Newer Beta-lactam Antibiotics: Doripenem, Ceftobiprole, Ceftaroline, and Cefepime

Jose A. Bazan, DO\textsuperscript{a}, Stanley I. Martin, MD\textsuperscript{b}, Kenneth M. Kaye, MD\textsuperscript{c,}*

Beta-lactam (\(\beta\)-lactam) antibiotics have been, and remain, the cornerstone of therapy for many life-threatening infections. Over the years, newer formulations have allowed clinicians to better provide broad empiric coverage and to use targeted therapy against commonly encountered gram-positive and gram-negative bacteria. For the most part, \(\beta\)-lactam antibiotics have evolved concomitantly with global antimicrobial resistance patterns. However, the emergence of pathogens like methicillin-resistant \textit{Staphylococcus aureus} (MRSA), penicillin-intermediate and penicillin-resistant \textit{Streptococcus pneumoniae}, multidrug-resistant (MDR) \textit{Pseudomonas aeruginosa}, and extended-spectrum \(\beta\)-lactamase (ESBL)–producing gram-negative enteric organisms have provided new challenges, and the evolution of new \(\beta\)-lactams has slowed. This article focuses on the agents doripenem, ceftobiprole, and ceftaroline. At this writing, ceftobiprole and ceftaroline have yet to be approved for use in the United States. In addition, this article summarizes recent developments regarding the potential increased mortality observed with the use of cefepime compared with that of other agents in the treatment of some infections.

\textsuperscript{a} Clinical and Research Fellow, Division of Infectious Diseases, The Ohio State University Medical Center, N1129 Doan Hall, 410 West 10th Avenue, Columbus, OH 43210, USA
\textsuperscript{b} Division of Infectious Diseases, The Ohio State University Medical Center, N1148 Doan Hall, 410 West 10th Avenue, Columbus, OH 43210, USA
\textsuperscript{c} Division of Infectious Diseases, Harvard Medical School, Channing Laboratory, Brigham and Women’s Hospital, 181 Longwood Avenue, Boston, MA 02115, USA
* Corresponding author.
E-mail address: kkaye@rics.bwh.harvard.edu (K.M. Kaye).

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Since the introduction of imipenem-cilastatin more than 20 years ago, the use of carbapenems such as meropenem, ertapenem, and most recently doripenem has become more common in the face of infections caused by increasingly MDR bacteria. Doripenem (formerly S-4661), a parenteral 1-β-methyl carbapenem, is the newest agent in the family, and it received approval by the US Food and Drug Administration (FDA) in 2007 for the treatment of complicated intra-abdominal infections (IAIs) and complicated urinary tract infections (UTIs).1 Doripenem binds to penicillin-binding proteins (PBPs) and leads to the inhibition of bacterial cell wall synthesis.1,2 Similar to other β-lactams, its bactericidal activity is directly related to the time the concentration of free drug exceeds the minimum inhibitory concentration (MIC) of the bacteria (% fT > MIC).1,3 Unlike imipenem, its 1-β-methyl side chain confers stability in the face of renal dihydropeptidases.4

Similar to other carbapenems, doripenem exhibits a low degree of plasma protein binding. Imipenem-cilastatin, meropenem, and doripenem have ~20%, ~2%, and ~8% protein binding, respectively.5–7 The metabolism of doripenem occurs through the actions of renal dihydropeptidase-I and undergoes renal excretion by a combination of glomerular filtration and active tubular secretion (78.7% unchanged drug and 18.5% inactive metabolites).1,7 The normal plasma elimination half-life is approximately 1 hour, and the usual dose for patients who have normal renal function is 500 mg infused intravenously (i.v.) for 1 hour every 8 hours.1,3,7,8 This dosing regimen has been shown to achieve the fT > MIC target of 35% for susceptible organisms that have an MIC that is 1 μg/mL or less. For organisms that have an MIC that is 2 μg/mL or greater, the same target fT > MIC can be achieved by increasing the infusion time (>1 hour) without increasing the total daily dose, given the stability of the drug at room temperature.3,7,9 Dosing requires adjustment in the setting of moderate renal dysfunction. For patients who have a creatinine clearance (CrCl) of 30 to 50 mL/min, 250 mg i.v. every 8 hours is recommended, and for a CrCl of 10 to 30 mL/min, 250 mg i.v. every 12 hours is recommended.1,7 There are no established parameters at this time for dosing in patients who have a CrCl of less than 10 mL/min and those undergoing hemodialysis.1,7

