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Spectrum and Potency of Ceftobiprole Against Leading North American Pathogens Producing Community- and Hospital-Acquired Pneumonia (2005-2007)

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Amended Abstract

Objectives: To establish ceftobiprole (BPR; a parenteral cephalosporin approved in four countries for complicated skin and skin-structure infections [CSSI] and under development for community- [CA] and hospital-acquired [HA] respiratory tract pathogens) potency and spectrum. BPR is active against MRSA and other Gram-positive and –negative pathogens, making it an attractive candidate for broad-spectrum therapy. Results assessing potency of BPR against commonly occurring CA- and HA-pneumonia pathogens in North America (NA) are presented.

Methods: A total of 5,108 non-duplicate isolates causing clinically-significant CA- and HA- pneumonia infections were collected from over 25 medical centers in NA participating in a BPR surveillance program (2005-2007). Susceptibility (S) testing was performed using CLSI methods (M07-A8, 2009) by the central monitoring laboratory.

Results: BPR inhibited the CA-RTI pathogens HI and SPN at ≤0.25 and ≤1 mg/L, respectively. Overall SA strains had MIC_{90} at 2 mg/L, however the MIC_{90} for oxacillin (OXA)-S strains was four-fold lower (0.5 mg/L). Coverage against Gram-negative bacilli causing HA-RTI showed EC was nearly identical for the three agents (Table; 97-98% inhibited at ≤4 mg/L). FEP provided enhanced coverage against KSP (90%) at ≤8 mg/L vs. 83% for BPR and 88% for CAZ. BPR and FEP were superior to CAZ against ESP. Against PSA, BPR was equal in potency to FEP (MIC_{90}, 8 mg/L) and two-fold more potent than CAZ against ASP, although the % inhibited for these agents at ≤2/≤4/≤8 mg/L was similar (67-92/60-90/66-87%, respectively).

	BPR MIC (mg/L)		Cum. % inhibited at MIC (mg/L)					
Organism (no. tested)	50%	90%	≤0.25	0.5	1	2	4	8
Community-acquired								
H. influenzae (HI; 883)	≤0.06	≤0.06	100	-	-	-	-	-
S. pneumoniae (SPN; 1,912)	≤0.06	0.5	88.9	98.5	100	-	-	-
Hospital-acquired								
S. aureus (SA; 938)	0.5	2	26.7	54.2	89.3	100	-	-
P. aeruginosa (PSA; 492)	4	>8	1.2	5.7	25	45.1	60.2	77.9
Klebsiella spp. (KSP; 228)	≤0.06	>8	75.9	77.6	79.4	80.3	81.1	82.5
Enterobacter spp. (EBS; 155)	≤0.06	8	75.5	78.1	80.7	85.8	89.7	91.6
Acinetobacter spp. (ASP; 122)	>8	>8	10.7	21.3	30.3	33.6	36.1	36.1

Conclusions: Ceftobiprole is a new β-lactam with antimicrobial activity against pathogens causing CA- and HA-pneumonia, similar to that of extended-spectrum cephems but including MRSA. These characteristics warrant continued evaluation of ceftobiprole as empiric therapy for treating bacterial pneumonia.

Introduction

Community-acquired (CAP) and nosocomial (healthcare-acquired [HAP], ventilator-associated [VAP]) pneumonia (NP) are significant causes of patient morbidity and mortality, and have become much more difficult to manage via the escalating resistances being detected among all pathogen groups, including *Streptococcus pneumoniae* and *Haemophilus influenzae* among CAP pathogens and *Staphylococcus aureus*, Enterobacteriaceae, and non-fermentative Gram-negative bacilli among NP pathogens. The decrease in utility of many older agents such as penicillins, cephalosporins, β-lactamase inhibitor combinations and even carbapenems, among many other classes of antimicrobics, has created a critical need for new agents. The search for compounds with greater potency, stability to common resistance mechanisms, favorable pharmacokinetic/pharmacodynamic (PK/PD) features and lower potential to select for resistance, is essential in addressing this situation.

