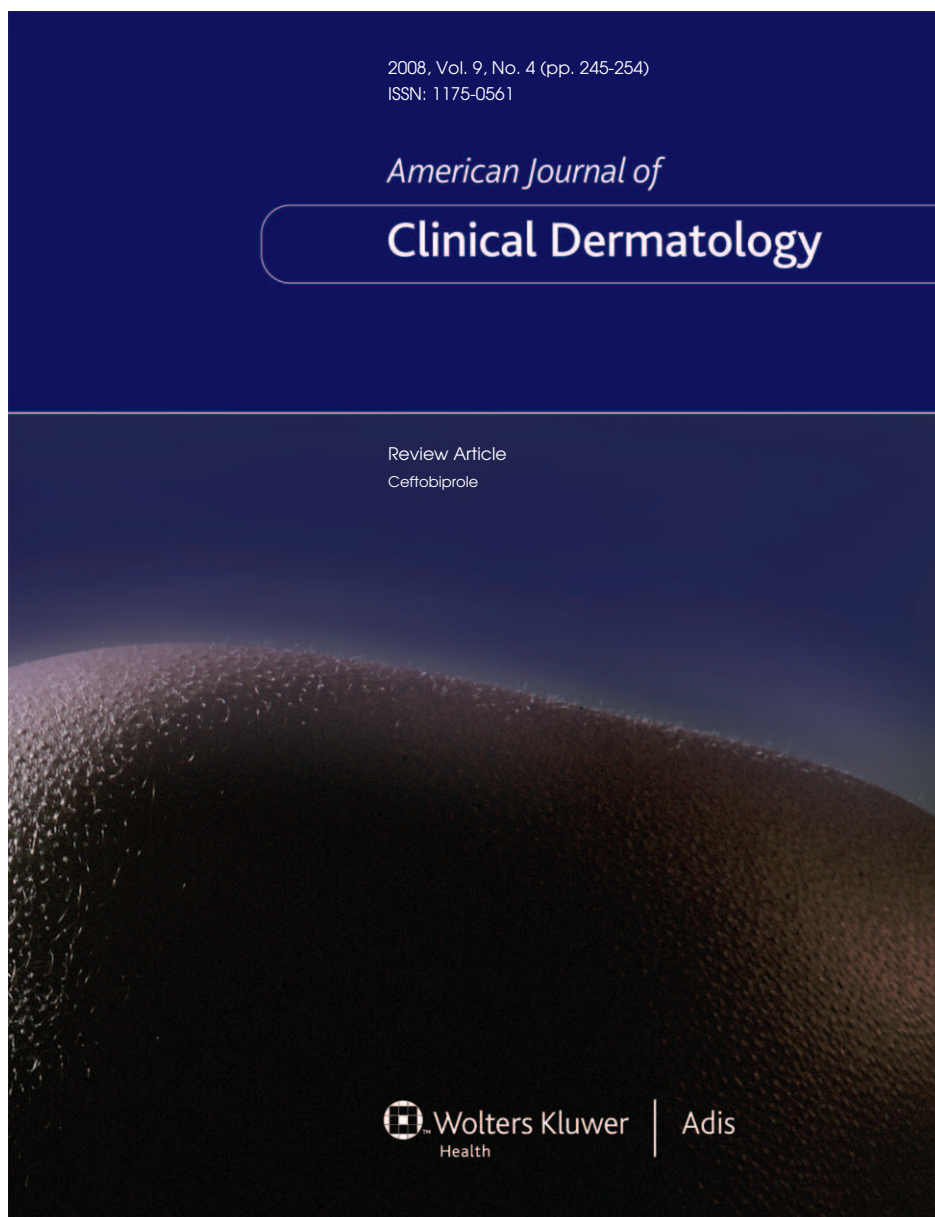


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Ceftobiprole

A Review of a Broad-Spectrum and Anti-MRSA Cephalosporin

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Abstract

Ceftobiprole, an investigational cephalosporin, is currently in phase III clinical development. Ceftobiprole is a broad-spectrum cephalosporin with demonstrated *in vitro* activity against Gram-positive cocci, including methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *S. epidermidis*, penicillin-resistant *S. pneumoniae*, *Enterococcus faecalis*, Gram-negative bacilli including AmpC-producing *Escherichia coli* and *Pseudomonas aeruginosa*, but excluding extended-spectrum β -lactamase-producing strains. Like cefotaxime, ceftriaxone, ceftazidime, and cefepime, ceftobiprole demonstrates limited activity against anaerobes such as *Bacteroides fragilis* and non-fragilis *Bacteroides* spp. In single-step and serial passage *in vitro* resistance development studies, ceftobiprole demonstrated a low propensity to select for resistant subpopulations. Ceftobiprole, like cefepime, is a weak inducer and a poor substrate for AmpC β -lactamases.

