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Worldwide Summary of Ceftobiprole Activity Against 59,695 Enterobacteriaceae and Non-Fermentative Gram-negative Bacilli

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Amended Abstract

Background: The broad-spectrum cephalosporin ceftobiprole (BPR) was tested against prevalent Gram-negative pathogens isolated worldwide during 2005-2009. BPR is an investigational drug under development for the treatment of complicated skin and skin structure infections (cSSSI) including infections by methicillin-resistant staphylococci. We report on the activity of BPR against Enterobacteriaceae (ENT) and non-fermentative (NF) Gram-negative (GN) pathogens in this collection.

Methods: During 2005-2009, a total of 59,695 consecutive, non-duplicate isolates from a variety of infections were collected from the following regions (n countries; n isolates): Asia Pacific (12; 14,884), Europe (14; 19,958), Latin America (4; 8,330), and North America (1; 16,523). Susceptibility (S) testing was performed by CLSI methods (M07-A8 and M100-S20-U).

Results: The activity against ENT and individual species was bimodal with an $MIC_{50/90}$ of ≤0.06/>8 µg/ml. As with other extended-spectrum cephalosporins, BPR showed limited activity against ceftazidime (CAZ) non-susceptible (NS) ENT. BPR was very active against CAZ-S ENT. BPR showed moderate activity against *Pseudomonas aeruginosa* (PA) and *Acinetobacter* spp. (ACIN) with 61 and 34% inhibited at a MIC value of ≤4 µg/ml, respectively. BPR was not active against *Stenotrophomonas maltophilia*.

Conclusion: BPR exhibited excellent potency against all ENT species that were CAZ-S in this very large geographically and temporally (including contemporary [2009]) diverse collection of isolates. BPR was moderately active against PA and ACIN. This data demonstrates the potential of BPR for targeted therapy of ENT and NF-GN pathogens in cSSSI.

Introduction

Ceftobiprole is a broad spectrum cephalosporin with potent activity against commonly occurring Gram-positive and –negative bacterial pathogens including resistant strains. The compound is stable to many commonly occurring β-lactamases, and has a strong affinity for penicillin-binding proteins, including PBP2′ (PBP2a), which mediates resistance to β-lactams in methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci (MR-CoNS). Ceftobiprole is also known to display *in vitro* activity against most Enterobacteriaceae and *Pseudomonas aeruginosa*, similar to that of other advanced generation cephems and β-lactam/β-lactamase inhibitor combinations.

Following encouraging results from preclinical and early phase clinical studies, ceftobiprole is in Phase III clinical development for the treatment of complicated skin and skin structure infections (cSSSI) and hospital-acquired bacterial pneumonia (HABP).

In this study, we report *in vitro* testing results from a very large collection of Gram-negative pathogens isolated worldwide during 2005-2009 comparing ceftobiprole activity with that of other β-lactam agents and members of several antimicrobial classes used in the empiric or directed therapy of cSSSI and HABP.

Methods

Bacterial Strain Collection. During 2005-2009, a total of 59,695 consecutive, non-duplicate Gram-negative pathogens from a variety of infections (including cSSSI and HABP) were collected from 159 medical centers (31 countries) in four geographic regions representing five continents (Table 1). Species identifications were performed by the submitting laboratories with confirmation performed by the central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA).

Susceptibility Test Methods. All isolates were tested for susceptibility by reference broth microdilution methods using the Clinical Laboratory Standards Institute recommendations (CLSI; M07-A8, 2009). Susceptibility testing was performed by using validated broth microdilution panels manufactured by TREK Diagnostics Systems/Sensititre (Cleveland, Ohio, USA). Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S20-U, 2010) quality control (QC) strains, including *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853. Categorical interpretation of comparator MIC values was performed according to CLSI (M100-S20-U, 2010) criteria, when available.