Ceftobiprole is an anti–methicillin-resistant *S. aureus* (anti-MRSA) cephalosporin with potent activity against Gram-positive and –negative bacteria. Ceftobiprole is stable to many β-lactamases and has a strong affinity for penicillin-binding proteins (PBP), including PBP2 (PBP2a) which mediates resistance to β-lactams in MRSA and coagulase-negative staphylococci, and PBP2x which is associated with penicillin resistance in pneumococci. Ceftobiprole is therefore an attractive therapeutic candidate given this unique spectrum, its safety profile characteristic of most β-lactams, and its predominantly bactericidal activity. Ceftobiprole also displays antibacterial activity against Enterobacteriaceae and many *Pseudomonas aeruginosa* isolates. The agent has been approved for the treatment of complicated skin and skin-structure infections in four countries and is under regulatory review in a number of other countries around the world. Additionally it is under development for various types of pneumonia.

The objective of the current study was to examine the susceptibility profiles and antibiograms of ceftobiprole and comparator agents tested against contemporary pathogens isolated in North America from patients with CAP, NP, HAP, and VAP during 2005-2007. These case isolates came from the Global Ceftobiprole Surveillance Program and numbered 5,108 total strains, all tested by reference susceptibility test methods.

Materials and Methods

Organisms Tested

Consecutive, non-duplicate clinical isolates from respiratory tract infections (CAP, NP, HAP, and VAP) were collected from North American sites in 2005-2007. This collection numbered 5,108 strains from more than 25 medical centers each year in the United States (USA) and Canada. This component of the Global Ceftobiprole Surveillance Program utilized significant isolates processed by a central reference monitor (JMI Laboratories, North Liberty, Iowa, USA) using GLP-compliant Clinical and Laboratory Standards Institute (CLSI; formerly the NCCLS) methods.

Susceptibility Test Methods

All strains were tested by the broth microdilution method using validated commercially prepared panels (TREK Diagnostics, Cleveland, OH, USA) in cation-adjusted Mueller-Hinton broth (with 5% lysed horse blood added for testing of streptococci and Haemophilus Test Medium for testing of *H. influenzae*) against a variety of antimicrobial agents representing the most common classes and examples of drugs used in the empiric or directed treatment of the indicated pathogen. Interpretation of MIC results was in accordance with published CLSI criteria, where available. Enterobacteriaceae with elevated MICs (≤2 mg/L) for ceftazidime and/or ceftriaxone and/or aztreonam were considered as extended-spectrum β-lactamase (ESBL)–producing phenotypes. Quality control (QC) strains utilized included *Escherichia coli* ATCC 25922 and 35218, *P. aeruginosa* ATCC 27853, *H. influenzae* ATCC 49247, *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619. All QC values were within published limits (Anderegg, et al., 2004).

Results

- Among the 5,108 tested North American strains the dominant species (*S. pneumoniae* and *H. influenzae)* were from CAP cases (**Tables 1** and **2**) and the overall rank order (top 10) was: *S. pneumoniae* (1,912) > *S. aureus* (938) > *H. influenzae* (883) > *P. aeruginosa* (492) > *Klebsiella* species (228) > *Enterobacter* species (155) > *Acinetobacter* species (122) > *Serratia* species (110) > *E. coli* (103) > *Stenotrophomonas maltophilia* (79).
- Ceftobiprole exhibited excellent potencies against Gram-positive respiratory tract pathogens: *S. pneumoniae* (MIC_{90}, 0.5 mg/L), *S. aureus* (MIC_{90}, 2 mg/L), and β-hemolytic streptococci (MIC_{90}, ≤0.06 mg/L); see **Table 1**.
- Ceftobiprole was very active against *S. pneumoniae* that were non-susceptible to penicillin ($MIC_{50/90}$ at 0.5/1 mg/L) and MRSA ($MIC_{50/90}$ at 1/2 mg/L). However, the MIC_{90} for ceftobiprole for both resistance subsets was four-fold greater than penicillin-susceptible and methicillin-susceptible *S. aureus* (MSSA) populations (**Table 3**).
- Ceftobiprole was very active against 883 tested *H. influenzae* (MIC_{90}, ≤0.06 mg/L), and its potency was not significantly influenced by β-lactamase production (**Table 3**).

