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In Vitro Activity of Ceftaroline Tested Against Leading Gram-Positive and Gram-Negative European Bacterial Pathogens Collected in 2009

M. CASTANHEIRA, R.N. JONES, H.S. SADER

JMI Laboratories, North Liberty, Iowa, USA

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JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
ph. 319.665.3370, fax 319.665.3371
helio-sader@jmilabs.com

Amended Abstract

Objective: To evaluate the activity of ceftaroline (CPT) against prevalent Gram-positive and -negative pathogens isolated in Europe during 2009. CPT is a novel, parenteral, broad-spectrum cephalosporin exhibiting bactericidal activity against methicillin-resistant *S. aureus* (MRSA) and multidrug-resistant *S. pneumoniae*, as well as against common Gram-negative pathogens.

Methods: A total of 4212 consecutive, nonduplicate isolates from bloodstream, skin and skin structure, and respiratory tract infections were collected from 24 medical centres in Europe, Turkey, and Israel during 2009. Species identification was confirmed by the central monitoring laboratory and all isolates were tested for susceptibility (S) to CPT and comparator agents using reference CLSI broth microdilution methods.

Results: CPT inhibited 99.9% of *S. aureus* strains (22.5% were MRSA) at ≤2 mg/L. One MRSA strain (0.1% of all *S. aureus* strains tested) exhibited an MIC of 4 mg/L upon initial testing, but repeat testing showed its MIC to be 2 mg/L. CPT MIC_{90} of MRSA strains was 2 mg/L, at least 16-fold lower than both ceftriaxone (CRO) and cefepime (FEP). CPT activity against coagulase-negative staphylococci (CoNS; 83.3% methicillin resistant) was similar to that against *S. aureus*. CPT inhibited all tested *S. pneumoniae* at ≤0.25 mg/L. Against 19 (3.9%) penicillin-resistant pneumococci (MIC ≥2 mg/L), CPT MIC_{50} and MIC_{90} values were 4- to 32-fold lower than values for all other beta-lactams. All β-haemolytic streptococci (BHS) and all but one viridans group streptococci (VGS) were inhibited at ≤0.25 and ≤0.5 mg/L, respectively. CPT MIC_{90} values for BHS and VGS (0.03 and 0.06 mg/L, respectively) were lower than those of penicillin, CRO, and FEP against these streptococci groups. CPT activity against Enterobacteriaceae (MIC_{50} 0.12 mg/L) was similar to CRO and FEP (MIC_{50}S ≤0.25 and ≤0.12 mg/L, respectively). Extended-spectrum beta-lactamase (ESBL) phenotype was observed in 12.2% of *E. coli* and 20.0% of *Klebsiella* spp., and all cephalosporins tested showed limited activity against ESBL-producing strains. *H. influenzae* strains were highly S to CPT (MIC_{90}, 0.015 mg/L).

	Cumulative % at CPT MIC (mg/L)					MIC (mg/L)	
Organism (no. tested)	**≤0.25**	**0.5**	**1**	**2**	**4**	**50%**	**90%**
S. aureus (1,200)	69.0	86.4	97.1	100.0	-	0.25	1
MRSA (270)	2.9	40.0	87.4	100.0	-	1	2
CoNS (432)	54.6	84.9	92.8	100.0	-	0.25	1
S. pneumoniae[a] (485)	100.0	-	-	-	-	≤0.008	0.12
BHS (195)	100.0	-	-	-	-	≤0.008	0.03
VGS (80)	97.5	98.8	98.8	98.8	100.0	0.03	0.06
E. faecalis (357)	-	2.2	28.3	65.8	72.5	2	8
E. coli (788)	75.2	81.7	85.6	87.8	89.0	0.12	16
Klebsiella spp. (294)	69.7	75.1	78.6	80.3	81.3	0.12	>32
Enterobacter spp. (146)	52.7	60.3	63.7	68.5	69.9	0.25	>32
H. influenzae (235)	100.0	-	-	-	-	≤0.008	0.015

a. Includes 19 (3.9%) penicillin-resistant strains (MIC ≥2 mg/L)

Conclusions: CPT demonstrated enhanced activity against European staphylococci, including MRSA, different streptococcal groups, and *H. influenzae*. CPT also demonstrated activity against Enterobacteriaceae that is similar to currently available broad-spectrum cephalosporins.

