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Antimicrobial Activity of Ceftaroline-Avibactam Tested Against Contemporary Clinical Isolates from USA Medical Centers (2011)

HS SADER, RK FLAMM, JM STREIT, RN JONES

JMI Laboratories, North Liberty, Iowa, USA

Helio S. Sader, MD, PhD
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
ph. 319.665.3370
fax 319.665.3371
helio-sader@jmilabs.com

Abstract

Background: Ceftaroline is a broad-spectrum cephalosporin active against Gram-positive (including MRSA and multidrug-resistant *S. pneumoniae*) and common Gram-negative organisms. Avibactam is a novel non-β-lactam β-lactamase inhibitor of Ambler class A, C, and D enzymes.

Methods: Isolates were consecutively collected in 2011 from 67 USA medical centers from all 9 CDC Census Regions (4-10/region). Susceptibility testing for ceftaroline-avibactam (avibactam at fixed 4 μg/mL), ceftaroline, and comparators was performed by CLSI broth microdilution methods for 11,676 strains.

Results: Ceftaroline-avibactam was highly active against *Klebsiella* spp. (MIC_{90}, 0.25 μg/mL), including ESBL-phenotype (MIC_{90}, 0.5 μg/mL) and meropenem-non-S strains (MIC_{90}, 1 μg/mL). All *E. coli*, including ESBL-phenotype strains (MIC_{90}, 0.12 μg/mL), were inhibited at ceftaroline-avibactam MIC of ≤0.5 μg/mL. Ceftaroline-avibactam was also active against *Enterobacter* spp. (MIC_{90}, 0.12 – 0.25 μg/mL), *Citrobacter* spp. (MIC_{90}, 0.12 μg/mL), *M. morganii* (MIC_{90}, 0.12 μg/mL), and *S. marcescens* (MIC_{90}, 1 μg/mL). Highest ceftaroline-avibactam MIC among MSSA and MRSA were 0.5 and 2 μg/mL, respectively. Penicillin-resistant ($MIC_{50/90}$, 0.12/0.25 μg/mL) and levofloxacin-non-susceptible ($MIC_{50/90}$, 0.06/0.12 μg/mL) *S. pneumoniae* were ceftaroline-avibactam-susceptible. Ceftaroline-avibactam was 8- to 16-fold more active than ceftriaxone against MSSA and penicillin-resistant *S. pneumoniae*; the highest ceftaroline-avibactam MIC value was only 0.5 μg/mL for both organisms. 98.8% of *H. influenzae* were inhibited at ceftaroline-avibactam MIC of ≤0.015 μg/mL (highest ceftaroline-avibactam MIC was only 0.06 μg/mL). β-hemolytic and viridans group streptococci had ceftaroline-avibactam MIC_{90}s of ≤0.015 and 0.12 μg/mL, respectively.

Conclusions: Ceftaroline-avibactam was highly active against Enterobacteriaceae producing KPC, various ESBL types, and AmpC (chromosomal- or plasmid-mediated) enzymes. Ceftaroline-avibactam and ceftaroline were the most potent β-lactam agents tested against staphylococci and streptococci collected from USA hospitals. MRSA and penicillin-resistant *S. pneumoniae* were particularly susceptible to ceftaroline-avibactam and ceftaroline.

Introduction

Ceftaroline fosamil is the prodrug form of ceftaroline, a cephalosporin with broad-spectrum *in vitro* activity. Ceftaroline has demonstrated bactericidal activity against organisms most frequently responsible for community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin-structure infections (ABSSSIs), including multidrug-resistant *Streptococcus pneumoniae* and methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA). Ceftaroline is also active against most Enterobacteriaceae species but, like other cephalosporins, has limited activity against isolates producing extended-spectrum β-lactamases (ESBLs), cephalosporinases and carbapenemases. However, the spectrum of activity of ceftaroline is further combined with avibactam.

