

Emerging agents to combat complicated and resistant infections: focus on ceftobiprole

César Bustos¹
Jose L Del Pozo^{1,2}

¹Division of Infectious Diseases,

²Division of Clinical Microbiology,
Clínica Universidad de Navarra, Spain

Abstract: Antimicrobial resistance is a global concern. Over the past few years, considerable efforts and resources have been expended to detect, monitor, and understand at the basic level the many different facets of emerging and increasing resistance. Development of new antimicrobial agents has been matched by the development of new mechanisms of resistance by bacteria. Current antibiotics act at a variety of sites within the target bacteria, including the cross-linking enzymes in the cell wall, various ribosomal enzymes, nucleic acid polymerases, and folate synthesis. Ceftobiprole is a novel parenteral cephalosporin with high affinity for most penicillin-binding proteins, including the *mecA* product penicillin-binding protein 2a, rendering it active against methicillin-resistant staphylococci. Its in vitro activity against staphylococci and multiresistant pneumococci, combined with its Gram-negative spectrum comparable to that of other extended-spectrum cephalosporins, its stability against a wide range of beta-lactamases, and its pharmacokinetic and safety profiles make ceftobiprole an attractive and well tolerated new antimicrobial agent. The US Food and Drug Administration granted ceftobiprole medocartil fast-track status in 2003 for the treatment of complicated skin infections and skin structure infections due to methicillin-resistant staphylococci, and subsequently extended this to treatment of hospital-acquired pneumonia, including ventilator-associated pneumonia due to suspected or proven methicillin-resistant *Staphylococcus aureus*.

Keywords: ceftobiprole, methicillin-resistant staphylococci, skin infection, hospital acquired pneumonia

Introduction

Since the introduction of antimicrobial agents in the 1940s, antibiotic resistance has become an increasing problem. Today, multiple-antibiotic resistance is commonly associated with a number of clinically important pathogens. Four general mechanisms of resistance have been shown. Target site alterations, inactivation of antimicrobials, alterations in cell wall permeability that deny access to antimicrobials and efflux mechanisms that pump the antimicrobial out of the cell before it can reach its target site. Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a cause of infection not only in healthcare settings but also in the community. Skin and soft tissue infections are most common, but invasive manifestations also occur. Strains of MRSA circulating in the community generally are susceptible to a number of non beta-lactam antimicrobial agents, although resistance patterns may vary temporally and geographically. Ceftobiprole, the active principle of the water-soluble prodrug BAL 5788 is a novel parenteral cephalosporin with high affinity for most penicillin-binding proteins (PBP), including the *mecA* product PBP2a, and stability

Correspondence: Jose L Del Pozo
Divisions of Clinical Microbiology and
Infectious Diseases, Clínica Universidad
de Navarra, Spain
Tel +3 494 829 6500
Email jdelpozo@unav.es

to almost all class A and C beta-lactamases.¹ Ceftobiprole is currently undergoing evaluation by the US Food and Drug Administration for the treatment of complicated skin and skin structure infections and community-acquired and healthcare-associated pneumonia. Two Phase III multicenter trials^{2,3} have demonstrated non-inferiority in complicated skin and skin structure infections when tested against vancomycin in primarily Gram-positive bacterial infections, and when tested against vancomycin plus ceftazidime in Gram-positive and Gram-negative bacterial infections. Two other Phase III clinical trials to assess ceftobiprole's efficacy in community-acquired pneumonia and nosocomial pneumonia have also concluded. While the drug met the non-inferiority criteria for community-acquired pneumonia and nosocomial pneumonia involving non-ventilator associated pneumonia, ceftobiprole was less effective than the comparator in ventilator associated pneumonia subjects.⁴

In vitro antibacterial activity: ceftobiprole and the penicillin-binding proteins (PBP)

Ceftobiprole is a new member of the pyrrolidinone-3-ylidenemethyl cephem series of cephalosporins. The antibacterial effects of ceftobiprole are mediated through blockage of the final steps of cell wall (peptidoglycan) biosynthesis.⁵ Ceftobiprole exhibits potent binding to PBPs from Gram-positive bacteria, including those with decreased beta-lactam sensitivity, such as PBP2a in MRSA (unlike ceftriaxone and ceftazidime), and PBP2x (the primary cephalosporin targets) in penicillin-resistant *Streptococcus pneumoniae* (ceftobiprole had an eight fold-higher binding affinity for a mutated PBP2x than ceftriaxone).⁶ In *Escherichia coli*, ceftobiprole exhibits strong binding to PBP2 and PBP3 (the primary targets for monobactams and most cephalosporins). Ceftobiprole exhibits a binding profile similar to those of cefepime and ceftazidime in *Pseudomonas aeruginosa* but with an enhanced binding to PBP2.⁶ This profile contributes to the broad-spectrum antibacterial activity against gram-negative and gram-positive bacteria of this cephalosporin. No breakpoints have been established for ceftobiprole, but based on minimum inhibitory concentration (MIC) distribution and pharmacokinetic/pharmacodynamic information, Mouton et al⁷ proposed a provisional breakpoint of ≤ 4 $\mu\text{g}/\text{mL}$ for susceptible Gram-positive microorganisms. This breakpoint may not be applicable to Gram-negative bacteria. The Clinical and Laboratory Standards Institute

has published acceptable limits for quality control strains for disk diffusion and MIC testing.^{8,9}

Spectrum of activity

Ceftobiprole is active against *S. aureus*, including MRSA and vancomycin-intermediate *S. aureus* (VISA), coagulase-negative staphylococci (CNS), *Enterococcus* species (including vancomycin-resistant but not ampicillin-resistant enterococci), pneumococci, some anaerobes, and Gram-negative bacilli (with similar activity to third- and fourth-generation cephalosporins, with the exception of *Proteus vulgaris*).^{5,10-14} Ceftobiprole is not active against extended-spectrum beta-lactamase (ESBL) producing strains of *Enterobacteriaceae*.^{13,15,16} Published MIC data for a range of microorganisms are shown in Table 1.

