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Antimicrobial Activity of Ceftobiprole versus Other Currently Marketed Cephalosporins and β-Lactams When Tested against Contemporary Gram-Positive and -Negative Organisms Collected from Europe (2015)

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Abstract

Background: Ceftobiprole (active form of the prodrug ceftobiprole medocaril) is a fifth-generation cephalosporin with an expanded spectrum and potent activity against Gram-positive and -negative bacteria. It is approved for marketing in various European countries for the treatment of hospital-acquired pneumonia (excluding ventilator-associated pneumonia) and community-acquired pneumonia in adults. Ceftobiprole is active *in vitro* against methicillin-resistant staphylococci, including *Staphylococcus aureus* (MRSA) and multidrug-resistant *Streptococcus pneumoniae*. It is generally β-lactamase stable with activity against *Enterobacteriaceae* and *Pseudomonas aeruginosa*.

Materials/methods: A total of 12,240 clinically relevant isolates (1 per patient episode) were collected from patients at 37 medical centres located in Europe (34), Turkey (2), and Israel (1) in 2015. Isolates were from multiple infection sites, including bloodstream, respiratory, skin and soft tissue, urinary tract, and others. Susceptibility testing of ceftobiprole, comparators, and quality-control organisms using broth microdilution panels followed Clinical and Laboratory Standards Institute guidelines. EUCAST interpretive criteria were applied.

Results: Ceftobiprole and ceftaroline were highly active when tested against 2,588 *S. aureus* isolates (22.4% methicillin resistant). Against MRSA, the percentage of susceptibility to ceftobiprole ($MIC_{50/90}$; 2/2 mg/L; 96.5% susceptible) was higher than for ceftaroline ($MIC_{50/90}$; 1/2 mg/L; 86.2% susceptible). All MRSA isolates were susceptible to linezolid and vancomycin. Ceftobiprole ($MIC_{50/90}$; 0.5/2 mg/L) and ceftaroline ($MIC_{50/90}$; 0.25/1 mg/L) also demonstrated potent activity against coagulase-negative staphylococci. Good potency was demonstrated by ceftobiprole against *Enterococcus faecalis* ($MIC_{50/90}$ values of 0.5/2 mg/L), while ceftaroline was 4-fold less active against these strains, with MIC_{50} and MIC_{90} values of 2 and 8 mg/L, respectively. All *E. faecalis* isolates were susceptible to daptomycin and tigecycline. Ceftobiprole, ceftaroline, and ampicillin displayed limited activity against *E. faecium* isolates (MIC_{50}; >4 mg/L), regardless of vancomycin susceptibility. Of the β-lactam agents tested, ceftobiprole (99.3% susceptible), ceftaroline (99.9% susceptible), and imipenem (100.0% susceptible) were the most active against *S. pneumoniae*. A high degree of potency was shown by ceftobiprole against viridans group streptococci ($MIC_{50/90}$; 0.06/0.25 mg/L) and β-haemolytic streptococci (MIC_{50}; 0.03 mg/L). For *Enterobacteriaceae*, 73.8% of isolates tested were susceptible to ceftobiprole, which was similar to the rates for cefepime (78.2%), ceftazidime (74.2%), and ceftriaxone (73.3%) and greater than ceftaroline (66.1%). Ceftobiprole and ceftaroline inhibited 70.4% and 20.0% of *P. aeruginosa* at ≤ 4 mg/L, respectively, while cefepime and ceftazidime exhibited 82.6% and 77.0% susceptibility. Ceftobiprole inhibited all isolates of *Haemophilus influenzae* and *Moraxella catarrhalis* at ≤ 0.5 mg/L, while ceftaroline inhibited all isolates at ≤0.25 mg/L.

Conclusions: Ceftobiprole was active *in vitro* against a broad range of clinically relevant Gram-positive and Gram-negative bacterial isolates from Europe, Turkey, and Israel. Ceftobiprole *in vitro* offers advantages in potency and spectrum when compared to currently marketed cephalosporins and other β-lactams.