Ceftobiprole medocartil, the prodrug of ceftobiprole, is converted by plasma esterases to ceftobiprole in <30 minutes. Peak serum concentrations of ceftobiprole observed at the end of a single 30-minute infusion were 35.5 μ g/mL for a 500-mg dose and 59.6 μ g/mL for a 750-mg dose. The volume of distribution of ceftobiprole is 0.26 L/kg ($\approx$ 18 L), protein binding is 16%, and its serum half-life is approximately 3.5 hours. Ceftobiprole is renally excreted ($\approx$ 70% in the active form) and systemic clearance correlates with creatinine clearance, meaning that dosage adjustment is required in patients with renal dysfunction. Ceftobiprole has a modest post-antibiotic effect (PAE) of $\approx$ 0.5 hours for MRSA and a longer PAE of approximately 2 hours for penicillin-resistant pneumococci. Ceftobiprole, when administered intravenously at 500 mg once every 8 hours (2-hour infusion), has a >90% probability of achieving $fT_{>MIC}$ (free drug concentration exceeds the minimum inhibitory concentration [MIC]) for 40% and 60%, respectively, of the dosing interval for isolates with ceftobiprole MIC $\leq$ 4 and $\leq$ 2 mg/L, respectively.

Currently, only limited clinical trial data are published for ceftobiprole. In a phase III trial, 784 patients with Gram-positive skin infections were randomized to treatment with either ceftobiprole 500 mg or vancomycin 1 g, each administered twice daily for 7–14 days; 93.3% of patients were clinically cured with ceftobiprole compared with 93.5% receiving vancomycin, and the eradication rate for MRSA infections was 91.8% for ceftobiprole compared with 90% for vancomycin. A phase III, randomized, double-blind, multicenter trial compared ceftobiprole 500 mg every 8 hours with vancomycin 1 g every 12 hours plus ceftazidime 1 g every 8 hours in patients with complicated skin and skin structure infections. Of the 828 patients enrolled, 31% had diabetic foot infections, 30% had abscesses, and 22% had wounds. No difference in clinical cure was reported in the clinically evaluable, intent-to-treat and microbiologically evaluable populations with cure rates of 90.5%, 81.9%, and 90.8%, respectively, in the ceftobiprole-treated patients and 90.2%, 80.8%, and 90.5%, respectively, in the vancomycin plus ceftazidime-treated group. Microbiologic eradication of Gram-positive cocci methicillin-susceptible *S. aureus* (MSSA) [ceftobiprole 91% vs vancomycin plus ceftazidime 92%] and MRSA (ceftobiprole 87% vs vancomycin plus ceftazidime 80%), as well as Gram-negative bacilli, *E. coli* (ceftobiprole 89% vs vancomycin plus ceftazidime 92%), and *P. aeruginosa* (ceftobiprole 87% vs vancomycin plus ceftazidime 100%), was not significantly different between groups. Similar cures rates in the microbiologically evaluable population occurred in both groups for Pantone-Valentine leukocidin (PVL)-positive MSSA and PVL-positive MRSA.

Currently, ceftobiprole has completed phase III trials for complicated skin and skin structure infections due to MRSA and nosocomial pneumonia due to suspected or proven MRSA; phase III trials are also ongoing in community-acquired pneumonia. Ceftobiprole has so far demonstrated a good safety profile in preliminary studies with similar tolerability to comparators. The broad-spectrum activity of ceftobiprole may allow it to be used as monotherapy in situations where a combination of antibacterials might be required. Further clinical studies are needed to determine the efficacy and safety of ceftobiprole and to define its role in patient care.

With the increasing incidence of infections caused by antimicrobial-resistant pathogens, there is an ongoing need for new antimicrobials. However, few new antimicrobial agents have been approved and made available for the treatment of patients in the past 20 years. Between 1983 and 1987, 16 new antimicrobials were approved by the US FDA, and only 11 new antimicrobials were approved between 1998 and 2005.^[1]

There are limited options for the treatment of patients with serious invasive infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and multi-drug-resistant *Streptococcus pneumoniae*.^[1–12] These options include vancomycin and newer agents such as linezolid and daptomycin, although daptomycin is not an option for *S. pneumoniae* respiratory tract infections because of inactivation by surfactant. Ceftobiprole, a cephalosporin, is currently in phase III clinical development. Ceftobiprole medocartil is the water-soluble prodrug of ceftobiprole, and is being jointly developed by Basilea Pharmaceutica AG and Johnson and Johnson Pharmaceutical Research and Development L.L.C.^[3] Ceftobiprole has an anti-Gram-positive spectrum that includes MRSA, while maintaining broad anti-Gram-negative activity,^[4] and is resistant to certain β -lactamases produced by Gram-positive and -negative pathogens.

This article reviews the available data on ceftobiprole regarding chemistry, mechanisms of action and resistance, *in vitro* activity, pharmacokinetic and pharmacodynamic properties, and efficacy and safety in clinical trials. In the chemistry, microbiology, and

pharmacokinetics sections, ceftobiprole is compared with ceftazidime, cefepime, cefotaxime, and ceftriaxone.

We performed a literature search of PubMed and MEDLINE for any article on ceftobiprole; scientific meetings were also searched for abstracts on ceftobiprole from 2000 to 2007 inclusive. Johnson and Johnson was contacted to provide clinical trial data.

1. Chemistry

Cephalosporins have a bicyclic ring structure containing a four-membered β -lactam ring fused to a six-membered dihydrothiazine ring. Third-generation cephalosporins such as ceftazidime, ceftriaxone, and cefotaxime contain an aminothiazole ring, which enhances the penetration of cephalosporins through the outer membrane of Gram-negative bacteria (figure 1). Cefepime is a fourth-generation oximino-cephalosporin. It is a zwitterion, with a positively charged substituent at position 3 and a negatively charged carboxylate group at position 4 (figure 1).

