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Antimicrobial Activity of Ceftobiprole When Tested against Contemporary Isolates from US Medical Centers (2016)

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https://www.jmilabs.com/data/posters/ASMMicrobe17-ceftobiprole-US-2016.pdf

Abstract

Background: Ceftobiprole medocaril (prodrug of ceftobiprole) is a fifth-generation cephalosporin approved for use in multiple European countries for the treatment of hospital-acquired pneumonia (excluding ventilator-associated pneumonia) and community-acquired pneumonia in adults. While not approved in the United States, ceftobiprole medocaril has qualified infectious disease product (QIDP) status, and Phase 3 studies supported by BARDA are planned to start in 2017. In this study, the activity of ceftobiprole and comparator agents was evaluated against recent US clinical isolates (2016).

Methods: Approximately 12,000 bacterial clinical isolates (1 per patient infection episode) were collected from patients in 30 medical centers in the US. The majority of isolates were from bloodstream, respiratory, skin and soft tissue, and urinary tract infections. Ceftobiprole and comparator agents were susceptibility (S) tested against clinical isolates and QC strains following CLSI methods. CLSI and EUCAST interpretive criteria were applied according to current guidelines.

Results: Ceftobiprole was very active against gram-positive bacteria. For *Staphylococcus aureus*, the MIC$_{50/90}$ for ceftobiprole was 0.5/2 mg/L (99.7%S, EUCAST criteria). For methicillin-susceptible *S. aureus,* the MIC$_{50/90}$ was 0.5/0.5 mg/L (100.0%S), and for methicillin-resistant *S. aureus,* the MIC$_{50/90}$ was 1/2 mg/L (99.3%S). Against coagulase-negative staphylococci, the MIC$_{50/90}$ for ceftobiprole was 0.5/1 mg/L with 97.7% of isolates at ≤2 mg/L. Ceftobiprole was active against *Enterococcus faecalis* (MIC$_{50/90}$, 0.5/2 mg/L) but not against *E. faecium* (MIC$_{50/90}$, >4/>4 mg/L). Susceptibility to ceftobiprole for *Streptococcus pneumoniae* was 99.7% (MIC$_{50/90}$, 0.015/0.5 mg/L); 2.1% of *S. pneumoniae* were nonsusceptible (NS) to ceftriaxone, and 3% were NS to penicillin. Against β-haemolytic streptococci and viridans group streptococci, the ceftobiprole MIC$_{50/90}$ were 0.015/0.03 mg/L and 0.06/0.25 mg/L, respectively. Susceptibility of *Enterobacteriaceae* to ceftobiprole was 82.5%, and a total of 72.7% of *Pseudomonas aeruginosa* were inhibited by ceftobiprole at ≤4 mg/L (85.9%, ≤8 mg/L).

Conclusions: Ceftobiprole was active against clinically relevant gram-positive and gram-negative isolates collected at US medical centers during 2016. The broad-spectrum activity of ceftobiprole, including its activity against multidrug-resistant staphylococci and streptococci, indicates that further study is warranted in infections where such organisms occur.

Introduction

- Ceftobiprole is a parenteral fifth-generation cephalosporin that is active against gram-positive and gram-negative bacteria
- Ceftobiprole has shown potent activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* and has shown activity against *Enterobacteriaceae* and *Pseudomonas aeruginosa*
- Ceftobiprole is not approved by the Food and Drug Administration (FDA) for use in the US; it has received national licenses for treating adult patients with community- and hospital-acquired pneumonia, excluding ventilator-associated pneumonia, in Austria, Belgium, Denmark, Finland, France, Germany, Italy, Luxembourg, Norway, Spain, Sweden, Switzerland, and the United Kingdom
- Ceftobiprole is currently in Phase 3 development to support indications for acute bacterial skin and skin structure infections and *S. aureus* bacteremia, supported by BARDA
- This study evaluated ceftobiprole and comparator antimicrobial agents when tested against 12,001 isolates collected in 2016 at 30 US medical centers across 9 census areas

