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Antimicrobial Activity of Ceftaroline and Comparator Agents Tested Against Bacterial Isolates from Patients with Bacteremia in United States Medical Centers (2012)

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Abstract

Background: Ceftaroline (CPT), the active metabolite of the prodrug CPT fosamil, is a cephalosporin with potent activity against methicillin-resistant *S. aureus* (MRSA). CPT fosamil was approved by the United States (USA) Food and Drug Administration in 2010. CPT and comparators were tested against contemporary pathogens causing bacteremia in USA hospitals.

Methods: 3,590 organisms from the 2012 AWARE CPT surveillance program were isolated from patients with bacteremia. Pathogens were collected in 163 medical centers and tested for susceptibility (S) against CPT and comparators by the CLSI broth microdilution method. S interpretations and ESBL-phenotype were determined per CLSI guidelines.

Results: 45.6% of *S. aureus* isolates were MRSA. CPT was very active against methicillin-S *S. aureus* (MSSA; MIC_{90}, 0.25 µg/mL; 100.0% S) and MRSA (MIC_{90}, 1 µg/mL; 92.6% S). Against MSSA, CPT was 16-, 4- and 4-fold more active than ceftriaxone, linezolid and vancomycin, respectively. Coagulase-negative staphylococci (CoNS; 62.3% MR-CoNS) were very CPT-S (MIC_{90}, 0.5 µg/mL). CPT ($MIC_{50/90}$, ≤0.015/0.12 µg/mL; 100.0% S) was 8-fold more potent than ceftriaxone (CRO; $MIC_{50/90}$, ≤0.06/1 µg/mL; 94.2% S) against *S. pneumoniae* (SPN) and very active against CRO-non-S SPN strains (MIC_{90}, 0.25 µg/mL). CPT was very active against viridans group (MIC_{90}, 0.06 µg/mL) and β-hemolytic streptococci (highest MIC only 0.03 µg/mL). CPT exhibited good activity against non-ESBL-phenotype strains of *E. coli* and *Klebsiella* spp. (KSP; $MIC_{50/90}$, 0.12/0.5 µg/mL for both organisms), but limited activity against ESBL-producing strains. 24.5% of ESBL-phenotype KSP strains were meropenem-resistant. CPT was very active against *H. influenzae* ($MIC_{50/90}$, ≤0.015/0.03 µg/mL), *P. mirabilis* ($MIC_{50/90}$, 0.12/0.5 µg/mL), and ceftazidime-S *E. cloacae* ($MIC_{50/90}$, 0.25/0.5 µg/mL), but showed moderate activity against *S. marcescens* ($MIC_{50/90}$, 1/2 µg/mL), *M. morganii* ($MIC_{50/90}$, 0.12/32 µg/mL) and *E. faecalis* ($MIC_{50/90}$, 2/8 µg/mL).

Conclusions: CPT demonstrated in vitro activity against gram-positive organisms, including MRSA and CRO-non-S SPN strains, and non-ESBL-phenotype Enterobacteriaceae causing bacteremia in USA hospitals.

Introduction

The increased complexity of patients requiring hospitalization and the widespread use of indwelling devices has created higher risks for nosocomial bloodstream infection (BSI), which is one of the most serious nosocomial infections. Furthermore, the increasing rates of antimicrobial resistance are creating dilemmas for treatment of BSI patients, requiring the development of new therapeutic options, advanced diagnostic tests and preventive technologies/strategies. Despite such advances, accurate empiric treatment remains critical to minimize inappropriate antimicrobial therapy that may lead to poor clinical outcome. *Staphylococcus aureus*, especially oxacillin (methicillin)-resistant strains (MRSA), represents a major cause of BSI, and prompt and appropriate antibacterial therapy plays an important role in the management of MRSA infections. Vancomycin has been used for treatment of MRSA infections for more than 40 years, and although susceptibility rates remain high (>99%) in the United States (USA) and worldwide, there have been increasing reports of treatment failure, which could be related to increased vancomycin MIC occurrences within the susceptibility range (2 µg/mL).