Introduction

Ceftaroline fosamil (formerly PPI-0903 and TAK-599) is an N-phosphonoamino water-soluble prodrug cephalosporin possessing broad-spectrum antimicrobial activity. Its bioactive form, ceftaroline, is released in vivo upon hydrolysis of the phosphonate group. This parenteral cephalosporin has demonstrated high affinity for penicillin-binding proteins (PBPs) 1a, 2a, 2b, and 2x and bactericidal activity against Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Streptococcus pneumoniae* (MDRSP), while also retaining activity against many Gram-negative bacilli.

Ceftaroline fosamil is currently under review for approval in the US. Encouraging results have been reported from phase II and III trials on the efficacy and safety of ceftaroline fosamil for treatment of complicated skin and skin structure infections (cSSSI) and from phase III community-acquired bacterial pneumonia (CABP) trials for the treatment of infections caused by Gram-positive pathogens, including multidrug-resistant staphylococci and streptococci and common Gram-negative species, including *Haemophilus influenzae*.

The present study was conducted to evaluate and compare the in vitro antimicrobial activity and spectrum of ceftaroline with those of other commonly used agents against clinical bacterial isolates from European medical centers (2009), including those with common resistance phenotypes.

Materials and Methods

Bacterial Isolates

A total of 4212 nonduplicate clinically significant isolates were consecutively collected in 2009 from 24 medical centers in 9 European countries, Turkey, and Israel. Gram-positive strains included *S. aureus* (n=1200; 22.5% MRSA), coagulase-negative staphylococci (CoNS; n=432; 83.3% oxacillin-resistant), *S. pneumoniae* (n=485), β-haemolytic streptococci (n=195), viridans group streptococci (n=80), and *Enterococcus faecalis* (n=357). Gram-negative strains included *Escherichia coli* (n=788; 11.9% extended-spectrum β-lactamase [ESBL] phenotype), *Klebsiella* spp. (n=294; 20.7% ESBL phenotype), *Enterobacter* spp. (n=146; 20.8% AmpC phenotype), and *H. influenzae* (n=235; 17.9% β-lactamase positive).

Susceptibility Testing

Broth microdilution methods were performed according to the Clinical and Laboratory Standards Institute (CLSI; M07-A8, 2009) to determine the antimicrobial susceptibility of each organism. Validated MIC panels manufactured by TREK Diagnostics (Cleveland, Ohio, USA) were used. All strains were tested in cation-adjusted Mueller-Hinton (MH) broth with the exception of *Streptococcus* spp. (MH broth supplemented with 2-5% lysed horse blood) and *H. influenzae* (Haemophilus Test Medium). Susceptibility percentage rates were based on the CLSI M100-S20 and EUCAST breakpoints. Concurrent testing of ATCC quality control (QC) strains included: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *E. coli* ATCC 25922, *E. coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 27853, *S. pneumoniae* ATCC 49619, and *H. influenzae* ATCC 49247.

