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Antimicrobial Activity of Ceftobiprole, a Novel Anti–Methicillin-Resistant *S. aureus* (MRSA) Cephalosporin, Tested Against Skin and Skin-Structure Infection Pathogens (North America)

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Amended Abstract

Objectives: To establish ceftobiprole (BPR) activity for this parenteral cephalosporin approved in four countries and under European and US regulatory review for complicated skin and skin-structure infections (SSSI). 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 SSSI pathogens in North America (NA) are presented.

Methods: Non-duplicate clinically-significant SSSI isolates (1,472) were collected from over 28 medical centers in NA participating in a BPR surveillance program (2005-2007). Identifications were confirmed by the central monitoring laboratory and all isolates were susceptibility (S) tested using CLSI methods.

Results:

	MIC_{90} in mg/L (% at ≤2/≤4/≤8 mg/L)		
Species (no. tested)	BPR	CRO[a] or CAZ[b]	FEP
S. aureus (SA; 896)	1 (100/-/-)	>32 (15/49/51)[a]	>16 (40/57/76)
P. aeruginosa (PSA; 100)	8 (67/79/92)	>16 (66/83/87)[b]	8 (60/76/90)
E. coli (EC; 99)	≤0.06 (96/97/97)	≤1 (97/98/98)[b]	0.25 (98/98/98)
E. faecalis (EF; 60)	1 (100/-/-)	-	-
β-hemolytic streptococci (BHS; 52)	≤0.06 (100/-/-)	≤0.25 (100/-/-)[a]	≤0.12 (100/-/-)
Enterobacter spp. (ESP; 54)	8 (83/89/93)	>16 (63/65/70)[b]	4 (89/96/98)
Klebsiella spp. (KSP; 42)	>8 (83/83/83)	>16 (86/88/88)[b]	2 (90/90/90)
P. mirabilis (31)	≤0.06 (100/-/-)	≤1 (97/100/-)[b]	≤0.12 (100/-/-)

[a]CRO = ceftriaxone, [b]CAZ = ceftazidime, FEP = cefepime

BPR inhibited all SA, EF and BHS at ≤2, ≤1, and ≤0.12 mg/L, respectively. MIC_{90} values for oxacillin (OXA)-R SA strains were two-fold higher than for OXA-S strains (1 versus 0.5 mg/L). Coverage against EC was nearly identical for the three agents (Table; 97-98% inhibited at ≤4 mg/L). Whereas 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, although the % inhibited for these agents at ≤2/≤4/≤8 mg/L was similar (67-92/60-90/66-87%, respectively).

Conclusions: Ceftobiprole is a new β-lactam with recognized activity against NA SSSI pathogens, similar to that of extended-spectrum cephems but including MRSA. These characteristics warrant continued evaluation of ceftobiprole as empiric therapy for SSSI, including Gram-negative pathogens.

Introduction

Ceftobiprole, an expanded spectrum cephalosporin with potent activity against commonly occurring Gram-positive and –negative bacterial pathogens including resistant strains is under regulatory review for the treatment of complicated skin and skin-structure infections (SSSI) in a number of countries around the world. It has been approved for this indication in four countries including Canada and Switzerland. Additionally it is currently under development for community- and hospital-acquired pneumonia. The compound is stable to many commonly occurring β-lactamases, and has a strong affinity for penicillin-binding proteins (PBP), including PBP2 (PBP2a), which mediates resistance to β-lactams in methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci (MR-CoNS). It is therefore an attractive new therapeutic option given this unique spectrum, broad safety profile characteristic of most β-lactams, and predominant bactericidal activities. Ceftobiprole is also known to display *in vitro* activity against most Enterobacteriaceae and *Pseudomonas aeruginosa*, similar to that of advanced generation cephems and β-lactam/β-lactamase inhibitor combinations.

