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Antimicrobial Activity of Ceftobiprole Tested Against Leading European Bacterial Pathogens: Results From an International Surveillance Program (2005-2006)

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Abstract

Objectives: To evaluate potency of ceftobiprole (BPR) against the most serious and commonly occurring Gram-positive and -negative pathogens isolated in Europe. BPR, an investigational parenteral cephalosporin, is currently under regulatory review following completion of Phase 3 clinical trials. This agent is uniquely active against oxacillin-resistant (OXA-R) *Staphylococcus aureus* (MRSA), as well as other Gram-positive and -negative pathogens, making it an attractive candidate for broad-spectrum therapy.

Methods: Consecutive, non-duplicate isolates (17,206) from bloodstream, skin and skin-structure and respiratory tract infections were collected from medical centers in Europe (23), Turkey (2), and Israel (1) participating in the BPR Surveillance Program during 2005-2006. Identifications were confirmed by the central monitoring laboratory and all isolates were susceptibility (S) tested using CLSI methods against BPR and comparator agents.

Results: Results are in the Table. Among SA (27% OXA-R) and CoNS (75% OXA-R) isolates tested, BPR inhibited 100% at ≤4 and ≤8 mg/L, respectively. While BPR MIC_{90} values for OXA-R strains were elevated over those of OXA-S strains (8-fold), MIC_{90} values for other cephalosporins correspondingly increased ≥32-fold. BPR was 4-fold more potent when testing β-haemolytic streptococci (BHS) and SPN compared with ceftriaxone (CRO) or cefepime (FEP); all BHS were inhibited at ≤0.25 mg/L and >99% of SPN by 0.5 mg/L. BPR was similar in potency to ceftazidime (CAZ) and FEP (MIC_{50} values, ≤1 mg/L) against tested Enterobacteriaceae; coverage against EC was nearly identical for the three agents (94-95% inhibited at ≤4 mg/L). FEP provided enhanced coverage against KSP (90% at ≤8 mg/L vs. 78-84% for BPR and CAZ), although BPR and FEP had lower MIC values than CAZ against ESP. Cephalosporins were largely inactive against ESBL-producing EC and KSP. BPR was equal in potency to CAZ (MIC_{50}, 2 mg/L) against PSA and 2-fold more potent than FEP, although % inhibited for these agents at ≤2/4/8 mg/L were similar. None of these agents inhibited >49% of ASP at 8 mg/L.

	MIC_{90} (% at ≤2/4/8 mg/L)		
Species (no. tested)	BPR	CRO or CAZ	FEP
S. aureus (SA; 4028)	1 (>99/100/-)	>32 (39/72/75)[a]	>16 (66/76/81)
Coagulase-negative staphylococci (CoNS; 1840)	2 (93/>99/100)	>32 (22/33/47)[a]	>16 (41/62/77)
S. pneumoniae (SPN; 1528)	0.25 (100/-/-)	1 (>99/>99/100)[a]	1 (>99/>99/>99)
E. coli (EC; 2779)	0.12 (93/94/94)	≤1 (93/94/95)[b]	0.25 (94/95/96)
Klebsiella spp. (KSP; 883)	>8 (77/78/78)	>16 (80/81/84)[b]	16 (84/87/90)
Enterobacter spp. (ESP; 571)	>8 (81/84/87)	>16 (66/68/70)[b]	4 (88/92/96)
P. aeruginosa (PSA; 984)	>8 (54/65/79)	>16 (56/69/76)[b]	16 (49/66/80)
Acinetobacter spp. (ASP; 320)	>8 (41/41/42)	>16 (15/32/39)[b]	>16 (26/37/49)

[a] ceftriaxone; [b] ceftazidime

Conclusions: Ceftobiprole displays prominent activity against European staphylococci, including OXA-R strains. The compound also displayed activity against Enterobacteriaceae, similar to that of extended-spectrum cephalosporins, as well as against some non-fermentative bacilli. Given the breadth of its spectrum, ceftobiprole may be useful in those European institutions/regions where MRSA and PSA are both prevalent.

