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

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Beta-lactam (β-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, β-lactam antibiotics have evolved concomitantly with global antimicrobial resistance patterns. However, the emergence of pathogens like meticillin-resistant Staphylococcus aureus (MRSA), penicillin-intermediate and penicillin-resistant Streptococcus pneumoniae, multidrug-resistant (MDR) Pseudomonas aeruginosa, and extended-spectrum β-lactamase (ESBL)–producing gram-negative enteric organisms have provided new challenges, and the evolution of new β-lactams has slowed. This article focuses on the agents doripenem, ceftobiprole, and ceftaroline. 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.

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DORIPENEM

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). Doripenem binds to penicillin-binding proteins (PBPs) and leads to the inhibition of bacterial cell wall synthesis. 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 (% $f_T >$MIC). Unlike imipenem, its 1-β-methyl side chain confers stability in the face of renal dihydropeptidases.

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. 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). 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. This dosing regimen has been shown to achieve the $f_T >$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 $f_T >$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. 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. 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. Dosing of doripenem in the setting of renal replacement therapy (CRRT) is also not clearly defined. However, new data has recently emerged regarding the pharmacokinetic profile of doripenem in the setting of continuous venovenous hemofiltration and hemodiafiltration. According to Cirillo and colleagues, both types of CRRT significantly removed doripenem and its primary metabolite (M-1) when administered as a single 500 mg dose over 1 hour to patients with end-stage renal disease on hemodialysis. Nevertheless, these patients still demonstrated significantly higher plasma drug concentrations, higher area under the plasma concentration time curves (0–12 hour), and longer plasma elimination half lives compared to healthy individuals. These results demonstrate that commonly used CRRT modalities can have an additive effect on residual total body drug clearance. Additional data is needed to help define optimal dosing strategies in patients with CrCl less than 10 mL/min, hemodialysis, and CRRT.

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.

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. On the other hand, vancomycin-resistant Enterococcus faecium isolates were uniformly resistant to doripenem. 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.

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. Doripenem also displays excellent activity against common respiratory pathogens such as Haemophilus influenzae and Moraxella catarrhalis (including β-lactamase-producing strains). With regard to the nonfermenting, aerobic, gram-negative bacteria, doripenem had the greatest activity against wild-type strains of P aeruginosa that had an MIC50 and MIC90 of 0.5 μg/mL and 8 μg/mL, respectively. 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. 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. However, only 6.7% of Class B metallo-β-lactamase–producing strains of P aeruginosa strains were sensitive to doripenem. Doripenem was active against 75.8% of wild-type Acinetobacter baumanii and 20.8% of carbapenem-resistant Acinetobacter spp (MIC90 of 16 μg/mL and >32 μg/mL, respectively). Aeromonas spp isolates were sensitive to doripenem (MIC90 of 1 μg/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 (MIC90 of 8 μg/mL). Stenotrophomonas maltophilia showed marked resistance to all carbapenems, including doripenem (MIC90 >16 μg/mL). 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.

Carbapenems as a class are generally resistant to hydrolysis by β-lactamases. Doripenem demonstrates enhanced stability and resistance to hydrolysis by derepressed AmpC β-lactamases and ESBLs. Currently known mechanisms of decreased microbial susceptibility to doripenem include the production of metallo-β-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. 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. 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. 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 IAIs in the clinically evaluable (86.7% vs 86.6%) and microbiologically evaluable (85.9% vs 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. Another phase
3, randomized, double-blind, multicenter trial showed that doripenem was noninferior to levofloxacain 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. 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. Rea-Neto and colleagues 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. Chastre and colleagues 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 vs 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% vs 57.7%).

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. Nevertheless, the epileptogenic potential of some carbapenems in patients who are at risk is a known potential side effect, particularly for imipenem-cilastatin. Doripenem may not be exempt from this risk, according to some postmarketing reports from outside the United States. However, a study evaluating the epileptogenic potential of doripenem administered i.v. or intracisternally in animal models failed to produce seizures.