Results

- Ceftaroline was highly active against *S. aureus*, with 100.0% of strains inhibited at ≤2 mg/L (Table 1). Against methicillin-susceptible *S. aureus* (MSSA), ceftaroline (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L) was 16-fold more active than ceftriaxone (MIC_{50}, 4 mg/L; Table 2)
- Against MRSA strains, ceftaroline (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L) was at least 64-fold more active than ceftriaxone, a comparator β-lactam with limited activity against MRSA (MIC_{50} and MIC_{90}, >32 mg/L). Ceftriaxone and other β-lactams showed very limited activity against MRSA. Ceftaroline activity against MRSA was similar to that of linezolid (MIC_{50} and MIC_{90}, 2 mg/L) and vancomycin (MIC_{50} and MIC_{90}1 mg/L; Table 2)
- Ceftaroline activity against CoNS was similar to that against *S. aureus*, with 99.1% of strains inhibited at ≤2 mg/L (Table 1). Four strains from 4 different countries showed highest ceftaroline MIC values at 4 mg/L
- Ceftaroline demonstrated strong activity against *S. pneumoniae* strains (MIC_{50} and MIC_{90}, ≤0.008 mg/L and 0.12 mg/L, respectively). Against 19 highly penicillin-resistant strains (MIC ≥4 mg/L), ceftaroline (MIC_{50} and MIC_{90}, 0.25 mg/L) was 8-fold more active than ceftriaxone (MIC_{50} and MIC_{90}, 2 mg/L). Of note, these strains showed high rates of resistance (≥68.4%) to erythromycin and clindamycin (Table 2)
- Ceftaroline demonstrated excellent activity against β-haemolytic streptococci (MIC_{50}, ≤0.008 mg/L and MIC_{90}, 0.03 mg/L) and viridans group streptococci (VGS; MIC_{50}, 0.03 mg/L and MIC_{90}, 0.06 mg/L) (Table 2). All VGS were inhibited at ceftaroline concentrations of 0.5 mg/L or lower, except for 1 strain from Turkey (Table 1)
- MICs of ceftaroline against *E. faecalis* ranged from 0.5 mg/L to >32 mg/L; 90.8% were inhibited by ≤8 mg/L. All *E. faecalis* strains were susceptible to ampicillin (MIC range, ≤1 mg/L to 8 mg/L), linezolid (MIC range, 0.25 mg/L to 2 mg/L), and daptomycin (MIC range, 0.12 mg/L to 4 mg/L), and 98.0% were susceptible to vancomycin (MIC range, 0.5 mg/L to >16 mg/L; Tables 1 and 2)

Table 1. Frequency of Occurrence of Ceftaroline MIC Values for All European Organisms Tested

	No. (cumulative %) of isolates inhibited at ceftaroline MIC (mg/L):											
Organisms (no. tested)	**≤0.008**	**0.015**	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**>8**
Gram-positive												
S. aureus (1,200)	2 (0.2)	0 (0.2)	2 (0.2)	5 (0.6)	64 (5.9)	757 (69.0)	209 (86.4)	129 (97.2)	34 (100.0)	-	-	-
Oxacillin-susceptible (930)	2 (0.2)	0 (0.2)	2 (0.2)	7 (0.8)	64 (7.6)	749 (88.2)	109 (99.9)	1 (100.0)	-	-	-	-
Oxacillin-resistant (270)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (3.0)	100 (40.0)	128 (87.4)	34 (100.0)	-	-	-
Coagulase-neg. staphylococci (432)	4 (0.9)	3 (1.6)	17 (5.6)	49 (16.9)	31 (24.1)	132 (54.6)	131 (85.0)	34 (92.8)	27 (99.1)	4 (100.0)	-	-
S. pneumoniae (485)	299 (61.7)	56 (73.2)	26 (78.6)	17 (82.1)	66 (95.7)	21 (100.0)	-	-	-	-	-	-
Penicillin-susc. (MIC, ≤2 mg/L; 466)	299 (64.2)	56 (76.2)	26 (81.8)	17 (85.4)	58 (97.9)	10 (100.0)	-	-	-	-	-	-
Penicillin-non-susc. (MIC, ≥4 mg/L; 19)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (42.1)	11 (100.0)	-	-	-	-	-	-
β-haemolytic streptococci (195)	98 (50.3)	70 (86.2)	27 (100.0)	-	-	-	-	-	-	-	-	-
Viridans group streptococci (80)	17 (21.3)	20 (46.3)	29 (82.5)	6 (90.0)	3 (93.8)	3 (97.5)	1 (98.8)	0 (98.8)	0 (98.8)	0 (98.8)	0 (98.8)	1 (100.0)
E. faecalis (357)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.2)	93 (28.3)	134 (65.8)	24 (72.6)	65 (90.8)	33 (100.0)
Gram-negative												
E. coli (788)	0 (0.0)	2 (0.3)	42 (5.6)	217 (33.1)	227 (61.9)	105 (75.3)	51 (81.7)	31 (85.7)	17 (87.8)	10 (89.1)	5 (89.7)	82 (100.0)
Klebsiella spp. (294)	0 (0.0)	0 (0.0)	5 (1.7)	64 (23.5)	94 (55.4)	42 (69.7)	16 (75.2)	10 (78.6)	5 (80.3)	3 (81.3)	4 (82.7)	51 (100.0)
Enterobacter spp. (146)	0 (0.0)	0 (0.0)	4 (2.7)	12 (11.0)	27 (29.5)	34 (52.7)	11 (60.3)	5 (63.7)	7 (68.5)	2 (69.9)	2 (71.2)	42 (100.0)
H. influenzae (235)	153 (65.1)	67 (93.6)	15 (100.0)	-	-	-	-	-	-	-	-	-
β-lactamase-negative (193)	140 (72.5)	47 (96.9)	6 (100.0)	-	-	-	-	-	-	-	-	-
β-lactamase-positive (42)	13 (31.0)	20 (78.6)	9 (100.0)	-	-	-	-	-	-	-	-	-