Staphylococcus species

Ceftobiprole has showed consistent activity against staphylococci in several studies with MICs for methicillin-resistant staphylococci higher than those for methicillin-susceptible staphylococci. In vitro activity against methicillin-resistant staphylococci appears to be a particularly valuable asset of this novel cephalosporin. The anti-staphylococcal activity of ceftobiprole was comparable to that of linezolid in one study.¹⁷ Ceftobiprole was shown to inhibit MRSA at ≤ 4 $\mu\text{g}/\text{mL}$.¹⁵ In this study, the higher ceftobiprole MIC values for *S. haemolyticus* and *S. saprophyticus* are consistent with those reported in another studies.^{18,19} Jones et al²⁰ tested ceftobiprole against 262 isolates of *Staphylococcus* species using agar dilution. All ceftobiprole MIC values were ≤ 2 $\mu\text{g}/\text{mL}$ for 146 isolates of *S. aureus* including MSSA (MIC₉₀, 1 $\mu\text{g}/\text{mL}$) and MRSA (MIC₉₀, 2 $\mu\text{g}/\text{mL}$). Denis et al⁶ reported ceftobiprole MIC₅₀ and MIC₉₀ values of 0.5 and 2 $\mu\text{g}/\text{mL}$, respectively against MRSA. Of a total of 1201 *S. aureus* (66% MRSA) and 460 CNS single-patient isolates, ceftobiprole MICs ranged from ≤ 0.12 to 1 $\mu\text{g}/\text{mL}$ for MSSA and 0.25 to 4 $\mu\text{g}/\text{mL}$ for MRSA.¹⁸ Ceftobiprole was active against 15,067 staphylococci isolates, inhibiting 100% of *S. aureus* and CNS at ≤ 4 and ≤ 8 $\mu\text{g}/\text{mL}$, respectively, although MIC₉₀ values of oxacillin-resistant isolates were 4- and 8-fold higher than those of oxacillin-susceptible isolates.²¹ Rouse et al²² showed that ceftobiprole had inhibitory activity similar to that of daptomycin, linezolid and vancomycin, and bactericidal activity similar to that of daptomycin and vancomycin against 37 isolates of MRSA and 51 isolates of methicillin-resistant CNS recovered from patients with endocarditis, and 31 isolates of MRSA and 65 isolates of methicillin-resistant coagulase-negative

Table I Antimicrobial activity of ceftobiprole against most common microorganism. Summary of published in vitro studies

| Microorganism | Number of isolates | MIC ₅₀ | MIC ₉₀ | References |
|--|--------------------|-------------------|-------------------|----------------------|
| MS <i>Staphylococcus aureus</i> | 7433 | 0.25–0.5 | <0.125–2 | 11,12,15,17,18,20,21 |
| MR <i>S. aureus</i> | 6553 | 0.5–2 | 0.12–4 | 11,12,15,17,18,20–22 |
| MS coagulase negative staphylococci | 965 | <0.12–1 | ≤0.015–1 | 11,18,20,21 |
| MR coagulase negative staphylococci | 3161 | 1 | 1–2 | 11,18,20–22 |
| <i>Enterococcus faecalis</i> | 2958 | 0.5 | 2–4 | 15,20,21 |
| <i>E. faecium</i> (ampicillin MIC ≤ 8 µg/mL) | 16 | 4 | 8 | 15 |
| <i>E. faecium</i> (ampicillin MIC ≥ 16 µg/mL) | 20 | >32 | >32 | 20 |
| Penicillin-susceptible <i>Streptococcus pneumoniae</i> | 3176 | 0.008–0.016 | 0.008–0.25 | 15,18,20,21,29 |
| Penicillin-intermediate <i>S. pneumoniae</i> | 265 | 0.06 | 0.12–0.5 | 18,20,29 |
| Penicillin-resistant <i>S. pneumoniae</i> | 1107 | 0.25–0.5 | 0.25–2 | 15,18,20,21,29 |
| <i>Moraxella catarrhalis</i> | 230 | ≤0.06–0.12 | 0.12–1 | 15,20,21 |
| <i>Haemophilus influenzae</i> | 1382 | ≤0.06–≤0.125 | ≤0.06–1 | 13,15,20,21 |
| <i>Neisseria gonorrhoeae</i> | 51 | 0.03 | 0.06–0.12 | 15,20 |
| <i>N. meningitidis</i> | 24 | ≤0.002 | 0.004 | 20 |
| ESBL-negative <i>Escherichia coli</i> | 1172 | 0.03–0.06 | 0.06 | 15,18,20 |
| ESBL-positive <i>E. coli</i> | 466 | 4–>32 | >8–>32 | 15,18,20,21 |
| ESBL-negative <i>Klebsiella pneumoniae</i> | 766 | 0.03–≤0.125 | 0.06–0.25 | 13,15,18,20 |
| ESBL-positive <i>K. pneumoniae</i> | 244 | 4–64 | >32–128 | 13,15,18,20 |
| AmpC-negative <i>Citrobacter freundii</i> | 368 | 0.06 | 1 | 18 |
| AmpC-positive <i>C. freundii</i> | 19 | 2 | >32 | 18 |
| AmpC-negative <i>Enterobacter cloacae</i> | 286 | 0.06 | 4 | 18 |
| AmpC-positive <i>E. cloacae</i> | 120 | 8 | >32 | 18 |
| <i>Proteus mirabilis</i> | 449 | ≤0.06 | ≤0.06–0.12 | 15,20,21 |
| ESBL-negative <i>P. vulgaris</i> | 427 | 0.03 | 0.06 | 18 |
| ESBL-positive <i>P. vulgaris</i> | 16 | >32 | >32 | 18 |
| <i>Morganella morganii</i> | 15 | 0.06 | 0.12 | 15 |
| <i>Serratia</i> species | 582 | ≤0.06–0.06 | 1–8 | 20,21 |
| Imipenem susceptible <i>Acinetobacter</i> species | 220 | 0.5 | >32 | 18 |
| Imipenem non-susceptible <i>Acinetobacter</i> species | 58 | >32 | >32 | 18 |
| <i>Burkholderia cepacia</i> | 22 | 8 | 64 | 14,20 |
| <i>Pseudomonas aeruginosa</i> | 2741 | 2–8 | 8–32 | 12–14,20,21,32 |
| Ceftazidime-resistant <i>P. aeruginosa</i> | 17 | 16 | >64 | 15 |
| <i>Stenotrophomonas maltophilia</i> | 32 | >32–>64 | >32–>64 | 14 |
| <i>Bacteroides fragilis</i> | 212 | 8–16 | 32–>128 | 12,15,20,34,35 |
| <i>Clostridium</i> species | 77 | 0.125–2 | ≤0.25–64 | 12,20,35 |
| <i>C. difficile</i> | 30 | 4 | 8 | 34 |
| <i>C. perfringens</i> | 30 | ≤0.016 | ≤0.016 | 34 |
| <i>Peptostreptococcus</i> species | 59 | 0.25 | 32 | 35 |
| <i>P. anaerobius</i> | 30 | 1–2 | 4–32 | 12,34 |
| <i>Finegoldia magna</i> | 50 | 0.12–0.25 | 0.25–0.5 | 12,34 |
| <i>Fusobacterium</i> species | 34 | 0.12 | 8 | 35 |
| <i>F. nucleatum</i> | 50 | ≤0.016 | ≤0.016 | 34 |
| <i>Prevotella</i> species | 44 | 0.12 | >128 | 35 |
| <i>P. bivia</i> | 47 | 4–16 | 64 | 12,34 |

Abbreviations: MIC, minimum inhibitory concentration; MS, methicillin susceptible; MR, methicillin resistant.

staphylococci from patients with bone and joint infection. Ceftobiprole has been shown to be uniformly active against the major epidemic MRSA clones, against highly oxacillin-resistant strains, against MRSA isolates with reduced susceptibility to vancomycin, and against MRSA strains carrying the enterococcal vancomycin resistance gene complex.^{23,24} Several studies^{25,26} have tested the activity of ceftobiprole against community-associated MRSA (CA-MRSA) (including the USA 300 strain) showing MIC₅₀ and MIC₉₀ values of 1 µg/mL.