Ceftobiprole has an oxyimino aminothiadiazolyl substituent linked to the 7-amino group of the bicyclic cephalosporin ring, and a vinylpyrrolidinone moiety at position 3^[5] (figure 2). The aminothiadiazolyl substituent affords ceftobiprole stability against many common penicillinases and broad-spectrum β -lactamases, while the vinylpyrrolidinone promotes binding to penicillin-binding protein 2a (PBP2a) in methicillin-resistant staphylococci.^[5]

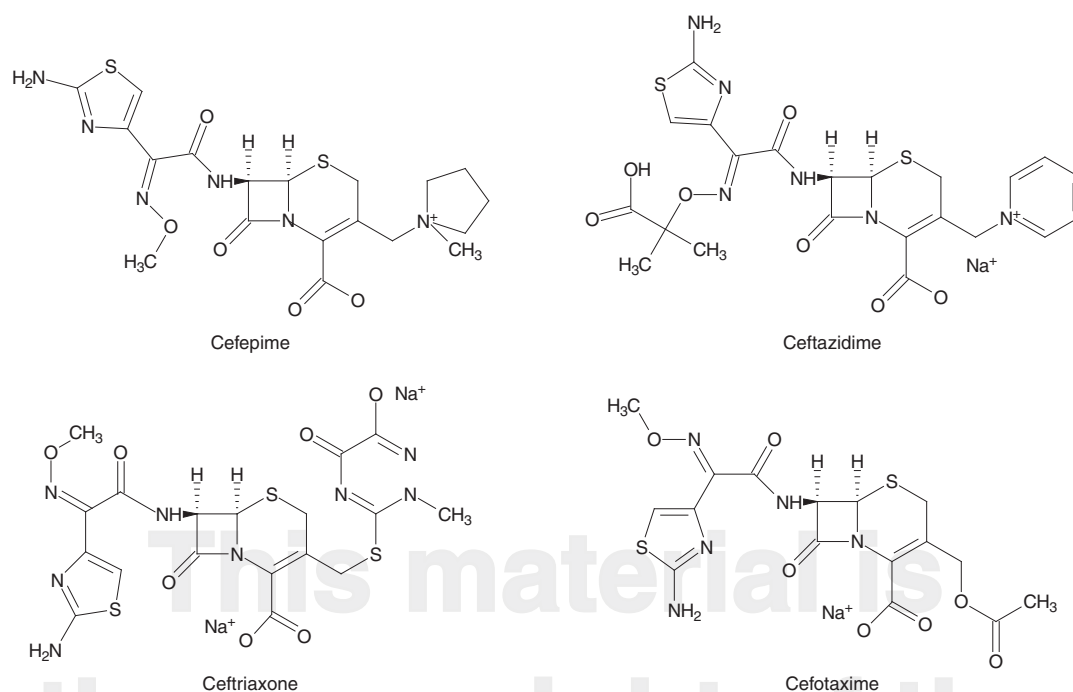


Fig. 1. Chemical structures of cefepime, ceftazidime, ceftriaxone, and cefotaxime.

2. Mechanism of Action

The mechanism of action of cephalosporins and penicillins is attributed to their ability to bind to PBPs and irreversibly inhibit peptidoglycan synthesis. Ceftobiprole is a unique β -lactam because of its ability to bind effectively to PBP2a, the β -lactam-insensitive PBP of MRSA, and to PBP2x in penicillin-resistant *S. pneumoniae*.^[3,4,13] PBP2a (also referred to as PBP2')

is responsible for the MRSA phenotype in staphylococci. Unlike other β -lactams, ceftobiprole binds to PBP2a with high affinity, rapidly forming a stable inhibitory complex.^[4] For example, the inhibitory concentration (IC_{50}) for PBP2a from the MRSA strain OC 3726 was 2 μ g/mL for ceftobiprole compared with >64 and >128 μ g/mL, respectively, for ceftriaxone and ceftazidime.^[13]

For penicillin-resistant *S. pneumoniae*, ceftobiprole was still able to bind to altered PBPs and form inhibitory complexes, but at

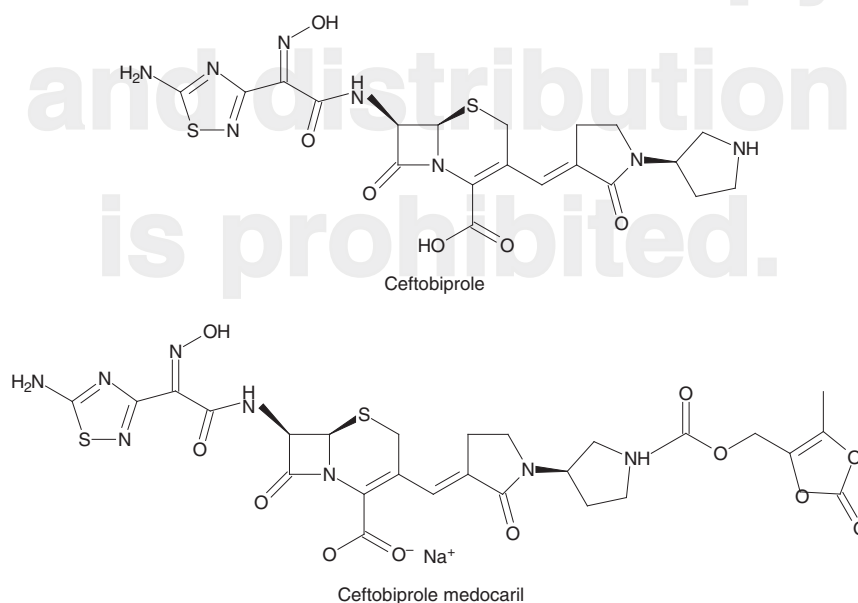


Fig. 2. Chemical structures of ceftobiprole and its prodrug ceftobiprole medocartil.