A number of studies have analyzed the in vitro activity of doripenem against bacterial isolates, using broth microdilution methods. The spectrum of antimicrobial activity of doripenem is similar to that of imipenem-cilastatin and meropenem for gram-positive and gram-negative bacteria.10–13

With regard to gram-positive bacteria, doripenem was the most active carbapenem against various isolates of methicillin-sensitive Staphylococcus aureus (MSSA) and methicillin-sensitive coagulase-negative staphylococci (MS-CoNS). It was twofold more active than meropenem or ertapenem against strains of Enterococcus faecalis and non-faecium enterococci, but twofold less active than imipenem-cilastatin.10 On the other hand, vancomycin-resistant Enterococcus faecium isolates were uniformly resistant to doripenem.10–14 Excellent in vitro activity has also been demonstrated against penicillin-susceptible, -intermediate, and -resistant Streptococcus pneumoniae, penicillin-susceptible and -resistant Streptococcus viridans, and the various β-hemolytic Streptococcus spp.10–13

Doripenem is active against Enterobacteriaceae. Its activity is similar to that of meropenem against wild-type (non-ESBL producing) and derepressed AmpC and ESBL-producing Enterobacteriaceae isolates.10–14 Doripenem also displays excellent activity against common respiratory pathogens such as Haemophilus influenzae and Moraxella catarrhalis (including β-lactamase-producing strains).10,12–14 With regard to the
nonfermenting, aerobic, gram-negative bacteria, doripenem had the greatest activity against wild-type strains of *P. aeruginosa* that had an MIC\(_{50}\) and MIC\(_{90}\) of 0.5 \(\mu\)g/mL and 8 \(\mu\)g/mL, respectively.\(^\text{10}\) In addition, doripenem may still retain activity against strains of *P. aeruginosa* that are resistant to other carbapenems. For instance, of 34 *P. aeruginosa* strains resistant to carbapenems, 29.4% were susceptible to doripenem, whereas none were susceptible to imipenem-cilastatin, and 2.9% were susceptible to meropenem.\(^\text{14}\) Notably, 44.1% of these same strains were sensitive to piperacillin-tazobactam, 29.4% were sensitive to cefepime, and 44.1% were sensitive to amikacin.\(^\text{14}\) However, only 6.7% of Class B metallo-\(\beta\)-lactamase–producing strains of *P. aeruginosa* strains were sensitive to doripenem.\(^\text{14}\) Doripenem was active against 75.8% of wild-type *Acinetobacter baumanii* and 20.8% of carbapenem-resistant *Acinetobacter* spp (MIC\(_{90}\) of 16 \(\mu\)g/mL and >32 \(\mu\)g/mL, respectively).\(^\text{13,14}\) *Aeromonas* spp isolates were sensitive to doripenem (MIC\(_{90}\) of 1 \(\mu\)g/mL), whereas doripenem’s activity against strains of *Burkholderia cepacia* was variable and less than that of meropenem but similar to that of imipenem-cilastatin (MIC\(_{90}\) of 8 \(\mu\)g/mL). *Stenotrophomonas maltophilia* showed marked resistance to all carbapenems, including doripenem (MIC\(_{90}\) >16 \(\mu\)g/mL).\(^\text{10}\) Finally, doripenem had good activity against anaerobic isolates of clinical importance such as *Bacteroides* spp, *Prevotella* spp, *Clostridium* spp, *Fusobacterium* spp, and anaerobic gram-positive cocci.\(^\text{15}\)

Carbapenems as a class are generally resistant to hydrolysis by \(\beta\)-lactamases. Doripenem demonstrates enhanced stability and resistance to hydrolysis by derepressed AmpC \(\beta\)-lactamases and ESBLs.\(^\text{16}\) Currently known mechanisms of decreased microbial susceptibility to doripenem include the production of metallo-\(\beta\)-lactamases such as IMP and VIM, decreased production or absence of the OprD outer membrane porin protein leading to decreased entry of the drug into the cell, and expression of multidrug efflux pumps that promote excretion of the drug out of the cell.\(^\text{7,16–20}\) Compared with the other carbapenems, doripenem has a higher threshold for selection of nonsusceptible mutants in vitro, and it seems that high-level resistance may require the coexistence of more than one resistance mechanism.\(^\text{7,16,17}\) At this time, some authors have suggested that it is unlikely that such complex alterations and multilevel mechanisms of resistance are selected in vivo during doripenem therapy.\(^\text{7,16–18,21}\)