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 non-inferiority comparative trials, doripenem has a place in the treatment of not only complicated IAIIs and complicated UTIs but also other health-care-associated infections such as HAP and VAP that are caused by susceptible pathogens. In July 16, 2008, the FDA’s Anti-Infective Drugs Advisory Committee voted in favor of doripenem’s clinical efficacy and safety for the treatment of HAP and VAP. At the time of writing, final FDA approval for these indications was pending.

Finally, doripenem may play a important role in the treatment of serious infections due to MDR gram negative pathogens. The emergence of carbapenemase-producing strains of \( K. pneumoniae \) (KPC) and carbapenem-resistant strains of \( P. aeruginosa \), presents a major challenge to clinicians given the limited antimicrobial options that are available to treat serious infections due to these organisms. New data are emerging about the potential utility of prolonged infusion doripenem to help treat such infections. Bulik and Nicolau analyzed the utility of prolonged infusion doripenem at doses known to simulate exposures in humans, for the treatment of thigh infection due to KPC-enzyme producing strains of \( K. pneumoniae \) in immunocompetent and
immunocompromised mice. Results demonstrated that in immunocompetent mice, 4-hour infusions of doripenem administered as 1 or 2 g every 8 hours, significantly decreased bacterial loads (~1 log CFU; \( P < .05 \)), while in immunocompromised mice, bacteriostatic effects were noted in isolates with MICs up to 8 \( \mu g/mL \) and 16 \( \mu g/mL \) respectively.\(^3\) Furthermore, a recent small retrospective study evaluated the use of doripenem 1 g i.v. every 8 hours infused over 4-hours combined with Fosfomycin 2 g i.v. every 8 hours for the treatment of HAP due to carbapenem-resistant \( P. aeruginosa \) (doripenem MICs of 4–8 mg/L). Results demonstrated that 6 of 8 patients (75%) experienced clinical cure or improvement. In patients in which follow-up microbiological evaluation was performed, eradication was documented in 6 of 7 patients (87%). Overall, there were no significant AEs that could be attributed to therapy.\(^3\) Additional clinical studies are needed to further define the role that extended-infusion doripenem will play in the treatment of infections due to MDR gram negatives, especially those that exhibit carbapenem resistance.

**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.\(^3\) It has been the rule that \( \beta \)-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.\(^3\),\(^4\) Cefotiboprole-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.\(^3\),\(^5\)–\(^7\) In addition, cefotiboprole also has affinity for PBP-2x in penicillin-resistant \( Streptococcus pneumoniae \) and for PBP-3 in \( Escherichia coli \) and \( P. aeruginosa \).\(^3\),\(^5\)–\(^9\) Cefotiboprole was initially approved for use in Canada and Switzerland but has now been withdrawn for reasons discussed at the end of this section.\(^4\)–\(^6\)

Cefotiboprole-medocaril, the inactive prodrug, is cleaved to the active compound of cefotiboprole, 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. Cefotiboprole primarily undergoes renal excretion, and the majority of the drug is recovered in the urine (~83% unchanged drug, ~0.3% prodrug, and ~0.8% inactive metabolites). The activity of cefotiboprole 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.\(^5\),\(^3\),\(^4\) 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 \( \mu g/mL \) or less and 1 \( \mu g/mL \) 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 \( \mu g/mL \) or less and 2 \( \mu g/mL \) or less, respectively, was greater than 90% with a dosage of 500 mg i.v. over 2 hours every 8 hours.\(^4\),\(^5\) 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.
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 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 oxacillin 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 ceftazidime 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 P aeruginosa was generally similar to other agents. Ceftobiprole inhibited 77.9% at concentrations that were 8 μg/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 Aeromonas spp, but not against Stenotrophomonas maltophilia, B cepacia, or Acinetobacter spp. It was readily active against wild-type and β-lactamase–producing strains of H influenzae and M catarrhalis. Finally, it does have some activity against most anaerobic gram-positive cocci such as Propionibacterium acnes, non-difficile Clostridium spp, and Porphyromonas spp. However, Peptostreptococcus anaerobius, Clostridium dificile, Prevotella spp, and Bacteroides spp were generally tolerant or resistant.