Table 2. Antimicrobial Activity of Ceftaroline and Comparator Agents Tested Against Bacterial Isolates From European Medical Centers

Organism (no. tested)/ Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
S. aureus (1200)					
Ceftaroline	0.25	1	≤0.008 – 4	- / -[b]	- / -
Oxacillin	0.5	>2	≤0.25 – >2	77.5 / 22.5	77.5 / 22.5
Ceftriaxone	4	>32	≤0.25 – >32	77.5 / 22.5	77.5 / 22.5
Imipenem	≤0.12	2	≤0.12 – >8	77.5 / 22.5	77.5 / 22.5
Erythromycin	0.5	>2	≤0.25 – >2	72.3 / 26.5	73.3 / 26.5
Clindamycin	≤0.25	0.5	≤0.25 – >2	90.3 / 9.3	89.6 / 9.7
Levofloxacin	≤0.5	>4	≤0.5 – >4	74.9 / 24.9	74.9 / 24.9
TMP/SMX[c]	≤0.5	≤0.5	≤0.5 – >2	98.8 / 1.2	98.8 / 1.2
Linezolid	2	2	0.5 – 2	100.0 / -	100.0 / 0.0
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
Oxacillin-susceptible (930)					
Ceftaroline	0.25	0.5	≤0.008 – 1	- / -	- / -
Ceftriaxone	4	4	≤0.25 – 16	99.8 / 0.0	100.0 / 0.0
Imipenem	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / 0.0	100.0 / 0.0
Erythromycin	0.5	>2	≤0.25 – >2	83.3 / 15.4	84.4 / 15.4
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	97.0 / 2.7	96.2 / 3.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	94.1 / 5.8	94.1 / 5.8
TMP/SMX	≤0.5	≤0.5	≤0.5 – >2	99.1 / 0.9	99.1 / 0.9
Linezolid	2	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
Oxacillin-resistant (270)					
Ceftaroline	1	2	0.25 – 4	- / -	- / -
Ceftriaxone	>32	>32	4 – >32	0.0 / 100.0	0.0 / 100.0
Imipenem	1	>8	≤0.12 – >8	0.0 / 100.0	0.0 / 100.0
Erythromycin	>2	>2	≤0.25 – >2	34.4 / 64.8	35.2 / 64.8
Clindamycin	≤0.25	>2	≤0.25 – >2	67.4 / 31.9	66.7 / 32.6
Levofloxacin	>4	>4	≤0.5 – >4	8.9 / 90.7	8.9 / 90.7
TMP/SMX	≤0.5	≤0.5	≤0.5 – >2	97.8 / 2.2	97.8 / 2.2
Linezolid	2	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
Coagulase-negative staphylococci (432)					
Ceftaroline	0.25	1	≤0.008 – 4	- / -	- / -
Oxacillin	>2	>2	≤0.25 – >2	16.7 / 83.3	16.7 / 83.3
Ceftriaxone	16	>32	0.5 – >32	16.7 / 83.3	16.7 / 83.3
Imipenem	0.5	>8	≤0.12 – >8	16.7 / 83.3	16.7 / 83.3
Erythromycin	>2	>2	≤0.25 – >2	36.1 / 63.2	36.1 / 63.2
Clindamycin	≤0.25	>2	≤0.25 – >2	69.2 / 30.1	66.9 / 30.8
Levofloxacin	4	>4	≤0.5 – >4	42.1 / 54.6	42.1 / 54.6
TMP/SMX	≤0.5	>2	≤0.5 – >2	58.5 / 41.5	58.5 / 41.5
Linezolid	1	1	0.25 – 4	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	2	0.25 – 4	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0