In a phase 3, prospective, multicenter, randomized, double-blind, noninferiority study, doripenem was found to have clinical cure rates comparable to those of meropenem for the treatment of complicated IAI in the clinically evaluable (86.7% versus 86.6%) and microbiologically evaluable (85.9% versus 85.3%) cases at test-of-cure follow-up. In cases in which *P. aeruginosa* was isolated (n = 19), microbial eradication was similar for doripenem and meropenem. Patients who had infected necrotizing pancreatitis and pancreatic abscesses were excluded from the study.\(^\text{22}\) Another phase 3, randomized, double-blind, multicenter trial showed that doripenem was noninferior to levofloxacin for the treatment of complicated UTIs. Clinical cure rates in evaluable patients were 95.1% and 90.2% for the doripenem and levofloxacin groups, respectively.\(^\text{23}\) Doripenem has also been studied for the treatment of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) in two prospective, randomized, multicenter, and open-label studies.\(^\text{24,25}\) Rea-Neto and colleagues\(^\text{24}\) showed that doripenem was comparable and noninferior to piperacillin-tazobactam for the treatment of HAP and VAP. Cure rates for clinically evaluable patients were 81.3% and 79.8% for doripenem and piperacillin-tazobactam, respectively. Decreased susceptibility of *P. aeruginosa* isolates was seen in 26.9% of patients treated using piperacillin-tazobactam and 7.7% of patients treated using doripenem. The authors acknowledged, however, a low rate of study-drug monotherapy when infection with *P. aeruginosa* was suspected and severely ill and immunocompromised patients were
excluded.24 Chastre and colleagues25 showed that doripenem was noninferior to imipenem-cilastatin in the treatment of VAP, with comparable cure rates of 68.3% versus 64.8% in clinically evaluable patients. All-cause mortality was similar for both treatment arms at 28 days (10.8% for doripenem versus 9.5% for imipenem-cilastatin). In cases in which *P. aeruginosa* was isolated at baseline, both treatment arms had similar clinical cure and microbiological eradication rates. There was a trend toward better outcomes for patients who had higher baseline Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, which were more than 20 points higher in the doripenem group than in the imipenem-cilastatin group (70.4% versus 57.7%).25

In previous studies, doripenem showed a good safety and tolerability profile compared with drugs studied in other arms. The incidence of study-drug-related adverse events (AEs) ranged from 16% to 32% for doripenem and from 18% to 27% for various comparators. The most commonly reported AEs were nausea, emesis, diarrhea, headaches, phlebitis, rash, and transaminitis. No seizure events that could be directly attributed to doripenem were reported.22–25 Nevertheless, the epileptogenic potential of some carbapenems in patients who are at risk is a known potential side effect, particularly for imipenem-cilastatin.26 Doripenem may not be exempt from this risk, according to some postmarketing reports from outside the United States.1 However, a study evaluating the epileptogenic potential of doripenem administered i.v. or intracisternally in animal models failed to produce seizures.27

As the newest member of the carbapenem family, the role of doripenem may mirror that of meropenem more than any other carbapenem. They both have similar spectrums of antimicrobial activity and safety profiles. Based on the aforementioned noninferiority comparative trials, doripenem has a place in the treatment of not only complicated IAIs and complicated UTIs but also other health-care-associated infections such as HAP and VAP that are caused by susceptible pathogens. The true clinical efficacy of doripenem against strains of *Pseudomonas* that are resistant to other carbapenems remains unclear. Another area that may merit future research is the role of doripenem for the treatment of postneurosurgical meningitis caused by MDR gram-negative bacteria.

**CEFTOBIPROLE**

Since the emergence of the first MRSA isolate in the 1960s, the medical community has witnessed the widespread dissemination of MRSA and the burden that it can create in hospital wards and, most recently, surrounding communities.28 It has been the rule that β-lactams as a class are ineffective against MRSA because of alterations in the target binding site PBP-2a that is coded by the *mecA* gene of the *mec* type IV staphylococcal cassette chromosome.29,30 Ceftobiprole-medocaril (formerly BAL 5788, RO-5788) is a new, i.v.–administered, broad-spectrum pyrrolidinone cephalosporin that retains a high degree of affinity for PBP-2a.31–33 In addition, ceftobiprole also has affinity for PBP-2x in penicillin-resistant *Streptococcus pneumoniae* and for PBP-3 in *Escherichia coli* and *P. aeruginosa*.31,33–35 At the time of writing, ceftobiprole has been approved for use in Canada and Switzerland and is under review by the FDA in the United States.36