Avibactam (previously, NXL104) is a new non-β-lactam β-lactamase inhibitor currently in clinical development. Avibactam has very limited intrinsic antibacterial activity, but efficiently protects β-lactams from hydrolysis by a variety of strains producing Ambler class A, C, and some D enzymes, including ESBLs and KPC enzymes (carbapenemases). Thus, the addition of avibactam restores ceftaroline activity against Enterobacteriaceae strains that are resistant to broad-spectrum cephalosporins due to the production of these β-lactamases. We report the *in vitro* activity of ceftaroline combined with avibactam (fixed concentration of 4 μg/mL) against bacterial organisms isolated in USA medical centers in 2011 as part of a worldwide surveillance program.

Methods

Organisms collection: A total of 11,676 bacterial isolates were tested as listed in Table 1. Sixty-seven medical centers distributed across all nine USA Census Regions (4 to 10 medical centers per region) contributed clinical isolates for this surveillance program in 2011. Organisms were consecutively collected from clinical infections and target numbers of strains for each of the requested bacterial species/genus were predetermined in the study protocol. Isolates were sent to the coordinator laboratory (JMI Laboratories, North Liberty, Iowa, USA) for reference susceptibility testing. Only one strain per patient infection episode was included in the surveillance.

Susceptibility testing: Isolates were tested for susceptibility to ceftaroline-avibactam and multiple comparator agents by reference broth microdilution methods as described by Clinical and Laboratory Standards Institute (CLSI) M07-A9 (2012) and CLSI interpretations were based on M100-S22 and M45-A breakpoints, while ceftaroline interpretations were based on the breakpoint criteria established by the USA-FDA. Ceftaroline was combined with avibactam at a fixed concentration of 4 μg/mL. *S. pneumoniae* were tested in Mueller-Hinton broth supplemented with 3-5% lysed horse blood, and *H. influenzae* were tested in Haemophilus Test Media, whereas *S. aureus* isolates were tested in cation-adjusted Mueller-Hinton broth. Concurrent testing of quality control (QC) strains assured proper test conditions.

