In Vitro Activity of Ceftaroline Tested Against Recent Clinical Isolates from the United States (USA)

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Abstract

Background: Ceftaroline (CPT) is a novel parenteral cephalosporin with broad-spectrum activity that includes MRSA.

Methods: 4,723 isolates from 38 species/groups and various resistance (R) subsets were collected from patients in the USA mostly in 2008. *Enterobacteriaceae* strains with an ESBL phenotype or AmpC hyperproducers were not evaluated. Susceptibility (S) of CPT and comparators were determined by CLSI broth microdilution and agar dilution methods.

Results: CPT was very active against staphylococci, including strains R to oxacillin (OXA), vancomycin (VAN), mupirocin or linezolid. Against streptococci, including 40 *S. pneumoniae* with a penicillin MIC of ≥8 µg/mL (highest CPT MIC, 0.5 µg/mL) and other R subsets, CPT was highly potent. The highest CPT MIC for MRSA was 2 µg/mL ($MIC_{50/90}$, 0.5/1 µg/mL). VAN-R did not affect CPT activity against *E. faecalis* ($MIC_{50/90}$, 2/8 µg/mL). CPT was very active against non-ESBL, non-AmpC hyperproducer *Enterobacteriaceae* ($MIC_{50/90}$, 0.12/2 µg/mL). *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp. *P. mirabilis, Salmonella* spp. and *Shigella* spp. were S to CPT (MIC_{90}, 0.25-0.5 µg/mL), while indole-positive Proteae and *Serratia* spp. exhibited slightly higher CPT MIC values. CPT was very active against *H. influenzae*, including 104 ampicillin-R (β-lactamase[βL]-producing and βL-negative [BLNAR; MIC_{90}, 0.12 µg/mL) strains. MIC_{90} for *H. parainfluenzae* (24 strains), *M. catarrhalis* (101), *Pasteurella multocida* (51) and *N. meningitidis* (20) were 0.06, 0.12, 0.03 and ≤0.008 µg/mL, respectively. CPT showed limited activity against *Acinetobacter* spp. and *P. aeruginosa*.

Organism (no. tested)	Cumulative % inhibited at ceftaroline MIC (µg/mL) of: ≤0.06	0.12	0.25	0.5	1	2	4	8	16
S. aureus (325)	0.9	3.7	35.4	63.4	93.9	100.0	-	-	-
CoNS[a] (555)	30.6	39.3	54.8	82.3	94.1	99.8	100.0	-	-
S. pneumoniae (455)	55.2	79.6	95.0	100.0	-	-	-	-	-
E. faecalis (210)	0.0	0.0	0.5	3.3	22.4	61.4	85.7	98.6	100.0
β-haemolytic strep. (310)	100.0	-	-	-	-	-	-	-	-
Enterobacteriaceae (1,550)[b]	26.4	53.2	71.0	80.2	88.1	92.0	93.8	95.6	97.1
H. influenzae (315)	86.7	98.7	100.0	-	-	-	-	-	-
N. gonorrhoeae (107)	25.2	40.2	69.2	95.3	100.0	-	-	-	-

a. CoNS = coagulase negative staphylococci.
b. Isolates with ESBL phenotype or AmpC hyperproducer (ceftazidime MIC, ≥16 µg/mL) were excluded.

Conclusions: CPT showed potent activity against streptococci, staphylococci and *Haemophilus*, including strains with various R phenotypes. Wild-type *Enterobacteriaceae* were generally quite S to CPT.

Introduction

Ceftaroline is a novel, parenteral, broad-spectrum cephalosporin exhibiting bactericidal activity against Gram-positive organisms, including methicillin(oxacillin)-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Streptococcus pneumoniae* (MDRSP), as well as common Gram-negative pathogens. Ceftaroline is currently in phase III clinical development. Favorable results have been reported from phase II and III trials (CANVAS 1 and 2) on the efficacy and safety profile of ceftaroline for treatment of complicated skin and skin structure infections (cSSSI) and from phase III community-acquired bacterial pneumonia (CABP) trials (FOCUS 1 and 2).

The objective of this study was to evaluate the antimicrobial activity and spectrum of ceftaroline and comparator agents tested against clinical bacterial isolates, including common resistance phenotypes, recently collected in medical institutions geographically dispersed throughout the United States (USA).