higher ceftobiprole concentrations than were required for susceptible strains.^[13] In a penicillin-resistant strain of *S. pneumoniae* OC 8819, ceftobiprole bound with greater affinity to PBP2a and PBP2x (IC₅₀ values of 0.1 and 1 µg/mL, respectively) than ceftriaxone (IC₅₀ values of 0.5 and 8 µg/mL, respectively).^[13] In the same strain, ceftobiprole bound PBP1a with an IC₅₀ of 0.1 µg/mL, compared with an IC₅₀ of 0.02 µg/mL for ceftriaxone.^[13] In a penicillin-susceptible strain of *S. pneumoniae* OC 8865, ceftobiprole bound to PBP1a and 1b with IC₅₀ values of 0.03 and 0.05 µg/mL, respectively, similar to the IC₅₀ values for ceftriaxone (0.01 and 0.03 µg/mL, respectively).^[6]

Ceftobiprole also binds to PBPs of Gram-negative bacteria.^[13] For *Escherichia coli* MC4100, ceftobiprole, ceftriaxone, and cefepime demonstrated similar affinity for PBP2 (IC₅₀ values of 0.2, 0.2, and 0.6 µg/mL, respectively). For *Pseudomonas aeruginosa* PAO1, ceftobiprole had the greatest affinity for PBP2 (IC₅₀ 3 µg/mL); ceftazidime and cefepime bound with less affinity (IC₅₀ values of >32 and 8 µg/mL, respectively). For *E. coli* MC4100, ceftobiprole and ceftriaxone bound to PBP1a with greater affinity than ceftazidime and cefepime (IC₅₀ values of 0.3, 0.2, 1.1, and 2 µg/mL, respectively). However, ceftobiprole had a lower affinity for PBP1b of the same strain of *E. coli* (IC₅₀ 8 µg/mL) than ceftriaxone (IC₅₀ 0.5 µg/mL). For *P. aeruginosa* PAO1, ceftobiprole bound to PBP1a with an affinity identical to that of cefepime (IC₅₀ 0.1 µg/mL); ceftobiprole PBP1b IC₅₀ was 0.5 µg/mL compared with 2 µg/mL for cefepime. Ceftazidime bound to PBP1a and PBP1b of *P. aeruginosa* PAO1 with IC₅₀ values of 0.2 and 4 µg/mL, respectively. Ceftobiprole bound with good affinity to PBP3 (the main PBP associated with cephalosporin bacterial killing) of Gram-negative bacteria. For *P. aeruginosa* PAO1, ceftobiprole bound to PBP3 as well as ceftazidime and cefepime (IC₅₀ 0.1 µg/mL). For *E. coli* MC4100, ceftobiprole did not bind to PBP3 as well as ceftriaxone and ceftazidime, but was similar to cefepime (IC₅₀ values of 0.2, <0.01, 0.01, and 0.1 µg/mL, respectively).

3. Mechanism of Resistance

Ceftobiprole has demonstrated a low ability to select for resistant mutant subpopulations.^[14] No development of stable resistance to ceftobiprole by isolates of MRSA or penicillin-resistant *S. pneumoniae* (or *Haemophilus influenzae* or *Moraxella catarrhalis*) was observed during classical multiple passage studies using low transfer volumes.^[4] However, in a recent *in vitro* serial passage using both *mecA*-positive (MRSA) and *mecA*-negative *S. aureus* at high inocula in 300-mL transfer volumes, high-level ceftobiprole resistance developed in all three strains on day 28 of passaging.^[15] High-level ceftobiprole resistance in MRSA was associated with a combination of at least seven mutations in *mecA*, while resistance development in the non-*mecA* strain suggested an alternative mechanism of action related to one or several chromo-

somally encoded genes. In penicillin-resistant *S. pneumoniae*, PBPs are altered, reducing the binding affinity of β-lactams.^[4] Ceftobiprole demonstrates affinity for altered PBPs in penicillin-resistant *S. pneumoniae* and thus maintains activity.^[4,13] Ceftobiprole is stable to hydrolysis by staphylococcal penicillinases and the common TEM-1 and SHV-1 β-lactamases. It is relatively stable to class C β-lactamases and shows a low tendency to induce these enzymes.^[14,16] Ceftobiprole is susceptible to hydrolysis by rare class A cephalosporinases, many extended-spectrum derivatives of TEM and SHV β-lactamases, and class B metallo-β-lactamases.^[4,14,17] The spectrum of activity of ceftobiprole against many β-lactamase-producing Gram-negative bacteria, except *Proteus vulgaris*, resembles that of cefepime.^[4]