Options for successful antimicrobial treatment of SSSI are complicated by patient-specific risk factors (age, severity of disease, underlying co-morbidities, allergies), spectrum of pathogens responsible, organism-specific resistances (innate or acquired), pharmacokinetic/pharmacodynamic parameters of the drugs being utilized, and the anatomic site being targeted. Of all characteristics that may result in clinical failure, selection for, or acquisition of, resistance among the offending pathogens to existing antimicrobial agents is known to occur rapidly and spread globally, resulting in rising healthcare costs. With these changes there is a critical need to modify, and add to, our antimicrobial therapeutic armamentarium.

As ceftobiprole moves through the clinical development pathway, surveillance to detect emerging antimicrobial resistance becomes necessary to further characterize the spectrum and potency of this agent against contemporary SSSI pathogens. In this study, *in vitro* testing results from a global surveillance program were summarized for 2005 to 2007 in North America comparing activity with that of β-lactam agents and members of other antimicrobial classes used in the empiric or directed therapy of cutaneous infections.

Materials and Methods

Bacterial Strains Tested

Nearly 1,500 non-duplicate, consecutive clinical isolates were submitted from more than 28 sites annually, located in North America (USA and Canada). Those isolates (years 2005-2007) originated from patients having documented SSSI and were either nosocomial or community-acquired. Isolates were predominantly from adults (≥18 years) and mostly from male patients. Species identifications were performed by the submitting laboratories with confirmation performed by the central laboratory monitor. 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 NCCLS) methods.

Susceptibility Testing Methods

All strains were tested by the CLSI broth microdilution method using validated commercially prepared panels (TREK Diagnostics, Cleveland, Ohio, USA) in cation-adjusted Mueller-Hinton broth (with 5% lysed horse blood added for testing of streptococci or Haemophilus Test Medium for testing of other fastidious species) against a variety of antimicrobial agents representing the most common classes and examples of drugs used in the empiric or directed treatment of the SSSI indication. 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 and *P. aeruginosa* ATCC 27853,

Results

- *S. aureus* (**Table 1**) was the dominant pathogen recorded from this series of SSSI cases (60.9%; 50.0% MRSA, **Table 2**), and other Gram-positive species were enterococci (5.7%) and β-hemolytic streptococci (3.5%).

Table 1. Rank order of SSSI bacterial pathogens observed in the ceftobiprole surveillance program in North America (2005-2007); 1,472 isolates

Rank	Organism (no. isolates)	%
1.	*S. aureus* (896)	60.9
2.	*P. aeruginosa* (100)	6.8
3.	*E. coli* (99)	6.7
4.	*Enterococci* (84)	5.7
5.	*Enterobacter* species (54)	3.7
6.	β-hemolytic streptococci (52)	3.5
7.	*Klebsiella* species (42)	2.9
8.	*P. mirabilis* (31)	2.1
9.	*Acinetobacter* species (20)	1.4
10.	*Serratia* species (20)	1.4
11.	Others (74)	5.0

Table 2. Comparative *in vitro* antimicrobial activity of ceftobiprole tested against Gram-positive species among the top 10 pathogens (95.0% of isolates) associated with SSSI in North America