Materials and Methods

Organism Collection: The organisms tested were collected from patients in the USA in 2007 and 2008. Isolates from the bloodstream, skin and soft tissue, and respiratory tract were included. Isolates of unusual/rare species or organism resistance phenotypes were included, and may have been isolated earlier than 2007 and/or from other geographic areas.

Susceptibility Testing: The isolates were tested for susceptibility to ceftaroline and many comparator agents by reference broth microdilution or agar dilution (*Neisseria gonorrhoeae* only) tests followed by confirmatory techniques that included CLSI M100-S19 criteria. *S. pneumoniae* was tested in Mueller-Hinton broth supplemented with 3-5% lysed horse blood, and *Haemophilus influenzae* was tested in Haemophilus Test Media while *S. aureus* was tested in cation-adjusted Mueller-Hinton broth.

PCR screens with mechanism-specific primer sets were performed on certain strains with unusual resistance patterns. Concurrent testing of quality control (QC) strains determined that proper test conditions were applied. These QC strains included *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922 and 35218, *Pseudomonas aeruginosa* ATCC 27853, *S. pneumoniae* ATCC 49619, and *H. influenzae* ATCC 49247 and 49766.

Results

- Ceftaroline was active against *S. aureus* (325 strains) including MSSA, MRSA, and strains with decreased susceptibility to vancomycin (hVISA, VISA, and VRSA), linezolid (MIC, ≥8 µg/mL), quinupristin/dalfopristin (MIC, ≥2 µg/mL), and/or mupirocin (MIC, >256 µg/mL; Tables 1 and 2)
- Against MRSA, all isolates were inhibited at a ceftaroline MIC of ≤2 µg/mL ($MIC_{50/90}$, 0.5/1 µg/mL). Ceftaroline MIC results varied from 0.25 to 2 µg/mL for the hVISA/VISA/VRSA subset ($MIC_{50/90}$, 1/2 µg/mL), from 0.5 to 2 µg/mL among the linezolid-resistant subset (MIC_{50}, 1/2 µg/mL), from 0.06 to 1 µg/mL among quinupristin/dalfopristin nonsusceptible strains (MIC_{50}, 0.5/1 µg/mL), and from 0.25 to 2 µg/mL among mupirocin-resistant strains (MIC_{50}, 0.5/1 µg/mL; Table 2)
- Ceftaroline ($MIC_{50/90}$, 0.25 µg/mL) was 16-fold more active than ceftriaxone ($MIC_{50/90}$, 4 µg/mL) and 8- to 16-fold more active than cefepime ($MIC_{50/90}$, 2/4 µg/mL) against MSSA. The highest ceftaroline MIC value was only 0.5 µg/mL (Table 2)
- Ceftaroline was slightly more active against coagulase-negative staphylococci (CoNS) compared to *S. aureus*. Against oxacillin-susceptible *Staphylococcus epidermidis* ($MIC_{50/90}$, 0.06/0.12 µg/mL), ceftaroline was 16-fold more active than ceftriaxone and 8-fold more active than cefepime ($MIC_{50/90}$, 1/2 µg/mL for ceftriaxone and 0.5/1 µg/mL for cefepime). *Staphylococcus capitis* ($MIC_{50/90}$, 0.06/0.5 µg/mL), *Staphylococcus hominis* ($MIC_{50/90}$, 0.5/1 µg/mL), *Staphylococcus haemolyticus* ($MIC_{50/90}$, 1/2 µg/mL), as well as CoNS strains having reduced susceptibility to linezolid ($MIC_{50/90}$, 0.5/1 µg/mL), were very susceptible to ceftaroline (Table 2)
- Ceftaroline exhibited moderate in vitro activity against vancomycin-susceptible ($MIC_{50/90}$, 2/4 µg/mL) and vancomycin-resistant ($MIC_{50/90}$, 4/8 µg/mL) strains of ampicillin-susceptible *E. faecalis* (Table 2)
- Ceftaroline was 8- to 16-fold more active than ceftriaxone against penicillin-intermediate, penicillin-resistant, levofloxacin-nonsusceptible, and multidrug-resistant strains of *S. pneumoniae* (ceftaroline MIC_{90}, 0.06-0.25 µg/mL; Table 2). Ceftaroline was also highly active against *S. pneumoniae* with high-level resistance to penicillin (MIC, ≥8 µg/mL), with the highest ceftaroline MIC value of 0.5 µg/mL (Table 2)
- β-haemolytic streptococci and *Streptococcus gallolyticus* (formerly *Streptococcus bovis*) were markedly susceptible to ceftaroline (MIC_{90}, ≤0.008-0.03 µg/mL). Ceftaroline was also very active against almost 400 strains of various viridans group streptococci (4 groups; MIC_{90}, 0.03–0.12 µg/mL; Table 2)
- Ceftaroline was highly active against Gram-negative respiratory pathogens *H. influenzae* (including β-lactamase positive isolates and β-lactamase-negative ampicillin-resistant [BLNAR] *H. influenzae* strains), *Haemophilus parainfluenzae*, and *Moraxella catarrhalis* (MIC_{90}, 0.015-0.12 µg/mL; Table 3)
- Ceftaroline was very active against *Enterobacteriaceae* not expressing broad-spectrum β-lactamase activity (extended-spectrum β-lactamase [ESBL] or AmpC-derepressed), with MIC_{90} values ranging from 0.25 to 2 µg/mL, except for some indole-positive Proteae for which MIC_{90} values were >16 µg/mL (*Morganella morganii*, *Proteus vulgaris*, and *Providencia stuartii*; Table 4)
- Ceftaroline was active against *Pasteurella multocida* strains (MIC_{90}, 0.03 µg/mL), but exhibited limited in vitro activity against *Acinetobacter* spp. and *P. aeruginosa* (MIC_{50}, >16 µg/mL; Table 4)
- All *Neisseria meningitidis* isolates (20) were inhibited at ≤0.008 µg/mL of ceftaroline. Ceftaroline was also very active against *N. gonorrhoeae* (MIC_{90}, 0.5 µg/mL), including penicillin-resistant and ciprofloxacin-resistant strains (Table 5)