Results

- The activity of ceftobiprole against Enterobacteriaceae was bimodal with 72.1% of isolates being inhibited at a MIC value ≤0.06 µg/ml and 16.9 % having MIC values of >8 µg/ml (Table 2). Similar potencies and MIC distributions were observed for ceftazidime, cefepime, and ceftriaxone. This pattern, observed for all cephalosporin agents tested, is a reflection of their limited activity against CAZ-NS phenotype strains of *E. coli* (10.3%) and *Klebsiella pneumoniae* (26.8%, Table 3).

- Ceftobiprole was very active against 16,877 ceftazidime-susceptible *E. coli* ($MIC_{50/90}$, ≤0.06/≤0.06 µg/ml; Table 2), but not against 1,946 CAZ-NS *E. coli* ($MIC_{50/90}$, >8/>8 µg/ml; Table 3). Against all *E. coli*, resistance to comparator agents ranged from 0.1% for imipenem to 60.3% (CLSI criteria) for ampicillin and rates were much higher in CAZ-NS *E. coli* (Table 3).

- Ceftobiprole was very active against 6,689 ceftazidime-susceptible *K. pneumoniae* ($MIC_{50/90}$, ≤0.06 /0.12 µg/ml; Table 2), but not against 2,447 CAZ-NS isolates ($MIC_{50/90}$, >8/>8 µg/ml; Table 3). Overall, 3.6% of *K. pneumoniae* were resistant to imipenem rising to 13.0% (CLSI criteria) in the CAZ-NS subgroup (Table 3).

- Ceftobiprole was also very active against other Enterobacteriaceae tested, with *Enterobacter* spp., *Citrobacter* spp., *Proteus mirabilis*, indole-positive *Proteus* spp., *Serratia* spp., and *Salmonella* spp. all having a MIC_{50} value of ≤0.06 µg/ml.

- Against 9,876 *P. aeruginosa* (MIC_{50}, 4 µg/ml) and 4,962 *Acinetobacter* spp. (MIC_{50}, >8 µg/ml), ceftobiprole inhibited 61 and 34% of isolates, respectively (MIC, ≤4 µg/ml; Table 2). Ceftobiprole was not active against *Stenotrophomonas maltophilia* (MIC_{50}, >8 µg/ml) with <1% of isolates inhibited at a MIC of 8 µg/ml (Table 2).

Table 1. Distribution of 59,695 Gram-negative isolates and medical centers by geographic region and country

Region and country	Number of medical centers	Number of isolates	Region and country	Number of medical centers	Number of isolates
Asia Western Pacific (12 countries)	74	14884	Europe (14 countries)	30	19958
Latin America (4 countries)	10	8330	North America (1 country)	45	16523

Table 2. Cumulative percent inhibited distribution of ceftobiprole MIC values for 59,695 Gram-negative pathogens (2005-2009)

	Cumulative % inhibited at ceftobiprole MIC (µg/ml):							
Organism (no. of strains)	≤0.06	0.12	0.25	0.5	1	2	4	8
Enterobacteriaceae (42,297)[a]	72	77	79	80	81	82	82	83
E. coli (18,823)	81	83	85	85	86	86	86	86
CAZ-S[b] (16,877)	90	92	93	94	94	94	94	94
CAZ-NS[c] (1,946)	3	5	8	11	13	15	17	19
K. pneumoniae (9,136)	65	67	69	69	70	71	71	72
CAZ-S[b] (6,689)	88	91	92	93	94	94	95	95
CAZ-NS[c] (2,447)	2	3	3	4	5	6	7	9
Enterobacter spp. (5,647)	63	69	71	73	75	77	80	82
Serratia spp. (2,336)	59	80	85	89	91	91	92	93
Citrobacter spp. (1,030)	69	72	73	75	81	86	88	89
P. mirabilis (1,983)	87	89	89	90	91	91	91	92
Indole-positive *Proteus* spp. (920)	70	72	73	73	73	73	74	74
NF-GN pathogens (17,398)[d]	2	4	7	12	25	39	49	58
P. aeruginosa (9,876)	<1	<1	1	3	23	45	61	76
Acinetobacter spp. (4,962)	4	8	18	26	31	33	34	35
S. maltophilia (1418)	<1	<1	<1	<1	<1	<1	<1	0.3

a. Includes 2,421 Enterobacteriaceae isolates from species not listed in the table.
b. CAZ-S = ceftazidime susceptible (MIC ≤4) µg/ml.
c. CAZ-NS = ceftazidime non-susceptible (MIC >4) µg/ml.
d. Includes 1,142 NF-GN isolates from species not listed in the table.