Ceftobiprole-medocaril, the inactive prodrug, is cleaved to the active compound of ceftobiprole, diacetyl, and carbon dioxide by plasma esterases shortly after infusion. The degree of plasma protein binding has been reported to be ~16% to 38%, whereas the volume of distribution is similar to that of the extracellular fluid compartment in adults at steady state. Ceftobiprole primarily undergoes renal excretion, and the majority of the drug is recovered in the urine (~83% unchanged drug, ~0.3%
prodrg, and ~0.8% inactive metabolites). The activity of ceftobiprole depends on the length of time that the concentration of free drug is more than the MIC of the organism (% $fT > MIC$), and the mean serum half-life is approximately 3 to 4 hours. Based on Monte Carlo simulation analysis, the likelihood of achieving the target $fT > MIC$ of 30% and 50% for organisms with an MIC that is 2 μg/mL or less and 1 μg/mL or less, respectively, was greater than 90% with a dosage of 500 mg i.v. over 1 hour every 12-hours. Similarly, the likelihood of achieving the target $fT > MIC$ of 40% and 60% for organisms with an MIC that is 4 μg/mL or less and 2 μg/mL or less, respectively, was greater than 90% with a dosage of 500 mg i.v. over 2 hours every 8 hours. The current recommended dosage in the setting of normal renal function is 500 mg i.v. infused for 30 minutes to 2 hours every 8 to 12 hours, depending on the target percentage of $fT > MIC$ desired and type of infection being treated. Thus, treatment of polymicrobial diabetic foot infections and gram-positive or gram-negative HAP or VAP may require 500 mg i.v. for 2 hours every 8 hours, versus treatment of a complicated skin and soft-tissue infection (SSTI) caused by a gram-positive bacteria, which may only require 500 mg i.v. for 1 hour every 12 hours. Pharmacodynamic studies suggest that dose adjustments are required in the setting of mild to moderate renal dysfunction (CrCl ≤ 50 mL/min; 500 mg i.v. for 2 hours every 12 hours). Further data are needed regarding optimal dosing in the setting of severe renal dysfunction and hemodialysis. Ceftobiprole does not undergo significant hepatic metabolism, and no dose adjustments appear to be required in the setting of hepatic dysfunction.

The spectrum of antimicrobial activity of ceftobiprole is among the broadest of all currently available cephalosporins. As part of a longitudinal, global, resistance-surveillance program (SENTRY), Fritsche and colleagues analyzed the in vitro activity of ceftobiprole using broth microdilution methods in 40,675 common bacterial isolates. With regard to gram-positive bacteria, ceftobiprole readily inhibited MSSA and MRSA at concentrations that are 4 μg/mL or less (MIC₉₀ 0.5 μg/mL and 2 μg/mL, respectively). The activity of ceftobiprole against MSSA isolates was equal to that of oxacillin and daptomycin, and eightfold greater than that of cefepime and ceftriaxone. Its activity was at least eightfold greater than that of any other β-lactam against MRSA and equal to that of linezolid, but twofold to fourfold less than that of vancomycin, TMP-SMX, or daptomycin. Ceftobiprole inhibited more than 99% of MS-CoNS and methicillin-resistant coagulase-negative staphylococci (MR-CoNS) isolates at concentrations of 0.5 μg/mL and 4 μg/mL, respectively. Its activity against MR-CoNS was comparable to that of vancomycin. Ceftobiprole showed good activity against ampicillin-sensitive, ampicillin-resistant, and vancomycin-resistant strains of Enterococcus faecalis, β-hemolytic Streptococcus spp, Streptococcus viridans Bacillus spp, Listeria spp, and Streptococcus pneumoniae. Ceftobiprole inhibited 100% of penicillin-susceptible and penicillin-resistant Streptococcus pneumoniae at concentrations of 0.25 μg/mL and 2 μg/mL respectively. Ceftobiprole, however, did not show significant activity against Corynebacterium spp. It also has no documented in vitro activity against Enterococcus faecium isolates regardless of their vancomycin or ampicillin susceptibility profiles.