Ceftaroline fosamil is approved by the USA Food and Drug Administration (FDA) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) and by the European Medicines Agency (EMA) for similar indications. The active metabolite, ceftaroline, is a cephalosporin with potent bactericidal in vitro activity against resistant gram-positive organisms, including MRSA, and common gram-negative organisms. As part of the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Program, a global ceftaroline surveillance study, we evaluated the activity of ceftaroline tested against contemporary pathogens causing BSI in USA hospitals.

Methods

Organism collection: A total of 3,590 clinically significant, nonduplicate isolates were collected from patients hospitalized with BSI in 163 USA medical centers during 2012. These organisms included *S. aureus* (1,014 strains, 45.6% MRSA), coagulase-negative staphylococci (CoNS; 350), *Streptococcus pneumoniae* (417), viridans group streptococci (VGS; 224), β-hemolytic streptococci (BHS; 164), *Escherichia coli* (568, 12.7% ESBL-phenotype) and *Klebsiella* spp. (353, 13.9% ESBL-phenotype). Species identification was performed by the participant center and confirmed at the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) when necessary by Matrix-Assisted Laser Desorption Ionization-Time Of Flight Mass Spectrometry (MALDI-TOF MS) using the Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, USA) following manufacturer instructions.

Susceptibility testing methods: Broth microdilution tests conducted according to the Clinical and Laboratory Standards Institute (CLSI) methods were performed to determine antimicrobial susceptibility of ceftaroline and comparator antimicrobials used to treat BSI. Validated MIC panels were manufactured by ThermoFisher Scientific (Cleveland, Ohio, USA). *S. aureus* strains were tested in cation-adjusted Mueller-Hinton broth (CA-MHB). Fastidious streptococci were tested in CA-MHB supplemented with 2.5-5% lysed horse blood (CLSI M07-A9, 2012).

Quality control: Concurrent quality control (QC) testing was performed to assure proper test conditions and procedures. Susceptibility percentages and validation of QC results were based on CLSI guidelines and susceptibility breakpoints established by the CLSI (M100-S23; 2013).

Results

- Ceftaroline was very active against *S. aureus* overall ($MIC_{50/90}$, 0.25/1 µg/mL; 96.6% susceptible), including 45.6% of isolates that were MRSA
- Ceftaroline MIC values ranged from 0.12 to 2 µg/mL when tested against MRSA (MIC_{50} and MIC_{90}, 1 µg/mL) and 92.6% were inhibited at ceftaroline MIC of ≤1 µg/mL (Tables 1 and 2)
- When tested against oxacillin- (methicillin)-susceptible *S. aureus* (MSSA), ceftaroline (MIC_{50} and MIC_{90}, 0.25 µg/mL; highest MIC, 0.5 µg/mL) was 16-fold more active than ceftriaxone (MIC_{50} and MIC_{90}, 4 µg/mL) and four- to eight-fold more active than linezolid ($MIC_{50/90}$, 1/2 µg/mL) and vancomycin (MIC_{50} and MIC_{90}, 1 µg/mL; Table 2)
- CoNS (62.3% methicillin-resistant) strains were very susceptible to ceftaroline ($MIC_{50/90}$, 0.25/0.5 µg/mL; Tables 1 and 2)
- Ceftaroline was the most potent β-lactam tested against *S. pneumoniae* strains ($MIC_{50/90}$, ≤0.015/0.12 µg/mL; 100.0% susceptible). Ceftaroline (MIC_{50} and MIC_{90}, 0.25 µg/mL) was eight-fold more active than ceftriaxone (MIC_{50} and MIC_{90}, 2 µg/mL; data not shown) when tested against penicillin-non-susceptible (penicillin MIC, ≥4 µg/mL) pneumococci, and retained potent activity against ceftriaxone-non-susceptible strains (MIC_{50} and MIC_{90}, 0.25 µg/mL; 100.0% susceptible; Table 1)
- Ceftaroline was very active against viridans group ($MIC_{50/90}$, ≤0.015/0.06 µg/mL) and β-hemolytic streptococci (highest MIC only 0.03 µg/mL; Tables 1 and 2)
- Ceftaroline exhibited good activity against non-ESBL-phenotype strains of *E. coli* and *Klebsiella* spp. ($MIC_{50/90}$, 0.12/0.5 µg/mL for both organisms), but limited activity against ESBL-phenotype strains (Table 1). Among ESBL-phenotype *Klebsiella* spp., 24.5% of strains were meropenem-resistant (Table 2)
- Ceftaroline was very active against *Proteus mirabilis* ($MIC_{50/90}$, 0.12/0.5 µg/mL), ceftazidime-susceptible *Enterobacter cloacae* ($MIC_{50/90}$, 0.25/0.5 µg/mL), and *H. influenzae* ($MIC_{50/90}$, ≤0.015/0.03 µg/mL), but showed moderate activity against *Serratia marcescens* ($MIC_{50/90}$, 1/2 µg/mL), *Morganella morganii* ($MIC_{50/90}$, 0.12/32 µg/mL) and *Enterococcus faecalis* ($MIC_{50/90}$, 2/8 µg/mL, similar to ampicillin; see Tables 1 and 2.