Table 3. Antimicrobial activity of ceftobiprole and comparator agents when tested against 58,253[a] Gram-negative pathogens

Organism (no. tested)/ Antimicrobial agent	MIC in µg/ml			CLSI[b] %S / %R	EUCAST[b] %S / %R
	MIC_{50}	MIC_{90}	Range		
Enterobacteriaceae (42,297)					
Ceftobiprole	≤0.06	>8	≤0.06 – >8	- / -[c]	- / -
Ampicillin	>16	>16	≤1 – >16	24.4 / 70.2	- / 75.6
Ampicillin/sulbactam	16	>16	≤2 – >16	47.2 / 35.6	- / 52.8
Piperacillin/tazobactam	2	32	≤0.5 – >64	87.4 / 6.8	83.3 / 12.6
Cefepime	≤0.12	16	≤0.12 – >16	89.0 / 8.7	83.0 / 13.1
Ceftazidime	≤1	>16	≤1 – >16	83.6 / 14.4	79.1 / 16.4
Ceftriaxone	≤0.25	>32	≤0.25 – >32	77.9 / 21.1	77.9 / 21.1
Imipenem	0.25	1	≤0.12 – >8	93.2 / 2.2	97.8 / 0.6
Levofloxacin	≤0.5	>4	≤0.5 – >4	78.0 / 19.7	76.1 / 22.0
Tetracycline	≤2	>8	≤2 – >8	60.6 / 36.0	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	70.1 / 29.9	70.1 / 0.0
E. coli (18,823)					
Ceftobiprole	≤0.06	>8	≤0.06 – >8	- / -	- / -
Ampicillin	>16	>16	≤1 – >16	39.1 / 60.3	- / 60.9
Ampicillin/sulbactam	16	>16	≤2 – >16	45.9 / 32.5	- / 54.1
Piperacillin/tazobactam	2	16	≤0.5 – >64	92.7 / 3.3	88.9 / 7.3
Cefepime	≤0.12	16	≤0.12 – >16	90.0 / 7.9	85.9 / 11.9
Ceftazidime	≤1	8	≤1 – >16	89.7 / 8.5	85.3 / 10.3
Ceftriaxone	≤0.25	>32	≤0.25 – >32	84.2 / 15.4	84.2 / 15.4
Imipenem	≤0.12	0.25	≤0.12 – >8	99.7 / 0.1	99.9 / <0.1
Levofloxacin	≤0.5	>4	≤0.5 – >4	70.3 / 27.7	70.0 / 29.7
Tetracycline	≤2	>8	≤2 – >8	58.8 / 40.8	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	61.1 / 38.9	61.1 / 0.0
CAZ-NS[d] *E. coli* (1,946)					
Ceftobiprole	>8	>8	≤0.06 – >8	- / -	- / -
Ampicillin/sulbactam	>16	>16	≤2 – >16	4.0 / 83.1	- / 96.0
Piperacillin/tazobactam	16	>64	≤0.5 – >64	69.9 / 11.3	48.5 / 30.1
Cefepime	>16	>16	≤0.12 – >16	27.3 / 61.9	16.9 / 78.4
Ceftriaxone	>32	>32	≤0.25 – >32	1.5 / 96.8	1.5 / 96.8
Imipenem	0.25	0.5	≤0.12 – >8	98.0 / 1.1	98.9 / 0.2
Levofloxacin	>4	>4	≤0.5 – >4	15.6 / 81.6	15.3 / 84.4
Tetracycline	>8	>8	≤2 – >8	23.2 / 76.1	- / -
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5 – >2	31.6 / 68.4	31.6 / 0.0
K. pneumoniae (9,136)					
Ceftobiprole	≤0.06	>8	≤0.06 – >8	- / -	- / -
Ampicillin/sulbactam	8	>16	≤2 – >16	58.5 / 34.3	- / 41.5
Piperacillin/tazobactam	4	>64	≤0.5 – >64	78.8 / 14.2	73.0 / 21.2