Materials and Methods

- 12,001 bacterial isolates were collected prospectively from patients in 30 US medical centers across 9 census areas during 2016
  - Isolates were recovered from patients with bloodstream infections, community-acquired and nosocomial respiratory tract infections, skin and skin structure infections, urinary tract infection, intra-abdominal infections, and other infections (miscellaneous or undefined)
  - Isolates were identified by the submitting laboratories and were confirmed at the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) by matrix-assisted laser desorption ionization-time of flight mass spectrometry, when necessary, using the Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, USA)
- Ceftobiprole and comparators were tested in broth microdilution panels with clinical isolates and quality control organisms according to Clinical and Laboratory Standards Institute guidelines
  - Categorical interpretation criteria were CLSI (M100-S27 [2017]), EUCAST (2017), or US FDA when no EUCAST or CLSI criteria were available
  - Quality control organisms were tested concurrently with clinical isolates

Results

- MIC$_{50/90}$ for ceftobiprole when tested against *S. aureus* was 0.5/2 mg/L (99.7%S)
  - 43% of *S. aureus* isolates were MRSA (Table 2)
  - MIC$_{50/90}$ for MRSA and methicillin-susceptible *S. aureus* (MSSA) were 1/2 and 0.5/0.5 mg/L, respectively (Table 1)
  - Ceftobiprole and ceftaroline were the most potent cephalosporins tested against 1,670 MSSA isolates and were 8- to 16-fold more potent than ceftriaxone (data not shown)
  - 99.3% of MRSA isolates were susceptible to ceftobiprole while 96.4% were susceptible to ceftaroline (Table 2)
    - Erythromycin resistance (84.2%; CLSI interpretive criteria) and levofloxacin resistance (69.3%; CLSI) were high (Table 2)

Table 1.Cumulative frequency (percentage) of ceftobiprole activity (mg/L) when tested against gram-positive and gram-negative bacteria from US surveillance (2016)