Introduction

- Ceftobiprole is a parenteral fifth-generation cephalosporin that is active against Gram-positive and -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*
- This agent is administered as the prodrug ceftobiprole medocaril, which is rapidly hydrolyzed *in vivo* to the active form of ceftobiprole
- Ceftobiprole has received national licenses for the treatment of 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
- This study evaluated ceftobiprole and comparator antimicrobial agents against more than 12,000 isolates collected at 37 medical centres from patients in Europe, Turkey, and Israel during 2015

Materials and Methods

Bacterial isolates

- 12,240 bacterial isolates were collected prospectively from patients in 34 medical centres in Europe, 2 in Turkey, and 1 in Israel
- Isolate numbers ranged from 164 from Romania to 1,803 from Germany
  - Isolates were collected from a variety of infection types that included bloodstream, respiratory, skin and soft tissue, urinary, and others
  - Species identification was confirmed by matrix-assisted laser desorption ionization-time of flight mass spectrometry, when necessary, using the Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, USA) by following manufacturer instructions

Susceptibility testing

- Ceftobiprole, comparators, and quality-control organisms were tested according to Clinical and Laboratory Standards Institute guidelines using broth microdilution panels
  - EUCAST (2017) interpretive criteria were applied
- For *Klebsiella* spp., *Escherichia coli*, and *Proteus mirabilis* in this analysis, an extended-spectrum β-lactamase (ESBL) screen-positive phenotype was defined as an MIC of ≥2 mg/L for ceftazidime and/or ceftriaxone and/or aztreonam
  - Although other β-lactamases, such as *Amp*C and KPC, may also produce an “ESBL screening-positive phenotype,” these strains were grouped because they usually demonstrate resistance to various broad-spectrum β-lactam compounds

Results

- $MIC_{50/90}$ for ceftobiprole when tested against *S. aureus* was 0.5/2 mg/L (99.2% susceptible; Tables 1 and 2)
  - 22.4% of *S. aureus* isolates were methicillin-resistant *S. aureus* (MRSA)
  - $MIC_{50/90}$ for MRSA and methicillin-susceptible *S. aureus* (MSSA) were 2/2 and 0.5/0.5 mg/L, respectively (Tables 1 and 2)
  - Ceftobiprole and ceftaroline were the most potent cephalosporins tested against 2,009 MSSA isolates and were 8- to 16-fold more potent than ceftriaxone (data not shown)
  - Only 86.2% of MRSA isolates were susceptible to ceftaroline while 96.5% were susceptible to ceftobiprole (Table 2)
    - Erythromycin resistance (68.0%) and levofloxacin resistance (83.4%) were high (Table 2)
- $MIC_{50/90}$ for ceftobiprole against 526 isolates of coagulase-negative staphylococci (CoNS) was 0.5/2 mg/L and all MIC values were ≤8 mg/L (Tables 1 and 2)
  - $MIC_{50/90}$ for MR-CoNS and MS-CoNS were 1/4 and 0.12/0.5 mg/L, respectively (Tables 1 and 2)
  - Ceftaroline ($MIC_{50/90}$; 0.25/1 mg/L) and ceftobiprole ($MIC_{50/90}$; 0.5/2 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; n=411), but not against *E. faecium* ($MIC_{50/90}$; >4/>4 mg/L; n=235, Table 1)
- β-lactam agents that exhibited high levels of activity when tested against *S. pneumoniae* (n=833) included ceftobiprole ($MIC_{50/90}$; 0.015/0.5 mg/L; 99.3% susceptible), ceftaroline (99.9% susceptible), and imipenem (100.0% susceptible; Table 2)
- The $MIC_{50/90}$ for ceftobiprole against 498 isolates of β-haemolytic streptococci were 0.015/0.03 mg/L (highest MIC, 0.12 mg/L; Table 1)
- Ceftaroline, ceftobiprole, and meropenem were the most active β-lactam agents tested against viridans group streptococci ($MIC_{50/90}$; 0.015/0.06 mg/L for ceftaroline; $MIC_{50/90}$; 0.06/0.25 mg/L for ceftobiprole; $MIC_{50/90}$; 0.03/0.25 mg/L for meropenem; Table 1)
- All isolates of *H. influenzae* were inhibited at a ceftobiprole MIC at ≤0.5 mg/L (Table 1)
  - A total of 14.3% of isolates were β-lactamase positive (data not shown)
- A total of 73.8% 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 (99.3% for *E. coli* and for *K. pneumoniae*; Table 1)
  - Ceftobiprole demonstrated a susceptibility profile similar to that of other expanded spectrum cephalosporins
  - Susceptibility against *Enterobacteriaceae* for cefepime was 78.2%, 73.3% for ceftriaxone, and 74.2% for ceftazidime (Table 3)
- A total of 70.4% of *P. aeruginosa* isolates were inhibited at ≤4 mg/L and 82.3% at ≤8 mg/L, while cefepime and ceftazidime inhibited 82.6% and 77.0% of the isolates at their susceptibility breakpoints, respectively (Table 3)
- The activity of ceftobiprole against *Acinetobacter* spp. was limited (24.2% at ≤4 mg/L and 24.7% at 8 mg/L) (Table 1)
- Ceftobiprole was inactive against almost all *Stenotrophomonas maltophilia* isolates (Table 1)