With regard to the Enterobacteriaceae, ceftobiprole showed good activity against non-ESBL–producing Escherichia coli, Proteus mirabilis, Citrobacter spp, Serratia spp, and Salmonella spp isolates. Ceftobiprole was less active than cephepin against non-ESBL–producing Klebsiella pneumoniae, Enterobacter spp, and indole-positive Proteus spp, with 76.9%, 85.4%, and 72.2% of respective isolates being inhibited by drug concentrations that were 8 μg/mL or less. Similar to other extended-spectrum cephalosporins, ceftobiprole showed limited activity against ESBL-producing strains of Escherichia coli and Klebsiella pneumoniae.
The in vitro activity of ceftobiprole against nonfermenting, aerobic, gram-negative bacteria such as \textit{P. aeruginosa} was generally similar to other agents. Ceftobiprole inhibited 77.9\% at concentrations that were 8 \mu g/mL or less, whereas the percentage susceptible to ceftazidime was 75.5\%, imipenem 75.8\%, cefepime 79.4\%, meropenem 80.9\%, piperacillin-tazobactam 84.8\%, amikacin 87.4\%, and polymixin B 99.8\%. Ceftobiprole was active against \textit{Aeromonas} spp, but not against \textit{Stenotrophomonas maltophilia}, \textit{B. cepacia}, or \textit{Acinetobacter} spp. It was readily active against wild-type and \beta-lactamase--producing strains of \textit{H. influenzae} and \textit{M. catarrhalis}.\textsuperscript{33} Finally, it does have some activity against most anaerobic gram-positive cocci such as \textit{Propionibacterium acnes}, \textit{non-dificile Clostridium} spp, and \textit{Porphyromonas} spp. However, \textit{Peptostreptococcus anaerobius}, \textit{Clostridium difficile}, \textit{Prevotella} spp, and \textit{Bacteroides} spp were generally tolerant or resistant.\textsuperscript{45}

Ceftobiprole is generally resistant to hydrolysis by staphylococcal penicillinases, but not to ESBLs, carbapenemases, or OXA-10 \beta-lactamases produced by some MDR gram-negative bacteria. However, it is a poor substrate for Class A and SHV-1, and class C AmpC \beta-lactamases, demonstrating low rates of hydrolysis on exposure.\textsuperscript{46}

Ceftobiprole has been evaluated for the treatment of complicated SSTIs in phase 3 clinical trials. A randomized, double-blind, multicenter, noninferiority study compared ceftobiprole with vancomycin for the treatment of complicated SSTIs caused by gram-positive bacteria. The results showed comparable cure rates in clinically evaluable patients (93.3\% for ceftobiprole versus 93.5\% for vancomycin). In cases of documented MRSA infection, cure rates were similar for both treatment arms (91.8\% for ceftobiprole versus 90.0\% for vancomycin), including those caused by Panton-Valentin leukocidin (+) strains.\textsuperscript{41} A second randomized, double-blind, multicenter, noninferiority trial compared ceftobiprole with vancomycin plus ceftazidime for the treatment of complicated SSTIs. In contrast with the first trial, patients who had diabetic foot infections were included in this study. Among the clinically evaluable patients, cure rates were 90.5\% and 90.2\% for the ceftobiprole and vancomycin/ceftazidime arms, respectively. Comparable clinical cure rates were found in patients who had documented infections caused by MRSA (89.7\% for ceftobiprole versus 86.1\% for vancomycin/ceftazidime) and \textit{P. aeruginosa} (86.7\% for ceftobiprole versus 100\% for vancomycin/ceftazidime). Similarly, cure rates for patients who had diabetic foot infections were 86.2\% and 81.8\% for ceftobiprole and vancomycin/ceftazidime, respectively.\textsuperscript{42}

The incidence of at least one AE was 52\% for ceftobiprole and 51\% for vancomycin in the first study and 56\% for ceftobiprole and 57\% for vancomycin/ceftazidime group in the second. Nausea (14\%), vomiting (7\%), taste disturbance (8\%), and infusion-site reactions (9\%) were the most commonly reported AEs for the ceftobiprole arms.\textsuperscript{41,42}

Laboratory studies using a rabbit model of MRSA aortic valve endocarditis and tibial osteomyelitis showed promising results with the use of ceftobiprole.\textsuperscript{47,48} In addition, neutropenic-mouse-model studies have shown that ceftobiprole has excellent lung tissue penetration and achieves high concentrations in alveolar epithelial lining fluids that are much more than the MICs for various isolates of \textit{Staphylococcus aureus}, including MRSA.\textsuperscript{49}

Phase 3 clinical trials looking at the use of ceftobiprole for the treatment of community-acquired pneumonia, HAP, VAP, and neutropenic fever are currently under way.\textsuperscript{31} Additional prospective, randomized, multicenter studies are needed to address the role of ceftobiprole in the treatment of MRSA bacteremia, endocarditis, and bone and joint infections. Ceftobiprole is the first available \beta-lactam to show bactericidal activity against MRSA in addition to a wide array of gram-negative pathogens. Given its documented
clinical efficacy, microbial eradication rates, and safety profile in phase 3 trials of complicated SSTIs, ceftobiprole will likely be used in the increasingly complex fight against infections caused by MRSA and susceptible gram-negative pathogens.