Organism (no. tested)	Antimicrobial agent	MIC (mg/L) 50%	90%	Range	% by category[a] Susceptible/Resistant
S. aureus (896)	Ceftobiprole	0.5	1	≤0.06–2	-/- (100.0)[c]
	Oxacillin	2	>2	≤0.25–>2	50.0/50.0
	Daptomycin	0.25	0.5	≤0.06–1	100.0/-
	Levofloxacin	≤0.5	>4	≤0.5–>4	65.4/33.8
	Linezolid	1	2	0.12–2	100.0/-
	Tetracycline	≤2	≤2	≤2–>8	94.5/4.9
	Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5–>2	99.0/0.9
	Vancomycin	1	1	0.25–>2	100.0/0.0
E. faecalis (60)	Ceftobiprole	0.25	1	0.12–2	-/- (100.0)
	Ampicillin	≤1	2	≤1–2	100.0/0.0
	Daptomycin	1	1	0.25–2	100.0/0.0
	Gentamicin HL[d]	≤500	1000	≤500–>1000	76.7/23.3
	Levofloxacin	1	>4	≤0.5–>4	75.0/23.3
	Linezolid	1	2	0.5–2	100.0/0.0
	Quinupristin/dalfopristin	>2	>2	2–>2	0.0/95.0
	Teicoplanin	≤2	≤2	≤2–>16	98.3/1.7
	Vancomycin	1	2	0.5–>16	98.3/1.7
E. faecium (24)	Ceftobiprole	>8	>8	2–>8	-/- (12.5)
	Ampicillin	>16	>16	≤1–>16	12.5/87.5
	Daptomycin	2	2	0.5–4	100.0/-
	Gentamicin HL[d]	≤500	>1000	≤500–>1000	50.0/50.0
	Levofloxacin	>4	>4	≤0.5–>4	12.5/87.5
	Linezolid	1	2	1–2	100.0/0.0
	Quinupristin/dalfopristin	1	2	≤0.25–2	87.5/0.0
	Teicoplanin	>16	>16	≤2–>16	37.5/54.2
	Vancomycin	>16	>16	0.5–>16	33.3/66.7
S. pyogenes (31)	Ceftobiprole	≤0.06	≤0.06	≤0.06	-/- (100.0)
	Cefepime	≤0.12	≤0.12	≤0.12	100.0/-
	Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0/-
	Penicillin	≤0.015	≤0.015	≤0.015	100.0/-
	Erythromycin	≤0.25	≤0.25	≤0.25–2	96.8/3.2
	Clindamycin	≤0.25	≤0.25	≤0.25	100.0/0.0
	Levofloxacin	≤0.5	≤0.5	≤0.5–1	100.0/0.0
	Linezolid	0.5	1	0.25–2	100.0/-
	Vancomycin	0.25	0.5	0.25–0.5	100.0/-
S. agalactiae (13)	Ceftobiprole	≤0.06	≤0.06	≤0.06	-/- (100.0)
	Cefepime	≤0.12	≤0.12	≤0.12	100.0/-
	Ceftriaxone	≤0.25	0.25	≤0.25	100.0/-
	Penicillin	0.03	0.06	≤0.015–0.06	100.0/-
	Erythromycin	≤0.25	>2	≤0.25–>2	69.2/30.8
	Clindamycin	≤0.25	>2	≤0.25–>2	84.6/15.4
	Levofloxacin	≤0.5	1	≤0.5–1	100.0/-
	Linezolid	1	1	0.5–1	100.0/-
	Vancomycin	0.5	0.5	0.25–0.5	100.0/-
CoNS (16)	Ceftobiprole	0.5	1	0.12–1	-/- (100.0)
	Oxacillin	1	>2	≤0.25–>2	37.5/62.5
	Daptomycin	0.25	0.5	0.12–0.5	100.0/-
	Levofloxacin	≤0.5	>4	≤0.5–>4	62.5/25.0
	Linezolid	0.5	1	0.5–1	100.0/-
	Tetracycline	≤2	>8	≤2–>8	87.5/12.5
	Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5–>2	87.5/12.5
	Vancomycin	1	2	0.5–2	100.0/0.0

[a] Susceptibility breakpoints of the CLSI M100-S19 (2009), where available.
[b] - = no established breakpoint for the drug or category.
[c] % of ceftobiprole MICs at ≤4 mg/L for comparison purposes only.
[d] HL = high-level aminoglycoside resistance.