Ceftobiprole is generally resistant to hydrolysis by staphylococcal penicillinases, but not to ESBLs, carbapenemases, or OXA-10 β-lactamases produced by some MDR gram-negative bacteria. However, it is a poor substrate for Class A and
SHV-1, and class C AmpC β-lactamases, demonstrating low rates of hydrolysis on exposure.\textsuperscript{52}

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 vs 93.5\% for vancomycin). In cases of documented MRSA infection, cure rates were similar for both treatment arms (91.8\% for ceftobiprole vs 90.0\% for vancomycin), including those caused by Panton-Valentin leukocidin (+) strains.\textsuperscript{47} 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 vs 86.1\% for vancomycin/ceftazidime) and \textit{P aeruginosa} (86.7\% for ceftobiprole vs 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{48}

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{47,48}

Laboratory studies using a rabbit model of MRSA aortic valve endocarditis and tibial osteomyelitis showed promising results with the use of ceftobiprole.\textsuperscript{53,54} 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{55}

Phase 3 clinical trials looking at the use of ceftobiprole for the treatment of community-acquired pneumonia, HAP, and neutropenic fever have been completed and we are awaiting their respective results.\textsuperscript{56}

Ceftobiprole is the first available β-lactam to show bactericidal activity against MRSA in addition to a wide array of gram-negative pathogens. However, in November 28, 2008, the FDA notified the sponsor of ceftobiprole, Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD), that it could not approve the drug for the treatment of complicated SSTI and diabetic foot infections. The FDA cited that irregularities had been found in 10 of 49 clinical trial sites when it reviewed data from two major studies (BAP00154 and BAP00414) that were presented by the company as part of its New Drug Application (NDA). The FDA concluded that J&JPRD had failed to adequately monitor the clinical investigators from the sites in question, thereby making the available data unreliable or unverifiable. The failure to adequately monitor could have affected safety and primary efficacy data from these sites. Furthermore, additional data was requested by the FDA regarding the conclusion that ceftobiprole was non-inferior to the comparator arm in subsets of patients that had skin and soft tissue abscesses that were drained or diabetic foot infections. The FDA did provide recommendations to the company regarding the design and conduct of two new clinical trials to re-evaluate the safety and efficacy of ceftobiprole for the treatment of complicated SSTI’s.\textsuperscript{57,58} In 2010, the European Committee for Medicinal Products for Human Use (CHMP) concluded that ceftobiprole should not
be authorized for use.\textsuperscript{59} Since then, both Canada and Switzerland have discontinued the sale and use of ceftobiprole.\textsuperscript{60,61}

**CEFTAROLINE**

Ceftaroline is another $\beta$-lactam of the cephalosporin class that retains activity against MRSA. 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.\textsuperscript{62,63} 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 $\sim$2.6 hours, plasma protein binding is less than 20\%, and drug clearance occurs mainly by way of renal excretion, with $\sim$75\% of the drug recovered in the urine.\textsuperscript{64–68} 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.\textsuperscript{69,70,72}

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 more severe renal dysfunction (CrCl $>$30–50 mL/min; 400 mg i.v. for 1 hour every 12 hours, CrCl $>$515 to $<$30 mL/min 300 mg i.v. for 1 hour every 12 hours, end stage renal disease CrCl $<$15 mL/min including hemodialysis 200 mg i.v. over 1 hour every 12 hours [administer after hemodialysis on hemodialysis days]).\textsuperscript{71}

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 MIC$\textsubscript{90}$ of 2 $\mu$g/mL, which is similar to that of linezolid and slightly higher than that of vancomycin (MIC$\textsubscript{90}$ of 1 $\mu$g/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 MIC$\textsubscript{90}$ was 2 $\mu$g/mL, which is only slightly higher than that of linezolid, which had an MIC$\textsubscript{90}$ of 1 $\mu$g/mL.\textsuperscript{73} Similar results were noted in clinical isolates from the United States, in which ceftaroline was the most active cephalosporin against all staphylococci tested.\textsuperscript{74}