Results

- Using the USA-FDA breakpoint for ceftaroline susceptibility (≤0.5 μg/mL), ceftaroline-avibactam was among the most active agents tested against Enterobacteriaceae (Tables 2 and 3)
- Ceftaroline-avibactam was active against *Klebsiella* spp. ($MIC_{50/90}$, 0.06/0.25 μg/mL), including strains with an ESBL-phenotype ($MIC_{50/90}$, 0.12/0.5 μg/mL) and those with reduced susceptibility to carbapenems ($MIC_{50/90}$, 0.5/1 μg/mL; Tables 2 and 3). Among ESBL-phenotype *Klebsiella* spp., 26.2% of strains exhibited decreased susceptibility (MIC, ≥2 μg/mL) to meropenem (Table 3)
- All *Escherichia coli* isolates were susceptible to ceftaroline-avibactam ($MIC_{50/90}$, 0.03/0.06 μg/mL) when breakpoints established by the USA-FDA for ceftaroline were applied (Table 2). Furthermore, ceftaroline-avibactam exhibited potent activity against *E. coli* strains with an ESBL-phenotype ($MIC_{50/90}$, 0.03/0.12 μg/mL; Tables 2 and 3)
- Among *Enterobacter cloacae* strains, 96.3% were inhibited by ceftaroline-avibactam at ≤0.5 μg/mL (Table 2). Meropenem (MIC_{90}, ≤0.06 μg/mL; 98.2% susceptible) and tigecycline (MIC_{90}, 0.5 mg/L; 98.4% susceptible) were also very active against *E. cloacae* (Table 3). Among ceftazidime-non-susceptible (MIC, ≥8 μg/mL) *E. cloacae* strains, 83.8% and 96.3% of strains were inhibited at ceftaroline-avibactam MICs of ≤0.5 and ≤1 μg/mL, respectively (Table 2)
- Ceftaroline-avibactam was active against *Serratia marcescens* ($MIC_{50/90}$, 0.5/1 μg/mL), with 89.0% and 98.3% of strains being inhibited at MIC of ≤0.5 and ≤1 μg/mL, respectively, and inhibited all 231 *Proteus mirabilis* strains at ≤0.5 μg/mL ($MIC_{50/90}$, 0.06/0.12 mg/L; Tables 2 and 3)
- *Morganella morganii* ($MIC_{50/90}$, 0.03/0.12 μg/mL), *Citrobacter freundii* ($MIC_{50/90}$, 0.06/0.12 μg/mL), *Citrobacter koseri* ($MIC_{50/90}$, 0.06/0.12 μg/mL), and *Enterobacter aerogenes* ($MIC_{50/90}$, 0.06/0.12 μg/mL) were very susceptible to ceftaroline-avibactam (Table 2)
- Ceftaroline-avibactam ($MIC_{50/90}$, ≤0.015/0.12 μg/mL) and ceftaroline ($MIC_{50/90}$, ≤0.015/0.12 μg/mL) were the most potent β-lactams tested against *S. pneumoniae* (Table 4). The highest ceftaroline-avibactam MIC value observed was 0.5 μg/mL (19 strains [0.9%]; Table 2)
- Against penicillin-resistant (MIC, ≥2 μg/mL) pneumococci, ceftaroline-avibactam ($MIC_{50/90}$, 0.12/0.25 μg/mL; Table 2) was eight-fold more active than ceftriaxone (MIC_{50}, 1 μg/mL and MIC_{90}, 2 μg/mL) and 32- to 64-fold more potent than amoxicillin/clavulanic acid (MIC_{50} and MIC_{90}, 8 μg/mL; data not shown)
- Ceftaroline-avibactam was highly active against *H. influenzae*, *Haemophilus parainfluenzae* and *Moraxella catarrhalis* (MIC_{90}, ≤0.015 μg/mL for all three organisms; Table 2)
- Ceftaroline-avibactam (MIC_{50} and MIC_{90}, 0.25 μg/mL) was 16-fold more active than ceftriaxone (MIC_{50} and MIC_{90}, 4 μg/mL) and four-fold more active than linezolid (MIC_{50} and MIC_{90}, 1 μg/mL) when tested against oxacillin- (methicillin-) susceptible *S. aureus* (MSSA; data not shown). The highest ceftaroline-avibactam MIC value among MSSA strains was only 0.5 μg/mL and 99.0% of strains were inhibited at a ceftaroline-avibactam MIC of ≤0.25 μg/mL (Tables 2 and 5)
- Against MRSA ($MIC_{50/90}$, 0.5/1 μg/mL), 98.4% and 100.0% of strains were inhibited at ceftaroline-avibactam MIC values of ≤1 μg/mL and ≤2 μg/mL, respectively (Table 2). Ceftaroline and ceftaroline-avibactam exhibited very similar activities against MRSA strains (data not shown)
- Ceftaroline-avibactam was very potent against β-hemolytic streptococci with the MIC_{90} at ≤0.015 μg/mL. The highest ceftaroline-avibactam MIC among β-hemolytic streptococci was only 0.06 μg/mL (Tables 2 and 5).

Table 1. List of Organisms Evaluated as Part of the Ceftaroline-Avibactam Surveillance Program (2011)

Organism	No. of isolates
Citrobacter freundii	157
C. koseri	117
Enterobacter aerogenes	146
E. cloacae	383
Escherichia coli	726
Klebsiella oxytoca	245
K. pneumoniae	818
Morganella morganii	192
Proteus mirabilis	231
Serratia marcescens	237
Pseudomonas aeruginosa	213
Haemophilus influenzae	909
H. parainfluenzae	122
Moraxella catarrhalis	294
Staphylococcus aureus	2169
Coagulase negative staphylococci	645
Streptococcus pneumoniae	2149
S. pyogenes	491
S. agalactiae	561
S. dysgalactiae	92
Streptococcus anginosus group	74
other Viridans group streptococci	486
Enterococcus faecalis	219
Total	11676