Table 1. Summary of ceftaroline activity tested against bacterial isolates causing bloodstream infections in USA hospitals (2012)

Organism/subgroup	No. of Isolates	No. of isolates (cumulative %) inhibited at ceftaroline MIC (µg/mL) of: ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	>4
Staphylococcus aureus	1,014	--	1 (0.1)	2 (0.3)	46 (4.8)	486 (52.8)	236 (76.0)	209 (96.6)	34 (100.0)	--	--
MSSA	552	--	1 (0.2)	2 (0.5)	45 (8.7)	476 (94.9)	28 (100.0)	--	--	--	--
MRSA	462	--	--	--	1 (0.2)	10 (2.4)	208 (47.4)	209 (92.6)	34 (100.0)	--	--
Streptococcus pneumoniae	417	311 (74.6)	28 (81.3)	27 (87.8)	35 (96.2)	14 (99.5)	2 (100.0)	--	--	--	--
penicillin-non-susc. (MIC, ≥4 µg/mL)	24	--	--	--	10 (41.7)	12 (91.7)	2 (100.0)	--	--	--	--
ceftriaxone-non-susc. (MIC, ≥2 µg/mL)	24	--	--	--	11 (45.8)	11 (91.7)	2 (100.0)		--	--	--
Coagulase-negative staphylococci	350	4 (1.1)	11 (4.3)	80 (27.1)	54 (42.6)	105 (72.6)	86 (97.1)	10 (100.0)	--	--	--
Viridans group streptococci	224	116 (51.8)	64 (80.4)	22 (90.2)	12 (95.5)	4 (97.3)	5 (99.6)	1 (100.0)	--	--	--
β-hemolytic streptococci	164	155 (94.5)	9 (100.0)	--	--	--	--	--	--	--	--
Enterococcus faecalis	127	--	--	--	--	1 (0.8)	4 (3.9)	22 (21.3)	47 (58.3)	20 (74.0)	33 (100.0)
Enterobacteriaceae	1,269	8 (0.6)	91 (7.8)	327 (33.6)	337 (60.1)	145 (71.6)	98 (79.3)	51 (83.3)	19 (84.8)	17 (86.1)	176 (100.0)
Escherichia coli	568	5 (0.9)	66 (12.5)	168 (42.1)	150 (68.5)	53 (77.8)	34 (83.8)	15 (86.4)	3 (87.0)	5 (87.9)	69 (100.0)
non-ESBL-phenotype	496	5 (1.0)	66 (14.3)	168 (48.2)	149 (78.2)	53 (88.9)	34 (95.8)	15 (98.8)	2 (99.2)	3 (99.8)	1 (100.0)
ESBL-phenotype	72	--	--	--	1 (1.4)	0 (1.4)	0 (1.4)	0 (1.4)	1 (2.8)	2 (5.6)	68 (100.0)
Klebsiella spp.	353	2 (0.6)	18 (5.7)	109 (36.5)	96 (63.7)	46 (76.8)	27 (84.4)	6 (86.1)	2 (86.7)	4 (87.8)	43 (100.0)
non-ESBL-phenotype	304	2 (0.7)	18 (6.6)	109 (42.4)	96 (74.0)	46 (89.1)	27 (98.0)	6 (100.0)	--	--	--
ESBL-phenotype	49	--	--	--	--	--	--	--	2 (4.1)	4 (12.2)	43 (100.0)
Enterobacter cloacae	109	--	--	4 (3.7)	33 (33.9)	26 (57.8)	9 (66.1)	3 (68.8)	2 (70.6)	4 (74.3)	28 (100.0)
ceftazidime-susc. (MIC, ≤4 µg/mL)	80	--	--	4 (5.0)	33 (46.3)	26 (78.8)	9 (90.0)	3 (93.8)	2 (96.3)	3 (100.0)	--
ceftazidime-non-susc. (MIC, ≥8 µg/mL)	29	--	--	--	--	--	--	--	--	1 (3.4)	28 (100.0)
Enterobacter aerogenes	41	--	--	11 (26.8)	10 (51.2)	3 (58.5)	0 (58.5)	0 (58.5)	3 (65.9)	1 (68.3)	13 (100.0)
Proteus mirabilis	70	--	1 (1.4)	22 (32.9)	33 (80.0)	5 (87.1)	4 (92.9)	1 (94.3)	0 (94.3)	0 (94.3)	4 (100.0)
Serratia marcescens	55	--	--	--	--	2 (3.6)	19 (38.2)	24 (81.8)	5 (90.9)	2 (94.5)	3 (100.0)
Morganella morganii	23	1 (4.3)	2 (13.0)	7 (43.5)	2 (52.2)	2 (60.9)	4 (78.3)	0 (78.3)	1 (82.6)	0 (82.6)	4 (100.0)
Providencia spp.	20	--	4 (20.0)	3 (35.0)	5 (60.0)	1 (65.0)	0 (65.0)	1 (70.0)	1 (75.0)	0 (75.0)	5 (100.0)
Citrobacter freundii	14	--	--	--	2 (14.3)	5 (50.0)	1 (57.1)	0 (57.1)	0 (57.1)	0 (57.1)	6 (100.0)
Citrobacter koseri	11	--	--	3 (27.3)	6 (81.8)	1 (90.9)	0 (90.9)	0 (90.9)	0 (90.9)	1 (100.0)	--
Proteus vulgaris	5	--	--	--	--	1 (20.0)	0 (20.0)	1 (40.0)	2 (80.0)	0 (80.0)	1 (100.0)
Haemophilus influenzae	25	21 (84.0)	3 (96.0)	0 (96.0)	1 (100.0)	--	--	--	--	--	--