Table 1 Antimicrobial activity of ceftobiprole when tested against the main organisms and organism groups of isolates included as part of European surveillance studies for 2015

Organism / organism group (no. of isolates)	No. of isolates at MIC (mg/L; cumulative %)																	
	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	>	MIC_{50}	MIC_{90}
Staphylococcus aureus (2,588)						4 (0.2%)	2 (0.2%)	729 (28.7%)	1,301 (78.9%)	234 (88.0%)	291 (99.2%)	20 (100.0%)					0.5	2
MSSA (2,009)						4 (0.2%)	2 (0.3%)	7 (0.6%)	729 (36.9%)	1,267 (100.0%)							0.5	0.5
MRSA (579)									0 (0.0%)	34 (5.9%)	234 (46.3%)	291 (96.5%)	20 (100.0%)				2	2
Coagulase-negative staphylococci (526)						13 (2.5%)	20 (6.3%)	72 (20.0%)	64 (32.1%)	97 (50.6%)	164 (81.7%)	48 (90.9%)	45 (99.4%)	3 (100.0%)			0.5	2
MS-CoNS (190)						12 (6.3%)	20 (16.8%)	72 (54.7%)	57 (84.7%)	27 (98.9%)	2 (100.0%)						0.12	0.5
MR-CoNS (336)						1 (0.3%)	0 (0.3%)	0 (0.3%)	7 (2.4%)	70 (23.2%)	162 (71.4%)	48 (85.7%)	45 (99.1%)	3 (100.0%)			1	4
Enterococcus spp. (646)								60 (9.3%)	108 (26.0%)	165 (51.5%)	18 (54.3%)	37 (60.1%)	28 (64.4%)			230 (100.0%)	0.5	>4
Enterococcus faecalis (411)								60 (14.6%)	107 (40.6%)	161 (79.6%)	13 (83.0%)	32 (90.8%)	21 (95.9%)			17 (100.0%)	0.5	2
Enterococcus faecium (235)								0 (0.0%)	1 (0.4%)	4 (2.1%)	5 (4.3%)	5 (6.4%)	7 (9.4%)			213 (100.0%)	>4	>4
Streptococcus pneumoniae (833)			12 (1.4%)	290 (36.3%)	280 (69.9%)	55 (76.5%)	17 (78.5%)	22 (81.2%)	55 (87.8%)	96 (99.3%)	3 (99.6%)	3 (100.0%)					0.015	0.5
Viridans group streptococci (264)		0 (0.0%)	2 (0.8%)	13 (5.7%)	62 (29.2%)	48 (47.3%)	72 (74.6%)	28 (85.2%)	17 (91.7%)	9 (95.1%)	4 (98.5%)						0.06	0.25
Beta-haemolytic streptococci (498)	0 (0.0%)	2 (0.4%)	5 (1.4%)	206 (42.8%)	122 (67.3%)	160 (99.4%)	2 (99.8%)	1 (100.0%)			1						0.015	0.03
Enterobacteriaceae (4,646)				55 (1.2%)	589 (13.9%)	1,912 (55.0%)	585 (67.6%)	190 (71.7%)	99 (73.8%)	67 (75.3%)	40 (76.1%)	47 (77.2%)	48 (78.0%)	40 (78.4%)	19 (78.9%)	24 (79.4%)	978 (100.0%)	0.03	>16
Escherichia coli (2,123)				20 (0.9%)	314 (15.7%)	1,006 (63.1%)	254 (75.1%)	59 (77.9%)	23 (78.9%)	15 (79.7%)	5 (79.9%)	7 (80.2%)	3 (80.4%)	5 (80.6%)	7 (80.9%)	7 (81.2%)	405 (100.0%)	0.03	>16
ESBL-screen phenotype (467)				0 (0.0%)	1 (0.2%)	7 (1.7%)	7 (3.2%)	8 (4.9%)	8 (6.6%)	8 (8.6%)	4 (9.4%)	4 (10.3%)	3 (10.9%)	5 (12.0%)	7 (13.5%)	7 (15.0%)	404 (100.0%)	>16	>16
Non-ESBL-screen phenotype (1,656)				20 (1.2%)	313 (20.1%)	999 (60.4%)	247 (75.4%)	51 (78.4%)	15 (79.3%)	6 (79.7%)	1 (79.8%)	3 (79.9%)	0 (99.9%)	0 (99.9%)	0 (99.9%)	1 (100.0%)	0.03	0.06