Table 2. Summary of Ceftaroline-Avibactam Activity when Tested Against Selected Organisms from USA Medical Centers (2011)

Organism/antimicrobial agent (no. tested)	no. of strains (cumulative %) inhibited at MIC (μg/mL) of:									MIC_{50}	MIC_{90}
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4		
Klebsiella spp. (1063)	48 (4.5)	352 (37.6)	405 (75.7)	151 (89.9)	65 (96.0)	28 (98.7)	12 (99.8)	2 (100.0)	-	0.06	0.25
non-ESBL-phenotype (899)	42 (4.7)	341 (42.6)	374 (84.2)	107 (96.1)	29 (99.3)	6 (100.0)	-	-	-	0.06	0.12
ESBL-phenotype (164)	6 (3.7)	11 (10.4)	31 (29.3)	44 (56.1)	36 (78.0)	22 (91.5)	12 (98.8)	2 (100.0)	-	0.12	0.5
meropenem-non-susceptible (43)	-	-	2 (4.6)	7 (20.9)	9 (41.9)	12 (69.8)	11 (95.3)	2 (100.0)	-	0.5	1
Escherichia coli (726)	241 (33.2)	345 (80.7)	109 (95.7)	24 (99.0)	6 (99.9)	1 (100.0)	-	-	-	0.03	0.06
non-ESBL-phenotype (638)	228 (35.7)	314 (85.0)	88 (98.7)	7 (99.8)	1 (100.0)	-	-	-	-	0.03	0.06
ESBL-phenotype (88)	13 (14.8)	31 (50.0)	21 (73.9)	17 (93.2)	5 (98.9)	1 (100.0)	-	-	-	0.03	0.12
Enterobacter cloacae (383)	6 (1.6)	23 (7.6)	102 (34.2)	144 (71.8)	71 (90.3)	23 (96.3)	11 (99.2)	3 (100.0)	-	0.12	0.25
ceftazidime-susceptible (303)	6 (2.0)	23 (9.6)	101 (42.9)	131 (86.1)	36 (98.0)	5 (99.7)	1 (100.0)	-	-	0.12	0.25
ceftazidime-non-susceptible (80)	-	-	1 (1.3)	13 (17.5)	35 (61.3)	18 (83.8)	10 (96.3)	3 (100.0)	-	0.25	1
Serratia marcescens (237)	-	-	1 (0.4)	25 (11.0)	91 (49.4)	94 (89.0)	22 (98.3)	1 (98.7)	3 (100.0)	0.5	1
Proteus mirabilis (231)	-	39 (16.9)	142 (78.4)	42 (96.5)	7 (99.6)	1 (100.0)	-	-	-	0.06	0.12
Morganella morganii (192)	23 (12.0)	93 (60.4)	51 (87.0)	13 (93.8)	8 (97.9)	4 (100.0)	-	-	-	0.03	0.12
Citrobacter freundii (157)	1 (0.6)	28 (18.5)	75 (66.2)	39 (91.1)	8 (96.2)	1 (96.8)	4 (99.4)	1 (100.0)	-	0.06	0.12
Enterobacter aerogenes (146)	8 (5.5)	59 (45.9)	62 (88.4)	10 (95.2)	5 (98.6)	2 (100.0)	-	-	-	0.06	0.12
Citrobacter koseri (117)	12 (10.3)	45 (48.7)	46 (88.0)	8 (94.9)	4 (98.3)	1 (99.1)	1 (100.0)	-	-	0.06	0.12
Streptococcus pneumoniae (2149)	1278 (59.5)	190 (68.3)	185 (76.9)	365 (93.9)	112 (99.1)	19 (100.0)	-	-	-	≤0.015	0.12
Penicillin-resistant (MIC, ≥2 μg/mL; 502)	-	1 (0.2)	30 (6.2)	340 (73.9)	112 (96.2)	19 (100.0)	-	-	-	0.12	0.25
Haemophilus influenzae (909)	898 (98.8)	9 (99.8)	2 (100.0)	-	-	-	-	-	-	≤0.015	≤0.015
Moraxella catarrhalis (294)	288 (98.0)	5 (99.7)	1 (100.0)	-	-	-	-	-	-	≤0.015	≤0.015
Haemophilus parainfluenzae (122)	117 (95.9)	2 (97.5)	2 (99.2)	1 (100.0)	-	-	-	-	-	≤0.015	≤0.015
Staphylococcus aureus (2169)	1 (0.0)	1 (0.1)	10 (0.6)	304 (14.6)	827 (52.7)	792 (89.2)	217 (99.2)	17 (100.0)	-	0.25	1
MSSA (1098)	1 (0.1)	0 (0.1)	10 (1.0)	302 (28.5)	774 (99.0)	11 (100.0)	-	-	-	0.25	0.25
MRSA (1071)	-	1 (0.1)	0 (0.1)	2 (0.3)	53 (5.2)	781 (78.2)	217 (98.4)	17 (100.0)	-	0.5	1
β-hemolytic streptococci (1144)	1068 (93.4)	74 (99.8)	2 (100.0)	-	-	-	-	-	-	≤0.015	≤0.015
Viridans group streptococci (560)	283 (50.5)	160 (79.1)	53 (88.6)	36 (95.0)	13 (97.3)	9 (98.9)	6 (100.0)	-	-	≤0.015	0.12