Organism / organism group	No. of isolates at MIC (mg/L; cumulative %)																MIC_{50}	MIC_{90}
	≤0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>		
Staphylococcus aureus (2,930)						1 <0.1	2 0.1	10 0.4	609 21.2	1,122 59.5	865 89.0	312 99.7	9 100.0				0.5	2
MSSA (1,670)						1 0.1	2 0.2	10 0.8	607 37.1	1,048 99.9	2 100.0						0.5	0.5
MRSA (1,260)								0 0.0	2 0.2	74 6.0	863 74.5	312 99.3	9 100.0				1	2
Coagulase-negative staphylococci (439)						16 3.6	14 6.8	65 21.6	64 36.2	116 62.6	139 94.3	15 97.7	10 100.0				0.5	1
MS-CoNS (175)						16 9.1	14 17.1	63 53.1	48 80.6	27 96.0	7 100.0						0.12	0.5
MR-CoNS (264)							0 0.0	2 0.8	16 6.8	89 40.5	132 90.5	15 96.2	10 100.0				1	1
Enterococcus spp. (531)						8 1.5	4 2.3	19 5.8	57 16.6	159 46.5	67 59.1	59 70.2	20 74.0			138 100.0	1	>4
Enterococcus faecalis (347)						7 2.0	4 3.2	19 8.6	56 24.8	155 69.5	57 85.9	37 96.5	12 100.0				0.5	2
Vancomycin-susceptible (≤4 mg/L) (334)						7 2.1	4 3.3	18 8.7	54 24.9	152 70.4	57 87.4	34 97.6	8 100.0				0.5	2
Vancomycin-nonsusceptible (>4 mg/L) (13)							0 0.0	1 7.7	2 23.1	3 46.2	0 46.2	3 69.2	4 100.0				2	4
Enterococcus faecium (177)									0 0.0	2 1.1	9 6.2	21 18.1	7 22.0			138 100.0	>4	>4
Vancomycin-susceptible (≤4 mg/L) (61)									0 0.0	1 1.6	9 16.4	21 50.8	5 59.0			25 100.0	2	>4
Vancomycin-nonsusceptible (>4 mg/L) (116)									0 0.0	1 0.9	0 0.9	0 0.9	2 2.6			113 100.0	>4	>4
Streptococcus pneumoniae (698)	0 0.0	1 0.1	10 1.6	175 26.6	262 64.2	33 68.9	32 73.5	35 78.5	67 88.1	81 99.7	2 100.0						0.015	0.5
Penicillin-susceptible non-meningitis (≤2 mg/L) (677)	0 0.0	1 0.1	10 1.6	175 27.5	262 66.2	33 71.0	32 75.8	34 80.8	67 90.7	63 100.0							0.015	0.25
Penicillin-intermediate non-meningitis (=4 mg/L) (20)							0 0.0	1 5.0	0 5.0	18 95.0	1 100.0						0.5	0.5
Penicillin-resistant non-meningitis (≥8 mg/L) (1)										0 0.0	1 100.0							
Ceftriaxone-non-susceptible non-meningitis (>1 mg/L) (15)									0 0.0	13 86.7	2 100.0						0.5	1
Viridans group streptococci (127)		0 0.0	2 1.6	8 7.9	25 27.6	19 42.5	26 63.0	29 85.8	7 91.3	6 96.1	3 98.4	1 99.2				1 100.0	0.06	0.25
β-haemolytic streptococci (585)	0 0.0	2 0.3	5 1.2	184 32.6	174 62.4	208 97.9	10 99.7	2 100.0									0.015	0.03
Streptococcus pyogenes (276)	0 0.0	2 0.7	4 2.2	166 62.3	98 97.8	5 99.6	1 100.0										0.008	0.015
Streptococcus agalactiae (240)			0 0.0	2 0.8	28 12.5	199 95.4	9 99.2	2 100.0									0.03	0.03
Other β-haemolytic streptococci (69)		0 0.0	1 1.4	16 24.6	48 94.2	4 100.0											0.015	0.015
Enterobacteriaceae (4,469)				36 0.8	164 4.5	2,313 56.2	823 74.6	241 80.0	110 82.5	66 84.0	52 85.1	51 86.3	38 87.1	13 87.4	18 87.8	544 100.0	0.03	>16