Introduction

Emergence of resistance among commonly occurring bacterial pathogens has limited the utility of many penicillins, cephalosporins, and other antimicrobial classes, driving increased utilization of carbapenems for Gram-negatives and vancomycin, daptomycin, and linezolid for Gram-positive pathogens. The recent appearance of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is especially worrisome given the rapidity of clonal spread that has occurred, enhanced pathogenicity features, and the occurrence of such pathogens in populations without usual risk factors. There is a paucity of broad-spectrum agents in development that are able to simultaneously target resistant subsets of both Gram-positive and -negative species.

Ceftobiprole (previously known as BAL9141), an expanded-spectrum pyrrolidinone-3-ylidene-methyl cephalosporin has completed Phase 3 clinical development for the treatment of complicated skin and skin-structure infections (cSSSI), and is under regulatory review for this indication. This agent demonstrates antimicrobial qualities similar to those of the "third and fourth generation" cephalosporins, by being stable to most commonly-occurring Class A and some Class C β-lactamases and has a strong affinity for penicillin-binding proteins, including PBP2a which mediates resistance to β-lactams in methicillin-resistant staphylococci, and PBP2x which mediates penicillin resistance in *Streptococcus pneumoniae*. Ceftobiprole is bactericidal against staphylococci, and is associated with a very low frequency of emergent resistance among *S. aureus* strains. Ceftobiprole is also known to display activity against most Enterobacteriaceae, *Pseudomonas aeruginosa*, and many other species, including anaerobes. These characteristics make ceftobiprole an attractive therapeutic candidate given this unique spectrum, broad safety profile characteristic of most β-lactams, and predominantly bactericidal activities.

Previous *in-vitro* studies have focused on more limited populations of targeted species, including resistant subsets (especially MRSA), and have not presented a systematic overview of a large geographic sampling of isolates. Here we examine the susceptibility profiles and antibiograms of ceftobiprole and comparator agents tested against contemporary European clinical isolates (17,206) collected in a prevalence mode format during 2005-2006 as part of a longitudinal international resistance surveillance protocol.

Materials and Methods

Bacterial Isolates

Consecutive, non-duplicate clinically significant isolates (17,206) were submitted from laboratories in Europe (23), Turkey (2), and Israel (1) as part of a global antimicrobial resistance surveillance network and were tested in a central laboratory (JMI Laboratories, North Liberty, IA, USA) using reference methodologies. Isolates originated from patients with documented bloodstream, respiratory and skin and skin-structure infections. The distribution of leading species and strains is presented in **Table 1**.

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 *Haemophilus 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. Enterobacteriaceae with elevated MICs (≥2 mg/L) for ceftazidime and/or ceftriaxone and/or aztreonam were considered as extended-spectrum β-lactamase-producing phenotypes. Quality control strains utilized included *Escherichia coli* ATCC 25922 and 35218, *P. aeruginosa* ATCC 27853, *H. influenzae* ATCC 49247, *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29213 and *S. pneumoniae* ATCC 49619.