4. Microbiology

The *in vitro* activities of ceftobiprole and comparative agents versus Gram-positive aerobes, Gram-negative aerobes, and anaerobes are depicted in table I, table II, and table III, respectively. The data presented in tables I–III were pooled from all published sources that included ceftobiprole data.^[18–52] The minimum inhibitory concentration at which 50% of bacteria are inhibited (MIC₅₀) and the minimum inhibitory concentration at which 90% of bacteria are inhibited (MIC₉₀) for ceftobiprole tested against methicillin-susceptible *S. aureus* (MSSA) and methicillin-susceptible *S. epidermidis* are lower than those for cefotaxime, ceftriaxone, ceftazidime, and cefepime (table I). The MIC₅₀ and MIC₉₀ for ceftobiprole tested against MRSA and methicillin-resistant *S. epidermidis* demonstrate that unlike cefotaxime, ceftriaxone, ceftazidime, and cefepime, ceftobiprole is very active against these strains (table I). Ceftobiprole demonstrates *in vitro* activity against *Enterococcus faecalis* with an MIC₉₀ of 4 mg/L and is active against ampicillin-susceptible *E. faecium*, but is inactive against ampicillin-resistant *E. faecium* with an MIC₅₀ of >32 mg/L. Ceftobiprole is active against penicillin-resistant *S. pneumoniae* but its activity is less against penicillin-intermediate and -resistant *S. pneumoniae* than against penicillin-susceptible isolates. The MIC₅₀ and MIC₉₀ for ceftobiprole have been reported to be 0.008 and 0.015 mg/L, respectively, for *S. pyogenes*, 0.008 and 0.015 mg/L, respectively, for *S. agalactiae*, 0.06 and 0.12 mg/L, respectively, for *Streptococcus* spp. group C, and 0.008 and 0.06 mg/L, respectively, for *Streptococcus* spp. group G.^[49]

Based upon MIC₉₀ data, ceftobiprole has comparable *in vitro* activity to cefepime against several Gram-negative pathogens, including *H. influenzae*, *E. coli*, *K. pneumoniae*, and *P. aeruginosa* (table II). Like cefepime, ceftobiprole is poorly active against extended-spectrum β-lactamase-producing *E. coli*, *K. pneumoniae*, and *P. mirabilis*^[51] with MIC₉₀ values of >16 and >32 mg/L, respectively. Ceftobiprole appears more potent *in vitro* than cefepime against isolates of *M. catarrhalis*, *P. mirabilis*, and *Salmonella* spp. Against *P. aeruginosa*, ceftobiprole displays

Table I. *In vitro* activity of ceftobiprole and comparators against Gram-positive aerobic bacteria^[18-20,22-26,28-30,32,33,35-37,40-42,44,49-52]

Bacteria	Ceftobiprole		Cefotaxime		Ceftriaxone		Ceftazidime		Cefepime	
	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)
<i>Staphylococcus aureus</i> (MS)	0.5	0.5	2	2	4	4	16	16	4	4
<i>S. aureus</i> (MR)	1	2	>32	>32	>32	>32	>64	>64	>64	>64
<i>S. epidermidis</i> (MS)	0.5	0.5	8	32	8	32	16	32	4	32
<i>S. epidermidis</i> (MR)	1	2	>32	>32	>32	>32	>32	>32	>32	>32
<i>Enterococcus faecalis</i>	0.5	4	>32	>32	>32	>32	>64	>64	>64	>64
<i>E. faecium</i>	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
<i>Streptococcus pneumoniae</i> (PS)	≤0.015	≤0.015	0.015	0.06	0.015	0.06	2	8	0.03	0.06
<i>S. pneumoniae</i> (PI)	0.06	0.12	0.25	1	0.25	1	8	16	0.5	1
<i>S. pneumoniae</i> (PR)	0.25	0.25	1	2	1	4	8	16	1	2

MIC₅₀ = minimum inhibitory concentration at which 50% of bacteria are inhibited; **MIC₉₀** = minimum inhibitory concentration at which 90% of bacteria are inhibited; **MR** = methicillin-resistant; **MS** = methicillin-susceptible; **PI** = penicillin-intermediate (penicillin MIC 0.12–1 mg/L); **PR** = penicillin-resistant (penicillin MIC ≥2 mg/L); **PS** = penicillin-susceptible (penicillin MIC ≤0.06 mg/L).

slightly greater activity than cefepime and similar activity compared with ceftazidime. Ceftobiprole is not active against ceftazidime-resistant *P. aeruginosa*.

Like cefotaxime, ceftriaxone, ceftazidime, and cefepime, ceftobiprole demonstrates limited activity against anaerobes such as *Bacteroides fragilis* and non-*fragilis* *Bacteroides* spp. (table

III).^[27,29,38] Ceftobiprole demonstrates lower MICs for *Clostridium perfringens* and *C. difficile* than other cephalosporins but appears to be less active *in vitro* against isolates of *Fusobacterium* spp., *Prevotella* spp., and *Veillonella* spp. than cefotaxime and ceftriaxone (table III), especially against β-lactamase-producing isolates.

Table II. *In vitro* activity of ceftobiprole and comparators against Gram-negative aerobic bacteria^[13,14,16,18,20,21,29,31,34,39,40,43,47,49,52]