Table 1. Ceftaroline MIC Distributions of Gram-positive and Gram-negative Organisms Collected in USA Medical Centers

Organism (no. tested)	Cumulative % inhibited at ceftaroline MIC (µg/mL) of: ≤0.06	0.12	0.25	0.5	1	2[a]	4	8	16
Staphylococcus aureus (325)	0.9	3.7	35.4	63.4	93.9	100.0	-	-	-
Coag.-neg. staphylococci (555)	30.6	39.3	54.8	82.3	94.1	99.8	100.0	-	-
Strept. pneumoniae (455)	55.2	79.6	95.0	100.0	-	-	-	-	-
β-haemolytic streptococci (310)	100.0	-	-	-	-	-	-	-	-
Enterococcus faecalis (210)	0.0	0.0	0.5	3.3	22.4	61.4	85.7	98.6	100.0
Citrobacter koseri (104)[b]	33.7	81.7	88.5	96.2	99.0	100.0	-	-	-
Citrobacter freundii (107)[b]	3.7	36.5	77.6	90.7	94.4	96.3	97.2	99.1	99.1
Enterobacter cloacae (103)[b]	15.5	38.8	75.7	91.3	98.1	100.0	-	-	-
Enterobacter aerogenes (103)[b]	37.9	71.8	88.4	93.2	94.2	95.2	96.1	98.1	99.0
Escherichia coli (102)[b]	47.1	74.5	92.2	95.1	97.1	99.0	99.0	100.0	-
Klebsiella pneumoniae (102)[b]	50.0	73.5	88.2	95.1	100.0	-	-	-	-
Klebsiella oxytoca (102)[b]	20.6	51.0	83.3	94.1	99.0	99.0	99.0	100.0	-
Indole-positive Proteae (408)[b]	27.0	38.7	46.8	54.4	65.7	74.8	80.1	85.0	89.7
Proteus mirabilis (105)[b]	43.8	77.1	94.3	96.2	100.0	-	-	-	-
Serratia marcescens (106)[b]	0.0	0.0	7.6	42.5	79.3	92.5	95.3	97.2	99.1
Salmonella spp. (104)[b]	18.3	80.8	91.4	94.2	98.1	99.0	99.0	99.0	100.0
Shigella spp. (104)[b]	19.2	57.7	90.4	96.2	99.0	100.0	-	-	-
Haemophilus influenzae (315)	86.7	98.7	100.0	-	-	-	-	-	-
Neisseria gonorrhoeae (107)	25.2	40.2	69.2	95.3	100.0	-	-	-	-

a. Proposed susceptible breakpoint based on pharmacokinetic/pharmacodynamic and clinical data.
b. *Enterobacteriaceae* isolates with ESBL phenotype or AmpC hyperproducer (ceftazidime MIC, ≥16 µg/mL) were not included in the study.