Cefepime	≤0.12	>16	≤0.12 – >16	79.4 / 16.6	72.4 / 23.2
Ceftazidime	≤1	>16	≤1 – >16	73.2 / 24.0	69.2 / 26.8
Ceftriaxone	≤0.25	>32	≤0.25 – >32	69.6 / 29.8	69.6 / 29.8
Imipenem	0.25	0.5	≤0.12 – >8	95.4 / 3.6	96.4 / 2.2
Levofloxacin	≤0.5	>4	≤0.5 – >4	78.3 / 19.3	76.5 / 21.7
Tetracycline	≤2	>8	≤2 – >8	72.6 / 23.9	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	71.2 / 28.8	71.2 / 0.0
CAZ-NS[d] *K. pneumoniae* (2,447)					
Ceftobiprole	>8	>8	≤0.06 – >8	- / -	- / -
Ampicillin/sulbactam	>16	>16	≤2 – >16	2.1 / 91.9	- / 97.9
Piperacillin/tazobactam	64	>64	≤0.5 – >64	33.5 / 45.5	22.1 / 66.5
Cefepime	>16	>16	≤0.12 – >16	28.1 / 59.1	10.0 / 79.0
Ceftriaxone	>32	>32	≤0.25 – >32	1.9 / 96.7	1.9 / 96.7
Imipenem	0.25	8	≤0.12 – >8	84.2 / 13.0	87.0 / 8.3
Levofloxacin	>4	>4	≤0.5 – >4	34.8 / 59.6	31.5 / 65.2
Tetracycline	8	>8	≤2 – >8	48.0 / 45.7	- / -
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5 – >2	27.9 / 72.1	27.9 / 0.0
Enterobacter spp. (5,647)					
Ceftobiprole	≤0.06	>8	≤0.06 – >8	- / -	- / -
Ampicillin/sulbactam	>16	>16	≤2 – >16	27.5 / 52.0	- / 72.5
Piperacillin/tazobactam	4	>64	≤0.5 – >64	76.5 / 11.1	71.2 / 23.5
Cefepime	≤0.12	8	≤0.12 – >16	91.1 / 6.7	78.4 / 12.1
Ceftazidime	≤1	>16	≤1 – >16	67.7 / 29.4	62.6 / 32.3
Ceftriaxone	≤0.25	>32	≤0.25 – >32	62.7 / 35.4	62.7 / 35.4
Imipenem	0.5	1	≤0.12 – >8	90.9 / 1.8	98.2 / 0.4
Levofloxacin	≤0.5	>4	≤0.5 – >4	86.6 / 10.8	84.2 / 13.4
Tetracycline	≤2	>8	≤2 – >8	79.2 / 16.0	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	80.8 / 19.2	80.8 / 0.0
Citrobacter spp. (1,030)					
Ceftobiprole	≤0.06	>8	≤0.06 – >8	- / -	- / -
Ampicillin/sulbactam	8	>16	≤2 – >16	61.9 / 30.5	- / 38.1
Piperacillin/tazobactam	2	64	≤0.5 – >64	82.7 / 5.7	77.2 / 17.3
Cefepime	≤0.12	2	≤0.12 – >16	95.0 / 4.1	87.9 / 6.9
Ceftazidime	≤1	>16	≤1 – >16	74.9 / 23.6	71.1 / 25.1
Ceftriaxone	≤0.25	>32	≤0.25 – >32	71.9 / 27.1	71.9 / 27.1
Imipenem	0.5	1	≤0.12 – 8	95.8 / 0.2	99.8 / 0.0
Levofloxacin	≤0.5	2	≤0.5 – >4	90.0 / 7.8	85.6 / 10.0
Tetracycline	≤2	>8	≤2 – >8	81.7 / 15.6	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	83.1 / 16.9	83.1 / 0.0
P. mirabilis (1,984)					
Ceftobiprole	≤0.06	0.5	≤0.06 – >8	- / -	- / -
Ampicillin	2	>16	≤1 – >16	64.0 / 35.7	- / 36.0
