.12	≤0.12	99.6	≤2	≤2	98.6	≤0.5	≤0.5	100	[40]
		UTI	1998	≤0.12	≤0.12	100	0.25	0.5	99.9	0.12	0.25	100	[139]
	Latin America	BSI	1997-2000	≤0.12	0.25	97.1	0.25	0.5	95.6	0.12	0.25	100	[140]
		Mixture	1997-1998	≤0.12	≤0.12	99.2	≤0.12	0.25	98.1	0.25	0.5	100	[141]
		Mixture	2005-2006	≤0.12	0.25	96.0	≤1	≤1	95.0	≤0.12	0.25	100	[31]
	Europe	UTI	1998-1999	≤0.12	0.25	98.6	0.25	0.5	96.7	0.12	0.25	100	[142]
		Mixture	1998-2003	0.25	4	93.8	8	>16	60.6	≤0.5	≤0.5	100	[35]
		Mixture	2005-2006	16	>16	39.6	16	>16	39.6	0.25	0.5	100	[31]
	<i>Klebsiella</i> spp.	North America	Mixture	2007	≤0.12	16	89.9	0.25	>16	81.7	0.25	2	90.9
BSI, RT			1998-2004	≤0.12	0.25	99.0	≤2	≤2	95.1	≤0.5	≤0.5	99.7	[40]
RT			2000	≤0.12	0.25	99.5	0.25	8	NR	≤0.06	0.25	87.8	[143]
Latin America		UTI	1998	≤0.12	0.25	99.4	0.25	0.5	95.8	0.25	0.5	100	[139]
		BSI	1997-2000	0.25	>16	74.8	1	>16	64.0	0.25	0.5	99.8	[140]
		RT	1997-2000	<0.12	>16	76.1	0.5	>16	63.1	0.25	0.5	99.6	[144]
Europe		Mixture	1997-1998	<0.12	8	86.5	≤0.12	>16	81.3	0.5	1	99.9	[141]
		Mixture	2005-2006	≤0.12	>16	86.5	≤1	>16	81.7	0.25	0.5	97.2	[31]
		UTI	1998-1999	≤0.12	4	98.6	0.25	>16	87.3	0.25	0.5	100	[142]
<i>Klebsiella</i> spp. ESBL+		North America	Mixture	1998-2003	1	8	92.5	>16	>16	36.9	≤0.5	≤0.5	99.3
	Mixture		2005-2006	8	>16	51.4	>16	>16	33.0	0.25	0.5	99.3	[31]
	Mixture		2007	≤0.12	2	95.3	0.25	>16	78.8	0.5	2	97.6	[138]
	Latin America	BSI, RT	1998-2004	≤0.12	2	99.3	≤1	>16	78.4	≤0.5	1	100	[40]
		BSI	1997-2000	≤0.12	8	91.5	0.5	>16	68.4	0.5	1	99.7	[140]
		RT	1997-2000	0.12	>16	61.2	0.5	>16	63.4	0.5	2	100	[144]
	Europe	Mixture	1997-1998	≤0.12	4	95.2	0.25	>16	78.4	0.5	2	99.6	[141]
		Mixture	2005-2006	≤0.12	4	93.4	≤1	>16	71.1	0.5	2	98.4	[31]
		UTI	1998-1999	0.25	8	95.3	4	>16	51.2	0.5	2	100	[142]
	<i>Enterobacter</i> spp.	North America	Mixture	2007	≤0.12	2	95.3	0.25	>16	78.8	0.5	2	97.6
BSI, RT			1998-2004	≤0.12	2	99.3	≤1	>16	78.4	≤0.5	1	100	[40]
BSI			1997-2000	≤0.12	8	91.5	0.5	>16	68.4	0.5	1	99.7	[140]
Latin America		RT	1997-2000	0.12	>16	61.2	0.5	>16	63.4	0.5	2	100	[144]
		Mixture	1997-1998	≤0.12	4	95.2	0.25	>16	78.4	0.5	2	99.6	[141]
		Mixture	2005-2006	≤0.12	4	93.4	≤1	>16	71.1	0.5	2	98.4	[31]
Asia-Pacific		UTI	1998-1999	0.25	8	95.3	4	>16	51.2	0.5	2	100	[142]