Table 2. Activity of ceftaroline and comparator antimicrobial agents when tested against bacterial isolates causing blood stream infections in USA medical centers (2012)

Organism (no. tested) / Antimicrobial agent	MIC (µg/mL) 50%	90%	%S / % I / %R (CLSI)[a]
Staphylococcus aureus (1,014)			
Ceftaroline	0.25	1	96.6 / 3.4 / 0.0
Ceftriaxone	4	>8	54.4 / 0.0 / 45.6
Oxacillin	0.5	>2	54.4 / 0.0 / 45.6
Erythromycin	16	>16	43.3 / 2.9 / 53.8
Clindamycin	≤0.25	>2	81.6 / 0.2 / 18.3
Levofloxacin	0.25	>4	58.7 / 1.1 / 40.2
Tigecycline[b]	0.06	0.12	100.0 / - / -
Linezolid	1	1	100.0 / 0.0 / 0.0
Vancomycin	1	1	99.9 / 0.1 / 0.0
Daptomycin	0.25	0.5	100.0 / - / -
MSSA (552)			
Ceftaroline	0.25	0.25	100.0 / 0.0 / 0.0
Ceftriaxone	4	4	100.0 / 0.0 / 0.0
Erythromycin	0.25	>16	69.6 / 3.5 / 26.9
Clindamycin	≤0.25	≤0.25	95.1 / 0.2 / 4.7
Levofloxacin	0.25	2	89.5 / 0.5 / 10.0
Tigecycline[b]	0.06	0.06	100.0 / - / -
Linezolid	1	2	100.0 / 0.0 / 0.0
Vancomycin	1	1	100.0 / 0.0 / 0.0
Daptomycin	0.25	0.5	100.0 / - / -
MRSA (462)			
Ceftaroline	1	1	92.6 / 7.4 / 0.0
Erythromycin	>16	>16	11.9 / 2.4 / 85.7
Clindamycin	≤0.25	>2	65.5 / 0.0 / 34.5
Levofloxacin	>4	>4	21.9 / 1.7 / 76.4
Tigecycline[b]	0.06	0.12	100.0 / - / -
Linezolid	1	1	100.0 / 0.0 / 0.0
Vancomycin	1	1	99.8 / 0.2 / 0.0
Daptomycin	0.25	0.5	100.0 / - / -
CoNS (350)[c]			
Ceftaroline	0.25	0.5	- / - / -
Oxacillin	1	>2	37.7 / 0.0 / 62.3
Ceftriaxone	8	>8	37.7 / 0.0 / 62.3
Erythromycin	>16	>16	33.7 / 2.6 / 63.7
Clindamycin	≤0.25	>2	70.3 / 4.0 / 25.7
Levofloxacin	0.5	>4	51.3 / 0.0 / 48.7
Tigecycline[b]	0.06	0.12	- / - / -
Linezolid	0.5	1	98.0 / 0.0 / 2.0
Vancomycin	2	2	100.0 / 0.0 / 0.0
Daptomycin	0.25	0.5	99.7 / - / -
Streptococcus pneumoniae (417)			
Ceftaroline	≤0.015	0.12	100.0 / - / -
Ceftriaxone	≤0.06	1	94.2 / 5.3 / 0.5
Penicillin[d]	≤0.06	2	71.9 / 17.5 / 10.6
Amoxicillin/clavulanate	≤1	2	91.6 / 1.7 / 6.7
Erythromycin	≤0.12	>16	63.9 / 0.0 / 36.1
Clindamycin	≤0.25	>2	84.9 / 0.6 / 14.4
Levofloxacin	1	1	99.8 / 0.0 / 0.2
Linezolid	1	1	100.0 / - / -
Tigecycline[b]	0.03	0.03	99.8 / - / -
Vancomycin	0.25	0.5	100.0 / - / -
Penicillin-non-susceptible (MIC, ≥4 µg/mL; 24)			
Ceftaroline	0.25	0.25	100.0 / - / -
Amoxicillin/Clavulanate	8	8	0.0 / 0.0 / 100.0
Ceftriaxone	2	2	16.7 / 79.0 / 4.2
Erythromycin	>16	>16	0.0 / 0.0 / 100.0
Clindamycin	>2	>2	4.2 / 0.0 / 95.8
Levofloxacin	1	1	95.8 / 0.0 / 4.2
Linezolid	0.5	0.5	100.0 / - / -
Tigecycline[b]	0.03	0.06	100.0 / - / -
Vancomycin	0.25	0.5	100.0 / - / -