Bacteria	Ceftobiprole		Cefotaxime		Ceftriaxone		Ceftazidime		Cefepime	
	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)
<i>Haemophilus influenzae</i> ^a	0.06	0.06	≤0.008	≤0.03	≤0.008	≤0.03	0.12	0.25	≤0.06	0.12
<i>Moraxella catarrhalis</i>	0.06	0.5	0.12	0.5	0.12	0.5	0.25	0.5	0.5	2
<i>Escherichia coli</i>	0.03	0.06	≤0.25	≤0.25	≤0.25	≤0.25	≤0.12	0.25	≤0.12	≤0.12
<i>E. coli</i> (AmpC)	0.06	0.06	16	32	16	32	32	32	≤0.12	≤0.12
<i>E. coli</i> (ESBL)	32	>32	32	>32	32	>32	16	>32	4	>16
<i>Klebsiella oxytoca</i>	0.03	0.06	≤0.25	≤0.25	≤0.25	≤0.25	≤2	≤2	≤0.12	≤0.12
<i>K. pneumoniae</i>	0.03	0.06	≤0.25	≤0.25	≤0.25	≤0.25	≤2	≤2	≤0.12	≤0.12
<i>K. pneumoniae</i> (ESBL)	>32	>32	>32	>32	>32	>32	>16	>16	4	>16
<i>Proteus mirabilis</i>	≤0.015	0.03	0.25	0.5	≤0.25	0.5	≤2	≤2	≤0.12	0.5
<i>Serratia</i> spp.	0.06	0.5	0.25	8	≤0.25	8	≤2	8	≤0.12	0.5
<i>Actinobacter</i> spp.	32	>32	8	32	>32	>32	>16	>16	>16	>16
<i>Pseudomonas aeruginosa</i>	2	8	32	>64	>64	>64	2	8	2	16
<i>Salmonella</i> spp.	0.03	0.03	0.25	4	≤0.25	8	≤2	8	≤0.12	0.5
<i>Shigella</i> spp.	0.03	0.03	≤0.25	≤0.25	≤0.25	≤0.25	≤2	≤2	≤0.12	≤0.12
<i>Burkholderia cepacia</i>	8	64	16	64	16	64	16	16	8	32
<i>Stenotrophomonas maltophilia</i>	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32

a Includes β-lactamase-producing strains.

ESBL = extended-spectrum β-lactamase; **MIC₅₀** = minimum inhibitory concentration at which 50% of bacteria are inhibited; **MIC₉₀** = minimum inhibitory concentration at which 90% of bacteria are inhibited.

Table III. *In vitro* activity of ceftobiprole and comparators against anaerobic bacteria^[27,29,38,40]

Bacteria	Ceftobiprole		Cefotaxime		Ceftriaxone		Ceftazidime		Cefepime	
	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)
<i>Bacteroides fragilis</i>	16	>128	4	32	8	64	32	>128	64	>128
Other <i>Bacteroides</i> spp.	16	>128	4	64	8	>128	64	>128	32	128
<i>Clostridium difficile</i>	4	8	32	64	32	64	64	64	64	64
<i>C. perfringens</i>	≤0.016	≤0.016	2	4	2	8	4	16	4	8
<i>Fusobacterium</i> spp.	0.12	8	0.12	2	0.12	4	2	64	1	8
<i>Prevotella</i> spp.	0.12	>128	0.5	16	0.5	32	2	32	2	32
<i>Veillonella</i> spp.	0.5	>128	0.25	4	0.25	4	4	16	1	8

MIC₅₀ = minimum inhibitory concentration at which 50% of bacteria are inhibited; **MIC₉₀** = minimum inhibitory concentration at which 90% of bacteria are inhibited.

5. Pharmacokinetics

5.1 Absorption

Ceftobiprole is available only in parenteral form.^[6] The pharmacokinetic parameters of ceftobiprole and comparative agents are shown in table IV.^[53-64] Ceftobiprole medocaril, the prodrug of ceftobiprole, is converted by plasma esterases to ceftobiprole in <30 minutes.^[53] Peak serum concentrations of ceftobiprole following a 30-minute infusion were 35.5 µg/mL with a single 500-mg dose and 59.6 µg/mL with a single 750-mg dose. The decline in serum ceftobiprole concentrations is consistent with rapid distribution of the drug from the systemic circulation to other body compartments.^[53]

5.2 Distribution

The volume of distribution of ceftobiprole is 0.26 L/kg (≈18 L), approximately the volume of the extracellular water compartment in adults.^[53] Ceftobiprole is approximately 16% protein bound. Limited data are available regarding ceftobiprole tissue distribution.

5.3 Metabolism and Excretion

The serum half-life of ceftobiprole is approximately 3.5 hours.^[53] This half-life allows for twice-daily administration, with little or no drug accumulation. Preliminary results from a trial of 20 patients with complicated skin and skin structure infections demonstrated that twice-daily administration of 750 mg of ceftobiprole resulted in plasma concentrations above 2 µg/mL for >80% of the dosing interval.^[8] This dosage regimen is predicted to be efficacious in complicated skin and skin structure infections with MRSA.^[8] Ceftobiprole is renally excreted at a rate that approximates the glomerular filtration rate.^[53] In urine, >70% of ceftobiprole is excreted in the active form. Systemic clearance of ceftobiprole correlates with creatinine clearance, meaning that dosage adjustment is required in patients with renal dysfunction.^[8]

6. Pharmacodynamics

The pharmacodynamics of ceftobiprole have been studied in a number of trials.^[65-70] Ceftobiprole has a modest post-antibiotic effect (PAE) of ≈0.5 hours for MRSA and a PAE of ≈2 hours for penicillin-resistant pneumococci.^[65] *In vitro* pharmacodynamic

Table IV. Pharmacokinetic parameters of single doses of ceftobiprole and comparators^[40,53-64]

Drug	IV dosage (mg)	C _{max} (mg/L)	AUC (mg • h/L)	t _{1/2} (h)	Vd (L/kg)	% Protein binding	% Excreted unchanged
Ceftobiprole	750	59.6	135	3.5	0.26	16	>70
	500 ^a	35.5	76.6	3.5	NA	NA	77.5
Cefotaxime	1000	41	80	1.0	0.43	40	50
Ceftriaxone	1000	150	973	8 ^b	0.13	83–96 ^b	60
Ceftazidime	1000	80	170	1.8	0.29	10	90
Cefepime	1000	66.9	137	1.9	0.22	16	82

a Values for this dose are the means for five samples.

b Dose dependent.