Ampicillin/sulbactam	≤2	16	≤2 – >16	81.2 / 9.7	- / 18.8
Piperacillin/tazobactam	≤0.5	1	≤0.5 – >64	99.3 / 0.2	98.9 / 0.7
Cefepime	≤0.12	1	≤0.12 – >16	93.0 / 5.8	90.4 / 8.0
Ceftazidime	≤1	≤1	≤1 – >16	96.0 / 3.2	93.4 / 4.0
Ceftriaxone	≤0.25	2	≤0.25 – >32	89.5 / 9.2	89.5 / 9.2
Imipenem	1	2	≤0.12 – >8	56.3 / 8.7	91.3 / 0.1
Levofloxacin	≤0.5	>4	≤0.5 – >4	79.8 / 16.1	72.9 / 20.2
Tetracycline	>8	>8	≤2 – >8	1.8 / 97.9	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	65.4 / 34.6	65.4 / 0.0
Indole-positive *Proteus* spp. (920)					
Ceftobiprole	≤0.06	>8	≤0.06 – >8	- / -	- / -
Ampicillin/sulbactam	16	>16	≤2 – >16	30.9 / 32.4	- / 69.1
Piperacillin/tazobactam	≤0.5	4	≤0.5 – >64	97.9 / 0.9	97.1 / 2.1
Cefepime	≤0.12	1	≤0.12 – >16	93.4 / 4.9	90.3 / 7.9
Ceftazidime	≤1	8	≤1 – >16	87.4 / 8.6	75.9 / 12.6
Ceftriaxone	≤0.25	8	≤0.25 – >32	76.7 / 16.6	76.7 / 16.6
Imipenem	2	4	≤0.12 – 8	30.3 / 27.9	72.1 / 0.0
Levofloxacin	≤0.5	>4	≤0.5 – >4	75.9 / 19.3	71.5 / 24.1
Tetracycline	>8	>8	≤2 – >8	35.8 / 56.7	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	71.2 / 28.8	71.2 / 0.0
Serratia spp. (2,336)					
Ceftobiprole	≤0.06	1	≤0.06 – >8	- / -	- / -
Ampicillin/sulbactam	>16	>16	≤2 – >16	10.2 / 68.5	- / 89.8
Piperacillin/tazobactam	2	16	≤0.5 – >64	91.8 / 1.9	88.6 / 8.2
Cefepime	≤0.12	1	≤0.12 – >16	96.4 / 2.9	92.6 / 4.4
Ceftazidime	≤1	2	≤1 – >16	95.0 / 3.9	89.8 / 5.0
Ceftriaxone	≤0.25	16	≤0.25 – >32	81.6 / 15.8	81.6 / 15.8
Imipenem	1	2	≤0.12 – >8	87.8 / 1.2	98.8 / 0.2
Levofloxacin	≤0.5	2	≤0.5 – >4	93.4 / 4.3	87.3 / 6.6
Tetracycline	>8	>8	≤2 – >8	6.7 / 66.7	- / -
Trimethoprim/sulfamethoxazole	≤0.5	2	≤0.5 – >2	91.4 / 8.6	91.4 / 0.0
P. aeruginosa (9,876)					
Ceftobiprole	4	>8	≤0.06 – >8	- / -	- / -
Aztreonam	8	>16	≤0.12 – >16	63.2 / 22.6	3.6 / 22.6
Piperacillin/tazobactam	8	>64	≤0.5 – >64	81.6 / 18.4	68.4 / 31.6
Ticarcillin/clavulanate	32	>128	≤16 – >128	66.7 / 33.3	15.2 / 84.8
Cefepime	4	>16	≤0.12 – >16	75.6 / 13.2	75.6 / 24.4
Ceftazidime	4	>16	≤1 – >16	73.1 / 21.3	73.1 / 26.9
Imipenem	2	>8	≤0.12 – >8	74.5 / 18.8	74.5 / 18.8
Levofloxacin	1	>4	≤0.5 – >4	67.1 / 27.9	59.6 / 32.9
Amikacin	≤2	>32	≤4 – >32	87.2 / 10.1	83.3 / 12.8
Tobramycin	0.5	>16	≤0.25 – >16	80.1 / 19.1	80.1 / 19.9
Polymyxin B	1	1	≤0.5 – >4	99.8 / 0.1	- / -