Escherichia coli (1,747)				0 0.0	54 3.1	1,062 63.9	264 79.0	40 81.3	21 82.5	6 82.8	7 83.2	0 83.2	2 83.3	2 83.5	3 83.6	286 100.0	0.03	>16
ESBL-phenotype (330)					0 0.0	9 2.7	5 4.2	6 6.1	7 8.2	4 9.4	6 11.2	0 11.2	2 11.8	2 12.4	3 13.3	286 100.0	>16	>16
Non-ESBL-phenotype (1,417)				0 0.0	54 3.8	1,053 78.1	259 96.4	34 98.8	14 99.8	2 99.9	1 100.0						0.03	0.06
Klebsiella pneumoniae (959)				0 0.0	49 5.1	579 65.5	139 80.0	25 82.6	8 83.4	5 83.9	5 84.5	11 85.6	1 85.7	0 85.7	4 86.1	133 100.0	0.03	>16
ESBL-phenotype (168)					0 0.0	4 2.4	2 3.6	3 5.4	3 7.1	2 8.3	5 11.3	11 17.9	1 18.5	0 18.5	4 20.8	133 100.0	>16	>16
Non-ESBL-phenotype (791)				0 0.0	49 6.2	575 78.9	137 96.2	22 99.0	5 99.6	3 100.0							0.03	0.06
Klebsiella oxytoca (232)					0 0.0	13 5.6	38 22.0	55 45.7	52 68.1	30 81.0	9 84.9	2 85.8	0 85.8	0 85.8	1 86.2	32 100.0	0.25	>16
ESBL-phenotype (33)										0 0.0	1 3.0	1 6.1	0 6.1	0 6.1	0 6.1	31 100.0	>16	>16
Non-ESBL-phenotype (199)					0 0.0	13 6.5	38 25.6	55 53.3	52 79.4	30 94.5	8 98.5	1 99.0	0 99.0	0 99.0	1 99.5	1 100.0	0.12	0.5
Enterobacter spp. (596)				0 0.0	10 1.7	252 44.0	162 71.1	39 77.7	14 80.0	8 81.4	15 83.9	24 87.9	28 92.6	9 94.1	6 95.1	29 100.0	0.06	4
Citrobacter spp. (219)				0 0.0	2 0.9	139 64.4	34 79.9	3 81.3	2 82.2	4 84.0	8 87.7	9 91.8	5 94.1	1 94.5	0 94.5	12 100.0	0.03	2
Proteus mirabilis (244)				0 0.0	29 11.9	164 79.1	33 92.6	7 95.5	1 95.9	0 95.9	0 95.9	0 95.9	0 95.9	0 95.9	1 96.3	9 100.0	0.03	0.06
Indole-positive Proteeae (192)				36 18.8	20 29.2	83 72.4	10 77.6	2 78.6	1 79.2	1 79.7	3 81.2	1 81.8	0 81.8	1 82.3	1 82.8	33 100.0	0.03	>16
Serratia spp. (239)					0 0.0	7 2.9	134 59.0	63 85.4	10 89.5	11 94.1	5 96.2	2 97.1	1 97.5	0 97.5	2 98.3	4 100.0	0.06	0.5
Pseudomonas aeruginosa (1,017)							0 0.0	2 0.2	4 0.6	23 2.9	188 21.3	326 53.4	196 72.7	135 85.9	97 95.5	46 100.0	2	16
Acinetobacter spp. (187)				1 0.5	4 2.7	3 4.3	3 5.9	10 11.2	32 28.3	32 45.5	17 54.5	6 57.8	7 61.5	4 63.6	5 66.3	63 100.0	1	>16
Stenotrophomonas maltophilia (191)															0 0.0	191 100.0	>16	>16
Haemophilus influenzae (450)				0 0.0	13 2.9	164 39.3	165 76.0	88 95.6	14 98.7	2 99.1	2 99.6					2 100.0	0.06	0.12
β-lactamase-positive (141)				0 0.0	1 0.7	49 35.5	59 77.3	24 94.3	4 97.2	2 98.6	1 99.3					1 100.0	0.06	0.12
β-lactamase-negative (309)				0 0.0	12 3.9	115 41.1	106 75.4	64 96.1	10 99.4	0 99.4	1 99.7					1 100.0	0.06	0.12
Haemophilus parainfluenzae (11)				1 9.1	0 9.1	4 45.5	1 54.5	3 81.8	2 100.0								0.06	0.25
Moraxella catarrhalis (237)				9 3.8	10 8.0	37 23.6	43 41.8	58 66.2	63 92.8	16 99.6	0 99.6					1 100.0	0.12	0.25