Table 1. Ceftobiprole and selected comparison agents tested against Gram-positive pathogens causing various types of pneumonia in North America (2005-2007); 2,871 strains

		MIC (mg/L)			% by category[a]
Organism (no. tested)	Antimicrobial agent	50%	90%	Range	Susceptible/Resistant
S. pneumoniae (1,912)	Ceftobiprole	≤0.06	0.5	≤0.06–1	-[b]/-(100.0)[c]
	Cefepime	≤0.12	1	≤0.12–4	92.9/0.5
	Ceftriaxone	≤0.25	1	≤0.25–16	94.5/1.7
	Penicillin	≤0.03	4	≤0.03–>4	88.6/0.7
	Erythromycin	≤0.25	>2	≤0.25–>2	63.3/36.2
	Clindamycin	≤0.25	>2	≤0.25–>2	81.6/27.9
	Levofloxacin	1	1	≤0.5–>4	99.2/0.5
	Linezolid	1	1	≤0.12–2	100.0/-
	Vancomycin	≤1	≤1	≤1	100.0/-
S. aureus (938)	Ceftobiprole	0.5	2	0.12–2	-[b]/-(100.0)[c]
	Oxacillin	>2	>2	≤0.25–>2	42.2/57.8
	Daptomycin	0.25	0.5	≤0.06–1	100.0/-
	Levofloxacin	4	>4	≤0.5–>4	45.8/53.4
	Linezolid	1	2	0.25—4	100.0/-
	Tetracycline	≤2	≤2	≤2–>8	94.5/4.9
	Trimethoprim/ sulfamethoxazole	≤0.5	≤0.5	≤0.5–>2	97.3/23
	Vancomycin	1	1	≤0.12–2	100.0/0.0
β-*hemolytic streptococci* (21)	Ceftobiprole	≤0.06	≤0.06	≤0.06	-[b]/-(100.0)[c]
	Cefepime	≤0.12	≤0.12	≤0.12–0.25	100.0/-
	Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0/-
	Penicillin	≤0.015	0.03	≤0.015–0.06	100.0/-
	Erythromycin	≤0.25	2	≤0.25–>2	76.2/23.8
	Clindamycin	≤0.25	≤0.25	≤0.25–>2	95.2/4.8
	Levofloxacin	≤0.5	1	≤0.5–2	100.0/0.0
	Linezolid	1	1	0.5–1	100.0/-
	Vancomycin	0.25	0.5	0.25–0.5	100.0/-

[a] Criteria of CLSI M100-S19 (2009). For penicillin versus pneumococci, the breakpoint of ≤2 mg/L was applied representing high-dose treatments of pneumonia.
[b] - = no established breakpoint for this drug or category. [c] % at ≤4 mg/L for comparisons only.

Table 2. Ceftobiprole and selected comparison agents tested against Gram-negative bacilli that were associated with patients having various types of pneumonia in North America (2005-2007); 2,093 strains