Table 3. Comparison of In Vitro Activity of Ceftaroline and Selected Antimicrobial Agents Tested Against *Haemophilus* spp. and *M. catarrhalis*

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/resistant[a]
H. influenzae				
β-Lactamase-negative (110)				
Ceftaroline	≤0.008	0.015	≤0.008 – 0.25	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 1	100.0 / -
Ampicillin	≤1	≤1	≤1	100.0 / 0.0
Amoxicillin/clavulanate	≤2	≤2	≤2 – 4	100.0 / 0.0
β-Lactamase-positive (101)				
Ceftaroline	≤0.008	0.03	≤0.008 – 0.12	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / -
Ampicillin	>4	>4	2 – >4	0.0 / 97.0
Amoxicillin/clavulanate	≤2	≤2	≤2 – 4	100.0 / 0.0
β-Lactamase-negative, ampicillin-resistant (BLNAR; 104)				
Ceftaroline	0.06	0.12	≤0.008 – 0.25	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / -
Ampicillin	2	4	2 – >4	0.0 / 46.2
Amoxicillin/clavulanate	4	8	≤2 – >8	59.6 / 40.4
H. parainfluenzae (24)				
Ceftaroline	0.015	0.06	≤0.008 – 0.06	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0 / -
Ampicillin	≤1	2	≤1 – >4	87.5 / 8.3
Amoxicillin/clavulanate	≤2	≤2	≤2 – 4	100.0 / 0.0
M. catarrhalis (101)				
Ceftaroline	0.06	0.12	≤0.008 – 0.5	- / -
Ceftriaxone	0.25	1	≤0.008 – 2	100.0 / 0.0
Ampicillin	1	>4	≤0.5 – >4	- / -
Amoxicillin/clavulanate	0.12	0.25	≤0.06 – 0.5	100.0 / -

a. Criteria as published by the CLSI [2009].

Table 2. Comparison of In Vitro Activity of Ceftaroline and Selected Antimicrobial Agents Tested Against Gram-positive Organisms

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/ resistant[a]
S. aureus				
MSSA (102)				
Ceftaroline	0.25	0.25	0.03 – 0.5	- / -
Ceftriaxone	4	4	1 – 8	100.0 / 0.0
Cefepime	2	4	0.5 – 4	100.0 / 0.0
MRSA (105)				
Ceftaroline	0.5	1	0.5 – 2	- / -
Ceftriaxone	32	>32	8 – >32	0.0 / 100.0
Cefepime	16	>16	4 – >16	0.0 / 100.0
Reduced vancomycin susceptibility[b] (47)				
Ceftaroline	1	2	0.25 – 2	- / -
Ceftriaxone	>32	>32	2 – >32	14.9 / 85.1
Cefepime	>16	>16	1 – >16	14.9 / 85.1
Vancomycin	4	>16	1 – >16	36.2 / 14.9
Linezolid nonsusceptible (13)				
Ceftaroline	1	2	0.5 – 2	- / -
Ceftriaxone	>32	>32	16 – >32	0.0 / 100.0
Cefepime	>16	>16	4 – >16	0.0 / 100.0
Linezolid	>8	>8	8 – >8	0.0 / -
Quinupristin/dalfopristin nonsusceptible (12)				
Ceftaroline	0.5	1	0.06 – 1	- / -
Ceftriaxone	32	>32	2 – >32	41.7 / 58.3
Cefepime	8	>16	1 – >16	41.7 / 58.3
Quin/dalfo	2	2	2 – >2	0.0 / 8.3
Mupirocin-resistant (46)				
Ceftaroline	0.5	1	0.25 – 2	- / -
Ceftriaxone	32	>32	1 – >32	15.2 / 84.8
Cefepime	8	>16	2 – >16	15.2 / 84.8
Mupirocin	>256	>256	>256	- / -
S. epidermidis				
Oxacillin-susceptible (100)				
Ceftaroline	0.06	0.12	≤0.008 – 1	- / -
Ceftriaxone	1	2	≤0.5 – 16	98.0 / 0.0
Cefepime	0.5	1	≤0.12 – 4	100.0 / 0.0
Oxacillin-resistant (100)				
Ceftaroline	0.5	0.5	0.12 – 1	- / -
Ceftriaxone	16	>32	2 – >32	25.0 / 23.0
Cefepime	4	>16	0.5 – >16	74.0 / 17.0
S. hominis (101)				
Ceftaroline	0.5	1	0.03 – 1	- / -
Ceftriaxone	16	32	≤0.5 – >32	47.5 / 5.0
Cefepime	4	8	0.25 – >16	94.1 / 4.0
Oxacillin	>2	>2	≤0.25->2	32.7/67.3