Results

- Ceftobiprole inhibited 100% and >99% of tested *S. aureus* and coagulase-negative staphylococci (CoNS) at 4 mg/L, respectively, although MIC_{90} values for oxacillin-resistant strains were 4- and 8-fold higher than oxacillin-susceptible isolates for the two groups (**Tables 1** and **2**).
- Ceftobiprole was also broadly active against *S. pneumoniae* and β-haemolytic streptococci, inhibiting 100% of isolates at ≤0.5 mg/L; some viridans group streptococci that originated from pediatric patients in Turkey had elevated ceftobiprole MIC values (>8 mg/L; 3.8%) and were clonally related.
- While the majority of *E. faecalis* strains (94.8%) were inhibited by ceftobiprole at ≤4 mg/L, the agent was generally inactive against *Enterococcus faecium*.
- Ceftobiprole was similar in potency to the "third- and fourth-generation" cephems (MIC_{50} values, ≤0.06 mg/L) for the tested Enterobacteriaceae but, similar to these other agents, was generally inactive against ESBL-producing strains (up to 8.0% of *E. coli* and 22.9% of *Klebsiella* spp. based upon phenotype; **Table 3**).
- Whereas cefepime provided enhanced coverage against *Klebsiella* spp. (89.6% at ≤8 mg/L vs. 78.1-83.6% for ceftobiprole and ceftazidime, respectively), ceftobiprole and cefepime were superior to ceftazidime against *Enterobacter* spp. and *Citrobacter* spp.
- Against *P. aeruginosa*, ceftobiprole was equal in potency to ceftazidime (MIC_{50}, 2 mg/L) and 2-fold more active than cefepime; the percentages inhibited at ≤2/4/8 mg/L were similar among the three agents (54/65/79, 56/69/76 and 49/66/80, respectively; **Table 3**).
- None of these agents inhibited greater than 49% of *Acinetobacter* spp. at 8 mg/L; among comparator agents, only polymyxin B was uniformly active (>99% susceptible).
- *H. influenzae* were inhibited by all (100%) tested agents at current breakpoints except for ampicillin (84.6% susceptible; β-lactamase–negative, ampicillin-resistant strains were not detected), tetracycline (98.2%) and trimethoprim/sulfamethoxazole (72.7%). Ceftobiprole inhibited all strains at ≤0.25 mg/L.

Table 2. Antimicrobial activity of ceftobiprole and selected comparison agents tested against Gram-positive pathogens collected from European patients as part of the SENTRY Antimicrobial Surveillance program (2005-2006)

	MIC (mg/L)		Percentage by category
Organism/Antimicrobial agent (no. tested)	50%	90%	Susceptible/Resistant[a]
S. aureus (4028)			
Ceftobiprole	0.25	1	- / -[b]
Cefepime	2	>16	81.0 / 17.5
Ceftazidime	8	>16	71.8 / 22.5
Ceftriaxone	4	>32	74.6 / 17.6
Daptomycin	0.25	0.5	100.0 / -
Levofloxacin	≤0.5	>4	70.6 / 28.6
Linezolid	1	2	>99.9 / -
Oxacillin	0.5	>2	73.0 / 27.0
Tetracycline	≤2	≤2	91.4 / 7.8
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	98.6 / 1.4
Vancomycin	1	1	100.0 / 0.0
Coagulase-negative staphylococci (1840)			
Ceftobiprole	0.5	2	- / -
Cefepime	4	>16	76.8 / 15.2
Ceftazidime	16	>16	31.6 / 42.2
Ceftriaxone	16	>32	47.4 / 18.8
Daptomycin	0.25	0.5	99.7 / -
Levofloxacin	4	>4	42.0 / 50.0
Linezolid	1	1	99.9 / -
Oxacillin	>2	>2	25.4 / 74.6
Tetracycline	≤2	>8	82.0 / 16.5
Trimethoprim/sulfamethoxazole	≤0.5	>2	61.7 / 38.3
Vancomycin	1	2	100.0 / 0.0
E. faecalis (1062)			
Ceftobiprole	0.5	4	- / -
Ampicillin	≤1	2	99.1 / 0.9
Daptomycin	0.5	1	100.0 / -
Gentamicin (HL)	≤500	>1000	70.6 / 29.4
Levofloxacin	1	>4	66.9 / 32.5
Linezolid	1	2	100.0 / 0.0
Teicoplanin	≤2	≤2	99.4 / 0.5
Vancomycin	1	2	99.3 / 0.6
S. pneumoniae (1528)			
Ceftobiprole	≤0.06	0.25	- / -
Cefepime	≤0.12	1	97.6 / 0.2
Ceftriaxone	≤0.25	1	98.8 / 0.3
Clindamycin	≤0.25	>2	78.2 / 21.3
Ertapenem	≤1	≤1	100.0 / 0.0
Erythromycin	≤0.25	>2	68.5 / 31.0
Imipenem	≤0.12	0.25	84.1 / 1.2
Levofloxacin	1	1	97.8 / 2.0
Linezolid	1	1	100.0 / -
Penicillin	≤0.03	2	97.8 / 0.1[c]
Vancomycin	≤1	≤1	100.0 / -
β-haemolytic streptococci (673)			
Ceftobiprole	≤0.06	≤0.06	- / -
Cefepime	≤0.12	≤0.12	99.7 / -
Ceftriaxone	≤0.25	≤0.25	99.7 / -
Clindamycin	≤0.25	≤0.25	91.8 / 8.2
Daptomycin	≤0.06	0.25	100.0 / -
Erythromycin	0.25	>2	79.5 / 20.1
Levofloxacin	≤0.5	1	99.7 / 0.3
Linezolid	1	1	100.0 / -
Penicillin	≤0.015	0.06	100.0 / -
Vancomycin	0.25	0.5	100.0 / -
Viridans group streptococci (365)			
Ceftobiprole	≤0.06	0.5	- / -
Cefepime	≤0.12	2	89.0 / 8.0
Ceftriaxone	≤0.25	2	89.0 / 8.2
Clindamycin	≤0.25	1	89.9 / 10.1
Daptomycin	0.25	0.5	100.0 / -
Erythromycin	≤0.25	>2	62.7 / 34.5
Levofloxacin	1	1	98.1 / 1.6
Linezolid	0.5	1	100.0 / -
Penicillin	0.06	2	77.0 / 8.5
Vancomycin	0.5	0.5	100.0 / -