Organism (no. tested)/ Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
S. pneumoniae (485)					
Ceftaroline	≤0.008	0.12	≤0.008 – 0.25	- / -	- / -
Penicillin[d]	≤0.03	2	≤0.03 – 8	96.1 / 0.2	- / -
Penicillin[e]	≤0.03	2	≤0.03 – 8	72.0 / 15.3	72.0 / 3.9
Ceftriaxone	≤0.25	1	≤0.25 – 4	92.8 / 0.4	82.9 / 0.4
Erythromycin	≤0.25	>2	≤0.25 – >2	74.2 / 25.4	74.2 / 25.4
Clindamycin	≤0.25	>2	≤0.25 – >2	81.4 / 17.9	82.1 / 17.9
Levofloxacin	1	1	≤0.5 – >4	99.0 / 0.4	99.0 / 1.0
Linezolid	1	1	≤0.12 – 2	100.0 / -	100.0 / 0.0
Vancomycin	≤1	≤1	≤1	100.0 / -	100.0 / 0.0
Daptomycin	0.12	0.25	≤0.06 – 0.5	- / -	- / -
Penicillin-susceptible (MIC, ≤2 mg/L; 466)[d]					
Ceftaroline	≤0.008	0.12	≤0.008 – 0.25	- / -	- / -
Ceftriaxone	≤0.25	1	≤0.25 – 4	95.5 / 0.2	86.1 / 0.2
Erythromycin	≤0.25	>2	≤0.25 – >2	76.2 / 23.4	76.2 / 23.4
Clindamycin	≤0.25	>2	≤0.25 – >2	83.5 / 15.9	84.1 / 15.9
Levofloxacin	1	1	≤0.5 – >4	98.9 / 0.4	98.9 / 1.1
Linezolid	1	1	≤0.12 – 2	100.0 / -	100.0 / 0.0
Vancomycin	≤1	≤1	≤1	100.0 / -	100.0 / 0.0
Daptomycin	0.12	0.25	≤0.06 – 0.5	- / -	- / -
Penicillin-non-susceptible (MIC, ≥4 mg/L; 19)[e]					
Ceftaroline	0.25	0.25	0.12 – 0.25	- / -	- / -
Ceftriaxone	2	2	≤0.25 – 4	26.3 / 5.3	5.3 / 5.3
Erythromycin	>2	>2	≤0.25 – >2	26.3 / 73.7	26.3 / 73.7
Clindamycin	>2	>2	≤0.25 – >2	31.6 / 68.4	31.6 / 68.4
Levofloxacin	1	2	1 – 2	100.0 / 0.0	100.0 / 0.0
Linezolid	0.5	1	0.5 – 1	100.0 / -	100.0 / 0.0
Vancomycin	≤1	≤1	≤1	100.0 / -	100.0 / 0.0
Daptomycin	0.12	0.25	0.12 – 0.25	- / -	- / -
β-haemolytic streptococci (195)					
Ceftaroline	≤0.008	0.03	≤0.008 – 0.03	- / -	- / -
Penicillin	≤0.015	0.06	≤0.015 – 0.12	100.0 / -	100.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	>2	≤0.25 – >2	81.5 / 16.9	81.5 / 16.9
Clindamycin	≤0.25	0.5	≤0.25 – >2	89.7 / 9.3	90.7 / 9.3
Levofloxacin	≤0.5	1	≤0.5 – 2	100.0 / 0.0	93.8 / 0.0
Linezolid	1	1	0.5 – 2	100.0 / -	100.0 / 0.0
Vancomycin	0.5	0.5	0.25 – 1	100.0 / -	100.0 / 0.0
Daptomycin	0.12	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Viridans group streptococci (80)					
Ceftaroline	0.03	0.06	≤0.008 – 16	- / -	- / -
Penicillin	0.06	0.5	≤0.015 – 32	76.3 / 3.8	86.3 / 3.8
Ceftriaxone	≤0.25	1	≤0.25 – >32	93.8 / 2.5	88.8 / 11.3
Erythromycin	≤0.25	>2	≤0.25 – >2	70.0 / 30.0	- / -
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	95.0 / 3.8	96.3 / 3.8
Levofloxacin	1	2	≤0.5 – >4	98.8 / 1.3	- / -
Linezolid	1	1	0.12 – 2	100.0 / -	- / -
Vancomycin	0.5	1	0.25 – 1	100.0 / -	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	- / -