Based on its in vitro activity, ceftobiprole may have sufficient activity to be efficacious in human infections caused by *S. aureus* and CNS, including those caused by methicillin- and vancomycin-resistant isolates.

Enterococcus species

Ceftobiprole has been shown to be equivalent to ampicillin in activity against ampicillin-susceptible *Enterococcus faecalis* (ampicillin MIC₅₀ and MIC₉₀ 2 and 4 µg/mL, respectively, and ceftobiprole MIC₅₀ and MIC₉₀ 0.5 and 4 µg/mL, respectively) and *E. faecium* (ampicillin MIC₅₀ and MIC₉₀ of ≤8 µg/mL and ceftobiprole MIC₅₀ and MIC₉₀ 4 and 8 µg/mL, respectively).¹⁵ However, ceftobiprole lacks affinity against ampicillin-resistant enterococci as a result of poor affinity for PBP5, which is mutated and overexpressed in ampicillin-resistant enterococci.^{20,27} All beta-lactamase-producing and vancomycin-resistant isolates were inhibited at concentrations of <1 µg/mL using a standard inoculum in a study.²⁸ High-level resistance to aminoglycosides did not affect the in vitro activity of ceftobiprole.²⁸

In summary, ceftobiprole has shown in vitro bactericidal activity against ampicillin-susceptible enterococci, but has only modest activity against ampicillin-resistant *E. faecium*.

Streptococcus pneumoniae

The incidence of pneumococci resistant to penicillin and other beta-lactam antimicrobial agents, as well as non-beta-lactam antimicrobial agents, has increased worldwide at an alarming rate. It has been shown that ceftobiprole was highly active against penicillin-susceptible isolates of *S. pneumoniae* (MIC₉₀ 0.03 µg/mL).¹⁵ Ceftobiprole was active against 299 drug-susceptible and -resistant pneumococci, with MIC₅₀ and MIC₉₀ values of 0.016 and 0.016 µg/mL (penicillin-susceptible isolates), 0.06 and 0.5 µg/mL (penicillin-intermediate isolates) and 0.5 and 1.0 µg/mL (penicillin-resistant isolates), respectively.²⁹ Ceftobiprole MICs against *S. pneumoniae* were lower than those of ceftriaxone and cefuroxime in two

worldwide surveillance studies.^{18,21} As with ceftriaxone and cefuroxime, ceftobiprole MICs increased with increasing resistance to penicillin, but even among penicillin-resistant isolates, ceftobiprole MICs did not exceed 1 mcg/mL. It has been described that beta-lactam MIC values correlated closely with increases in the numbers of PBP1a, PBP2x and PBP2b substitutions.³⁰ Alpha- and beta-hemolytic streptococci have been shown to have low ceftobiprole MICs in several studies.^{15,20,21}

Penicillin-susceptible, -intermediate and -resistant isolates of *S. pneumoniae* are highly susceptible to ceftobiprole in vitro. Ceftobiprole may therefore be a therapeutic option for infections caused by pneumococci that are resistant to conventional cephalosporins. This renders ceftobiprole a promising candidate for empirical treatment of community- and hospital-acquired pneumonia.

Moraxella catarrhalis and Haemophilus influenzae

Ceftobiprole had MIC values 0.5 and 0.03 µg/mL for 40 beta-lactamase-producing and 9 beta-lactamase-non producing clinical isolates of *Moraxella catarrhalis*, respectively.¹⁰ Similar results were found in other studies.^{15,20} Ceftobiprole MIC₅₀ and MIC₉₀ values for 321 clinical isolates of *H. influenzae* were 0.06 and 0.25 µg/mL for 262 beta-lactamase-positive isolates, 0.03 and 0.25 µg/mL for 40 beta-lactamase-negative isolates, and 0.5 and 2.0 mcg/ml for 19 beta-lactamase-negative ampicillin-resistant isolates, respectively.¹⁰ Ceftriaxone MIC values for *H. influenzae* were usually at least 2-fold lower than those of ceftobiprole, whereas MIC values of amoxicillin (with or without clavulanate) were usually 2- to 4-fold higher than those of ceftobiprole. Cefpodoxime MIC values were similar to or slightly higher than those of ceftobiprole.¹⁰ Similar results were found in other studies.^{13,15} Results of these studies, combined with the excellent in vitro activity of ceftobiprole against *S. pneumoniae* and *M. catarrhalis*, make ceftobiprole a promising drug for the treatment of patients with community-acquired respiratory tract infections who require hospitalization.

Enterobacteriaceae

Ceftobiprole appears to have a unique pattern of Gram-negative PBP affinity. The major targets for ceftobiprole in *E. coli* appear to be PBP1b and PBP2, and not PBP3 (the target for ceftriaxone and other third-generation cephalosporins). High affinity for PBP2 appears to be a general, novel property of the pyrrolidinone-3-ylidenemethyl cepheems. PBP affinities

to and stability with different classes of beta-lactamases determine the antibacterial spectrum of ceftobiprole against Gram-negative pathogens. As with 3rd- and 4th-generation extended-spectrum cephalosporins, ceftobiprole was largely inactive against strains expressing ESBL enzymes. A lack of activity against *P. vulgaris* (MIC₅₀ and MIC₉₀ >32 µg/mL) results from efficient enzymatic hydrolysis (mediated by K1 beta-lactamase) of ceftobiprole by this microorganism. Ceftobiprole had similar in vitro activity to ceftriaxone against different isolates of Gram-negative Enterobacteriaceae.¹⁵ These results are consistent with those reported in other studies.^{12,13,20} Ceftobiprole showed more activity than ceftriaxone against *Citrobacter freundii* and against *Enterobacter cloacae*.^{20,31} This appears to be the result of relatively high-level stability toward broad-spectrum class A beta-lactamases produced by these two microorganisms. Ceftobiprole is more labile than cefepime to ESBLs; as a consequence, its inhibitory activity against ESBL-producing isolates is weaker. As shown in two in a surveillance studies,^{18,21} ceftobiprole was similar in potency to the third- and fourth-generation cepheims for the principle members of the Enterobacteriaceae. The decreased level of activity of both cefepime and ceftobiprole against ceftazidime non-susceptible and derepressed AmpC screen-positive isolates of *E. cloacae* and *Citrobacter* spp. is likely a reflection of their relative stability to class C beta-lactamases. As with other cephalosporins, the in vitro activity of ceftobiprole against ESBL screen-positive strains of *E. coli*, *Klebsiella pneumoniae* and *Pseudomonas mirabilis* was notably diminished. This finding is consistent with other studies and likely reflects the increased susceptibility of ceftobiprole and other cephalosporins to hydrolysis by mutated class A beta-lactamases (TEM- and SHV-type enzymes). Ceftobiprole was among the most active agents tested (MIC₉₀, ≤0.06 µg/mL) against *Salmonella* spp., *Shigella* spp. and *Vibrionaceae*.^{15,20,21}