- The MIC$_{50/90}$ for ceftobiprole against 439 coagulase-negative staphylococci (CoNS) isolates was 0.5/1 mg/L, and all MIC values were ≤4 mg/L (Table 1)
  - MIC$_{50/90}$ for MR-CoNS and MS-CoNS were 1/1 and 0.12/0.5 mg/L, respectively (Table 1)
- Ceftaroline (MIC$_{50/90}$, 0.25/0.5 mg/L) and ceftobiprole (MIC$_{50/90}$, 0.5/1 mg/L) were the most potent β-lactam agents tested against CoNS (Table 2)
- Ceftobiprole exhibited potent activity against *Enterococcus faecalis* (MIC$_{50/90}$, 0.5/2 mg/L), but not against *E. faecium* (MIC$_{50/90}$, >4/>4 mg/L; Table 1)
- Against *Streptococcus pneumoniae*, ceftobiprole (MIC$_{50/90}$, 0.015/0.5 mg/L; 99.7%S), ceftaroline (MIC$_{50/90}$, ≤0.008/0.12 mg/L; 100.0%S; CLSI), and penicillin (MIC$_{50/90}$, 0.015/2 mg/L; 97.0%S [CLSI parenteral non-meningitis interpretive criteria]; Table 2) were the most active agents

Table 2. Activity of ceftobiprole and comparator antimicrobial agents when tested against gram-positive bacteria from US surveillance (2016)