AUC = area under the plasma concentration-time curve; **C_{max}** = maximum plasma concentration; **IV** = intravenous; **NA** = information not available; **t_{1/2}** = half-life; **Vd** = volume of distribution.

studies comparing ceftobiprole, vancomycin, and linezolid against wild-type MRSA, vancomycin heteroresistant MRSA, community-associated (CA-MRSA), and vancomycin-tolerant MRSA strains showed that ceftobiprole and vancomycin were bactericidal against these strains while linezolid was bacteriostatic.^[69] As with other cephalosporins, the length of time that the serum concentration exceeds the MIC is considered to be the best index of antibacterial efficacy for ceftobiprole.^[65] For cephalosporins, studies have shown that a bacteriostatic effect is achieved when free drug concentrations exceed the MIC for 30% (30% $fT_{>MIC}$) of the dosing interval for staphylococci and 40% (40% $fT_{>MIC}$) of the dosing interval for Gram-negative bacilli.^[66] Furthermore, near-maximal organism kill is achieved at 50% and 60% $fT_{>MIC}$ for staphylococci and Gram-negative bacilli, respectively. In a neutropenic mouse pneumonia model, ceftobiprole was found to penetrate epithelial lining fluid well (60–94% of serum concentration).^[70] In this study, $fT_{>MIC}$ of $\approx 20\%$ was associated with maximal lung bacterial reductions of MSSA, hospital-acquired MRSA, and CA-MRSA.

When ceftobiprole was administered in a dose of 500 mg intravenously every 8 hours (2-hour infusion), the probabilities of achieving 40% and 60% $fT_{>MIC}$ exceeded 90% for MICs ≤ 4 and ≤ 2 mg/L, respectively.^[66] For ceftobiprole administered in a dose of 500 mg intravenously every 12 hours and 500 mg intravenously every 8 hours, the probability of achieving a near bactericidal effect (defined as 50% $fT_{>MIC}$) exceeded 90% for MSSA and MRSA. For ceftobiprole administered in a dose of 500 mg intravenously every 8 hours, the probability of achieving a near bactericidal effect (defined as 60% $fT_{>MIC}$) exceeded 90% for non-AmpC-producing Gram-negative bacilli. For AmpC-producing Gram-negative bacilli, the probability of achieving a static effect (defined as 40% $fT_{>MIC}$) was 89.8%. The probability of achieving a static effect against *P. aeruginosa* was 71.1%.

In vitro time kill studies showed that combinations of ceftobiprole with either amikacin or levofloxacin were synergistic against *P. aeruginosa*.^[46] *In vitro* combinations of ceftobiprole

with aminoglycosides were found to be synergistic against *E. faecalis*.^[67] The potential for increased activity of ceftobiprole in combination with other agents with different mechanisms of action should be further explored *in vitro* and *in vivo*.

7. Clinical Trials

Although animal data and clinical perspectives on use of ceftobiprole are available,^[38,71-79] actual clinical trial data with ceftobiprole are rather limited. Animal data testing ceftobiprole have demonstrated microbiologic and clinical efficacy in pneumonia, endocarditis, and experimental foreign body infections caused by ceftobiprole-susceptible pathogens.^[71-75] A phase II clinical trial has been performed in which 750 mg of ceftobiprole was administered twice daily to hospitalized patients with complicated skin and skin structure infections.^[4] The preliminary results of this study showed good efficacy against streptococci, MSSA, and MRSA.

The first phase III trial of ceftobiprole to be completed was STRAUSS (Study of Resistant *Staphylococcus aureus* Skin and Skin Structure Infections).^[4,80] In this study, 784 patients with Gram-positive infections were randomized to treatment with either ceftobiprole 500 mg or vancomycin 1 g, each administered twice daily for 7–14 days (table V).^[80] Over 25% of patients who could be evaluated microbiologically were confirmed to have MRSA skin and skin structure infections. Of the 397 patients treated with ceftobiprole and 387 patients treated with vancomycin, 93.3% and 93.5%, respectively, were clinically cured. The response rate in MRSA infections was 91.8% for ceftobiprole and 90% for vancomycin. Furthermore, this study showed that ceftobiprole was safe and similarly well tolerated as vancomycin. Adverse event rates were comparable between the treatment groups.^[80]

Recently, a phase III, randomized, double-blind, multicenter trial compared ceftobiprole 500 mg every 8 hours with vancomycin 1 g every 12 hours plus ceftazidime 1 g every 8 hours in patients with complicated skin and skin structure infections.^[81,82]

Table V. Clinical trials involving ceftobiprole

Trial	No. of pts	Indication	Dosage regimen	Microbiologic response	Clinical response
STRAUSS ^[80] (phase III, randomized, comparative)	784	Gram-positive skin and skin structure infections	397 treated with ceftobiprole 500 mg bid for 7–14 d	91.8% eradication rate for ceftobiprole (MRSA only)	93.3% clinically cured with ceftobiprole
			387 treated with vancomycin 1 g bid for 7–14 d	90% eradication rate for vancomycin (MRSA only)	93.5% clinically cured with vancomycin
STRAUSS ^[81] (phase III, randomized, comparative)	828	Complicated skin and skin structure infections	547 treated with ceftobiprole 500 mg every 8 h ^a for 7–14 d	88% eradication rate for ceftobiprole (all organisms)	81.9% clinically cured with ceftobiprole
			281 treated with vancomycin 1 g every 12 h + ceftazidime 1 g every 8 h ^a for 7–14 d	89% eradication rate for vancomycin + ceftazidime (all organisms)	80.8% clinically cured with vancomycin + ceftazidime

a Infused over 2 h.

bid = twice daily; **MRSA** = methicillin-resistant *Staphylococcus aureus*; **pts** = patients.