Klebsiella pneumoniae (853)				4 (0.5%)	96 (11.7%)	247 (40.7%)	64 (48.2%)	21 (50.6%)	6 (51.2%)	1 (51.9%)	5 (52.1%)	5 (52.6%)	3 (53.0%)	2 (53.2%)	4 (53.7%)	395 (100.0%)	0.12	>16
ESBL-screen phenotype (421)					0 (0.0%)	2 (0.5%)	2 (1.0%)	3 (1.7%)	1 (1.9%)	6 (3.3%)	1 (3.6%)	4 (4.5%)	3 (5.2%)	2 (5.7%)	4 (6.4%)	394 (100.0%)	>16	>16
Non-ESBL-screen phenotype (432)				4 (0.9%)	96 (23.1%)	245 (79.9%)	62 (94.2%)	18 (98.4%)	4 (99.3%)	2 (99.3%)	0 (99.3%)	1 (99.5%)	0 (99.5%)	0 (99.5%)	1 (99.8%)	1 (100.0%)	0.03	0.06
Klebsiella oxytoca (188)				0 (0.0%)	2 (1.1%)	24 (13.8%)	27 (28.2%)	31 (44.7%)	39 (65.4%)	21 (76.6%)	9 (81.4%)	0 (81.4%)	0 (81.4%)	1 (81.9%)	1 (82.4%)	33 (100.0%)	0.25	>16
ESBL-screen phenotype (35)													0 (0.0%)	1 (2.9%)	1 (5.7%)	33 (100.0%)	>16	>16
Non-ESBL-screen phenotype (153)				0 (0.0%)	2 (1.3%)	24 (17.0%)	27 (34.6%)	31 (54.9%)	39 (80.4%)	21 (94.1%)	9 (100.0%)						0.12	0.5
Enterobacter spp. (501)				2 (0.4%)	29 (6.2%)	207 (47.5%)	88 (65.1%)	32 (69.5%)	9 (71.3%)	4 (72.1%)	11 (74.3%)	23 (78.8%)	26 (84.0%)	6 (85.2%)	6 (86.4%)	68 (100.0%)	0.06	>16
Citrobacter spp. (198)				0 (0.0%)	21 (10.6%)	122 (72.2%)	19 (81.8%)	4 (83.8%)	2 (83.8%)	1 (84.3%)	7 (85.4%)	8 (88.9%)	2 (92.9%)	1 (93.9%)	1 (94.4%)	2 (95.5%)	0.03	2
Proteus mirabilis (325)				6 (1.8%)	73 (24.3%)	177 (78.8%)	20 (84.9%)	9 (87.7%)	5 (88.3%)	2 (88.9%)	5 (90.5%)	2 (92.0%)	4 (93.2%)	2 (93.8%)	3 (94.8%)	1 (95.1%)	0.03	0.5
Indole-positive *Proteus* spp. (202)				22 (10.9%)	48 (34.7%)	82 (75.2%)	5 (77.2%)	0 (78.2%)	0 (78.2%)	0 (78.7%)	1 (79.2%)	0 (79.2%)	1 (79.7%)	0 (79.7%)	1 (80.2%)	38 (100.0%)	0.03	>16
Serratia spp. (203)				0 (0.0%)	4 (2.0%)	34 (18.7%)	98 (67.0%)	35 (85.2%)	37 (91.6%)	13 (95.1%)	1 (95.6%)	0 (95.6%)	0 (95.6%)	1 (96.1%)	0 (96.1%)	8 (100.0%)	0.06	0.25
Pseudomonas aeruginosa (1,064)							2 (0.2%)	8 (0.9%)	46 (5.3%)	315 (34.9%)	243 (57.7%)	135 (70.4%)	127 (82.3%)	45 (86.6%)		143 (100.0%)	2	>16
Acinetobacter spp. (356)							29 (8.1%)	30 (16.6%)	18 (21.6%)	6 (23.3%)	1 (23.6%)	2 (24.2%)	2 (24.7%)	1 (25.0%)	1 (25.3%)	259 (100.0%)	>16	>16
Stenotrophomonas maltophilia (159)												0 (0.0%)	1 (0.6%)	1 (1.3%)		157 (100.0%)	>16	>16
Haemophilus influenzae (428)				0 (0.0%)	38 (8.4%)	202 (55.6%)	144 (89.3%)	40 (98.6%)	5 (99.8%)	1 (100.0%)							0.03	0.12
Beta-lactamase-positive (61)				0 (0.0%)	3 (4.9%)	40 (70.5%)	13 (91.8%)	4 (98.4%)	1 (100.0%)								0.03	0.06
Beta-lactamase-negative (367)				0 (0.0%)	33 (9.0%)	162 (53.1%)	131 (88.8%)	36 (98.6%)	4 (99.7%)	1 (100.0%)							0.03	0.12
Haemophilus parainfluenzae (6)				0 (0.0%)	1 (16.7%)	3 (66.7%)	0 (66.7%)	1 (83.3%)	1 (100.0%)								0.03	—
Moraxella catarrhalis (226)					37 (16.4%)	36 (32.3%)	59 (58.4%)	74 (91.2%)	19 (99.6%)	1 (100.0%)							0.06	0.12