Organism	Region	Site of infection	Year(s) of collection	MIC (mg/l) [*]						Ref.			
				Cefepime			Ceftazidime				Imipenem		
				MIC ₅₀	MIC ₉₀	S (%)	MIC ₅₀	MIC ₉₀	S (%)		MIC ₅₀	MIC ₉₀	S (%)
<i>Proteus mirabilis</i>	North America	Mixture	2007	≤0.12	≤0.12	100	≤0.12	≤0.12	100	1	2	99.2	[138]
	Europe	Mixture	1997-1998	≤0.12	0.50	96.3	≤0.12	1	95.3	1	2	99.5	[141]
<i>Providencia</i> spp.	America and Europe	Mixture	2005-2006	≤0.12	0.25	94.3	≤1	NR	98.3	1	2	99.8	[31]
	Europe and Australia	Mixture	1999-2000	0.03	1	99.0	NR	NR	NR	2	8	98.0	[36]
<i>Morganella morganii</i>	Europe and Australia	Mixture	1999-2000	0.03	2	100	NR	NR	NR	4	8	92.0	[36]
<i>Salmonella</i> spp.	America and Europe	Mixture	2005-2006	≤0.12	≤0.12	100	≤1	≤1	98.1	0.25	0.5	100	[31]
<i>Citrobacter</i> spp.	America and Europe	Mixture	2005-2006	≤0.12	1	98.3	≤1	>16	75.9	0.5	1	99.6	[31]
<i>Serratia</i> spp.	America and Europe	Mixture	2005-2006	≤0.12	0.5	97.5	≤1	2	95.2	1	2	99.8	[31]

BSI: Bloodstream infection; ESBL⁺: Extended-spectrum β-lactamase-producing organisms; NR: Not reported; RT: Respiratory tract infection; S: Susceptibility; UTI: Urinary tract infection.

* Results were interpreted according to Clinical and Laboratory Standards Institute criteria.

Table 3

MICs (mg/l) of, and susceptibility to, cefepime, ceftazidime and imipenem among clinical populations of Gram-negative non-Enterobacteriaceae

Organism	Region	Site of infection	Year(s) of collection	MIC (mg/l)*						Ref.				
				Cefepime		Ceftazidime (Ceftriaxone) [†]		Imipenem						
				MIC ₅₀	MIC ₉₀	S (%)	MIC ₅₀	MIC ₉₀	S (%)		MIC ₅₀	MIC ₉₀	S (%)	
<i>Acinetobacter</i> spp.	North America	Mixture	2007	4	16	85.7	2	>16	>16	83.3	2	16	77.5	[138]
	Latin America	Mixture	1997-2001	>16	>16	35.2	>16	>16	>16	28.5	1	>8	86.9	[145]
<i>Pseudomonas aeruginosa</i>	America and Europe	BSI	1997-2000	16	>16	45.4	>16	>16	>16	39.0	0.5	8	89.1	[140]
		RT	1997-2000	>16	>16	26.4	>16	>16	>16	16.7	1	>8	84.9	[144]
	North America	Mixture	2005-2006	16	>16	44.1	>16	>16	>16	34.8	1	>8	72.4	[30]
		Mixture	2007	4	16	85.7	2	>16	>16	83.3	2	16	77.5	[138]
		BSI, RT	1998-2004	2	8	90.8	2	16	16	87.3	1	2	94.4	[40]
		RT	2000	4	16	80.5	4	>16	>16	78.3	1	8	85.6	[143]
Latin America	UTI	1998	4	8	91.2	4	>16	>16	85.8	0.25	0.5	100	[139]	
	Mixture [§]	2001	4	16	80.1	≤2	>16	>16	77.0	1	>8	78.3	[146]	
	RT [¶]	1996-2001	2	16	84.1	2	32	32	84.1	1	16	86.6	[147]	
	RT [#]	NR	64	256	15.0	64	>512	>512	27.0	32	128	30.0	[148]	
<i>Burkholderia cepacia</i>	Latin America	RT ^{**}	NR	64	256	10.0	128	>512	>512	16.0	32	64	21.0	[148]
		BSI	1997-2000	4	>16	72.1	4	>16	>16	69.4	1	>8	84.5	[140]
	America and Europe	RT	1997-2000	8	>16	61.2	4	>16	>16	61.2	2	>8	69.2	[144]
		Mixture [§]	2002	4	>256	55.4	>192	>256	>256	31.4	2	>32	57.3	[149]
	Asia-Pacific	Mixture	2005-2006	4	>16	79.4	2	>16	>16	75.5	1	>8	75.8	[31]
		UTI	1998-1999	4	16	76.4	4	>16	>16	77.4	2	8	88.7	[142]
<i>Stenotrophomonas maltophilia</i>	America and Europe	Mixture	2003	8	16	85.0	4	4	4	90.0	4	8	65.0	[150]
		RT [¶]	1996-2001	16	128	47.0	4	16	16	82.4	4	16	50.0	[147]
	World	RT	NR	256	>256	10.0	16	>512	>512	43.0	32	128	9.0	[148]
	America and Europe	Mixture	1997-2003	16	>16	27.6	8	>16	>16	52.9	>8	>8	100	[151]
<i>Haemophilus influenzae</i>	North America	Mixture	2004	>16	>16	9.4	16	>16	>16	45.3	>8	>8	1.9	[152]
		BSI, RT	1998-2004	≤0.06	0.12	100	≤0.25	1	93.7	NR	NR	NR	NR	[40]
	America and Europe	RT	1998-2004	≤0.06	0.12	100	≤0.06	≤0.06	100	100	NR	NR	NR	[153]
		Mixture	2005-2006	≤0.12	≤0.12	100	≤0.25	≤0.25	100	100	0.5	1	100	[31]