Organism (no. tested)/ Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Enterococcus faecalis (357)					
Ceftaroline	2	8	0.5 – >32	- / -	- / -
Ampicillin	≤1	2	≤1 – 8	100.0 / 0.0	99.7 / 0.0
Erythromycin	>2	>2	≤0.25 – >2	7.3 / 56.9	- / -
Levofloxacin	2	>4	≤0.5 – >4	64.1 / 35.0	- / -
Linezolid	2	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	2	0.5 – >16	98.0 / 1.7	98.0 / 1.7
Daptomycin	1	2	0.12 – 4	100.0 / -	- / -
Escherichia coli (788)					
Ceftaroline	0.12	16	0.015 – >32	- / -	- / -
Ceftriaxone	≤0.25	8	≤0.25 – >32	90.9 / 7.4	88.8 / 10.8
Ceftazidime	≤1	2	≤1 – >16	95.3 / 2.3	89.3 / 4.7
Cefepime	≤0.12	1	≤0.12 – >16	95.1 / 3.3	90.2 / 4.9
Imipenem	0.25	0.25	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	16	≤0.5 – >64	92.0 / 2.9	89.1 / 8.0
Levofloxacin	≤0.5	>4	≤0.5 – >4	76.1 / 22.6	75.8 / 23.9
Amikacin	2	8	0.5 – >32	99.0 / 0.5	97.5 / 1.0
Klebsiella spp. (294)					
Ceftaroline	0.12	>32	0.03 – >32	- / -	- / -
Ceftriaxone	≤0.25	>32	≤0.25 – >32	85.4 / 13.6	82.3 / 17.0
Ceftazidime	≤1	>16	≤1 – >16	84.5 / 13.4	82.1 / 15.5
Cefepime	≤0.12	>16	≤0.12 – >16	87.4 / 10.2	85.0 / 12.6
Imipenem	0.25	0.5	≤0.12 – >8	97.6 / 2.4	96.9 / 2.4
Piperacillin/tazobactam	2	>64	≤0.5 – >64	83.0 / 10.9	78.2 / 17.0
Levofloxacin	≤0.5	4	≤0.5 – >4	87.1 / 8.8	85.4 / 12.9
Amikacin	1	4	0.5 – >32	96.9 / 1.7	94.9 / 3.1
Enterobacter spp. (146)					
Ceftaroline	0.25	>32	0.03 – >32	- / -	- / -
Ceftriaxone	≤0.25	>32	≤0.25 – >32	74.7 / 12.3	64.4 / 32.2
Ceftazidime	≤1	>16	≤1 – >16	70.1 / 20.8	66.0 / 29.9
Cefepime	≤0.12	2	≤0.12 – >16	95.9 / 2.7	89.0 / 4.1
Imipenem	0.5	1	≤0.12 – >8	98.6 / 0.7	97.9 / 0.7
Piperacillin/tazobactam	4	64	≤0.5 – >64	72.6 / 9.6	68.5 / 27.4
Levofloxacin	≤0.5	4	≤0.5 – >4	89.0 / 6.8	89.0 / 11.0
Amikacin	1	2	≤0.25 – 16	100.0 / 0.0	99.3 / 0.0
Haemophilus influenzae (235)					
Ceftaroline	≤0.008	0.015	≤0.008 – 0.03	- / -	- / -
Ampicillin	≤1	>16	≤1 – >16	82.1 / 17.4	82.1 / 17.9
Amoxicillin/clavulanate	≤1	2	≤1 – 4	100.0 / 0.0	89.4 / 10.6
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 1	100.0 / -	0.0 / 100.0
Cefuroxime	≤2	≤2	≤2 – >8	99.1 / 0.4	63.8 / 6.8
Azithromycin	1	2	≤0.5 – >4	99.5 / -	0.0 / 0.5
Levofloxacin	≤0.5	≤0.5	≤0.5	100.0 / -	100.0 / 0.0
TMP/SMX	≤0.5	>2	≤0.5 – >2	71.9 / 21.7	71.9 / 25.5