- Ceftobiprole was very active against all *S. aureus* (MIC_{90}, 1 mg/L; all MIC results at ≤2 mg/L), ampicillin-susceptible *Enterococcus faecalis* (MIC_{90}, 1 mg/L), *Streptococcus pyogenes* and *Streptococcus agalactiae* (MIC_{90}, ≤0.06 mg/L), and a limited number (16) of CoNS (MIC_{90}, 1 mg/L; see **Table 2**).
- Daptomycin, linezolid, and vancomycin also exhibited excellent coverage of Gram-positive pathogens, except vancomycin when tested against *Enterococcus faecium* (33.3% susceptibility; **Table 2**).
- **Table 3** shows ceftobiprole potencies tested against 7 of the top 10 SSSI pathogens (366 Gram-negative bacilli). Ceftobiprole was active against *E. coli, Enterobacter* species, *Klebsiella* species, *Proteus mirabilis,* and *Serratia* species (MIC_{50} results at ≤0.06 mg/L), but had decreased potency versus *P. aeruginosa* ($MIC_{50/90}$, 2/8 mg/L, and *Acinetobacter* species ($MIC_{50/90}$, >8/>8 mg/L).
- Resistant subsets shown in **Table 4** note the excellent ceftobiprole activity against MRSA (MIC_{90}, 1 mg/L). However, ESBL phenotype strains of *E. coli* and *Klebsiella* species were generally resistant to ceftobiprole, having MIC_{50} and MIC_{90} values at >8 mg/L.
- Other tested agents having broad-spectrum coverage of the Gram-negative SSSI pathogens were: cefepime (MIC_{90} range, ≤0.12–8 mg/L), and imipenem (MIC_{90} range, 0.25–8 mg/L). The above ranges exclude *Acinetobacter* species where the susceptibility rates were only 30.0–45.0 %, except for polymyxin B (100.0%).

Table 3. Comparative *in vitro* antimicrobial activity of ceftobiprole tested against Gram-negative species among the top 10 pathogens (95.0% of isolates) associated with SSSI in North America

Organism (no. tested)	Antimicrobial agent	MIC (mg/L) 50%	90%	Range	% by category[a] Susceptible/Resistant
P. aeruginosa (100)	Ceftobiprole	2	8	0.25–>8	-/- (79.0)[c]
	Cefepime	2	8	0.25–>16	90.0/3.0
	Ceftazidime	2	>16	≤1–>16	87.0/13.0
	Imipenem	2	8	0.25–>8	86.0/9.0
	Piperacillin/tazobactam	4	>64	≤0.5–>64	88.0/12.0
	Amikacin	2	4	0.5–>32	97.0/2.0
	Levofloxacin	≤0.5	>4	≤0.5–>4	75.0/20.0
	Polymyxin B	1	1	≤0.5–2	100.0/-
E. coli (99)	Ceftobiprole	≤0.06	≤0.06	≤0.06–>8	-/- (97.0)
	Cefepime	≤0.12	0.25	≤0.12–>16	98.0/1.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25–>32	96.0/4.0
	Ceftazidime	≤1	≤1	≤1–16	98.0/2.0
	Imipenem	0.25	0.25	≤0.12–1	100.0/0.0
	Levofloxacin	≤0.5	>4	≤0.5–>4	75.8/24.2
	Tetracycline	≤2	>8	≤2–>8	66.7/32.3
	Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5–>2	68.7/31.3
Enterobacter species (54)	Ceftobiprole	≤0.06	8	≤0.06–>8	-/- (89.0)
	Cefepime	≤0.12	4	≤0.12–16	98.2/0.0
	Ceftriaxone	≤0.25	>32	≤0.25–>32	61.1/37.0
	Ceftazidime	≤1	>16	≤1–>16	63.0/37.0
	Imipenem	0.5	1	≤0.12–>8	96.3/1.9
	Levofloxacin	≤0.5	4	≤0.5–>4	89.0/9.3
	Tetracycline	≤2	8	≤2–>8	87.0/7.4
	Trimethoprim/sulfamethoxazole	≤0.5	1	≤0.5–>2	87.0/9.3
Klebsiella species (42)	Ceftobiprole	≤0.06	>8	≤0.06–>8	-/- (83.3)
	Cefepime	≤0.12	2	≤0.012–>16	90.5/4.8
	Ceftriaxone	≤0.25	16	≤0.25–>32	85.7/14.3
	Ceftazidime	≤1	>16	≤1–>16	88.1/11.9
	Imipenem	0.25	0.5	≤0.12–>8	92.9/2.4
	Levofloxacin	≤0.5	≤0.5	≤0.5–>4	92.9/7.1
	Tetracycline	≤2	4	≤2–>8	90.5/9.5
	Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5–>2	85.7/14.3
P. mirabilis (31)	Ceftobiprole	≤0.06	≤0.06	≤0.06–>2	-/- (100.0)
	Cefepime	≤0.12	≤0.12	≤0.12–0.5	100.0/0.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25–2	96.8/0.0
	Ceftazidime	≤1	≤1	≤1–4	100.0/0.0
	Imipenem	0.5	2	≤0.12–4	100.0/0.0
	Levofloxacin	≤0.5	2	≤0.5–>4	96.8/3.2
	Tetracycline	>8	>8	0.0/100.0	
	Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5–>2	93.6/6.4
Serratia species (20)	Ceftobiprole	≤0.06	0.12	≤0.06–0.5	-/- (100.0)
	Cefepime	≤0.12	0.25	≤0.12–0.25	100.0/0.0
	Ceftriaxone	≤0.25	1	≤0.25–2	95.0/0.0
	Ceftazidime	≤1	≤1	≤1	100.0/0.0
	Imipenem	0.5	1	0.25–2	100.0/0.0
	Levofloxacin	≤0.5	1	≤0.5–>4	95.0/5.0
	Tetracycline	>8	>8	8–>8	0.0/70.0
	Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5–>2	90.0/10.0
Acinetobacter species (20)	Ceftobiprole	>8	>8	0.12–>8	-/- (45.0)
	Cefepime	>16	>16	1–>16	35.0/60.0
	Ceftazidime	>16	>16	4–>16	35.0/60.0
	Imipenem	8	>8	≤0.12–>8	45.0/40.0
	Ampicillin/sulbactam	16	>16	≤2–>16	40.0/35.0
	Piperacillin/tazobactam	>64	>64	≤0.5–>64	30.0/60.0
	Levofloxacin	>4	>4	≤0.5–>4	35.0/65.0
	Polymyxin B	≤0.5	≤0.5	≤0.5–2	100.0/0.0