Organism	Region	Site of infection	Year(s) of collection	MIC (mg/l) [*]						Ref.
				Cefepime		Ceftazidime (Ceftriaxone) [‡]		Imipenem		
				MIC ₅₀	S (%)	MIC ₅₀	S (%)	MIC ₅₀	S (%)	
<i>Moraxella catarrhalis</i>	North America	BSI, RT	1998-2004	0.5	NR	≤0.25	NR	NR	NR	[40]
<i>Neisseria gonorrhoeae</i>	Asia	STDs	2003	0.12	NR	0.03	0.06	NR	NR	[154]
<i>Neisseria meningitidis</i>	Europe and Australia	Mixture	1999-2000	0.03	NR	0.06	0.06	<0.06	0.12	[36]

BSI: Bloodstream infection; NR: Not reported; RT: Respiratory tract infection; S: Susceptibility; STD: Sexually transmitted disease; UTI: Urinary tract infection.

^{*} Results were interpreted according to Clinical and Laboratory Standards Institute criteria.

[‡] For *H. influenzae* ceftriaxone MICs were shown.

[§] Intensive care unit patients.

[¶] Cystic fibrosis patients.

[#] Mucoid isolates.

^{**} Nonmucoid isolates.

Table 4
MICs (mg/l) of, and susceptibility to, cefepime, ceftazidime and imipenem among clinical populations of Gram-positive organisms

Organism	Region	Site of infection	Year(s) of collection	MIC (mg/l)*						Ref.			
				Cefepime			Ceftazidime (Ceftriaxone)†				Imipenem		
				MIC ₅₀	MIC ₉₀	S (%)	MIC ₅₀	MIC ₉₀	S (%)		MIC ₅₀	MIC ₉₀	S (%)
<i>Staphylococcus aureus</i>	North America	Mixture	2007	2	4	100 [§]	8	16	89.3	0.03	0.06	100	[138]
		BSI, RT	1998-1904	2	4	100 [§]	8	16	86.7	NR	NR	NR	[40]
		SSTI	2000	4	>16	83.9 [¶]	8	>16	75.0	≤0.06	4	92.1	[155]
	Latin America	RT	1997-1900	>16	>16	46.7 [¶]	NR	NR	NR	NR	NR	NR	[144]
		BSI	1997-1900	4	>16	69.4 [¶]	8	>16	56.4	≤0.06	>8	69.4	[140]
		Mixture	2005-2006	2	4	99.9	8	8	96.5	≤0.12	≤0.12	>99.9	[31] [§]
Coagulase-negative <i>Staphylococcus</i> spp.	North America	Mixture	2007	1	2	100 [§]	4	16	88.2	2	4	98.1	[138]
		BSI, RT	1998-1904	1	2	100 [§]	8	8	94.0	NR	NR	NR	[40]
	Latin America	BSI	1997-1900	4	>16	24.7 [¶]	>16	>16	24.7	0.5	>8	24.7	[140]
	Europe and Australia	Mixture	1999-1900	0.03	0.06	100	0.06	0.06	100	0.008	0.008	100	[36]
<i>Streptococcus pyogenes</i>	North America	BSI, RT	1998-1904	≤0.12	≤0.12	100	≤0.25	≤0.25	100	NR	NR	NR	[40]
		Mixture	1998-1903	≤0.12	1	94.1	0.12	0.5	93.6	NR	NR	NR	[35]
<i>Viridans streptococci</i>	North America	Mixture	2005-2006	0.5	2	99.9	4	8	96.8	≤0.12	≤0.12	100	[31] [§]
	North America	Mixture	2007	≤0.12	1	96.0	≤0.25	1	95.2	≤0.15	0.25	88.1	[138]
<i>Streptococcus pneumoniae</i>	North America	Mixture	2001-02	≤0.12	1	96.6	0.03	0.03	99.8	≤0.06	≤0.06	NR	[42]
		Mixture	1998-04	0.25	1	99.2	0.25	1	98.7	≤0.06	0.12	NR	[42] [#]
	Europe	RT	1999-03	≤0.06	1	98.4	0.03	1	99.1	0.25	0.5	NR	[41] ^{**}
	BSI, RT	1998-04	≤0.12	1	93.7	≤0.25	1	93.7	NR	NR	NR	[40]	
	RT	1998-04	≤0.06	0.5	99.2	0.03	0.5	99.5	NR	NR	NR	[153]	
	Mixture	2005-06	≤0.12	1	96.3	≤0.25	1	97.5	NR	NR	NR	[31]	
	RT	1999-03	≤0.06	1	98.4	0.03	1	99.1	NR	NR	NR	[39]	