Acinetobacter spp. (4,962)					
Ceftobiprole	>8	>8	≤0.06 – >8	- / -	- / -
Piperacillin/tazobactam	>64	>64	≤0.5 – >64	37.5 / 62.5	- / -
Ticarcillin/clavulanate	>128	>128	≤16 – >128	29.0 / 60.5	- / -
Cefepime	>16	>16	≤0.12 – >16	35.8 / 54.0	- / -
Ceftazidime	>16	>16	≤1 – >16	32.4 / 61.8	- / -
Imipenem	2	>8	≤0.12 – >8	56.8 / 39.2	51.7 / 39.2
Levofloxacin	>4	>4	≤0.5 – >4	34.3 / 59.2	33.2 / 65.7
Amikacin	>32	>32	≤4 – >32	45.0 / 51.1	42.5 / 55.0
Tobramycin	4	>16	≤0.25 – >16	50.7 / 46.9	50.7 / 49.3
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5 – >2	39.0 / 61.0	39.0 / 0.0
Polymyxin B	≤0.5	≤0.5	≤0.5 – >4	99.3 / 0.7	- / -
S. maltophilia (1,418)					
Ceftobiprole	>8	>8	≤0.06 – >8	- / -	- / -
Ticarcillin/clavulanate	32	>128	≤16 – >128	36.8 / 27.6	- / -
Cefepime	>16	>16	≤0.12 – >16	- / -	- / -
Ceftazidime	16	>16	≤1 – >16	43.0 / 43.4	- / -
Imipenem	>8	>8	0.5 – >8	- / -	- / -
Levofloxacin	1	4	≤0.5 – >4	81.7 / 9.0	- / -
Trimethoprim/sulfamethoxazole	≤0.5	1	≤0.5 – >2	96.2 / 3.8	100.0 / 0.0
Polymyxin B	2	>4	≤0.5 – >4	- / -	- / -

a. Number of isolates (58,253) differs from total number in the overall study (59,695) as a number of species have not been reported in the table because of low isolate numbers.
b. Criteria as published by the CLSI [2010] and EUCAST [2010].
c. = No breakpoint has been established.
d. CAZ-NS = ceftazidime non-susceptible (MIC >4) µg/ml.

Conclusions

- Ceftobiprole exhibited excellent potency against all Enterobacteriaceae that were ceftazidime susceptible in this very large geographically and temporally (including contemporary [2009]) diverse collection of organisms.
- Ceftobiprole had more limited activity against *P. aeruginosa* and *Acinetobacter* spp, and ceftazidime non-susceptible phenotypes, as observed with other marketed broad-spectrum cephalosporins. Ceftobiprole was not active against *S. maltophilia*.
- This data expands the definition of ceftobiprole activity against the majority of contemporary Enterobacteriaceae and non-fermentative Gram-negative bacilli on a global scale. This anti-MRSA parenteral cephalosporin is potentially useful as empiric or targeted therapy to treat patients with cSSSI and HABP.

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