Table 2 Activity of ceftobiprole and comparator antimicrobial agents when tested against Gram-positive pathogens from Europe, Turkey, and Israel (2015)

Organism (no. of isolates) / antimicrobial agent	MIC_{50}	MIC_{90}	EUCAST* %S	EUCAST* %R
S. aureus (2,588)				
Ceftobiprole	0.5	2	99.2	0.8
Ceftaroline	0.25	1	96.9	3.1
Ceftriaxone	4	>8	—[3]	—
Clindamycin	≤0.25	≤0.25	91.6	8.1
Daptomycin	0.25	0.5	100.0	0.0
Erythromycin	0.25	>8	71.4	27.2
Gentamicin	≤1	≤1	94.7	5.3
Levofloxacin	0.25	>4	77.6	22.0
Linezolid	1	1	100.0	0.0
Oxacillin	0.5	>2	77.6	22.4
Tetracycline	≤0.5	≤0.5	92.2	7.7
Tigecycline	0.06	0.12	100.0	0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	99.8	0.1
Vancomycin	0.5	1	100.0	0.0
MRSA (579)				
Ceftobiprole	2	2	96.5	3.5
Ceftaroline	1	2	86.2	13.8
Ceftriaxone	>8	>8	—	—
Clindamycin	≤0.25	>2	68.6	31.3
Daptomycin	0.25	0.5	100.0	0.0
Erythromycin	>8	>8	30.3	68.0
Gentamicin	≤1	>8	85.7	14.3
Levofloxacin	>4	>4	16.1	83.4
Linezolid	1	1	100.0	0.0
Tetracycline	≤0.5	>8	85.8	14.2
Tigecycline	0.12	0.12	100.0	0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	99.3	0.3
Vancomycin	0.5	1	100.0	0.0
Coagulase-negative staphylococci (526)				
Ceftobiprole	0.5	2	—	—
Ceftaroline	0.25	1	—	—
Ceftriaxone	>8	>8	—	—
Clindamycin	≤0.25	>2	75.1	23.6
Daptomycin	0.5	0.5	100.0	0.0
Erythromycin	>8	>8	39.2	59.9
Gentamicin	≤1	>8	55.5	44.5
Levofloxacin	2	>4	49.6	45.2
Linezolid	0.5	1	99.4	0.6
Oxacillin	>2	>2	36.1	63.9
Tetracycline	≤0.5	>8	82.5	16.0
Tigecycline	0.06	0.25	100.0	0.0
Trimethoprim-sulfamethoxazole	≤0.5	>4	70.7	13.3
Vancomycin	1	2	100.0	0.0
Enterococcus spp. (646)				
Ceftobiprole	0.5	>4	—	—
Ampicillin	1	>8	66.9	33.1
Ceftaroline	2	>8	—	—
Daptomycin	1	2	—	—
Levofloxacin	2	>4	51.9	48.1[4]
Linezolid	1	2	99.7	0.3
Teicoplanin	≤2	≤2	94.0	6.0
Tigecycline	0.06	0.12	100.0	0.0