[a] Breakpoint criteria are those from CLSI [2008]; [b] = no breakpoint established.
[c] Breakpoints are for penicillin (parenteral) non-meningitis; CLSI M100-S18 [2008].

Table 3. *In-vitro* activity of ceftobiprole in comparison to selected antimicrobial agents tested against ranking Gram-negative pathogens collected from European patients as part of the SENTRY Antimicrobial Surveillance program (2005-2006)

	MIC (mg/L)		Percentage by category
Organism/Antimicrobial agent (no. tested)	50%	90%	Susceptible/Resistant[a]
E. coli (2779)			
Ceftobiprole	≤0.06	0.12	- / -[b]
Ampicillin	>16	>16	46.1 / 53.2
Cefepime	≤0.12	0.25	96.0 / 3.1
Ceftazidime	≤1	≤1	95.4 / 2.7 (8.0)[c]
Ceftriaxone	≤0.25	≤0.25	93.6 / 5.8 (7.3)
Imipenem	≤0.12	0.25	100.0 / 0.0
Levofloxacin	≤0.5	>4	78.9 / 17.4
Piperacillin/tazobactam	2	8	93.8 / 2.6
Tetracycline	≤2	>8	63.0 / 36.3
Trimethoprim/sulfamethoxazole	≤0.5	>2	69.0 / 31.0
Klebsiella spp. (883)			
Ceftobiprole	≤0.06	>8	- / -
Ampicillin	>16	>16	5.0 / 79.2
Cefepime	≤0.12	16	89.6 / 7.8
Ceftazidime	≤1	>16	83.6 / 13.5 (22.2)
Ceftriaxone	≤0.25	>32	82.0 / 12.5 (22.9)
Imipenem	0.25	0.5	98.9 / 0.6
Levofloxacin	≤0.5	>4	87.4 / 10.8
Piperacillin/tazobactam	2	>64	82.1 / 13.7
Tetracycline	≤2	>8	79.6 / 18.5
Trimethoprim/sulfamethoxazole	≤0.5	>2	79.8 / 20.2
Enterobacter spp. (571)			
Ceftobiprole	≤0.06	>8	- / -
Ampicillin	>16	>16	6.1 / 85.6
Cefepime	≤0.12	4	96.0 / 3.2
Ceftazidime	≤1	>16	70.0 / 25.3
Ceftriaxone	≤0.25	>32	72.2 / 16.5
Imipenem	0.5	2	97.4 / 1.1
Levofloxacin	≤0.5	>4	85.3 / 12.3
Piperacillin/tazobactam	2	64	75.3 / 9.5
Tetracycline	≤2	8	83.7 / 9.5
Trimethoprim/sulfamethoxazole	≤0.5	>2	86.3 / 13.7
Proteus mirabilis (203)			
Ceftobiprole	≤0.06	≤0.06	- / -
Ampicillin	≤1	>16	62.6 / 37.4
Cefepime	≤0.12	≤0.12	97.5 / 2.5
Ceftazidime	≤1	≤1	96.6 / 3.0 (5.9)
Ceftriaxone	≤0.25	≤0.25	95.1 / 3.0 (5.9)
Imipenem	1	2	99.5 / 0.5
Levofloxacin	≤0.5	2	90.6 / 7.9
Piperacillin/tazobactam	≤0.5	1	98.5 / 0.0
Tetracycline	>8	>8	2.0 / 97.5
Trimethoprim/sulfamethoxazole	≤0.5	>2	66.0 / 34.0
Indole-positive Proteae (146)			
Ceftobiprole	≤0.06	>8	- / -