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/ resistant[a]
S. haemolyticus (102)				
Ceftaroline	1	2	0.03 – 4	- / -
Ceftriaxone	>32	>32	1 – >32	16.7 / 61.8
Cefepime	>16	>16	0.25 – >16	36.3 / 53.9
Oxacillin	>2	>2	≤0.25 – >2	11.8 / 88.2
S. capitis (101)				
Ceftaroline	0.06	0.5	0.015 – 2	- / -
Ceftriaxone	2	>32	≤0.5 – >32	78.2 / 11.9
Cefepime	0.5	16	≤0.12 – >16	89.1 / 8.9
Oxacillin	≤0.25	>2	≤0.25 – >2	63.4 / 36.6
Linezolid-nonsusceptible CoNS (51)				
Ceftaroline	0.5	1	0.06 – 2	- / -
Ceftriaxone	32	>32	1 – >32	7.8 / 92.2
Cefepime	8	>16	0.25 – >16	7.8 / 92.2
Oxacillin	>2	>2	≤0.25 – >2	7.8 / 92.2
E. faecalis				
Vancomycin-susceptible (102)				
Ceftaroline	2	4	0.25 – 16	- / -
Ceftriaxone	>32	>32	>32	- / -
Cefepime	>16	>16	16 – >16	- / -
Ampicillin	≤2	≤2	≤2 – 4	100.0 / 0.0
Vancomycin-resistant (108)				
Ceftaroline	4	8	0.5 – 16	- / -
Ceftriaxone	>32	>32	16 – >32	- / -
Cefepime	>16	>16	16 – >16	- / -
Ampicillin	≤2	≤2	≤2 – 4	100.0 / 0.0
S. pneumoniae				
Penicillin-susceptible (MIC, ≤0.06 µg/mL; 102)				
Ceftaroline	≤0.008	0.03	≤0.008 – 0.06	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / 0.0
Amoxicillin/clavulanate	≤1	≤1	≤1 – 2	100.0 / 0.0
Penicillin-intermediate (MIC, 0.12 – 1 µg/mL; 102)				
Ceftaroline	0.03	0.06	≤0.008 – 0.12	- / -
Ceftriaxone	≤0.25	1	≤0.25 – 2	99.0 / 0.0
Amoxicillin/clavulanate	≤1	≤1	≤1 – 2	100.0 / 0.0
Penicillin-resistant (MIC, >2 µg/mL; 100)				
Ceftaroline	0.12	0.25	0.03 – 0.5	- / -
Ceftriaxone	1	2	≤0.25 – 8	69.0 / 7.0
Penicillin[c]	2	4	2 – >4	53.0 / 3.0
Amoxicillin/clavulanate	8	8	≤1 – >8	28.0 / 51.0
High-level penicillin-resistant (MIC, ≥8 µg/mL; 40)				
Ceftaroline	0.25	0.5	0.06 – 0.5	- / -
Ceftriaxone	4	8	1 – 16	5.0 / 72.5
Amoxicillin/clavulanate	>8	>8	2 – >8	2.5 / 97.5