Viridans group streptococci[e] (224)			
Ceftaroline	≤0.015	0.06	- / - / -
Ceftriaxone	0.12	1	92.4 / 4.8 / 2.7
Penicillin	≤0.06	1	66.1 / 30.9 / 3.1
Erythromycin	1	>16	39.7 / 2.3 / 58.0
Clindamycin	≤0.25	>2	87.4 / 0.8 / 11.7
Levofloxacin	1	2	90.2 / 2.2 / 7.6
Linezolid	0.5	1	100.0 / - / -
Tigecycline[b]	0.03	0.06	100.0 / - / -
Vancomycin	0.5	0.5	100.0 / - / -
Daptomycin	0.25	1	100.0 / - / -
β-hemolytic streptococci[f] (164)			
Ceftaroline	≤0.015	≤0.015	- / - / -
Ceftriaxone	≤0.06	0.12	100.0 / - / -
Penicillin	≤0.06	≤0.06	100.0 / - / -
Erythromycin	≤0.12	>16	59.8 / 1.2 / 39.0
Clindamycin	≤0.25	>2	75.6 / 0.7 / 23.8
Levofloxacin	0.5	1	99.4 / 0.6 / 0.0
Linezolid	1	1	100.0 / - / -
Tigecycline[b]	0.03	0.03	100.0 / - / -
Vancomycin	0.5	0.5	100.0 / - / -
Daptomycin	0.12	0.25	100.0 / - / -
Enterobacteriaceae[g] (1,269)			
Ceftaroline	0.12	>32	79.3 / 4.0 / 16.7
Ceftriaxone	≤0.06	>8	85.2 / 0.7 / 14.1
Ceftazidime	0.12	16	87.9 / 1.8 / 10.3
Piperacillin/tazobactam	2	16	91.9 / 3.3 / 4.8
Meropenem	≤0.06	≤0.06	99.0 / 0.1 / 0.9
Levofloxacin	≤0.12	>4	80.3 / 1.2 / 18.5
Gentamicin	≤1	8	89.7 / 0.8 / 9.5
Tigecycline[b]	0.25	1	98.6 / 1.4 / 0.0
Escherichia coli (568)			
Ceftaroline	0.12	>32	83.8 / 2.7 / 13.6
Ceftriaxone	≤0.06	>8	87.9 / 0.0 / 12.1
Ceftazidime	0.12	4	90.3 / 1.4 / 8.3
Piperacillin/tazobactam	2	8	94.5 / 1.8 / 3.7
Meropenem	≤0.06	≤0.06	99.8 / 0.2 / 0.0
Levofloxacin	≤0.12	>4	70.0 / 0.4 / 29.6
Gentamicin	≤1	>8	85.4 / 0.1 / 14.5
Tigecycline[b]	0.12	0.12	100.0 / 0.0 / 0.0
ESBL-phenotype (72)			
Ceftaroline	>32	>32	1.4 / 0.0 / 98.6
Ceftriaxone	>8	>8	4.2 / 0.0 / 95.8
Ceftazidime	16	>32	23.6 / 11.1 / 65.3
Piperacillin/tazobactam	8	>64	75.0 / 8.3 / 16.7
Meropenem	≤0.06	≤0.06	98.6 / 1.4 / 0.0
Levofloxacin	>4	>4	23.6 / 1.4 / 75.0
Gentamicin	2	>8	57.7 / 1.5 / 40.8
Tigecycline[b]	0.12	0.25	100.0 / 0.0 / 0.0
Klebsiella spp.[h] (353)			
Ceftaroline	0.12	>32	84.4 / 1.6 / 13.9
Ceftriaxone	≤0.06	>8	87.0 / 0.0 / 13.0
Ceftazidime	0.12	16	88.1 / 1.4 / 10.5
Piperacillin/tazobactam	4	16	90.9 / 2.3 / 6.8
Meropenem	≤0.06	≤0.06	96.6 / 0.0 / 3.4
Levofloxacin	≤0.12	4	89.5 / 1.2 / 9.3
Gentamicin	≤1	≤1	93.5 / 1.1 / 5.4
Tigecycline[b]	0.25	1	99.4 / 0.6 / 0.0
ESBL-phenotype[i] (49)			
Ceftaroline	>32	>32	0.0 / 0.0 / 100.0
Ceftriaxone	>8	>8	6.1 / 0.0 / 93.9
Ceftazidime	32	>32	14.3 / 10.2 / 75.5
Piperacillin/tazobactam	64	>64	36.7 / 14.3 / 49.0
Meropenem	≤0.06	>8	75.5 / 0.0 / 24.5
Levofloxacin	>4	>4	36.7 / 4.1 / 59.2
Gentamicin	4	>8	55.1 / 8.2 / 36.7