Ampicillin	>16	>16	20.5 / 78.1
Cefepime	≤0.12	≤0.12	97.9 / 1.4
Ceftazidime	≤1	2	93.8 / 2.1
Ceftriaxone	≤0.25	2	97.3 / 2.1
Imipenem	2	4	100.0 / 0.0
Levofloxacin	≤0.5	4	84.9 / 8.9
Piperacillin/tazobactam	≤0.5	2	99.3 / 0.7
Tetracycline	>8	>8	30.8 / 53.4
Trimethoprim/sulfamethoxazole	≤0.5	>2	80.1 / 19.9
Citrobacter spp. (115)			
Ceftobiprole	≤0.06	1	- / -
Ampicillin	>16	>16	8.7 / 77.4
Cefepime	≤0.12	1	98.3 / 0.9
Ceftazidime	≤1	>16	76.5 / 20.9
Ceftriaxone	≤0.25	32	75.7 / 7.8
Imipenem	0.5	1	99.1 / 0.0
Levofloxacin	≤0.5	2	92.2 / 7.0
Piperacillin/tazobactam	2	64	81.7 / 6.1
Tetracycline	≤2	>8	85.2 / 13.9
Trimethoprim/sulfamethoxazole	≤0.5	>2	82.6 / 17.4
Serratia spp. (205)			
Ceftobiprole	≤0.06	0.5	- / -
Ampicillin	>16	>16	4.4 / 86.8
Cefepime	≤0.12	1	98.0 / 2.0
Ceftazidime	≤1	2	96.1 / 3.4
Ceftriaxone	≤0.25	16	86.8 / 4.4
Imipenem	1	1	100.0 / 0.0
Levofloxacin	≤0.5	2	93.7 / 2.0
Piperacillin/tazobactam	2	32	82.4 / 2.0
Tetracycline	>8	>8	9.3 / 54.6
Trimethoprim/sulfamethoxazole	≤0.5	>2	89.3 / 10.7
P. aeruginosa (984)			
Ceftobiprole	2	>8	- / -
Amikacin	≤4	16	90.1 / 6.0
Aztreonam	8	>16	66.9 / 19.6
Cefepime	4	16	79.9 / 9.2
Ceftazidime	2	>16	75.9 / 18.7
Imipenem	1	>8	76.1 / 15.9
Levofloxacin	≤0.5	>4	69.2 / 26.5
Piperacillin/tazobactam	8	>64	83.4 / 16.6
Polymyxin B	1	1	99.5 / 0.5
Tobramycin	0.5	>16	79.7 / 19.3
Acinetobacter spp. (320)			
Ceftobiprole	>8	>8	- / -
Amikacin	>32	>32	46.3 / 50.6
Ampicillin/sulbactam	16	>16	49.4 / 40.6
Cefepime	16	>16	49.4 / 33.1
Ceftazidime	>16	>16	39.4 / 51.9
Imipenem	1	>8	68.1 / 28.4
Levofloxacin	4	>4	40.6 / 45.6
Piperacillin/tazobactam	>64	>64	40.0 / 52.5
Polymyxin B	≤0.5	≤0.5	99.4 / 0.6
Tobramycin	2	>16	55.0 / 41.9
Trimethoprim/sulfamethoxazole	>2	>2	41.6 / 58.4
H. influenzae (384)			
Ceftobiprole	≤0.06	≤0.06	- / -
Amoxicillin/clavulanate	≤1	≤1	100.0 / 0.0
Ampicillin	≤1	16	84.6 / 14.1
Cefepime	≤0.12	≤0.12	100.0 / -
Ceftriaxone	≤0.25	≤0.25	100.0 / -
Imipenem	0.5	1	100.0 / -
Levofloxacin	≤0.5	≤0.5	100.0 / -
Piperacillin/tazobactam	≤0.5	≤0.5	100.0 / 0.0
Tetracycline	≤2	≤2	98.2 / 1.0
Trimethoprim/sulfamethoxazole	≤0.5	>2	72.7 / 23.4