***Pseudomonas aeruginosa* and other non-fermenting Gram-negative bacilli**

Ceftobiprole appears to have in vitro antipseudomonal activity resembling that of cefepime, at least against isolates susceptible to ceftazidime.¹⁵ The presence of ceftobiprole's 7-aminothiadiazolylhydroxyimino side chain cannot explain this activity because most cephalosporins bearing this substituent do not inhibit *P. aeruginosa*. This finding suggests that the positively charged 3 substituent may contribute to the antipseudomonal activity of ceftobiprole. However, cross-resistance between ceftazidime, cefepime,

and ceftobiprole exists for most, but not all, *P. aeruginosa* isolates.^{15,32} Ceftobiprole MIC₉₀ values of 8 to 16 µg/mL for ceftazidime-susceptible *P. aeruginosa*, while MIC₉₀ values of 16 to >64 µg/mL for ceftazidime-resistant isolates have been reported.^{12,13,15,20} In the surveillance study published by Fristche et al²¹ ceftobiprole was equal in potency to ceftazidime and 2-fold more potent than cefepime against *P. aeruginosa*. Pillar et al¹⁸ reported that, as was observed with *Enterobacteriaceae*, the activity of ceftobiprole and cefepime against *P. aeruginosa* and *Acinetobacter* spp. was also dependent on the expression of beta-lactam resistance. MICs of both ceftobiprole and cefepime increased significantly among ceftazidime non-susceptible *P. aeruginosa*. The activity of ceftobiprole against other nonfermenting Gram-negative bacilli tested was most similar to that of imipenem in terms of MIC₅₀ and MIC₉₀ values in a study.¹⁴ Ceftobiprole was particularly active against *Agrobacterium radiobacter* (MIC₉₀, 0.25 µg/mL), *Alcaligenes faecalis* (MIC₉₀, 2 µg/mL), *Bordetella bronchiseptica* (MIC₉₀, 4 µg/mL), *Ochrobactrum anthropi* (MIC₉₀, 2 µg/mL), *Pseudomonas oryzaehabitans* (MIC₉₀, 0.25 µg/mL), *Ralstonia pickettii* (MIC₉₀, 4 µg/mL) and *Weeksella virosa* (MIC₉₀, 2 µg/mL). Imipenem, however, had superior activity against *Achromobacter xylosoxidans*, *Acinetobacter baumannii*, *Brevundimonas vesicularis*, *Burkholderia cepacia* complex, *Comamonas acidovorans*, *P. aeruginosa* and *Pseudomonas stutzeri*. Cefepime was more active against *Chryseobacterium indologenes*, *Sphingomonas* species and *P. aeruginosa*. Ceftobiprole MIC₅₀ and MIC₉₀ values of 2 to 32 and 16 to >32 µg/mL have been reported for *Acinetobacter baumannii* species,^{14,16} and MIC₅₀ and MIC₉₀ values of ≤0.06 for *Acinetobacter lwoffii*.¹⁶

Ceftobiprole is largely inactive against *Stenotrophomonas maltophilia*, *Burkholderia cepacia* and *Chryseobacterium meningosepticum*.^{14,33}

Based on in vitro studies, ceftobiprole may be potent enough to be of clinical utility against most of the species evaluated apart from *S. maltophilia* and *C. meningosepticum*. Ceftobiprole appears to have similar in vitro activity to ceftazidime and cefepime against ceftazidime-susceptible *P. aeruginosa* (although ceftobiprole MIC values may be a dilution higher than those of ceftazidime and cefepime in some cases). Ceftobiprole lacks activity against ceftazidime-resistant *P. aeruginosa* isolates.

Anaerobic bacteria

Ceftobiprole had good activity against a wide range of Gram-positive and -negative anaerobes isolated from diabetic foot

infections.¹² In this study, all *Propionibacterium acnes* isolates had MIC values ≤ 0.25 $\mu\text{g/mL}$. *Clostridium* species had MIC values ≤ 1 $\mu\text{g/mL}$ (except for one isolate of *Clostridium innocuum* and one isolate of *Clostridium clostridioforme*). Ceftobiprole activity against *Clostridium* species has species variability with *Clostridium perfringens* typically having low MIC values.^{34,35} Peptostreptococci had MIC values ≤ 1 $\mu\text{g/mL}$ with the exception of 10 isolates of *Peptostreptococcus anaerobius* (MIC₉₀, 4 $\mu\text{g/mL}$).^{12,34} However, Wootton et al³⁵ reported MIC₉₀ of 32 $\mu\text{g/mL}$ for *Peptostreptococcus* species. Ceftobiprole has been highly active against *Finegoldia magna* isolates (MIC₉₀ ≤ 0.5 $\mu\text{g/mL}$).^{12,34} Ceftobiprole has been shown active (MIC ≤ 0.016 –4 $\mu\text{g/mL}$) against Gram-positive beta-lactamase-negative isolates (other than *C. difficile* and *P. anaerobius* isolates) and against *Fusobacterium nucleatum* (including both beta-lactamase-positive and -negative isolates).³⁴ Wootton et al³⁵ reported higher MIC values for *Fusobacterium* species, including *F. nucleatum*, *F. russi*, *F. necroforum* and *F. mortiferum* (MIC₉₀, 8 $\mu\text{g/mL}$). Ceftobiprole's activity against Gram-negative anaerobes is species dependent.¹² While *Porphyromonas asaccharolytica* and *Porphyromonas somerae* had MIC values ≤ 0.125 $\mu\text{g/mL}$, *Prevotella bivia* and *Prevotella melaninogenica* had higher MIC values (64 and 16 $\mu\text{g/mL}$, respectively).^{12,34,35} High MIC values of ceftobiprole (≥ 32 $\mu\text{g/mL}$) have been reported for *Bacteroides fragilis* group, possibly due to chromosomal beta-lactamase activity. MIC₉₀ values against non-*fragilis* *Bacteroides* species of ≥ 32 $\mu\text{g/mL}$ have also been reported.^{34,35}

These studies indicate that ceftobiprole is active against many Gram-positive anaerobes in vitro. Its activity against Gram-negative anaerobes is species-dependent, being less active against the majority of beta-lactamase-producing Gram-negative anaerobes. The activity of ceftobiprole against *F. nucleatum* and *C. perfringens* may be useful in the empirical treatment of complicated skin and skin structure infections as well as oropharyngeal abscesses and aspiration pneumonia (although it has limited activity against *Prevotella* species). However, its poor activity against *Bacteroides* species is a limitation for empirical treatment of intra-abdominal infections.