Table 3. Activity of Ceftaroline-Avibactam, Ceftaroline and Comparator Antimicrobial Agents when Tested Against Enterobacteriaceae

Organism/antimicrobial agent (no. tested)	MIC (μg/mL)		%S / %I / %R	
	MIC_{50}	MIC_{90}	CLSI[a]	EUCAST[a]
Klebsiella spp[b] (1,063)				
Ceftaroline-avibactam	0.06	0.25	- / - / -	- / - / -
Ceftaroline[c]	0.12	>32	81.6 / 2.8 / 15.6	- / - / -
Ceftriaxone	≤0.06	>8	85.5 / 0.9 / 13.6	85.5 / 0.9 / 13.6
Ceftazidime	0.12	16	88.0 / 0.5 / 11.5	86.3 / 1.7 / 12.0
Ampicillin/sulbactam	8	>32	70.5 / 0.0 / 29.5	70.5 / 0.0 / 29.5
Piperacillin/tazobactam	2	>64	88.0 / 1.6 / 10.4	82.4 / 5.6 / 12.0
Meropenem	≤0.06	≤0.06	96.0 / 0.1 / 3.9	96.1 / 0.0 / 3.9
Tigecycline[d]	0.25	1	98.5 / 1.3 / 0.2	94.6 / 3.9 / 1.5
Gentamicin	≤1	2	92.8 / 1.7 / 5.5	91.7 / 1.1 / 7.2
Levofloxacin	≤0.12	>4	88.4 / 1.1 / 10.5	87.4 / 1.0 / 11.6
Non-ESBL-phenotype[e] (899)				
Ceftaroline-avibactam	0.06	0.12	- / - / -	- / - / -
Ceftaroline[c]	0.12	0.5	96.2 / 3.0 / 0.8	- / - / -
Ceftriaxone	≤0.06	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Ceftazidime	0.12	0.5	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Ampicillin/sulbactam	4	16	83.0 / 11.4 / 5.6	83.0 / 0.0 / 17.0
Piperacillin/tazobactam	2	8	99.1 / 0.3 / 0.6	94.1 / 5.0 / 0.9
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Tigecycline[d]	0.25	0.5	98.9 / 0.8 / 0.2	95.8 / 3.1 / 1.1
Gentamicin	≤1	≤1	99.1 / 0.2 / 0.7	99.1 / 0.0 / 0.9
Levofloxacin	≤0.12	0.5	98.2 / 0.8 / 1.0	97.4 / 0.8 / 1.8
ESBL-phenotype[f] (164)				
Ceftaroline-avibactam	0.12	0.5	- / - / -	- / - / -
Ceftaroline[c]	>32	>32	1.2 / 1.8 / 97.0	- / - / -
Ceftriaxone	>8	>8	6.1 / 5.5 / 88.4	6.1 / 5.5 / 88.4
Ceftazidime	>32	>32	22.0 / 3.6 / 74.4	11.0 / 11.0 / 78.0
Ampicillin/sulbactam	>32	>32	1.8 / 8.6 / 89.6	1.8 / 8.0 / 98.2
Piperacillin/tazobactam	>64	>64	26.8 / 8.6 / 64.6	18.3 / 8.5 / 73.2
Meropenem	≤0.06	>8	73.8 / 1.2 / 25.0	75.0 / 4.3 / 20.7
Tigecycline[d]	0.5	2	96.3 / 3.7 / 0.0	88.4 / 7.8 / 3.7