BSI: Bloodstream infection; NR: Not reported; RT: Respiratory tract infection; S: Susceptibility; SSTI: Skin and soft tissue infection.

* Results were interpreted according to Clinical and Laboratory Standards Institute criteria.

‡ For all streptococci, ceftriaxone MICs were shown.

§ All strains were oxacillin-susceptible.

¶ Susceptibility was predicted by the oxacillin results.

Considering only penicillin-intermediate strains.

** Considering only penicillin-resistant strains.

Table 5
Cefepime MICs interpretative breakpoints: comparison between CLSI and EUCAST criteria

Organism	CLSI (MIC, mg/l)			EUCAST (MIC, mg/l)		
	S	I	R	S	I	R
<i>Gram-negative</i>						
<i>Acinetobacter</i> spp.	≤8	16	≥32		IU	
<i>Burkholderia cepacia</i>		NA			IU	
Enterobacteriaceae*	≤8	16	≥32	≤1	2-8	≥16
<i>Haemophilus</i> spp.	≤2			≤0.25		≥0.5
<i>Moraxella catarrhalis</i>		NA		≤0.25		≥0.5
<i>Neisseria gonorrhoeae</i>	≤0.5				IU	
<i>Neisseria meningitidis</i>		NA			IU	
<i>Pseudomonas</i> spp.	≤8	16	≥32	≤8		≥16
<i>Stenotrophomonas maltophilia</i>		NA			IU	
<i>Gram-positive</i>						
<i>Enterococcus</i> spp.		NA			IU	
<i>Staphylococcus</i> spp.	≤8	16	≥32		‡	
<i>Streptococcus pneumoniae</i>						
Nonmeningitis	≤1	2	≥4	≤1	2	≥4
Meningitis	≤0.5	1	≥2			
<i>Streptococcus</i> spp.						
β-hemolytic group	≤0.5			≤0.5		≥1
Viridans group	≤1	2	≥4	≤0.5		≥1

CLSI: Clinical and Laboratory Standards Institute; EUCAST: European Committee on Antimicrobial Susceptibility Testing; I: Intermediate; IU: Inappropriate use; NA: Not available; R: Resistant; S: Susceptible.

* According to CLSI criteria, confirmed *E. coli*, *Klebsiella* spp. and *P. mirabilis* ESBL producers should be reported as resistant to all cephalosporins and aztreonam independently of MIC values [28]. Notably, criteria for the remaining Enterobacteriaceae have not been established.

‡ Susceptibility to cefepime, as with other cephalosporins, is inferred from the methicillin susceptibility.