Resistance studies

In an in vitro study, ceftobiprole was refractory to hydrolysis by the common staphylococcal PC1 beta-lactamase, the class TEM-1 beta-lactamase, and the class C AmpC beta-lactamase, but was labile to hydrolysis by class B, class D, and class A ESBL.³⁶ Experiments involving prolonged serial

transfer of staphylococci in the presence of subinhibitory concentrations of ceftobiprole or comparators and assessing single-step mutation frequencies suggest that staphylococci are relatively refractory to development of endogenous resistance to ceftobiprole.³⁷ Serial passage with increasing concentrations of ceftobiprole performed with 3 MRSA isolates and 1 MSSA isolate suggests that development of resistance to ceftobiprole due to chromosomal mutations occurs with low frequency, if ever, in MRSA.¹⁵ However, a recent study³⁸ demonstrated that MRSA can develop high-level ceftobiprole resistance in vitro mediated by mutations in PBP2a. Ceftobiprole did not select for *S. pneumoniae* clones with MIC values exceeding 1 mcg/ml during up to 50 days serial passage in the presence of subinhibitory concentrations of ceftobiprole, and single-passage selection experiments showed varying rates of endogenous emergence of resistance to ceftobiprole from 1.7×10^{-3} to 1.2×10^{-8} , at the MIC to $<1.4 \times 10^{-8}$ to $<1 \times 10^{-9}$ at 8 times the MIC.²⁹ Ceftobiprole is a poor substrate for class C beta-lactamases and is hydrolyzed at very low rates compared to cephalothin or penicillin G. It is more readily hydrolyzed by class A cephalosporinase from *P. vulgaris* and by ESBLs (TEM derivatives). In *Enterobacteriaceae*, ceftobiprole, cefepime and ceftazidime generally cause less induction of AmpC beta-lactamases than cefoxitin and imipenem. Ceftobiprole is not readily hydrolyzed by AmpC enzymes, suggesting that transient induction of AmpC enzymes may not be a major contributing factor to resistance among Gram-negative bacteria.³⁶ Finally, to date, emergence of ceftobiprole resistance has not been reported in animal or human studies. However this is an issue that deserves careful monitoring.

Ceftobiprole in experimental animal models

In keeping with its in vitro activity, ceftobiprole medocaril showed activity in an experimental mouse septicemia model against a variety of pathogens (MSSA, MRSA, *S. pyogenes*, *S. pneumoniae*, *E. coli*, *K. pneumoniae*, *C. freundii*, *S. marcescens* and *P. mirabilis*).¹⁵ Against the MRSA strain, ceftobiprole was superior to vancomycin. Ceftobiprole medocaril was superior to ceftriaxone and vancomycin against MSSA. Ceftobiprole medocaril showed in vivo activity against three penicillin-resistant strains of *S. pneumoniae*, including a strain with reduced in vitro susceptibility to third-generation cephalosporins. Ceftobiprole medocaril exhibited good in vivo activity against group A streptococci and *E. coli*. Ceftobiprole medocaril was more active than vancomycin and linezolid against the vancomycin-susceptible

strain in an experimental *S. aureus* mouse abscess model.¹⁵ Ceftobiprole medocartil was also active against VISA, as this pathogen was eliminated from most animals. Ceftobiprole medocartil was more active than vancomycin or amoxicillin-clavulanic acid against MRSA in a rat experimental endocarditis model.³⁷ Ceftobiprole medocartil and vancomycin were equally active in a rabbit model of aortic valve endocarditis against MRSA, whereas ceftobiprole medocartil was more active than vancomycin against a VISA strain.³⁹ No difference was found between animals treated with ceftobiprole medocartil and those treated with vancomycin in a rat tissue cage model of chronic MRSA foreign-body infection.⁴⁰ No differences were found in the microbiological cure among 4 weeks treatment with ceftobiprole medocartil, vancomycin or linezolid in a rabbit model of MRSA tibial osteomyelitis.⁴¹ Ceftobiprole medocartil had comparable activity to that of ampicillin against four strains of *E. faecalis* (including beta-lactamase producing and vancomycin resistant strains in a mouse peritonitis model).⁴² In an immunocompetent murine pneumonia model, ceftobiprole medocartil activity was similar to that of ceftriaxone and cefepime against *H. influenzae* and ESBL-nonproducing strains of *E. cloacae* and *K. pneumoniae*. For ESBL-producing *K. pneumoniae*, no differences were detected between no treatment and treatment with ceftobiprole medocartil, ceftriaxone or cefepime.⁴³

These models confirm the *in vivo* activity of ceftobiprole against Gram-negative bacteria (except for ESBL-producing Gram-negative bacilli and *P. vulgaris*). There are limited published experimental animal trials evaluating ceftobiprole's activity against *P. aeruginosa*.

Pharmacokinetic profile

Because ceftobiprole is not sufficiently soluble in water to be used for parenteral administration in humans, it is administered as a water-soluble prodrug, ceftobiprole medocartil. Ceftobiprole medocartil is rapidly converted by plasma esterases to ceftobiprole. The safety and pharmacokinetics of ceftobiprole medocartil were evaluated in a double-blind, single ascending-dose study (following doses of 125, 250, 500, 750 or 1000 mg) in 40 healthy male subjects. Peak levels of the active drug in plasma were observed at the end of the 30-min infusion. Afterwards, concentrations in plasma declined in a biphasic manner consistent with a rapid distribution of ceftobiprole from the systemic circulation into other body compartments. The apparent volume of distribution (18–20 L) was similar to the values reported for other beta-lactams. The clearance (4.1–5.1 L/h), volume of distribution (18–20 L), and half-life in the post-distribution