**CEFTAROLINE**

Ceftaroline is another β-lactam of the cephalosporin class that retains activity against MRSA. At the time of this writing, ceftaroline remains investigational and is not yet approved for use. Ceftaroline fosamil (formerly PPI-0903M, formerly TAK-599) is a new, water-soluble, i.v.-administered, N-phosphono–type cephalosporin that undergoes hydrolysis of the phosphate group and is rapidly converted to its active compound in vivo after parenteral administration in animal models. In addition, it has a high degree of affinity for PBP-2a, with documented anti-MRSA activity.50,51 The pharmacokinetic and pharmacodynamic profiles of ceftaroline have been analyzed in murine models of thigh, lung, and aortic valve infection, and in healthy human volunteers and patients who had complicated SSTIs. The results of these studies show that the mean serum half-life is ~2.6 hours, plasma protein binding is less than 20%, and drug clearance occurs mainly by way of renal excretion, with ~75% of the drug recovered in the urine.52–56 The current dosing regimen used in patients who have normal renal function in phase 2 and 3 clinical trials is 600 mg i.v. infused for 1 hour every 12 hours.57,58 Dosage adjustments are not required in the setting of mild renal dysfunction (CrCl >50–80 mL/min), but should be undertaken for patients who have moderate renal dysfunction (CrCl >30–50 mL/min; 400 mg i.v. for 1 hour every 12 hours). No specific recommendations regarding dosing in the setting of severe renal dysfunction (CrCl < 30 mL/min) or hemodialysis are available at this time.56

Analysis of the in vitro activity of ceftaroline against various clinical and laboratory bacterial isolates from various parts of the world using broth microdilution methods showed that it has excellent activity against MSSA, MRSA, MS-CoNS, and MR-CoNS. Activity was fourfold greater than that of vancomycin and 16 fold greater than that of ceftriaxone or cefepime against MSSA isolates. When tested against 102 MRSA isolates, ceftaroline had an MIC90 of 2 µg/mL, which is similar to that of linezolid and slightly higher than that of vancomycin (MIC90 of 1 µg/mL). Activity was also documented against vancomycin-intermediate strains of Staphylococcus aureus. For 100 isolates of vancomycin-intermediate strains of Staphylococcus aureus tested, the ceftaroline MIC90 was 2 µg/mL, which is only slightly higher than that of linezolid, which had an MIC90 of 1 µg/mL.59 Similar results were noted in clinical isolates from the United States, in which ceftaroline was the most active cephalosporin against all staphylococci tested.60 Other gram-positive bacteria that showed susceptibility to ceftaroline included Streptococcus pneumoniae (ceftaroline MIC90: penicillin-susceptible, ≤ 0.016 µg/mL; penicillin-intermediate, 0.06 µg/mL; penicillin-resistant, 0.25 µg/mL), β-hemolytic streptococci spp, and Streptococcus viridans. Ceftaroline was less active than vancomycin, imipenem–cilastatin, and levofloxacin against Bacillus spp. Ceftaroline showed only marginal activity against Enterococcus faecalis and was not effective against Enterococcus faecium (ceftaroline MIC90 for vancomycin-susceptible and vancomycin-resistant strains, >32 µg/mL).59

Ceftaroline displayed significant activity against the Enterobacteriaceae. Non-ESBL–producing strains were uniformly susceptible, whereas ESBL–producing strains of Escherichia coli, K pneumoniae, and P mirabilis were resistant. Among the nonfermenting, gram-negative bacteria, ceftaroline showed only minimal activity against certain isolates of P aeruginosa and A baumanii (ceftaroline MIC90 of 16 and MIC90 >32 µg/mL for both organisms) and was not active against Alcaligenes spp or...
Stenotrophomonas maltophilia. On the other hand, ceftaroline showed excellent activity against *Neisseria meningitidis*, *M catarrhalis*, and both β-lactamase–producing and non–β-lactamase–producing strains of *H influenzae*. In terms of anaerobic activity, it has significant effect against *Peptostreptococcus* spp, *Propionibacterium* spp, and non-*difficile Clostridium* spp. It has minimal to no activity against *Bacteroides fragilis* and *Prevotella* spp.59