		MIC (mg/L)			% by category[a]
Organism (no. tested)	Antimicrobial agent	50%	90%	Range	Susceptible/Resistant
H. influenzae (883)	Ceftobiprole	≤0.06	≤0.06	≤0.06–0.25	-[b]/-(100.0)[c]
	Cefepime	≤0.12	≤0.12	≤0.12–0.5	100.0/-
	Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0/-
	Amoxicillin/clavulanate	≤1	≤1	≤1–4	100.0/0.0
	Ampicillin	≤1	>16	≤1–>16	73.5/25.5
	Clarithromycin	8	16	≤0.25–>32	78.8/2.2
	Levofloxacin	≤0.5	≤0.5	≤0.5	100.0/0.0
	Tetracycline	≤2	≤2	≤2–>8	98.5/0.9
	Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5–>2	77.8/19.4
P. aeruginosa (492)	Ceftobiprole	4	>8	0.25–>8	-/-(60.2)
	Cefepime	4	16	0.25–>16	78.0/7.3
	Ceftazidime	4	>16	≤1–>16	74.6/19.9
	Imipenem	2	>8	0.25–>8	75.4/15.9
	Piperacillin/tazobactam	8	>64	≤0.5–>64	81.5/18.5
	Amikacin	≤4	16	≤4–>32	92.3/5.3
	Levofloxacin	2	>8	≤0.5–>4	66.3/26.2
	Polymyxin B	1	1	≤0.5–2	100.0/0.0
Klebsiella species (228)	Ceftobiprole	≤0.06	>8	≤0.06–>8	-/-(81.1)
	Cefepime	≤0.12	4	≤0.12–>16	93.4/3.9
	Ceftriaxone	≤0.25	32	≤0.25–>32	81.5/17.1
	Ceftazidime	≤1	>16	≤1–>16	86.8/12.3
	Imipenem	0.25	0.5	≤0.12–>8	94.3/4.4
	Levofloxacin	≤0.5	>4	≤0.5–>4	85.1/13.2
	Tetracycline	≤2	>8	≤2–>8	80.7/13.2
	Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5–>2	77.6/19.3
Enterobacter species (155)	Ceftobiprole	≤0.06	8	≤0.06–>8	-/-(89.7)
	Cefepime	≤0.12	2	≤0.12–>16	97.4/1.9
	Ceftriaxone	≤0.25	>32	≤0.25–>32	69.0/29.0
	Ceftazidime	≤1	>16	≤1–>16	72.3/27.1
	Imipenem	0.5	2	≤0.12–>8	99.4/0.6
	Levofloxacin	≤0.5	4	≤0.5–>4	88.4/6.4
	Tetracycline	≤2	>8	≤2–>8	83.9/11.0
	Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5–>2	82.6/11.0
Acinetobacter species (122)	Ceftobiprole	>8	>8	≤0.06–>8	-/-(36.1)
	Cefepime	>16	>16	0.5–>16	30.3/52.5
	Ceftazidime	>16	>16	≤1–>16	23.0/69.7
	Imipenem	4	>8	≤0.12–>8	51.6/29.5
	Ampicillin/sulbactam	16	>16	≤2–>16	48.4/41.0
	Piperacillin/tazobactam	>64	>4	≤0.5–>64	28.7/51.6
	Levofloxacin	>4	>4	≤0.5–>4	23.8/71.3
	Polymyxin B	≤0.5	≤0.5	≤0.5–>4	97.5/2.5
Serratia species (110)	Ceftobiprole	≤0.06	1	≤0.06–>8	-/-(94.6)
	Cefepime	≤0.12	0.5	≤0.12–8	100.0/0.0
	Ceftriaxone	≤0.25	4	0.25–>32	84.6/12.7
	Ceftazidime	≤1	≤1	≤1–>16	93.6/5.4
	Imipenem	1	2	≤0.12–2	100.0/0.0
	Levofloxacin	≤0.5	2	≤0.5–>4	95.5/1.8
	Tetracycline	>8	>8	≤2–>8	6.4/58.2
	Trimethoprim/sulfamethoxazole	≤0.5	2	≤0.5–>2	85.5/10.9
E. coli (103)	Ceftobiprole	≤0.06	0.25	≤0.06–>8	-/-(94.2)
	Cefepime	≤0.12	0.25	≤0.12–>16	94.2/3.9
	Ceftriaxone	≤0.25	≤0.25	≤0.25–>32	91.3/7.8
	Ceftazidime	≤1	≤1	≤1–>16	92.2/7.8
	Imipenem	≤0.12	0.25	≤0.12–0.5	100.0/0.0
	Levofloxacin	≤0.5	>4	≤0.5–>4	68.0/31.1
	Tetracycline	≤2	>8	≤2–>8	71.8/28.2
	Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5–>2	73.8/26.2