phase (3 hours) remained constant over the dose range.⁴⁴ Results of a multiple-dose study indicate that ceftobiprole has stable pharmacokinetic properties over an 8-day course of dosing, with low intersubject variability.⁴⁵ Overall results agreed with data reported by the same group in a single ascending-dose study. A strong correlation between the time that the concentration remains above the MIC ($T > MIC$) and effect has been demonstrated in both *in vitro* and experimental animal model studies.^{46,47} In a single-dose study performed following infusion of ceftobiprole medocartil at 500 and 1000 mg, total concentrations were above the MIC of 4 *Bacteroides* for 5 to 7 hours, corresponding to a $T > MIC$ of 42% to 58% of a 12-hour interval, assuming twice-daily dosing, for 500 and 1000 mg, respectively.⁴⁴ For ceftobiprole medocartil 500 mg every 12 hours, the probabilities of achieving 30% and 50% $T > MIC$ exceeded 90% for MIC values of ≤ 2 mcg/ml and ≤ 1 μ g/mL, respectively. And for ceftobiprole medocartil 500 mg every 8 hours, the probabilities of achieving 40 and 60% $T > MIC$ exceeded 90% for MIC values of 4 μ g/mL and ≤ 2 μ g/mL, respectively. For both regimens, the probability of achieving a near bactericidal effect (50% $T > MIC$ in Gram-positive and 60% in Gram-negative microorganisms) exceeded 90% for MSSA and MRSA and non-AmpC-producing Gram-negative microorganisms.⁴⁸ The skin and skin structure infections regimen (ceftobiprole medocartil 500 mg intravenously every 12 hours) and nosocomial pneumonia regimen (ceftobiprole medocartil 500 mg intravenously every 8 hours) both demonstrated a high probability of achieving a maximal bactericidal effect against both MSSA and MRSA isolates. When mixed infections containing both gram-negative and gram-positive microorganisms are suspected, a regimen of 500 mg intravenously every 8 hours may be appropriate.⁴⁹ Although lung concentrations of ceftobiprole have not been measured in humans, a study in leukopenic female Swiss albino mice demonstrated lower lung than serum concentrations of ceftobiprole but a longer ceftobiprole half-life in lungs versus serum.⁵⁰ Ceftobiprole is predominantly eliminated in the urine.⁴⁴ The highest urine drug concentrations are observed within 2 hours after the start of the infusion, and urine concentrations correlate with dose. Glomerular filtration of the active metabolite appears to be predominantly responsible for removal of free drug from the systemic circulation.⁴⁴ Lodise et al⁴⁸ analyzed a total of 150 Phase I/II subjects in order to determine the optimal renal dose adjustment for intravenous ceftobiprole medocartil. Ceftobiprole medocartil 500 mg intravenously every 12 hours was determined to be the most appropriate

regimen for those with a CrCl \leq 50 mL/min. Dosing for patients receiving hemodialysis/hemofiltration remains to be addressed in the published literature. Ceftobiprole medocaril is not hepatically metabolized.

Post-antibiotic effect

It has been described that the effect of sub-MIC concentrations on growth during the post-antibiotic effect (PAE) was longer than the PAE in a study,⁵¹ suggesting that continued exposure to sub-MIC levels of ceftobiprole following a supra-inhibitory level may allow for continued suppression of growth in vivo. The mean PAE for 3 *S. pneumoniae* was 1.8 h (range 1.4–3.1 hours) and did not differ by penicillin susceptibility.⁵¹ Staphylococcal PAEs were slightly lower for methicillin-susceptible isolates (mean, 0.4 hours; range, 0–0.8 hours) than for methicillin-resistant isolates (mean, 1.0 hours; range, 0–1.8 hours). The PAEs for the vancomycin-susceptible isolates (mean, 0.6 hours; range, 0–1.1 hours) did not differ from those for vancomycin-intermediate and -resistant isolates (mean, 1.0 hours; range, 0–1.8 hours). Three *E. faecalis* isolates had a mean PAE of 0.4 hours (0–0.9 hours). These findings support the twice-daily dosing of ceftobiprole for infections caused by Gram-positive cocci.

Adverse events

In the Schmitt-Hoffmann studies,^{44,45} 8 subjects dosed with ceftobiprole experienced 10 adverse effects. Of these, 7 were reported as mild taste disturbances, described by subjects as a caramel-like taste experienced during the infusion period (attributed to conversion of the prodrug to ceftobiprole plus diacetyl, the latter being a natural product which has a caramel-like taste). The remaining 3 adverse effects were mild nausea (2 subjects) and moderate vomiting (1 subject). None of the adverse effects were severe or serious, and none required treatment.

Clinical studies

Two recently published multicenter non-inferiority trials involving more than 1500 patients with skin and soft tissue infections have shown cure rates similar to those of the comparators (vancomycin or vancomycin plus ceftazidime). The Study of Resistant *S. aureus* Skin and Skin Structure Infections (STRAUSS) trial³ was a multicenter, randomized, double-blind clinical trial involving patients with complicated skin and skin structure infections in whom Gram-positive pathogens were documented and/or suspected based on microscopic examination. The primary

objective was to compare clinical cure rates 7 to 14 days after completion of therapy with ceftobiprole medocaril (500 mg intravenously every 12 h) or vancomycin (1 g intravenously every 12 hours). The predominant pathogen was *S. aureus* (37% of which were MRSA). The Gram-negative isolates included Enterobacteriaceae (37), *Pseudomonas* species (6) and *A. baumannii* (2). Overall cure rates in the ceftobiprole-treated (n = 282) and vancomycin-treated (n = 277) subjects in the clinically evaluable population were similar (93.3% and 93.5%, respectively). Cure rates in the ceftobiprole-treated (n = 61) and vancomycin-treated (n = 60) subjects in the clinically evaluable population with MRSA infections were 91.8% and 90.0%, respectively. Serious treatment-related adverse events were 1% in the ceftobiprole-treated group and 3% in the vancomycin-treated group. Rates of therapy discontinuation due to treatment-related adverse events were comparable in the two groups.

A second ceftobiprole phase III skin and skin structure infection double-blind study (STRAUSS 2) reportedly enrolled 828 patients who were either treated with ceftobiprole medocaril or the combination of ceftazidime plus vancomycin (2:1 randomization).² In this study, approximately one-third of patients had diabetic foot infections. A total of 91% of clinically evaluable patients were cured with ceftobiprole medocaril compared to 90% of patients treated with combination therapy. The clinical response in those with diabetic foot infection was 86% and 82% for ceftobiprole medocaril versus combination therapy, respectively. More than 20% of microbiologically evaluable patients had MRSA infections. A phase III clinical trial for nosocomial pneumonia (CHOPIN) has also been completed but results have not been published; a trial for community acquired pneumonia is ongoing.

Conclusions

MRSA has assumed increased importance in both community-acquired and nosocomial infections. A broad-spectrum agent with bactericidal activity against MRSA is an attractive treatment option. Ceftobiprole medocaril is a broad-spectrum cephalosporin with in vitro activity against MRSA that has demonstrated favorable results in two phase III trials in complicated skin and skin structure infections which included subjects with MRSA infections. Ceftobiprole exhibits in vitro activity against many bacteria that cause hospital- and community-acquired infections, including methicillin-resistant staphylococci. It has activity against *S. aureus*, including MRSA and VISA, CNS, *Enterococcus* species (but not ampicillin-resistant

enterococci), pneumococci and some anaerobes; it also has activity against Gram-negative bacilli similar to that of available third- and fourth-generation cephalosporins. Ceftobiprole appears to be relatively refractory to development of endogenous resistance. Ceftobiprole is not active against ESBL-producing Gram-negative bacilli or *P. vulgaris*, and its activity against *P. aeruginosa* has not yet been adequately evaluated in vivo. Ceftobiprole has received fast-track status from the FDA; further clinical studies are warranted to evaluate its efficacy and safety in patients with infections beyond those of skin and skin structures.

Disclosures

The authors disclose no conflicts of interest.