Of 828 patients enrolled, 31% had diabetic foot infections, 30% had abscesses, and 22% had infected wounds.^[81] No difference in clinical cure was reported in the clinically evaluable, intent-to-treat, and microbiologically evaluable populations with cure being reported in 90.5%, 81.9%, and 90.8%, respectively, of the ceftobiprole-treated patients and 90.2%, 80.8%, and 90.5%, respectively, of the vancomycin plus ceftazidime-treated group. Microbiologic eradication of MSSA (ceftobiprole 91% vs vancomycin plus ceftazidime 92%) and MRSA (ceftobiprole 87% vs vancomycin plus ceftazidime 80%) was similar between treatment groups. Similar cure rates in the microbiologically evaluable population occurred in both groups for Panton-Valentine leukocidin (PVL)-positive MSSA and PVL-positive MRSA.^[82] For all patients in whom Gram-negative bacteria were isolated at baseline, the clinical cure rate was 87.9% (109/124) for ceftobiprole and 89.7% (61/68) for vancomycin plus ceftazidime, and the microbiologic eradication rates were 84.7% (105/124) for ceftobiprole and 83.8% (57/68) for vancomycin plus ceftazidime.^[81] Furthermore, the cure rates reported for clinically evaluable patients were 89.2% (33/37) in the ceftobiprole arm versus 92.3% (24/26) for vancomycin plus ceftazidime in patients with *E. coli* isolated at baseline and 86.7% (18/20) for ceftobiprole and 100% (9/9) for vancomycin plus ceftazidime in patients with *P. aeruginosa* isolated at baseline. Ceftobiprole was reported to be safe and similarly well tolerated as vancomycin plus ceftazidime with discontinuation rates due to treatment-related adverse effects of 4% in each group. Although these results are encouraging, more data are required, especially with regard to *P. aeruginosa* infections, to fully assess the effectiveness of ceftobiprole.

Phase III trials assessing ceftobiprole as a treatment in patients with complicated skin and skin structure infections (including diabetic foot infections), nosocomial pneumonia, and community-acquired pneumonia have been completed. These trials have assessed ceftobiprole in patients with infections caused by a broad spectrum of pathogens, including MRSA and most of the important Gram-negative pathogens that are leading causes of skin and lower respiratory tract disease.

8. Adverse Effects/Drug Interactions

Ceftobiprole has, in general, demonstrated a good safety profile in preliminary studies.^[7] One episode of syncope was reported, but this was not attributed to ceftobiprole. No other serious adverse effects were reported.

Ceftobiprole was similarly well tolerated as vancomycin in patients with skin and soft tissue infections caused by Gram-positive infections.^[4,8,80,81] The most common adverse effects were nausea (14%) and taste disturbance (8%).^[80] Mild to moderate nausea and vomiting were the most frequent adverse effects in a phase II study of 35 hospitalized patients with complicated skin infections requiring surgical intervention.^[80] A characteristic event

during the infusion period of ceftobiprole in these studies was a caramel-like taste, which is thought to be due to the conversion of the prodrug ceftobiprole medocaryl to ceftobiprole plus diacetyl.^[53] Diacetyl is a natural product known also as a food additive that imparts a caramel-like or buttery flavor.^[7,53] Other adverse events reported included headache and a mild-to-moderate increase in ALT reported in three patients receiving multiple doses of ceftobiprole 750 mg.^[7] Except for the taste disturbance, the frequency of adverse events was not clearly related to the dose of ceftobiprole.^[53] Furthermore, no ECG abnormalities and no clinically relevant changes in laboratory parameters or vital signs have been reported.^[53]

9. Role of Ceftobiprole in Therapy and Conclusion

The broad spectrum of activity of ceftobiprole, which includes Gram-positive cocci, MRSA, penicillin-resistant *S. pneumoniae* and *E. faecalis*, together with comparable activity to cefepime against Gram-negative bacilli, including AmpC-producing *E. coli* (but not extended-spectrum β -lactamase-producing isolates) and *P. aeruginosa*, may make it an ideal alternative to complex multiple antibacterial regimens for the treatment of nosocomial infections, such as hospital and ventilator-associated pneumonia, and polymicrobial infections. Ceftobiprole may also have a unique role to play in the treatment of community-acquired pneumonia in the setting of CA-MRSA. Specifically, ceftobiprole may be used in place of a third-generation cephalosporin together with vancomycin (or linezolid) for empiric treatment of community-acquired pneumonia when CA-MRSA is a possible pathogen. Finally, ceftobiprole has proven to be efficacious in the treatment of complicated skin and skin structure infections and preliminary safety data appear promising for this new antibacterial. Further clinical studies are needed to determine the efficacy and safety of ceftobiprole in patients and to define its role in patient care.

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