Gentamicin	2	>8	57.9 / 10.4 / 31.7	51.2 / 6.7 / 42.1
Levofloxacin	>4	>4	34.8 / 2.4 / 62.8	32.3 / 2.5 / 65.2
E. coli (726)				
Ceftaroline-avibactam	0.03	0.06	- / - / -	- / - / -
Ceftaroline[c]	0.12	32	83.1 / 2.6 / 14.3	- / - / -
Ceftriaxone	≤0.06	>8	89.1 / 0.3 / 10.6	89.1 / 0.3 / 10.6
Ceftazidime	0.12	2	91.7 / 1.3 / 7.0	89.3 / 2.4 / 8.3
Ampicillin/sulbactam	8	>32	50.1 / 23.8 / 26.1	50.1 / 0.0 / 49.9
Piperacillin/tazobactam	2	8	93.8 / 3.9 / 4.3	91.7 / 2.1 / 6.2
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Tigecycline[d]	0.12	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Gentamicin	≤1	>8	87.3 / 0.6 / 12.1	86.5 / 0.8 / 12.7
Levofloxacin	≤0.12	>4	69.6 / 0.5 / 29.9	69.3 / 0.3 / 30.4
Non-ESBL-phenotype (638)				
Ceftaroline-avibactam	0.03	0.06	- / - / -	- / - / -
Ceftaroline[c]	0.12	0.5	93.3 / 2.9 / 3.8	- / - / -
Ceftriaxone	≤0.06	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Ceftazidime	0.12	0.25	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Ampicillin/sulbactam	8	32	55.7 / 24.8 / 19.5	55.7 / 0.0 / 44.3
Piperacillin/tazobactam	2	4	96.4 / 1.1 / 2.5	95.9 / 0.5 / 3.6
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Tigecycline[d]	0.06	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Gentamicin	≤1	8	89.7 / 0.6 / 9.7	89.0 / 0.7 / 10.3
Levofloxacin	≤0.12	>4	76.6 / 0.5 / 22.9	76.3 / 0.3 / 23.4
ESBL-phenotype (88)				
Ceftaroline-avibactam	0.03	0.12	- / - / -	- / - / -
Ceftaroline[c]	>32	>32	9.1 / 0.0 / 90.9	- / - / -
Ceftriaxone	>8	>8	10.2 / 2.3 / 87.5	10.2 / 2.3 / 87.5
Ceftazidime	16	>32	31.8 / 10.2 / 58.0	11.4 / 20.4 / 68.2
Ampicillin/sulbactam	32	>32	9.1 / 17.0 / 73.9	9.1 / 0.0 / 90.9
Piperacillin/tazobactam	8	>64	75.0 / 8.0 / 17.0	61.4 / 13.6 / 25.0
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Tigecycline[d]	0.12	0.25	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Gentamicin	≤1	>8	70.5 / 0.0 / 29.5	68.2 / 2.2 / 29.5
Levofloxacin	>4	>4	18.2 / 1.1 / 80.7	18.2 / 0.0 / 81.8