[a] Breakpoint criteria are those from CLSI [2008]; [b] = no breakpoint established. [c] Percentages in parentheses are those meeting CLSI [CLSI, 2008] ESBL screening criteria for MIC values ≥2 mg/L.

Table 1. Cumulative MIC frequency distributions of ceftobiprole when tested against ranking pathogens (17,206 total isolates) of contemporary isolates originating from patients in European medical centers (2005-2006)

	Cumulative % inhibited at each MIC (mg/L)							
Organism group (no. tested)	≤0.06	0.12	0.25	0.5	1	2	4	8
S. aureus (4028)	<1	2	55	78	92	>99	100	-
Oxacillin-susceptible (2942)	<1	3	75	>99	>99	100	-	-
Oxacillin-resistant (1086)	<1	<1	<1	20	70	97	100	-
Coagulase-negative staphylococci (1840)	6	19	30	55	83	93	>99	100
Oxacillin-susceptible (468)	20	71	98	100	-	-	-	-
Oxacillin-resistant (1372)	<1	1	6	39	77	91	>99	100
E. faecalis (1062)	<1	12	32	65	75	90	95	98
β-haemolytic streptococci (673)	>99	>99	100	-	-	-	-	-
S. pneumoniae (1528)	78	81	93	>99	>99	100	-	-
Viridans group streptococci (365)	77	86	90	91	93	95	96	96
E. coli (2779)	90	91	92	93	93	93	94	94
Klebsiella spp. (883)	63	68	72	74	76	77	78	78
Enterobacter spp. (571)	67	70	73	75	77	81	84	87
Citrobacter spp. (115)	70	76	77	84	91	96	96	96
Serratia spp. (205)	61	74	83	91	94	94	95	95
Salmonella spp. (59)	97	100	-	-	-	-	-	-
P. mirabilis (203)	92	93	94	95	96	96	96	97
Indole-positive Proteae (146)	74	74	74	74	74	74	74	75
P. aeruginosa (984)	<1	<1	1	6	34	54	65	79
Acinetobacter spp. (320)	9	16	25	35	39	41	41	42
H. influenzae (384)	98	>99	100	-	-	-	-	-

Conclusions

- **Among Gram-positive bacterial pathogens recovered from patients hospitalized in European medical centers (2005-2006), ceftobiprole inhibited all (100%) of tested *S. aureus* at ≤4 mg/L and CoNS at ≤8 mg/L; and all *S. pneumoniae*, all β-haemolytic streptococci and 91% of viridians group streptococci at ≤0.5 mg/L.**
- **Ceftobiprole also maintained activity against the most commonly occurring Enterobacteriaceae (exception, ESBL-positive strains) and many *P. aeruginosa*, being equal in potency to ceftazidime (MIC_{50}, 2 mg/L) and 2-fold more active than cefepime against this species.**
- **Ceftobiprole is unique among currently utilized cephalosporins in retaining activity against leading European pathogens responsible for skin and skin-structure, bloodstream, and community-associated respiratory tract infections, including those pathogens routinely resistant to other β-lactams such as MRSA and *E. faecalis* (Table 2).**
- **These characteristics warrant continued evaluation of the agent as empiric therapy, especially in those institutions/regions where MRSA and *P. aeruginosa* may be prevalent.**

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