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/ resistant[a]
Levofloxacin-nonsusceptible (53)				
Ceftaroline	0.015	0.12	≤0.008 – 0.5	- / -
Ceftriaxone	≤0.25	2	≤0.25 – 4	88.7 / 1.9
Amoxicillin/clavulanate	≤1	4	≤1 – >8	83.0 / 9.4
Levofloxacin	>4	>4	4 – >4	0.0 / 84.9
Multidrug-resistant[d] (127)				
Ceftaroline	0.12	0.25	≤0.008 – 0.5	- / -
Ceftriaxone	1	4	≤0.25 – 8	54.3 / 15.0
Amoxicillin/clavulanate	8	>8	≤1 – >8	34.6 / 55.1
β-Haemolytic streptococci				
Group A (*S. pyogenes*; 102)				
Ceftaroline	≤0.008	≤0.008	≤0.008 – 0.015	- / -
Ceftriaxone	≤0.5	≤0.5	≤0.5	100.0 / -
Cefepime	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / -
Group B (*S. agalactiae*;104)				
Ceftaroline	0.015	0.03	≤0.008 – 0.03	- / -
Ceftriaxone	≤0.5	≤0.5	≤0.5	100.0 / -
Cefepime	≤0.12	≤0.12	≤0.12	100.0 / -
Other β-haemolytic streptococci[e] (104)				
Ceftaroline	≤0.008	0.015	≤0.008 – 0.06	- / -
Ceftriaxone	≤0.5	≤0.5	≤0.5	100.0 / -
Cefepime	≤0.12	0.5	≤0.12 – 1	99.0 / -
S. gallolyticus (101)				
Ceftaroline	≤0.008	0.015	≤0.008 – 0.03	- / -
Ceftriaxone	≤0.5	≤0.5	≤0.5	100.0 / 0.0
Cefepime	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / 0.0
Viridans group streptococci				
S. anginosus / *milleri* group[f] (103)				
Ceftaroline	0.015	0.03	≤0.008 – 0.12	- / -
Ceftriaxone	≤0.5	≤0.5	≤0.5 – 1	100.0 / 0.0
Cefepime	0.25	0.5	≤0.12 – 1	100.0 / 0.0
Penicillin	0.06	0.12	≤0.015 – 2	95.1 / 0.0
S. mitis group[g] (104)				
Ceftaroline	0.015	0.12	≤0.008 – 1	- / -
Ceftriaxone	≤0.5	1	≤0.5 – 16	90.4 / 3.8
Cefepime	≤0.12	1	≤0.12 – 8	90.4 / 3.8
Penicillin	0.12	2	≤0.015 – 32	66.3 / 6.7
S. mutans group[h] (76)				
Ceftaroline	≤0.008	0.03	≤0.008 – 0.25	- / -
Ceftriaxone	≤0.5	≤0.5	≤0.5 – 4	94.7 / 1.3
Cefepime	≤0.12	0.25	≤0.12 – 8	96.1 / 1.3
Penicillin	≤0.015	0.12	≤0.015 – 4	92.1 / 1.3
S. salivarius group[i] (114)				
Ceftaroline	≤0.008	0.03	≤0.008 – 0.06	- / -
Ceftriaxone	≤0.5	≤0.5	≤0.5 – 1	100.0 / 0.0
Cefepime	≤0.12	0.25	≤0.12 – 1	100.0 / 0.0
Penicillin	0.06	0.5	≤0.015 – 2	78.1 / 0.0

a. Criteria as published by the CLSI [2009].
b. Includes: hVISA (17 strains), VISA (23 strains), and VRSA (7 strains).
c. Criteria as published by CLSI [2009] for penicillin parental (nonmeningitidis).
d. Include strains resistant to at least 2 of the following antimicrobial agents: penicillin (MIC ≥8µg/mL), cefuroxime (MIC ≥4 µg/mL), erythromycin (MIC ≥1 µg/mL), tetracycline (MIC ≥8 µg/mL), trimethoprim/sulfamethoxazole (MIC ≥4/76 µg/mL), and levofloxacin (MIC ≥8 µg/mL).
e. Includes: *Streptococcus dysgalactiae* (9 strains), *Streptococcus equi* (1 strain), *Streptococcus equisimilis* (1 strain), Group C *Streptococcus* (29 strains), Group F *Streptococcus* (11 strains), and Group G *Streptococcus* (53 strains).
f. Includes: *Streptococcus anginosus* (30 strains), *Streptococcus constellatus* (19 strains), *Streptococcus intermedius* (17 strains), and *Streptococcus milleri* (37 strains).
g. Includes: *Streptococcus gordonii* (4 strains), *Streptococcus mitis* (66 strains), *Streptococcus oralis* (8 strains), *Streptococcus parasanguinis* (12 strains), and *Streptococcus sanguinis* (14 strains).
h. Includes: *Streptococcus mutans* (75 strains) and *Streptococcus sobrinus* (1 strain). Isolates collected earlier than 2007 and/or outside USA were included in this group.
i. Includes: *Streptococcus salivarius* (114 strains). Isolates collected earlier than 2007 and/or outside USA were included in this group.