Phase 2 and 3 clinical trials have been done to compare the safety and efficacy of ceftaroline with that of vancomycin with or without aztreonam for the treatment of SSTIs in randomized and observer-blinded studies. In the phase 2 study, the clinical cure rate was 96.7% for ceftaroline and 88.9% for standard therapy.57 In the phase 3 study, overall cure rates were 91.1% for ceftaroline and 93.3% for standard therapy in the clinically evaluable patient population. With respect to MRSA, similar clinical and microbiological cure rates were observed for both treatment arms (94.9% and 94.9% for ceftaroline versus 95.1% and 91.8% for vancomycin/aztreonam).58

In phase 2 and 3 comparative clinical trials, ceftaroline proved to be a well-tolerated drug and showed a good safety profile.57,58 In the phase 2 study, the incidence of reported AEs was similar for both treatment groups (61.2% for ceftaroline versus 56.3% for standard therapy), with the great majority of AEs being mild in nature (87.9% for ceftaroline versus 70.8% for standard therapy). The most commonly reported ceftaroline-related AEs in this study were crystalluria (9% for ceftaroline versus 15.6% for standard therapy) and elevated serum creatinine phosphokinase levels (7.5% for ceftaroline and 6.3% for standard therapy).57 In the phase 3 study, both treatment arms had comparable rates of possibly and probably study-drug-related AEs (43.2% for ceftaroline versus 47% for standard therapy). Similar to the first study, the majority of AEs were mild in nature. The most commonly reported AEs were nausea (5.7% for ceftaroline and 4.6% for standard therapy), headache (5.1% for ceftaroline and 3.7% for standard therapy), and generalized pruritus (3.7% for ceftaroline and 4.6% for standard therapy).58

As with ceftobiprole, future clinical trials should help clarify ceftaroline’s role among the new anti-MRSA β-lactams and determine its place in the treatment of community- and hospital-acquired infections such as pneumonia, bacteremia, endocarditis, and bone and joint infections.

**CEFEPIME**

This section on cefepime summarizes recent data from two comprehensive meta-analyses that put into question the safety and efficacy of cefepime and led to an FDA review regarding possible increased mortality risk from the use of cefepime.61,62 This section also highlights reports of side effects such as neurotoxicity in the setting of renal failure.63–65

Since its introduction into clinical use more than a decade ago, cefepime, which is a broad-spectrum, antipseudomonal, fourth generation oxyimino-cephalosporin, has been one of the first-line agents for the empiric treatment of patients who have neutropenic fever. It is currently FDA approved for the treatment of moderate to severe pneumonia, uncomplicated and complicated UTIs, complicated IAIs, and uncomplicated SSTIs caused by susceptible bacteria.65 Given its broad spectrum of antimicrobial activity, its stability in the face of inducible β-lactamases, and its higher threshold for selection of hyperproducing strains of chromosomally mediated β-lactamases, cefepime has been considered an appropriate agent for the treatment of severe gram-negative infections.66–68 In addition, it also has superior activity against *Streptococcus pneumoniae* and staphylococci (methicillin-sensitive strains) compared with
other extended-spectrum late-generation cephalosporins.\textsuperscript{69–71} Cefepime has been for the most part a fairly well-tolerated drug, with most reported AEs being categorized as mild and statistically similar to those for the comparator arms in phase 3 clinical trials.\textsuperscript{72} In addition, it has a low incidence of allergic cross-reactivity with penicillin and ceftazidime because of its unique side chain structure.\textsuperscript{73} A comprehensive review of cefepime’s dosing regimens, pharmacodynamic and pharmacokinetic properties, metabolism and elimination, and spectrum of antimicrobial coverage has been published in \textit{Infectious Disease Clinics of North America}.\textsuperscript{74}

In 2002, the FDA reviewed data submitted by the manufacturer of cefepime and approved an addition to cefepime’s label warning about the increased risk for neurotoxicity, especially in the setting of renal failure.\textsuperscript{64} The data were based on postmarketing reports that included episodes of encephalopathy, myoclonus, and seizures. Most of these cases were in patients who had renal dysfunction for whom administered doses exceeded recommendations. Some events, however, were also reported in patients who received renal-adjusted doses of cefepime. Discontinuation of the offending drug, or hemodialysis in some cases, led to resolution of symptoms in most patients.\textsuperscript{63–65}