Table 6
Pharmacokinetic parameters of cefepime in healthy adults and patients with different renal insufficiency levels

Patient	Dose (g)	Administration	C _{max} (mg/l)	Half-life (h)	AUC (mg h/l)	Cl _T (ml/min)	Cl _R (ml/min)	%X _u	Ref.
Healthy adults	0.25	iv. 30 min	16.3 ± 2.4	1.9 ± 0.2	34 ± 3 [*]	122 ± 10	96 ± 19	78.4 ± 11.3	[47] [‡]
Healthy adults	0.5	iv. 30 min	31.6 ± 2.9	1.8 ± 0.2	62 ± 6 [*]	136 ± 13	116 ± 11	85.6 ± 2.9	[47] [‡]
Healthy adults	1	iv. 30 min	66.9 ± 4.6	1.9 ± 0.2	137 ± 9 [*]	122 ± 8	103 ± 5	84.2 ± 2.2	[47] [‡]
Healthy adults	2	iv. 30 min	133 ± 35.5	1.8 ± 0.2	263 ± 33 [*]	128 ± 16	104 ± 12	81.3 ± 6.9	[47] [‡]
Healthy adults	0.5	im.	13.9 ± 3.4	1.4 ± 0.9	60.0 ± 8.0	NR	NR	NR	[156] [§]
Healthy adults	1	im.	29.6 ± 4.4	1.6 ± 0.4	137.0 ± 11.0	NR	NR	NR	[156] [§]
Healthy adults	2	im.	57.5 ± 9.5	1.5 ± 0.4	262.0 ± 23.0	NR	NR	NR	[156] [§]
Infected patients: ClCr > 100 ml/min	2 every 12 h	iv. 30 min	259 ± 287	3.1 ± 2.6	734 ± 344 [¶]	117 ± 72	NR	NR	[58] [§]
Infected patients: ClCr 60-100 ml/min	2 every 12 h	iv. 30 min	167 ± 124	7.6 ± 5.2	1138 ± 540 [¶]	73 ± 37	NR	NR	[58] [§]
Infected patients: ClCr < 60 ml/min	1-2 every 24 h	iv. 30 min	207 ± 295	12.1 ± 6.3	845 ± 296 [¶]	43 ± 18	NR	NR	[58] [§]

%X_u: Percentage of dose recovered in urine; Cl_R: Renal clearance; Cl_T: Total body clearance; im.: Intramuscular administration; iv.: Intravenous administration; NR: Not reported.

* AUC_{0-∞}.

[‡]Data obtained after the 30-min infusion.

[§]Data obtained at the steady state.

[¶]AUC₂₄.

Summary of results of a systematic review and meta-analysis of 57 clinical trials evaluating efficacy and safety of cefepime

Table 7

Outcome index	Statistical comparison (number of clinical trials)	Cefepime (n/N patients)	Comparator (n/N patients)	RR (95% CI)	p-value
All-cause mortality by comparator drug	Total (n = 41)	309/3931	220/3457	1.26 (1.08-1.49)	0.005
	Cefepime vs ceftazidime (n = 23)	167/2006	116/1625	1.20 (0.96-1.50)	0.11
	Cefepime vs piperacillin-tazobactam (n = 3)	30/398	15/416	2.14 (1.17-3.89)	0.01
All-cause mortality by comparator infection	Cefepime vs imipenem or meropenem (n = 6)	73/808	62/802	1.20 (0.88-1.63)	0.24
	Cefepime vs ceftriaxone or cefotaxime (n = 9)	39/719	27/614	1.24 (0.77-1.99)	0.38
	Total (n = 41)	309/3931	220/3457	1.26 (1.08-1.49)	0.005
Clinical failure by comparator infection	Neutropenic fever (n = 19)	130/2043	87/1928	1.42 (1.09-1.84)	0.009
	Pneumonia (n = 10)	110/953	84/767	1.15 (1.89-1.48)	0.29
	Urinary tract/gynecological infections (n = 2)	0/308	0/222	NE	NA
Clinical failure by comparator infection	Other infections (n = 10)	69/627	49/540	1.20 (0.85-1.69)	0.3
	Total (n = 55)	1715/4656	1628/4215	0.98 (0.93-1.03)	0.37
	Neutropenic fever (n = 20)	1258/2258	1178/2152	1.00 (0.96-1.05)	0.88
Clinical failure by comparator infection	Community-acquired pneumonia (n = 15)	107/829	105/658	0.78 (0.61-1.00)	0.05
	Hospital-acquired pneumonia (n = 3)	132/294	142/292	0.92 (0.77-1.09)	0.34
	Urinary tract/gynecological infections (n = 5)	41/397	22/276	1.12 (0.69-1.81)	0.66
Clinical failure by comparator infection	Meningitis (n = 2)	34/146	37/152	0.96 (0.64-1.44)	0.85
	Other infections (n = 10)	143/732	144/685	0.97 (0.79-1.19)	0.77

CI: Confidence interval; NA: Not applicable; NE: Not estimable; RR: Relative risk. Data from [97].