Tigecycline[b]	0.5	2	98.0 / 2.0 / 0.0
Proteus mirabilis (70)			
Ceftaroline	0.12	0.5	92.9 / 1.3 / 5.7
Ceftriaxone	≤0.06	≤0.06	94.3 / 1.4 / 4.3
Ceftazidime	0.06	0.12	98.6 / 1.4 / 0.0
Piperacillin/tazobactam	≤0.5	1	100.0 / 0.0 / 0.0
Meropenem	≤0.06	0.12	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	>4	65.7 / 7.2 / 27.1
Gentamicin	≤1	>8	84.3 / 2.8 / 12.9
Tigecycline[b]	2	4	87.1 / 12.9 / 0.0
Enterobacter cloacae (109)			
Ceftaroline	0.25	>32	66.1 / 2.7 / 31.2
Ceftriaxone	0.5	>8	67.9 / 2.7 / 29.4
Ceftazidime	0.5	>32	73.4 / 3.7 / 22.9
Piperacillin/tazobactam	4	64	81.7 / 10.0 / 8.3
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	0.5	99.1 / 0.9 / 0.0
Gentamicin	≤1	≤1	96.3 / 0.0 / 3.7
Tigecycline[b]	0.25	1	97.2 / 2.8 / 0.0
Enterobacter aerogenes (41)			
Ceftaroline	0.12	>32	58.5 / 0.0 / 41.5
Ceftriaxone	0.25	>8	56.1 / 4.9 / 39.0
Ceftazidime	0.25	32	61.0 / 7.3 / 31.7
Piperacillin/tazobactam	4	64	70.7 / 19.5 / 9.8
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	1	92.7 / 2.3 / 4.9
Gentamicin	≤1	≤1	100.0 / 0.0 / 0.0
Tigecycline[b]	0.25	1	97.6 / 2.4 / 0.0
Serratia marcescens (55)			
Ceftaroline	1	2	38.2 / 43.5 / 18.2
Ceftriaxone	0.25	1	90.9 / 0.0 / 9.1
Ceftazidime	0.25	0.5	100.0 / 0.0 / 0.0
Piperacillin/tazobactam	2	4	98.2 / 1.8 / 0.0
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	0.25	100.0 / 0.0 / 0.0
Gentamicin	≤1	2	94.5 / 0.0 / 5.5
Tigecycline[b]	0.5	1	100.0 / 0.0 / 0.0
Morganella morganii (23)			
Ceftaroline	0.12	32	78.3 / 0.0 / 21.7
Ceftriaxone	≤0.06	2	82.6 / 8.7 / 8.7
Ceftazidime	0.06	16	82.6 / 4.4 / 13.0
Piperacillin/tazobactam	≤0.5	2	100.0 / 0.0 / 0.0
Meropenem	≤0.06	0.12	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	>4	69.6 / 8.7 / 21.7
Gentamicin	≤1	>8	87.0 / 0.0 / 13.0
Tigecycline[b]	0.5	1	95.7 / 4.3 / 0.0
Providencia spp.[j] (20)			
Ceftaroline	0.12	16	65.0 / 5.0 / 30.0
Ceftriaxone	≤0.06	0.25	90.0 / 5.0 / 5.0
Ceftazidime	0.12	2	95.0 / 0.0 / 5.0
Piperacillin/tazobactam	1	4	95.0 / 0.0 / 5.0
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0
Levofloxacin	0.25	>4	70.0 / 0.0 / 30.0
Gentamicin	2	8	80.0 / 20.0 / 0.0
Tigecycline[b]	1	2	95.0 / 5.0 / 0.0
Haemophilus influenzae (25)			
Ceftaroline	≤0.015	0.03	100.0 / - / -
Ceftriaxone	≤0.06	≤0.06	100.0 / - / -
Cefuroxime	1	4	95.8 / 4.2 / 0.0
Ampicillin	≤0.25	1	92.0 / 4.0 / 4.0
Amoxicillin/clavulanate	≤1	2	100.0 / 0.0 / 0.0
Piperacillin/tazobactam	≤0.5	≤0.5	100.0 / 0.0 / 0.0
Azithromycin	1	2	100.0 / - / -
Levofloxacin	≤0.12	≤0.12	100.0 / - / -