Recent data from two comprehensive systematic reviews and meta-analyses of randomized controlled trials, both from the same group, have put into question cefepime’s efficacy and safety compared with that of other broad-spectrum β-lactams.\textsuperscript{61,62} The first meta-analysis reviewed the results of 33 studies to determine if the outcomes of patients who had neutropenic fever were influenced by the choice of initial empiric β-lactam therapy.\textsuperscript{61} The primary outcome was all-cause mortality assessed at 30 days posttreatment. The results showed that patients who received cefepime (17 trials, \( n = 3,123 \) patients) had a higher and more statistically significant 30 day all-cause mortality compared with patients who received other antipseudomonal β-lactams (\( P = .02 \)). However, no significant differences were noted with regard to secondary outcomes analyzed, such as treatment failure, microbiological failure, infection-related mortality, antibiotic modification, addition of vancomycin, addition of antifungal agents, bacterial superinfections, any other superinfections, or AEs. The authors of that study compared piperacillin-tazobactam with cefepime (4 trials) and found no differences in all-cause mortality. However, they stated that the latter results were hampered by a lack of substantial methodologic data that would allow definitive conclusions for this particular analysis.\textsuperscript{61}

The second meta-analysis, by Yahav and colleagues,\textsuperscript{62} reviewed the results of 57 studies in which cefepime was compared with other β-lactams to assess all-cause mortality at 30 days posttreatment as the primary outcome. Randomized trials were subdivided based on the comparator drug used and the type of infection for which the patient was being treated. Similar to the first meta-analysis, the authors found that in the 41 studies (38 of which were clinical trials) for which all-cause mortality was available, patients treated using cefepime had an overall higher and more statistically significant all-cause mortality compared with patients treated using other β-lactams, despite similar baseline risk factors for mortality (\( P = .005 \)). This difference was most significant when cefepime was compared with piperacillin-tazobactam (relative risk [RR] 2.14; \( P = .01 \)), but it was seen for all comparator drugs. The authors also concluded that except for cases of UTIs, all-cause mortality was higher for cefepime than for the comparator drugs with regard to the type of infection being treated.\textsuperscript{62}

Yahav and colleagues offered some possible explanations for their findings. First, they stated that cefepime-induced neurotoxicity may have been underrecognized in the pool of patients that was analyzed, which in turn may have contributed to the overall higher all-cause mortality observed. Second, they argued that other factors such as
inoculum, inadequate targeted-tissue concentrations, and pharmacodynamics (inter-
mittent versus continuous cefepime dosing) may have played a role in the results.61,62

These reports have some limitations, however. In particular, complete all-cause
mortality results were lacking in some of the trials analyzed, and potential patient
selection bias might not have been fully accounted for in the meta-analysis. The
FDA is reviewing the safety data on cefepime further and requested support from Bris-
tol-Meyers Squibb, the manufacturer of cefepime (Maxipime), with the goal of reach-
ing a conclusion and releasing further recommendations to the public in the near
future.75,76

SUMMARY

The advent of novel cephalosporins with anti-MRSA activity such as ceftobiprole and
ceftaroline is an exciting new development. MRSA is a major and growing problem in
infectious diseases, and the addition of cephalosporins with activity against this
organism will be greeted with high anticipation if and when they are FDA approved.
Doripenem is also a welcome addition to the carbapenems, and its use will most likely
mirror that of meropenem. However, based on the currently available data, it is difficult
to recommend the use of doripenem rather than meropenem. Despite the fact the in
vitro results seem to suggest that doripenem may retain activity against some carba-
penem-resistant strains of P aeruginosa, it is not clear whether this has any in vivo clin-
ical relevance. The authors of this article hope that future phase 3 clinical trials will help
expand potential FDA-approved indications for these and any other upcoming β-lac-
tams that might be in the early stages of development. The FDA recently updated its
recommendations regarding cefepime. The FDA independently conducted both trial-
level (n = 88 trials; including 24 neutropenic fever trials) and patient-level (n = 35 trials)
meta-analyses and concluded there was no statistically significant difference in 30 day
all cause mortality between the cefepime and comparator treatment arms (adjusted
risk difference 5-38 per 1000 population, 95% C.I. −1.53–12.28 and 4.83 per 1000
population, 95% C.I. −4.72–14.38 respectively). Based on these findings, the FDA is-
sued a statement that cefepime should retain its status as a first-line treatment option
for already approved indications, including the treatment of neutropenic fever. Never-
theless, both the FDA and the manufacturer of cefepime (Bristo-Myers Squibb) will
continue to perform independent safety reviews on the drug based on hospital
utilization data. According to the FDA, it may take a year before such findings are
made public.75,76,77

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