Other gram-positive bacteria that showed susceptibility to ceftaroline included *Streptococcus pneumoniae* (ceftaroline MIC$\textsubscript{90}$: penicillin-susceptible, $\leq$0.016 $\mu$g/mL; penicillin-intermediate, 0.06 $\mu$g/mL; penicillin-resistant, 0.25 $\mu$g/mL), $\beta$-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 MIC$\textsubscript{90}$ for vancomycin-susceptible and vancomycin-resistant strains, $>$32 $\mu$g/mL).\textsuperscript{73}

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 baumannii* (ceftaroline MIC$\textsubscript{50}$ of 16 and MIC$\textsubscript{90}$ $>$32 $\mu$g/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.73

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 complicated 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 an integrated analysis of two phase 3 studies, the overall cure rates were 91.6% for ceftaroline and 92.7% 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 (93.4% and 92.3% for ceftaroline vs 94.3% and 93.7% for vancomycin/aztreonam).70

In phase 2 and 3 comparative clinical trials for the treatment of complicated SSTIs, 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 vs 56.3% for standard therapy), with the great majority of AEs being mild in nature (87.9% for ceftaroline vs 70.8% for standard therapy). The most commonly reported ceftaroline-related AEs in this study were crystalluria (9% for ceftaroline vs 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 studies, both treatment arms had comparable rates of any reported AE after starting therapy (44.7% for ceftaroline vs 47.5% for standard therapy). Similar to the phase 2 study, the majority of AEs were mild in nature. The most commonly reported study-drug related AEs were nausea (5.9% vs 5.1%), diarrhea (4.9% vs 3.8%), and pruritus (3.5% vs 8.2%) in the ceftaroline and standard therapy arms respectively.70

An integrated analysis of two phase 3 clinical trials comparing ceftaroline to ceftriaxone for the treatment of community-acquired pneumonia (CAP) in hospitalized (non-ICU) patients, demonstrated that clinical cure rates were comparable between both treatment arms in the clinically evaluable patients (84.3% vs 77.7% respectively). The per-patient microbiological cure rates were 87% and 81% for ceftaroline and standard therapy respectively. Furthermore, clinical cure rates in microbiologically evaluable patients infected with non-MDR *Streptococcus pneumoniae*, MDR *Streptococcus pneumoniae*, or MSSA were 85.7%, 100%, and 72% for ceftaroline compared to 69.5%, 25%, and 55.6% for standard therapy respectively. No conclusions could be reached regarding efficacy of ceftaroline for the treatment of CAP due to MRSA as patients with suspected or documented infection with this pathogen were excluded from the study.71

Ceftaroline was well tolerated in both phase 3 CAP studies and had comparable incidence of any AE to ceftriaxone (47% vs 45.7%), most of which were mild in nature. The most commonly reported AEs in the ceftaroline arm compared to the standard therapy arm were diarrhea (4.2% vs 2.6%), headache (3.4% vs 1.5%), and insomnia (3.1% vs 2.3%). There were no differences between treatment arms with regards to other relatively infrequent AEs, including QT-interval, hepatobiliary, renal, and/or hematologic abnormalities.71

Based on the aforementioned studies, the FDA approved ceftaroline fosamil for the treatment of acute bacterial SSTI and CAP in adult patients ≥18 years-old. A prospective randomized study that will assess the efficacy of ceftaroline for the treatment of CAP in patients at high risk for MRSA should be scheduled to start by the end of
2011. There is also preliminary in-vitro and in-vivo animal model data emerging on the potential use of NXL-104, a new experimental β-lactamase inhibitor, in combination with ceftaroline for the treatment of infections due to ESBL, AmpC β-lactamase, and KPC-enzyme producing Enterobacteriaceae. Phase 1 trials using this combination are currently in development.

**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. This section also highlights reports of side effects such as neurotoxicity in the setting of renal failure.