[a] Criteria of CLSI M100-S19 (2009). [b] - = no established breakpoint for the drug or category. [c] % at ≤4 mg/L for comparison purposes only.

- Ceftobiprole was active against wild-type (WT) populations of *Klebsiella* species, *Enterobacter* species, *Serratia* species, and *E. coli* (all MIC_{50}, ≤0.06 mg/L; **Table 2**). Also this anti-MRSA cephem was quite potent versus *Citrobacter* species (MIC_{90}, 2 mg/L), *Proteus mirabilis* (MIC_{90}, ≤0.06 mg/L), and *Moraxella catarrhalis* (MIC_{90}, 0.12 mg/L; data not shown).
- Ceftobiprole, in contrast to Enterobacteriaceae results above (**Table 2**), had limited coverage of *P. aeruginosa* (MIC_{50}, 4 mg/L), *Acinetobacter* species (MIC_{50}, >8 mg/L), and *S. maltophilia* (MIC_{50}, >8 mg/L; data not shown).
- **Table 3** illustrates that ceftobiprole has significantly less activity (MIC_{50}, >8 mg/L) against *E. coli* and *Klebsiella* species isolates with an ESBL phenotype (see **Table 2**).

Table 3. Ceftobiprole MIC distributions against key pathogens in North America including resistance subsets (2005-2007)

	Cumulative % of inhibited at MIC (mg/L)							
Organism group (no. tested)	≤0.06	0.12	0.25	0.5	1	2	4	8
S. pneumoniae								
Penicillin-S (1,684)	82.1	86.9	97.7	99.9	100.0	-	-	-
Penicillin-NS (218)	0.5	0.5	20.2	88.1	100.0	-	-	-
S. aureus								
MSSA (396)	0.0	1.5	62.9	100.0	-	-	-	-
MRSA (542)	0.0	0.0	0.2	20.7	81.6	100	-	-
H. influenzae								
BLT- (647)	98.6	100.0	-	-	-	-	-	-
BLT+ (234)	97.4	98.7	100.0	-	-	-	-	-
E. coli								
ESBL (11)	18.2	27.3	27.3	27.3	36.4	36.4	45.5	45.5
Klebsiella species								
ESBL (446)	0.0	0.0	0.0	2.2	4.4	4.4	6.5	13

BLT = β-lactamase test, S = susceptible, NS = non-susceptible, MRSA = methicillin-resistant, MSSA = methicillin-S, ESBL = phenotype per CLSI criteria (2009), could include KPC or pAmp C enzymes.

Conclusions

- **Ceftobiprole demonstrated high potencies against bacterial pathogens associated with CAP.**
  - **– *S. pneumoniae* (all MIC values at ≤1 mg/L)**
  - **– *H. influenzae* (all MIC values at ≤0.25 mg/L)**
  - **– *S. aureus* (all MIC values at ≤2 mg/L)**
- **WT Enterobacteriaceae were very ceftobiprole-susceptible (MIC_{50}, ≤0.06 mg/L), but MIC_{90} results were compromised by hydrolysis caused by prevalent β-lactamases (ESBL, pAmp C, hyper-expressed Amp C, serine carbapenemases).**
- **Ceftobiprole coverage (% susceptible) of the most common non-fermentative Gram-negative bacilli was limited (MIC_{90} results at >8 mg/L).**
- **Many North American CAP isolates (2005-2007) remain highly susceptible to ceftobiprole.**

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