Table 4. Comparison of In Vitro Activity of Ceftaroline and Selected Antimicrobial Agents Tested Against *Enterobacteriaceae* and Selected Nonfermentative Gram-negative Bacilli

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/ resistant[a]
C. koseri (104)				
Ceftaroline	0.12	0.5	0.015 – 2	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / 0.0
Ceftazidime	≤2	≤2	≤2	100.0 / 0.0
Cefepime	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / 0.0
C. freundii (107)				
Ceftaroline	0.25	0.5	0.06 – >16	- / -
Ceftriaxone	≤0.25	0.5	≤0.25 – 2	100.0 / 0.0
Ceftazidime	≤2	≤2	≤2 – 8	100.0 / 0.0
Cefepime	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / 0.0
E. cloacae (103)				
Ceftaroline	0.25	0.5	0.015 – 2	- / -
Ceftriaxone	≤0.25	0.5	≤0.25 – 4	100.0 / 0.0
Ceftazidime	≤2	≤2	≤2 – 8	100.0 / 0.0
Cefepime	≤0.12	0.25	≤0.12 – 0.5	100.0 / 0.0
E. aerogenes (103)				
Ceftaroline	0.12	0.5	0.03 – >16	- / -
Ceftriaxone	≤0.25	0.5	≤0.25 – 8	100.0 / 0.0
Ceftazidime	≤2	≤2	≤2 – 8	100.0 / 0.0
Cefepime	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / 0.0
E. coli (102)				
Ceftaroline	0.12	0.25	0.015 – 8	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0 / 0.0
Ceftazidime	≤2	≤2	≤2	100.0 / 0.0
Cefepime	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / 0.0
K. pneumoniae (102)				
Ceftaroline	0.06	0.5	0.015 – 1	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / 0.0
Ceftazidime	≤2	≤2	≤2	100.0 / 0.0
Cefepime	≤0.12	0.25	≤0.12 – 1	100.0 / 0.0

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/ resistant[a]
K. oxytoca (102)				
Ceftaroline	0.12	0.5	0.03 – 8	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / 0.0
Ceftazidime	≤2	≤2	≤2	100.0 / 0.0
Cefepime	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / 0.0
M. morganii (101)				
Ceftaroline	0.12	>16	0.03 – >16	- / -
Ceftriaxone	≤0.25	0.5	≤0.25 – 4	100.0 / 0.0
Ceftazidime	≤2	4	≤2 – 8	100.0 / 0.0
Cefepime	≤0.12	≤0.12	≤0.12 – 1	100.0 / 0.0
P. vulgaris (100)				
Ceftaroline	1	>16	0.06 – >16	- / -
Ceftriaxone	≤0.25	4	≤0.25 – 4	100.0 / 0.0
Ceftazidime	≤2	≤2	≤2	100.0 / 0.0
Cefepime	≤0.12	0.25	≤0.12 – 1	100.0 / 0.0
P. rettgeri (102)				
Ceftaroline	0.06	1	0.03 – >16	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 2	100.0 / 0.0
Ceftazidime	≤2	≤2	≤2 – 4	100.0 / 0.0
Cefepime	≤0.12	≤0.12	≤0.12 – 2	100.0 / 0.0
P. stuartii (105)				
Ceftaroline	2	16	0.03 – >16	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 1	100.0 / 0.0
Ceftazidime	≤2	≤2	≤2 – 8	100.0 / 0.0
Cefepime	≤0.12	0.25	≤0.12 – 0.5	100.0 / 0.0
P. mirabilis (105)				
Ceftaroline	0.12	0.25	0.03 – 1	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0 / 0.0
Ceftazidime	≤2	≤2	≤2	100.0 / 0.0
Cefepime	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / 0.0