Organism (no.)/ antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a]		EUCAST[a]	
			%S	%R	%S	%R
***Staphylococcus aureus* (2,930)**						
Ceftobiprole	0.5	2			99.7	0.3
Ceftaroline	0.25	1	98.5	<0.1	98.5	1.5
Ceftriaxone	4	>8	57.0	43.0		
Clindamycin	≤0.25	>2	85.3	14.5	85.2	14.7
Daptomycin	0.25	0.5	>99.9		>99.9	<0.1
Erythromycin	4	>8	43.3	49.7	44.0	53.1
Gentamicin	≤1	≤1	97.7	2.1	97.5	2.5
Levofloxacin	0.25	>4	62.6	35.5	62.6	37.4
Linezolid	1	1	100.0	0.0	100.0	0.0
Oxacillin	0.5	>2	57.0	43.0	57.0	43.0
Tetracycline	≤0.5	≤0.5	96.3	3.1	94.0	4.8
Tigecycline	0.06	0.12	100.0		100.0	0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	97.9	2.1	97.9	2.0
Vancomycin	0.5	1	100.0	0.0	100.0	0.0
MRSA (1,260)						
Ceftobiprole	1	2			99.3	0.7
Ceftaroline	0.5	1	96.4	0.1	96.4	3.6
Ceftriaxone	>8	>8	0.0	100.0		
Clindamycin	≤0.25	>2	71.0	28.7	71.0	29.0
Daptomycin	0.5	0.5	99.9		99.9	0.1
Erythromycin	>8	>8	11.1	84.2	11.7	86.7
Gentamicin	≤1	≤1	95.9	3.9	95.8	4.2
Levofloxacin	4	>4	27.8	69.3	27.8	72.2
Linezolid	1	1	100.0	0.0	100.0	0.0
Oxacillin	>2	>2	0.0	100.0	0.0	100.0
Tetracycline	≤0.5	1	95.7	3.7	92.8	5.2
Tigecycline	0.06	0.12	100.0		100.0	0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	95.8	4.2	95.8	4.0
Vancomycin	0.5	1	100.0	0.0	100.0	0.0
Coagulase-negative staphylococci (439)						
Ceftobiprole	0.5	1				
Ceftaroline	0.25	0.5				
Ceftriaxone	8	>8	39.9	60.1		
Clindamycin	≤0.25	>2	70.2	28.9	69.2	29.8
Daptomycin	0.25	0.5	100.0		100.0	0.0
Erythromycin	>8	>8	39.2	57.2	40.3	58.3
Gentamicin	≤1	>8	77.2	20.7	75.6	24.4
Levofloxacin	0.25	>4	60.4	38.0	60.4	39.6
Linezolid	0.5	1	97.7	2.3	97.7	2.3
Oxacillin	2	>2	39.9	60.1	42.8	57.2
Tetracycline	≤0.5	>8	85.6	13.9	83.6	15.0
Tigecycline	0.06	0.12			100.0	0.0
Trimethoprim-sulfamethoxazole	≤0.5	>4	70.2	29.8	70.2	10.5
Vancomycin	1	2	100.0	0.0	100.0	0.0
***Enterococcus faecalis* (347)**						
Ceftobiprole	0.5	2				
Ampicillin	1	2	100.0	0.0	100.0	0.0
Ceftaroline	2	8				
Daptomycin	1	1	100.0			
Levofloxacin	1	>4	76.1	23.6	76.4	23.6[b]
Linezolid	1	1	100.0	0.0	100.0	0.0
Teicoplanin	≤0.5	≤0.5	96.3	3.7	96.0	4.0
Tigecycline	0.06	0.12	100.0		100.0	0.0
Vancomycin	1	2	96.3	3.7	96.3	3.7
***Streptococcus pneumoniae* (698)**						
Ceftobiprole	0.015	0.5			99.7	0.3
Ceftaroline	≤0.008	0.12	100.0		99.7	0.3
Ceftriaxone	0.03	1	97.8	0.3[b]		
Clindamycin	≤0.25	>2	85.0	14.6	85.4	14.6
Erythromycin	0.06	>32	53.3	45.8	53.3	45.8
Levofloxacin	1	1	99.0	0.9	99.0	1.0
Linezolid	1	2	100.0		100.0	0.0
Penicillin	0.015	2	97.0	0.1[c]		
Tetracycline	≤0.25	>8	79.7	20.1	79.7	20.1
Trimethoprim-sulfamethoxazole	0.25	>4	72.3	17.2	78.2	17.2
Vancomycin	0.25	0.25	100.0		100.0	0.0
β-haemolytic streptococci (585)						
Ceftobiprole	0.015	0.03				
Ceftaroline	≤0.008	0.015	100.0		100.0	0.0
Ceftriaxone	0.03	0.06	100.0		100.0	0.0
Clindamycin	≤0.25	>2	83.2	16.2	83.8	16.2
Daptomycin	≤0.06	0.25	100.0		100.0	0.0
Erythromycin	0.03	>32	67.3	32.0	67.3	32.0
Levofloxacin	0.5	1	99.8	0.2	99.8	0.2
Linezolid	1	1	100.0		100.0	0.0
Meropenem	≤0.008	0.06	100.0		100.0	0.0
Penicillin	0.015	0.06	100.0		100.0	0.0
Tetracycline	0.5	>8	53.4	45.2	52.2	46.6
Vancomycin	0.25	0.5	100.0		100.0	0.0
Viridans group streptococci (127)						
Ceftobiprole	0.06	0.25				
Ceftaroline	0.015	0.06				
Ceftriaxone	0.12	0.5	94.5	3.1	91.3	8.7
Clindamycin	≤0.25	>2	82.7	15.7	84.3	15.7
Daptomycin	0.25	1	100.0			
Erythromycin	0.03	>32	53.5	44.9		
Levofloxacin	1	2	92.9	7.1		
Linezolid	1	1	100.0			
Meropenem	0.03	0.5	95.3		100.0	0.0
Penicillin	0.06	1	74.0	3.1	83.5	3.1
Tetracycline	1	>8	56.7	38.6		
Vancomycin	0.5	0.5	100.0		100.0	0.0