a. Criteria as published by the CLSI [2013].
b. USA-FDA breakpoints were applied when available [Tygacil Product Insert, 2012].
c. Includes: *Staphylococcus auricularis* (one strain), *S. capitis* (26 strains), *S. caprae* (three strains), *S. cohnii* (three strains), *S. epidermidis* (216 strains), *S. haemolyticus* (17 strains), *S. hominis* (51 strains), *S. intermedius* (one strain), *S. lugdunensis* (10 strains), *S. pettenkoferi* (seven strains), *S. saprophyticus* (three strains), *S. simulans* (four strains), *S. warneri* (seven strains), and unspeciated coagulase-negative staphylococci (one strain).
d. Criteria as published by the CLSI [2013] for 'Penicillin oral penicillin V' (S≤0.06, I=0.12-1, R≥2 µg/mL).
e. Includes: *Streptococcus acidominimus* (one strain), *S. alactolyticus* (one strain), *S. anginosus* (20 strains), *S. bovis* group (5 strains), *Streptococcus constellatus* (6 strains), *Streptococcus cristatus* (2 strains), *Streptococcus equinus* (one strain), *S. gallolyticus* (two strains), *S. gordonii* (four strains), *S. intermedius* (one strain), *S. milleri* (2 strains), *S. mitis* (84 strains), *S. mitis* group (one strain), *S. mutans* (two strains), *S. oralis* (25 strains), *S. parasanguinis* (18 strains), *S. salivarius* (28 strains), *S. sanguinis* (13 strains), and unspeciated viridans group streptococci (eight strains).
f. Includes: Group A *Streptococcus* (56 strains), Group B *Streptococcus* (93 strains), and Group C *Streptococcus* (15 strains).
g. Includes: *Citrobacter freundii* (14 strains), *C. koseri* (11 strains), *Enterobacter aerogenes* (41 strains), *E. cloacae* (109 strains), *Escherichia coli* (568 strains), *Klebsiella oxytoca* (55 strains), *K. pneumoniae* (298 strains), *Morganella morganii* (23 strains), *Proteus mirabilis* (70 strains), *P. vulgaris* (five strains), *Providencia rettgeri* (12 strains), *P. stuartii* (eight strains), and *Serratia marcescens* (55 strains).
h. Includes: *Klebsiella oxytoca* (55 strains) and *K. pneumoniae* (298 strains).
i. Includes: *Klebsiella oxytoca* (four strains) and *K. pneumoniae* (45 strains).
j. Includes: *Providencia rettgeri* (12 strains) and *P. stuartii* (eight strains).