Vancomycin	1	2	93.2	6.8
Streptococcus pneumoniae (833)				
Ceftobiprole	0.015	0.5	99.3	0.7
Ceftaroline	≤0.008	0.12	99.9	0.1
Ceftriaxone	0.03	1	86.4	0.7
Clindamycin	≤0.12	>1	82.2	17.8
Erythromycin	0.03	>2	75.0	24.8
Imipenem	≤0.015	0.25	100.0	0.0
Levofloxacin	1	1	98.1	1.9
Linezolid	1	1	100.0	0.0
Penicillin	≤0.06	2	70.9	29.1[4]
			70.9	4.0[5]
Tetracycline	0.25	>4	76.1	23.5
Trimethoprim-sulfamethoxazole	≤0.5	4	77.0	18.0
Vancomycin	0.25	0.25	100.0	0.0
β-haemolytic streptococci (498)				
Ceftobiprole	0.015	0.03	—	—
Ceftaroline	≤0.008	0.015	100.0	0.0
Ceftriaxone	≤0.03	0.06	100.0	0.0
Clindamycin	0.06	0.25	90.6	9.4
Daptomycin	0.12	0.25	100.0	0.0
Erythromycin	≤0.03	4	83.3	15.9
Levofloxacin	0.5	1	97.0	1.4
Linezolid	1	1	100.0	0.0
Meropenem	≤0.008	0.06	100.0	0.0
Penicillin	≤0.03	0.06	100.0	0.0
Tetracycline	≤0.25	>8	52.8	47.0
Vancomycin	0.25	0.5	100.0	0.0
Viridans streptococci (264)				
Ceftobiprole	0.06	0.25	—	—
Ceftaroline	0.015	0.06	—	—
Ceftriaxone	0.12	0.5	92.4	7.6
Clindamycin	≤0.015	0.5	90.2	9.8
Daptomycin	0.25	0.5	—	—
Erythromycin	≤0.03	>4	—	—
Levofloxacin	1	2	—	—
Linezolid	0.5	1	—	—
Meropenem	0.03	0.25	100.0	0.0
Penicillin	0.06	1	82.6	3.4
Vancomycin	0.5	0.5	100.0	0.0

* Criteria as published by EUCAST [2017]
[3] No interpretive criteria
[4] Non-meningitis breakpoints used
[5] Meningitis breakpoints used

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 2015 surveillance study evaluating 12,040 bacterial organisms from Europe, Turkey, and Israel confirms earlier reports demonstrating the wide-spectrum nature of ceftobiprole activity

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Table 3 Activity of ceftobiprole and comparator antimicrobial agents when tested against Gram-negative pathogens from Europe, Turkey, and Israel (2015)