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/ resistant[a]
S. marcescens (106)				
Ceftaroline	1	2	0.25 – >16	- / -
Ceftriaxone	≤0.25	1	≤0.25 – 8	100.0 / 0.0
Ceftazidime	≤2	≤2	≤2	100.0 / 0.0
Cefepime	≤0.12	0.25	≤0.12 – 0.5	100.0 / 0.0
Salmonella spp. (104)				
Ceftaroline	0.12	0.25	0.06 – 16	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0 / 0.0
Ceftazidime	≤2	≤2	≤2	100.0 / 0.0
Cefepime	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / 0.0
Shigella spp. (104)				
Ceftaroline	0.12	0.25	0.03 – 2	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / 0.0
Ceftazidime	≤2	≤2	≤2	100.0 / 0.0
Cefepime	≤0.12	0.25	≤0.12 – 0.5	100.0 / 0.0
P. multocida (51)				
Ceftaroline	≤0.008	0.03	≤0.008 – 0.12	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	- / -
Ceftazidime	≤2	≤2	≤2 – 4	- / -0
Cefepime	≤0.12	0.5	≤0.12 – 2	- / -0
A. baumannii (101)				
Ceftaroline	>16	>16	2 – >16	- / -
Ceftriaxone	>32	>32	4 – >32	21.8 / 57.4
Ceftazidime	>16	>16	≤2 – >16	36.6 / 59.4
Cefepime	16	>16	0.5 – >16	34.7 / 48.5
P. aeruginosa (101)				
Ceftaroline	>16	>16	4 – >16	- / -
Ceftriaxone	>32	>32	16 – >32	0.0 / 78.2
Ceftazidime	4	>16	≤2 – >16	74.3 / 21.8
Cefepime	4	>16	1 – >16	76.2 / 10.9

a. Criteria as published by the CLSI [2009].

Table 5. Comparison of In Vitro Activity of Ceftaroline and Selected Antimicrobial Agents Tested Against *Neisseria* spp.

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/resistant[a]
N. meningitidis (20)				
Ceftaroline	≤0.008	≤0.008	≤0.008	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25	- / -
Cefepime	≤0.12	≤0.12	≤0.12	- / -
Penicillin	≤0.03	0.06	≤0.03-0.12	95.0 / 0.0
N. gonorrhoeae				
Penicillin-susceptible (8)				
Ceftaroline	0.015	-	0.004 – 0.06	- / -
Ceftriaxone	≤0.001	-	≤0.001 – 0.002	100.0 / -
Penicillin-intermediate (61)				
Ceftaroline	0.25	0.5	0.008 – 1	- / -
Ceftriaxone	0.015	0.06	0.004 – 0.12	100.0 / -
Penicillin-resistant (38)				
Ceftaroline	0.5	1	0.03 – 1	- / -
Ceftriaxone	0.03	0.12	0.004 – 0.12	100.0 / -
Ciprofloxacin-susceptible (44)				
Ceftaroline	0.06	0.5	0.004 – 1	- / -
Ceftriaxone	0.008	0.03	≤0.001 – 0.06	100.0 / -
Penicillin	0.25	1	0.015 – >4	18.2 / 9.1
Ciprofloxacin-intermediate (20)				
Ceftaroline	0.5	0.5	0.06 – 1	- / -
Ceftriaxone	0.06	0.12	0.008 – 0.12	100.0 / -
Penicillin	2	>4	1 – >4	0.0 / 80.0
Ciprofloxacin-resistant (43)				
Ceftaroline	0.25	0.5	0.008 – 1	- / -
Ceftriaxone	0.03	0.06	0.004 – 0.12	100.0 / -
Penicillin	1	>4	0.25 – >4	0.0 / 41.9
All strains (107)				
Ceftaroline	0.25	0.5	0.004 – 1	- / -
Ceftriaxone	0.015	0.12	≤0.001 – 0.12	100.0 / -
Penicillin	1	>4	0.015 – >4	7.5 / 35.5
Ciprofloxacin	0.25	>4	≤0.008 – >4	41.1 / 40.2

a. Criteria as published by the CLSI [2009].

Conclusions

- Ceftaroline was highly active against *S. aureus*, including MRSA (highest MIC, 2 µg/mL). Furthermore, resistance to vancomycin, linezolid, quinupristin/dalfopristin, or mupirocin did not appear to adversely affect ceftaroline activity against *S. aureus*
- Ceftaroline showed potent activity against *S. pneumoniae* and *H. influenzae*, including strains with various resistance phenotypes such as MDRSP
- Wild-type strains of *Enterobacteriaceae* (non-ESBL-producers and non-AmpC-hyperproducers) were generally susceptible to ceftaroline, with the exception of some indole-positive Proteae species
- Favorable results from the cSSSI and CABP clinical trials and the broad-spectrum antimicrobial profile of ceftaroline establish it as a promising and potentially effective therapeutic option in the treatment of various types of community-acquired and hospital-associated infections

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