References

- Bush K, Heep M, Macielag MJ, Noel GJ. Anti-MRSA beta-lactams in development, with a focus on ceftobiprole: the first anti-MRSA beta-lactam to demonstrate clinical efficacy. *Expert Opin Investig Drugs*. 2007;16(4):419–429.
- Noel GJ, Bush K, Bagchi P, Ianus J, Strauss RS. A randomized, double-blind trial comparing ceftobiprole medocaril with vancomycin plus ceftazidime for the treatment of patients with complicated skin and skin-structure infections. *Clin Infect Dis*. 2008;46(5):647–655.
- Noel GJ, Strauss RS, Amsler K, Heep M, Pypstra R, Solomkin JS. Results of a double-blind, randomized trial of ceftobiprole treatment of complicated skin and skin structure infections caused by gram-positive bacteria. *Antimicrob Agents Chemother*. 2008;52(1):37–44.
- El Solh A. Ceftobiprole: a new broad spectrum cephalosporin. *Expert Opin Pharmacother*. 2009;10(10):1675–1686.
- Deshpande L, Rhomberg PR, Fritsche TR, Sader HS, Jones RN. Bactericidal activity of BAL9141, a novel parenteral cephalosporin against contemporary Gram-positive and Gram-negative isolates. *Diagn Microbiol Infect Dis*. 2004;50(1):73–75.
- Davies TA, Page MG, Shang W, Andrew T, Kania M, Bush K. Binding of ceftobiprole and comparators to the penicillin-binding proteins of *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*. *Antimicrob Agents Chemother*. 2007;51(7):2621–2624.
- Mouton JW, Schmitt-Hoffmann A, Shapiro S, Nashed N, Punt NC. Use of Monte Carlo simulations to select therapeutic doses and provisional breakpoints of BAL9141. *Antimicrob Agents Chemother*. 2004;48(5):1713–1718.
- Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. 17th informational supplement. CLSI document M100-S17 [ISBN 1-56238-625-5]. Clinical and Laboratory Standards Institute, Wayne, PA, USA, 2007.
- Anderegg TR, Jones RN, Sader HS. Quality control guidelines for BAL9141 (Ro 63–9141), an investigational cephalosporin, when reference MIC and standardized disk diffusion susceptibility test methods are used. *J Clin Microbiol*. 2004;42(7):3356–3358.
- Bogdanovich T, Clark C, Ednie L, et al. Activities of ceftobiprole, a novel broad-spectrum cephalosporin, against *Haemophilus influenzae* and *Moraxella catarrhalis*. *Antimicrob Agents Chemother*. Jun 2006;50(6):2050–2057.
- Bogdanovich T, Ednie LM, Shapiro S, Appelbaum PC. Antistaphylococcal activity of ceftobiprole, a new broad-spectrum cephalosporin. *Antimicrob Agents Chemother*. 2005;49(10):4210–4219.
- Goldstein EJ, Citron DM, Merriam CV, Warren YA, Tyrrell KL, Fernandez HT. In vitro activity of ceftobiprole against aerobic and anaerobic strains isolated from diabetic foot infections. *Antimicrob Agents Chemother*. 2006;50(11):3959–3962.
- Issa NC, Rouse MS, Piper KE, Wilson WR, Steckelberg JM, Patel R. In vitro activity of BAL9141 against clinical isolates of gram-negative bacteria. *Diagn Microbiol Infect Dis*. 2004;48(1):73–75.
- Zbinden R, Punter V, von Graevenitz A. In vitro activities of BAL9141, a novel broad-spectrum pyrrolidinone cephalosporin, against gram-negative nonfermenters. *Antimicrob Agents Chemother*. 2002;46(3):871–874.
- Hebeisen P, Heinze-Krauss I, Angehrn P, Hohl P, Page MG, Then RL. In vitro and in vivo properties of Ro 63–9141, a novel broad-spectrum cephalosporin with activity against methicillin-resistant staphylococci. *Antimicrob Agents Chemother*. 2001;45(3):825–836.
- Jones ME. In-vitro profile of a new beta-lactam, ceftobiprole, with activity against methicillin-resistant *Staphylococcus aureus*. *Clin Microbiol Infect*. 2007;13 Suppl 2:17–24.
- von Eiff C, Friedrich AW, Becker K, Peters G. Comparative in vitro activity of ceftobiprole against staphylococci displaying normal and small-colony variant phenotypes. *Antimicrob Agents Chemother*. 2005;49(10):4372–4374.
- Pillar CM, Aranza MK, Shah D, Sahn DF. In vitro activity profile of ceftobiprole, an anti-MRSA cephalosporin, against recent gram-positive and gram-negative isolates of European origin. *J Antimicrob Chemother*. 2008;61(3):595–602.
- Srinivasan V, McGowan JE Jr, McAllister S, Tenover FC. In vitro activity of ceftobiprole against coagulase-negative staphylococci isolated in the USA. *Int J Antimicrob Agents*. 2008;31(3):294–296.
- Jones RN, Deshpande LM, Mutnick AH, Biedenbach DJ. In vitro evaluation of BAL9141, a novel parenteral cephalosporin active against oxacillin-resistant staphylococci. *J Antimicrob Chemother*. 2002;50(6):915–932.
- Fritsche TR, Sader HS, Jones RN. Antimicrobial activity of ceftobiprole, a novel anti-methicillin-resistant *Staphylococcus aureus* cephalosporin, tested against contemporary pathogens: results from the SENTRY Antimicrobial Surveillance Program (2005–2006). *Diagn Microbiol Infect Dis*. 2008;61(1):86–95.
- Rouse MS, Steckelberg JM, Patel R. In vitro activity of ceftobiprole, daptomycin, linezolid, and vancomycin against methicillin-resistant staphylococci associated with endocarditis and bone and joint infection. *Diagn Microbiol Infect Dis*. 2007;58(3):363–365.
- Chung M, Antignac A, Kim C, Tomasz A. Comparative study of the susceptibilities of major epidemic clones of methicillin-resistant *Staphylococcus aureus* to oxacillin and to the new broad-spectrum cephalosporin ceftobiprole. *Antimicrob Agents Chemother*. 2008;52(8):2709–2717.
- Lin G, Appelbaum PC. Activity of ceftobiprole compared with those of other agents against *Staphylococcus aureus* strains with different resistotypes by time-kill analysis. *Diagn Microbiol Infect Dis*. 2008;60(2):233–235.
- Leonard SN, Cheung CM, Rybak MJ. Activities of ceftobiprole, linezolid, vancomycin, and daptomycin against community-associated and hospital-associated methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2008;52(8):2974–2976.
- Yun HC, Ellis MW, Jorgensen JH. Activity of ceftobiprole against community-associated methicillin-resistant *Staphylococcus aureus* isolates recently recovered from US military trainees. *Diagn Microbiol Infect Dis*. 2007;59(4):463–466.
- Deshpande LM, Jones RN. Bactericidal activity and synergy studies of BAL9141, a novel pyrrolidinone-3-ylidenemethyl cephem, tested against streptococci, enterococci and methicillin-resistant staphylococci. *Clin Microbiol Infect*. 2003;9(11):1120–1124.
- Arias CA, Singh KV, Panesso D, Murray BE. Time-kill and synergism studies of ceftobiprole against *Enterococcus faecalis*, including beta-lactamase-producing and vancomycin-resistant isolates. *Antimicrob Agents Chemother*. 2007;51(6):2043–2047.