[a] Criteria as published by CLSI [2017] and EUCAST [2017]; CLSI tigecycline breakpoints do not exist so US FDA breakpoints were used
[b] CLSI non-meningitis breakpoint
[c] CLSI parenteral non-meningitis breakpoint

- Ceftaroline, ceftobiprole, and meropenem were the most active β-lactam agents when tested against viridans group streptococci (MIC$_{50/90}$, 0.015/0.06 mg/L; MIC$_{50/90}$, 0.06/0.25 mg/L; and MIC$_{50/90}$, 0.03/0.5 mg/L, respectively [Table 2])
- The MIC$_{50/90}$ values for ceftobiprole against β-haemolytic streptococci were 0.015/0.03 mg/L (highest MIC, 0.12 mg/L; Table 1)
- Ceftobiprole was highly active against *H. influenzae* and *Moraxella catarrhalis* isolates, exhibiting MIC$_{50/90}$ values of 0.06/0.12 mg/L and 0.012/0.25 mg/L, respectively (Table 1)
  - A total of 31.3% of *H. influenzae* isolates were β-lactamase positive (data not shown)
- A total of 82.5% of *Enterobacteriaceae* isolates were susceptible to ceftobiprole (MIC$_{50/90,}$ 0.03/>16 mg/L; Tables 1 and 3)
  - Non-ESBL screen phenotype *E. coli* and *K. pneumoniae* were mostly susceptible to ceftobiprole (99.8% for *E. coli* and 99.6% for *K. pneumoniae;* data not shown)
  - Ceftobiprole demonstrated a susceptibility profile similar to other expanded spectrum cephalosporins
  - *Enterobacteriaceae* were 88.8%S to cefepime, 81.9%S to ceftriaxone, and 85.9%S to ceftazidime (Table 3)
- Ceftobiprole inhibited 72.7% of *P. aeruginosa* isolates at ≤4 mg/L and inhibited 85.9% at ≤8 mg/L, while cefepime and ceftazidime inhibited 85.5% and 86.0% of *P. aeruginosa* isolates, respectively, at their susceptibility breakpoints (Tables 1 and 3)
- The activity of ceftobiprole against *Acinetobacter* spp. was limited (61.5% at ≤4 mg/L and 63.6% at ≤8 mg/L; Table 1)
- Ceftobiprole was inactive against almost all *Stenotrophomonas maltophilia* isolates (Table 1)

Conclusions

- Ceftobiprole demonstrated potent *in vitro* activity against gram-positive multidrug-resistant pathogens, including MRSA and drug-resistant *S. pneumoniae*
- Ceftobiprole *in vitro* activity against gram-negative pathogens, including *Enterobacteriaceae* and *P. aeruginosa,* was similar to other cephalosporins such as ceftazidime and cefepime
- Overall, the *in vitro* results of this 2016 surveillance study evaluating 12,001 bacterial organisms from across 9 US census areas confirm earlier reports demonstrating the broad-spectrum activity of ceftobiprole and its value in further study involving infections where multidrug-resistant pathogens may occur

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References

Clinical and Laboratory Standards Institute (2015). *M07-A10. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard—tenth edition*. Wayne, PA: CLSI.

Clinical and Laboratory Standards Institute (2017). *M100-S27. Performance standards for antimicrobial susceptibility testing: 27th informational supplement.* Wayne, PA: CLSI.

EUCAST (2017). Breakpoint tables for interpretation of MICs and zone diameters. Version 7.0, January 2017. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 2017.

Farrell DJ, Flamm RK, Sader HS, et al. (2014). Ceftobiprole activity against over 60,000 clinical bacterial pathogens isolated in Europe, Turkey, and Israel from 2005 to 2010. *Antimicrob Agents Chemother* 58: 3882–3888.