Organism (no. of isolates) / antimicrobial agent	MIC_{50}	MIC_{90}	EUCAST* %S	EUCAST* %R
Haemophilus influenzae (428)				
Ceftobiprole	0.03	0.12	—[3]	—
Amoxicillin-clavulanic acid	0.5	2	98.4	1.6
Azithromycin	0.5	1	1.4	0.2
Cefepime	0.06	0.12	99.5	0.5
Ceftaroline	0.008	0.015	98.6	1.4
Ceftriaxone	≤0.015	≤0.015	100.0	0.0
Imipenem	0.5	1	97.4	2.6
Levofloxacin	≤0.015	≤0.015	100.0	0.0
Piperacillin-tazobactam	≤0.015	0.03	98.4	1.6
Tetracycline	0.5	0.5	99.8	0.2
Trimethoprim-sulfamethoxazole	0.06	>4	70.1	26.9
Enterobacteriaceae (4,646)				
Ceftobiprole	0.03	>16	73.8	26.2
Aztreonam	≤0.12	>16	74.6	22.8
Cefepime	0.06	>64	78.2	18.0
Ceftaroline	0.25	>32	66.1	33.9
Ceftazidime	0.25	>32	74.2	21.8
Ceftriaxone	≤0.06	>8	73.3	26.0
Gentamicin	0.5	>8	85.7	13.8
Imipenem	≤0.12	1	96.3	1.4
Levofloxacin	0.06	>4	73.6	24.5
Meropenem	0.03	0.06	97.1	1.9
Piperacillin-tazobactam	2	64	81.7	14.4
Tigecycline	0.25	1	92.2	17.4
Trimethoprim-sulfamethoxazole	≤0.5	>4	68.4	30.7
Escherichia coli (2,123)				
Ceftobiprole	0.03	>16	78.9	21.1
Aztreonam	≤0.12	>16	78.8	18.9
Cefepime	0.06	64	79.5	17.0
Ceftaroline	0.12	>32	72.2	27.8
Ceftazidime	0.25	16	79.7	15.5
Ceftriaxone	≤0.06	>8	79.0	20.7
Gentamicin	0.5	>8	87.1	12.8
Imipenem	≤0.12	≤0.12	99.8	0.0
Levofloxacin	≤0.03	>4	68.0	31.5
Meropenem	≤0.015	0.03	99.8	0.1
Piperacillin-tazobactam	2	16	88.2	8.5
Tigecycline	0.12	0.25	99.8	0.0
Trimethoprim-sulfamethoxazole	≤0.5	>4	62.4	36.9
Klebsiella pneumoniae (853)				
Ceftobiprole	0.12	>16	51.2	48.8
Aztreonam	0.25	>16	52.1	46.9
Piperacillin-tazobactam	≤0.015	0.03	98.4	1.6
Ceftaroline	2	>32	48.5	51.5
Ceftazidime	1	>32	51.3	47.0
Ceftriaxone	0.25	>8	51.9	47.6
Gentamicin	0.25	>8	72.8	27.0
Imipenem	≤0.12	8	86.8	7.6
Levofloxacin	0.5	>4	62.0	34.9
Meropenem	0.03	8	85.6	9.7
Piperacillin-tazobactam	4	>128	61.3	32.9
Tigecycline	0.25	1	93.0	0.8
Trimethoprim-sulfamethoxazole	≤0.5	>4	56.9	42.0
Pseudomonas aeruginosa (1,064)				
Ceftobiprole	2	>16	—	—
Amikacin	4	32	84.2	10.2
Aztreonam	4	>16	5.7	16.6
Cefepime	2	16	82.6	17.4
Ceftaroline	16	>32	—	—
Ceftazidime	2	32	77.0	23.0
Colistin	≤0.5	1	99.9	0.1
Gentamicin	2	>8	78.8	21.2
Imipenem	1	>8	72.4	13.8
Levofloxacin	0.5	>4	60.9	30.8
Piperacillin-tazobactam	4	>64	72.9	27.1
Trimethoprim-sulfamethoxazole	4	>4	—	—

* Criteria as published by EUCAST [2017]
[3] No interpretive criteria