Since its introduction into clinical use more than a decade ago, cefepime, which is a broad-spectrum, antipseudomonal, fourth generation oximino-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. 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. In addition, it also has superior activity against *Streptococcus pneumoniae* and *staphylococci* (methicillin-sensitive strains) compared with other extended-spectrum late-generation cephalosporins. 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. In addition, it has a low incidence of allergic cross-reactivity with penicillin and ceftazidime because of its unique side chain structure. A comprehensive review of cefepime’s dosing regimens, pharmacodynamic and pharmacokinetic properties, metabolism and elimination, and spectrum of antimicrobial coverage has been published in *Infectious Disease Clinics of North America*.

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. 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.

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. 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. 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.83

The second meta-analysis, by Yahav and colleagues,84 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.84

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 (intermittent vs continuous cefepime dosing) may have played a role in the results.83,84

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 further reviewed the safety data on cefepime and requested support from Bristol-Meyers Squibb (BMS), the manufacturer of cefepime (Maxipime), with the goal of reaching a conclusion and releasing further recommendations to the public.87,88 On June 17, 2009 the FDA released a communication stating its conclusions regarding the use of cefepime for its approved indications. The FDA performed its own meta-analysis that included both trial- and patient-level data from 88 clinical trials. This meta-analysis included the 38 clinical trials reported in the meta-analysis by Yahav et al, but also an additional 50 clinical trials which were not included in the latter. The total number of patients included in the FDA meta-analysis was 9,467 and 8,288 for the cefepime and comparator-treatment arms respectively. Results from the trial-level meta-analysis demonstrated that there was no statistically significant difference in the 30 day all cause mortality between cefepime and comparator-treated patients (6.21% vs 6.00%; adjusted risk difference 5.38 / 1000 population, 95% CI: −1.53 – 12.28). The FDA also found no statistically significant difference in 30 day all cause mortality when it analyzed patient-level data from 35 clinical trials (5.63% vs 5.68%; adjusted risk difference 4.83 / 1000 population, 95% CI: −4.72 – 14.38). Finally, a meta-analysis from trial-level data obtained from 24 febrile neutropenia trials failed to demonstrate a statistically significant increase in mortality associated with the use of cefepime (adjusted risk difference 9.67 / 1000 population, 95% CI: −2.87 – 22.21). Further investigations by the FDA revealed that according to patient-level data from 7 comparative febrile neutropenia trials, the majority of deaths in cefepime-treated patients could be
attributed to underlying co-morbidities. Therefore, based on all these findings, the FDA concluded that cefepime should remain an appropriate treatment option for patients with approved indications for its use. Nevertheless, both the FDA and BMS will continue to perform independent safety reviews on the drug based on hospital utilization data.99

SUMMARY

The advent and approval of ceftaroline, a cephalosporin with anti-MRSA activity, 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. The combination of ceftaroline with the new β-lactamase inhibitor NXL-104, also brings about much interest as it pertains to enhanced activity against ESBL and KPC-enzyme producing strains of Enterobacteriaceae. On the other hand, despite recent setbacks in its approval process at the FDA, ceftobiprole may one day still become available to clinicians and find its role in the treatment of serious infections due to MRSA and susceptible gram-negative organisms. Doripenem is also a welcome addition to the carbapenems, and its use will most likely mirror that of meropenem. Despite the fact the in vitro results seem to suggest that doripenem may retain activity against some carbapenem-resistant strains of *P aeruginosa*, it is not clear whether this has any in vivo clinical relevance. Nevertheless, more clinical data is needed regarding the use of prolonged-infusion doripenem for the treatment of serious infections due to MDR gram negative organisms, including carbapenem-resistant strains. Also, we are awaiting the final decision by the FDA regarding final approval of doripenem for the treatment of HAP and VAP. 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-lactams that might be in the early stages of development. Finally, the FDA updated its recommendations regarding cefepime. There were no statistically significant differences in 30 day all cause mortality between the cefepime and comparator treatment arms. Based on these findings, the FDA issued a statement that cefepime should retain its status as a treatment option for already approved indications, including the treatment of neutropenic fever.

REFERENCES