Conclusions

- Ceftaroline demonstrated potent activity against gram-positive organisms, including MRSA and ceftriaxone-non-susceptible *S. pneumoniae* strains, and non-ESBL-phenotype Enterobacteriaceae causing BSI in USA hospitals
- These in vitro data support the further clinical development of ceftaroline for treatment of BSI, especially those caused by MRSA and multidrug-resistant *S. pneumoniae*.

References

1. Clinical and Laboratory Standards Institute (2012). *M07-A9. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: ninth edition*. Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute (2013). *M100-S23. Performance standards for antimicrobial susceptibility testing: 23rd informational supplement.* Wayne, PA: CLSI.
3. Corey GR, Wilcox M, Talbot GH, Friedland HD, Baculik T, Witherell GW, Critchley I, Das AF, Thye D (2010). Integrated analysis of CANVAS 1 and 2: Phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. *Clin Infect Dis* 51: 641-650.
4. Drusano GL (2010). Pharmacodynamics of ceftaroline fosamil for complicated skin and skin structure infection: rationale for improved anti-methicillin-resistant *Staphylococcus aureus* activity. *J Antimicrob Chemother* 65 Suppl 4: iv33-iv39.
5. Flamm RK, Sader HS, Farrell DJ, Jones RN (2012). Summary of ceftaroline activity against pathogens in the United States, 2010: Report from the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Surveillance Program. *Antimicrob Agents Chemother* 56: 2933-2940.
6. Jones RN, Mendes RE, Sader HS (2010). Ceftaroline activity against pathogens associated with complicated skin and skin structure infections: Results from an international surveillance study. *J Antimicrob Chemother* 65 Suppl 4: iv17-iv31.
7. Mendes RE, Tsakris A, Sader HS, Jones RN, Biek D, McGhee P, Appelbaum PC, Kosowska-Shick K (2012). Characterization of methicillin-resistant *Staphylococcus aureus* displaying increased MICs of ceftaroline. *J Antimicrob Chemother* 67: 1321-1324.
8. Tygacil® Package Insert (2012). Available at www.tygacil.com. Accessed January 2013.

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