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

Conclusions

- **Ceftobiprole showed broad-spectrum activity against North American isolates of pathogens associated with SSSI, with greatest potency demonstrated against *S. aureus* (MIC_{90}, 1 mg/L), *E. faecalis* (MIC_{90}, 1 mg/L), and streptococcal species (MIC_{90}, ≤0.06 mg/L)**
- **The clear majority of Enterobacteriaceae were also inhibited by ceftobiprole, an activity most like those of ceftriaxone and ceftazidime.**
- **Ceftobiprole had more limited activity against *P. aeruginosa* and *Acinetobacter* species, eg, 120 of 1,472 strains (8.2% of SSSI isolates). Also some ESBL, serine carbapenemases, and Amp C-expressing strains may be resistant to ceftobiprole, as well as other parenteral cephalosporins.**
- **Ceftobiprole exhibits excellent coverage of Gram-positive pathogens including MRSA, and has activity against Gram-negative bacilli found in complicated SSSI comparable to the "third- or fourth-generation" cephalosporins. Monitoring of this novel parenteral agent should be sustained.**

Table 4. Ceftobiprole MIC distributions tested against selected resistance subsets among SSSI isolates from North America (2005-2007)

Organism Group (no. tested)	Cumulative % inhibited at MIC (mg/L) ≤0.06	0.12	0.25	0.5	1	2	4	8
MRSA (448)	0.2	0.2	0.5	20.3	93.5	100	-	-
E. coli, ESBL[a] (4)	0	0	0	25	25	25	25	25
Klebsiella species, ESBL[a] (7)	0	0	0	0	0	0	0	0

[a] ESBL criteria of the CLSI (MIC at ≥2 mg/L for aztreonam and/or ceftazidime and/or ceftriaxone).

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