Farrell DJ, Flamm RK, Sader HS, et al. (2014). Activity of ceftobiprole against methicillin-resistant *Staphylococcus aureus* (MRSA) strains with reduced susceptibility to daptomycin, linezolid, vancomycin and strains with defined SCC*mec* types. *Int J Antimicrob Agents* 43: 323–327.

Fritsche TR, Sader HS, Jones RN (2008). 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* 61: 86-95.

Rossolini GM, Dryden MS, Kozlov RS, et al. (2011). Comparative activity of ceftobiprole against gram-positive and gram-negative isolates from Europe and the Middle East: the CLASS study. *J Antimicrob Chemother* 66: 151–159.

Table 3. Activity of ceftobiprole and comparator antimicrobial agents when tested against gram-negative bacteria from US surveillance (2016)

Organism (no.)/ antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a]		EUCAST[a]	
			%S	%R	%S	%R
***Haemophilus influenzae* (450)**						
Ceftobiprole	0.06	0.12				
Amoxicillin-clavulanic acid	1	2	99.1	0.9	92.0	8.0
Ampicillin	1	>8	59.6	32.0	59.6	40.4
Azithromycin	0.5	1	98.9		0.7	1.1
Cefepime	0.06	0.25	100.0		97.6	2.4
Ceftaroline	0.015	0.03	99.6		92.0	8.0
Ceftriaxone	0.004	0.015	100.0		99.1	0.9
Imipenem	0.5	2	98.9		98.0	2.0
Levofloxacin	0.015	0.03	100.0		98.0	2.0
Piperacillin-tazobactam	0.015	0.06	100.0	0.0	92.0	8.0
Tetracycline	0.5	1	99.8	0.2	99.6	0.2
Tigecycline	0.12	0.25	96.7			
Trimethoprim-sulfamethoxazole	0.12	>4	66.4	31.3	66.4	32.7
***Moraxella catarrhalis* (237)**						
Ceftobiprole	0.12	0.25				
Amoxicillin-clavulanic acid	0.12	0.25	100.0	0.0	100.0	0.0
Azithromycin	0.015	0.03	99.6		99.6	0.4
Cefepime	0.5	2			100.0	0.0
Ceftaroline	0.12	0.25				
Ceftazidime	0.06	0.25	100.0			
Ceftriaxone	0.25	0.5	100.0		99.6	0.0
Imipenem	≤0.03	0.06			100.0	0.0
Levofloxacin	0.03	0.06	100.0		100.0	0.0
Tetracycline	0.25	0.5	100.0	0.0	100.0	0.0
Tigecycline	0.06	0.06				
Trimethoprim-sulfamethoxazole	0.12	0.25	97.0	0.0	97.0	1.3
***Enterobacteriaceae* (4,469)**						
Ceftobiprole	0.03	>16			82.5	17.5
Ampicillin-sulbactam	16	>32	47.8	35.5	47.8	52.2
Aztreonam	0.12	>16	85.3	13.3	83.2	14.7
Cefepime	≤0.12	4	88.8	8.9	87.1	9.9
Ceftaroline	0.12	>32	75.5	20.4	75.5	24.5
Ceftazidime	0.25	16	85.9	12.3	82.9	14.1
Ceftriaxone	≤0.06	>8	81.9	17.1	81.9	17.1
Colistin	0.25	>8			82.6	17.4
Gentamicin	0.5	2	90.8	8.3	90.3	9.2
Imipenem	≤0.12	1	92.8	2.1	97.9	0.6
Levofloxacin	0.06	>4	82.2	15.9	78.3	19.0
Meropenem	0.03	0.06	98.7	1.1	98.9	0.6
Piperacillin-tazobactam	2	16	91.6	4.7	87.9	8.4
Tigecycline	0.25	1	97.7	0.1	92.9	2.3
Trimethoprim-sulfamethoxazole	≤0.5	>4	78.1	21.9	78.1	21.3
***Escherichia coli* (1,747)**						
Ceftobiprole	0.03	>16			82.5	17.5
Ampicillin-sulbactam	16	>32	48.5	31.3	48.5	51.5
Aztreonam	0.12	>16	84.3	13.6	81.7	15.7
Cefepime	≤0.12	>16	84.1	13.4	83.2	14.9
Ceftaroline	0.12	>32	78.5	19.4	78.5	21.5
Ceftazidime	0.25	16	85.9	11.7	82.4	14.1
Ceftriaxone	≤0.06	>8	82.0	17.7	82.0	17.7
Colistin	0.12	0.25			99.6	0.4
Gentamicin	0.5	>8	86.9	12.9	86.7	13.1
Imipenem	≤0.12	≤0.12	99.9	0.1	99.9	0.0
Levofloxacin	≤0.03	>4	67.6	30.3	66.3	32.7
Meropenem	≤0.015	0.03	99.9	0.1	99.9	0.0
Piperacillin-tazobactam	2	8	95.1	2.7	91.8	4.9
Tigecycline	0.12	0.25	99.9	0.0	99.9	0.1
Trimethoprim-sulfamethoxazole	≤0.5	>4	64.9	35.1	64.9	34.3
***Klebsiella pneumoniae* (959)**						
Ceftobiprole	0.03	>16			83.4	16.6
Ampicillin-sulbactam	8	>32	71.7	19.7	71.7	28.3
Aztreonam	0.06	>16	85.6	13.9	84.3	14.4
Cefepime	≤0.12	>16	86.7	11.7	85.7	12.5
Ceftaroline	0.12	>32	80.4	17.5	80.4	19.6
Ceftazidime	0.25	>32	85.6	13.1	83.1	14.4
Ceftriaxone	≤0.06	>8	84.5	15.2	84.5	15.2
Colistin	0.12	0.25			98.4	1.6
Gentamicin	0.25	1	91.0	7.4	90.8	9.0
Imipenem	≤0.12	0.25	97.0	2.8	97.2	2.0
Levofloxacin	0.06	2	91.0	7.2	86.1	10.1
Meropenem	0.03	0.03	97.0	2.6	97.4	2.4
Piperacillin-tazobactam	2	16	90.6	6.3	84.9	9.4
Tigecycline	0.25	1	98.6	0.0	95.2	1.4
Trimethoprim-sulfamethoxazole	≤0.5	>4	82.2	17.8	82.2	17.3
***Enterobacter* spp. (596)**						
Ceftobiprole	0.06	4			80.0	20.0
Ampicillin-sulbactam	32	>32	13.1	65.0	13.1	86.9
Aztreonam	0.12	>16	73.2	25.0	71.3	26.8
Cefepime	≤0.12	2	92.6	3.9	86.2	4.9
Ceftaroline	0.25	>32	67.3	29.2	67.3	32.7
Ceftazidime	0.5	>32	71.8	26.5	69.6	28.2
Ceftriaxone	0.25	>8	69.1	29.4	69.1	29.4
Colistin	0.12	>8			85.0	15.0
Gentamicin	0.25	0.5	95.6	3.5	95.3	4.4
Imipenem	0.25	1	97.5	2.0	98.0	0.2
Levofloxacin	≤0.03	0.5	95.6	3.0	91.8	5.7
Meropenem	0.03	0.06	97.7	2.0	98.0	0.2
Piperacillin-tazobactam	2	64	78.8	9.1	75.1	21.2
Tigecycline	0.25	1	99.0	0.0	94.8	1.0
Trimethoprim-sulfamethoxazole	≤0.5	1	91.1	8.9	91.1	8.9
***Pseudomonas aeruginosa* (1,017)**						
Ceftobiprole	2	16				
Amikacin	4	8	96.7	2.0	91.5	3.3
Ampicillin-sulbactam	>32	>32				
Aztreonam	8	>16	72.3	17.0	5.9	17.0
Cefepime	2	16	85.5	2.9	85.5	14.5
Ceftaroline	16	>32				
Ceftazidime	2	16	86.0	9.6	86.0	14.0
Colistin	1	2	99.6	0.4	99.6	0.4
Gentamicin	2	8	86.5	7.0	86.5	13.5
Imipenem	1	8	78.1	18.3	81.7	8.9
Levofloxacin	0.5	4	76.3	16.2	66.7	33.3
Piperacillin-tazobactam	4	64	80.8	8.8	80.8	19.2
Tigecycline	>8	>8				
Trimethoprim-sulfamethoxazole	>4	>4				

[a] Criteria as published by CLSI [2017] and EUCAST [2017]; CLSI tigecycline breakpoints do not exist so US FDA breakpoints were used