a. Criteria as published by the CLSI [2009] and EUCAST [2009], for staphylococci only. β-lactam susceptibility should be directed by the oxacillin test results
b. - = No breakpoint has been established by CLSI or USA-FDA
c. Trimethoprim/sulfamethoxazole
d. Criteria as published by the CLSI [2009] for 'Penicillin parenteral (non-meningitis)'
e. Criteria as published by the CLSI [2009] for 'Penicillin (oral penicillin V)'

- Among the Enterobacteriaceae species tested, ceftaroline (MIC_{50}, 0.12-0.25 mg/L) had similar potency to that of ceftriaxone and cefepime (MIC_{50}, ≤0.12-0.25 mg/L) (Table 2). All cephalosporins tested showed limited activity against ESBL phenotype strains of *E. coli* (12.2%) and *Klebsiella* spp. (20.0%) (data not shown)
- *H. influenzae* were highly susceptible to ceftaroline, with MIC_{50} and MIC_{90} values of ≤0.008 and 0.015 mg/L, respectively. Among *H. influenzae* isolates evaluated in this study, 17.4% were resistant to ampicillin and only a 2-fold increase in MIC_{50} and MIC_{90} values was observed for ceftaroline when stratified by ampicillin resistance (Table 1)

Conclusions

- Ceftaroline demonstrated broad-spectrum antimicrobial activity against Gram-positive and Gram-negative bacterial pathogens, including methicillin-resistant staphylococci, penicillin-resistant streptococci, and ampicillin-resistant *H. influenzae*, isolated from European medical centers in 2009
- Ceftaroline has a significant potency advantage (at least 16-fold) compared with ceftriaxone and cefepime against MSSA. Ceftaroline was highly active against MRSA with >85% of isolates inhibited by ≤1 mg/L. (highest MIC, 2 mg/L)
- Greatest activity of ceftaroline (MICs of ≤0.12 mg/L) was observed against *H. influenzae*, β-haemolytic streptococci, viridans group streptococci, and *S. pneumoniae*
- Ceftaroline exhibits good activity against *E. coli*, *Klebsiella* spp., and *Enterobacter cloacae* isolates, but like many other broad-spectrum cephalosporins, shows limited inhibition of ESBL-producing and AmpC-derepressed strains
- These data suggest a potentially important clinical role for ceftaroline in the treatment of cSSSI and CAP infections, including those caused by pathogens resistant to β-lactams and other commonly used antimicrobials

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