29. Kosowska K, Hoellman DB, Lin G, et al. Antipneumococcal activity of ceftobiprole, a novel broad-spectrum cephalosporin. *Antimicrob Agents Chemother.* 2005;49(5):1932–1942.
30. Davies TA, Shang W, Bush K. Activities of ceftobiprole and other beta-lactams against *Streptococcus pneumoniae* clinical isolates from the United States with defined substitutions in penicillin-binding proteins PBP 1a, PBP 2b, and PBP 2x. *Antimicrob Agents Chemother.* 2006;50(7):2530–2532.
31. Hecker SJ, Cho IS, Glinka TW, et al. Discovery of MC-02,331, a new cephalosporin exhibiting potent activity against methicillin-resistant *Staphylococcus aureus*. *J Antibiot (Tokyo).* 1998;51(8):722–734.
32. Walkty A, Decorbey M, Nichol K, Karlowsky JA, Hoban DJ, Zhanel GG. In vitro activity of ceftobiprole against clinical isolates of *Pseudomonas aeruginosa* obtained from Canadian intensive care unit (ICU) patients as part of the CAN-ICU Study. *J Antimicrob Chemother.* 2008;62(1):206–208.
33. Thamlikitkul V, Trakulsomboon S. In vitro activity of ceftobiprole against *Burkholderia pseudomallei*. *J Antimicrob Chemother.* 2008;61(2):460–461.
34. Ednie L, Shapiro S, Appelbaum PC. Antianaerobe activity of ceftobiprole, a new broad-spectrum cephalosporin. *Diagn Microbiol Infect Dis.* 2007;58(1):133–136.
35. Wootton M, Bowker KE, Holt HA, MacGowan AP. BAL 9141, a new broad-spectrum pyrrolidinone cephalosporin: activity against clinically significant anaerobes in comparison with 10 other antimicrobials. *J Antimicrob Chemother.* 2002;49(3):535–539.
36. Queenan AM, Shang W, Kania M, Page MG, Bush K. Interactions of ceftobiprole with beta-lactamases from molecular classes A to D. *Antimicrob Agents Chemother.* 2007;51(9):3089–3095.
37. Entenza JM, Hohl P, Heinze-Krauss I, Glauser MP, Moreillon P. BAL9141, a novel extended-spectrum cephalosporin active against methicillin-resistant *Staphylococcus aureus* in treatment of experimental endocarditis. *Antimicrob Agents Chemother.* 2002;46(1):171–177.
38. Banerjee R, Gretes M, Basuino L, Strynadka N, Chambers HF. In vitro selection and characterization of ceftobiprole-resistant methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother.* 2008;52(6):2089–2096.
39. Chambers HF. Evaluation of ceftobiprole in a rabbit model of aortic valve endocarditis due to methicillin-resistant and vancomycin-intermediate *Staphylococcus aureus*. *Antimicrob Agents Chemother.* 2005;49(3):884–888.
40. Vaudaux P, Gjinovci A, Bento M, Li D, Schrenzel J, Lew DP. Intensive therapy with ceftobiprole medocartil of experimental foreign-body infection by methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother.* 2005;49(9):3789–3793.
41. Yin LY, Calhoun JH, Thomas JK, Shapiro S, Schmitt-Hoffmann A. Efficacies of ceftobiprole medocartil and comparators in a rabbit model of osteomyelitis due to methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother.* 2008;52(5):1618–1622.
42. Arias CA, Singh KV, Panesso D, Murray BE. Evaluation of ceftobiprole medocartil against *Enterococcus faecalis* in a mouse peritonitis model. *J Antimicrob Chemother.* 2007;60(3):594–598.
43. Rouse MS, Hein MM, Anguita-Alonso P, Steckelberg JM, Patel R. Ceftobiprole medocartil (BAL5788) treatment of experimental *Haemophilus influenzae*, *Enterobacter cloacae*, and *Klebsiella pneumoniae* murine pneumonia. *Diagn Microbiol Infect Dis.* 2006;55(4):333–336.
44. Schmitt-Hoffmann A, Roos B, Schleimer M, et al. Single-dose pharmacokinetics and safety of a novel broad-spectrum cephalosporin (BAL5788) in healthy volunteers. *Antimicrob Agents Chemother.* 2004;48(7):2570–2575.
45. Schmitt-Hoffmann A, Nyman L, Roos B, et al. Multiple-dose pharmacokinetics and safety of a novel broad-spectrum cephalosporin (BAL5788) in healthy volunteers. *Antimicrob Agents Chemother.* 2004;48(7):2576–2580.
46. Craig WA, Andes DR. In vivo pharmacodynamics of ceftobiprole against multiple bacterial pathogens in murine thigh and lung infection models. *Antimicrob Agents Chemother.* 2008;52(10):3492–3496.
47. Laohavaleeson S, Tessier PR, Nicolau DP. Pharmacodynamic characterization of ceftobiprole in experimental pneumonia caused by phenotypically diverse *Staphylococcus aureus* strains. *Antimicrob Agents Chemother.* 2008;52(7):2389–2394.
48. Lodise TP Jr, Pypstra R, Kahn JB, et al. Probability of target attainment for ceftobiprole as derived from a population pharmacokinetic analysis of 150 subjects. *Antimicrob Agents Chemother.* 2007;51(7):2378–2387.
49. Lodise TP, Patel N, Renaud-Mutart A, Gorodecky E, Fritsche TR, Jones RN. Pharmacokinetic and pharmacodynamic profile of ceftobiprole. *Diagn Microbiol Infect Dis.* 2008;61(1):96–102.
50. Azoulay-Dupuis E, Bedos JP, Mohler J, Schmitt-Hoffmann A, Schleimer M, Shapiro S. Efficacy of BAL5788, a prodrug of cephalosporin BAL9141, in a mouse model of acute pneumococcal pneumonia. *Antimicrob Agents Chemother.* 2004;48(4):1105–1111.
51. Pankuch GA, Appelbaum PC. Postantibiotic effect of ceftobiprole against 12 Gram-positive organisms. *Antimicrob Agents Chemother.* 2006;50(11):3956–3958.

Infection and Drug Resistance

Publish your work in this journal

Infection and Drug Resistance is an international, peer-reviewed open-access journal that focuses on the optimal treatment of infection (bacterial, fungal and viral) and the development and institution of preventive strategies to minimize the development and spread of resistance. The journal is specifically concerned with the epidemiology of antibiotic

Submit your manuscript here: <http://www.dovepress.com/infection-and-drug-resistance-journal>

resistance and the mechanisms of resistance development and diffusion in both hospitals and the community. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Dovepress