Table 4. Activity of Ceftaroline-Avibactam, Ceftaroline and Comparator Antimicrobial Agents when Tested Against *S. pneumoniae* and *H. influenzae*

Organism/antimicrobial agent (no. tested)	MIC (μg/mL)		%S / %I / %R	
	MIC_{50}	MIC_{90}	CLSI[a]	EUCAST[a]
S. pneumoniae (2,149)				
Ceftaroline-avibactam	≤0.015	0.12	- / - / -	- / - / -
Ceftaroline[b]	≤0.015	0.12	99.1 / - / -	- / - / -
Ceftriaxone	≤0.06	2	88.4 / 10.3 / 1.3	76.1 / 22.6 / 1.3
Penicillin[c]	≤0.06	4	85.2 / 12.8 / 1.9	- / - / -
Penicillin[d]	≤0.06	4	56.3 / 20.3 / 23.4	56.3 / 28.9 / 14.8
Amoxicillin/clavulanate	≤1	8	81.1 / 4.8 / 14.1	- / - / -
Erythromycin	≤0.12	>16	55.2 / 0.4 / 44.4	55.2 / 0.4 / 44.4
Clindamycin	≤0.25	>2	78.2 / 0.6 / 21.2	78.8 / 0.0 / 21.2
Levofloxacin	1	1	98.7 / <0.1 / 1.2	98.7 / 0.0 / 1.3
Trimethoprim/sulfamethoxazole	≤0.5	>4	65.1 / 8.8 / 26.1	69.8 / 4.1 / 26.1
Tetracycline	0.5	>8	74.2 / 0.2 / 25.6	73.8 / 0.4 / 25.8
Linezolid	1	1	100.0 / - / -	100.0 / 0.0 / 0.0
Vancomycin	0.25	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
H. influenzae (909)				
Ceftaroline-avibactam	≤0.015	≤0.015	- / - / -	- / - / -
Ceftaroline[b]	≤0.015	0.03	99.6 / - / -	- / - / -
Ceftriaxone	≤0.06	≤0.06	100.0 / - / -	100.0 / 0.0 / 0.0
Ampicillin	0.25	>8	73.0 / 0.0 / 27.0	73.0 / 0.0 / 27.0
Amoxicillin/clavulanate	≤1	≤1	99.9 / 0.0 / 0.1	90.2 / 0.0 / 9.8
Azithromycin	1	2	98.9 / - / -	1.2 / 97.7 / 1.1
Clarithromycin	8	16	81.3 / 17.0 / 1.7	1.9 / 98.1 / 0.0
Levofloxacin	≤0.12	≤0.12	100.0 / - / -	100.0 / 0.0 / 0.0

a. Criteria as published by the CLSI and EUCAST (2012).
b. USA-FDA breakpoints were applied when available [Teflaro® Prescribing Information, 2012].
c. Criteria as published by the CLSI [2012] for 'Penicillin parenteral (non-meningitis)'.
d. Criteria as published by the CLSI [2012] for 'Penicillin (oral penicillin V)'.

Table 5. Activity of Ceftaroline-Avibactam, Ceftaroline and Comparator Antimicrobial Agents when Tested Against *S. aureus* and β-hemolytic Streptococci

Organism/antimicrobial agent (no. tested)	MIC (μg/mL)		%S / %I / %R	
	MIC_{50}	MIC_{90}	CLSI[a]	EUCAST[a]
S. aureus (2,169)				
Ceftaroline-avibactam	0.25	1	- / - / -	- / - / -
Ceftaroline[b]	0.25	1	99.0 / - / -	- / - / -
Ceftriaxone	8	>8	49.4 / 1.2 / 49.4	50.6 / 0.0 / 49.4
Oxacillin	1	>2	50.6 / 0.0 / 49.4	50.6 / 0.0 / 49.4
Erythromycin	>16	>16	38.4 / 2.2 / 59.6	38.4 / 0.6 / 61.0
Clindamycin	≤0.25	>2	84.6 / <0.1 / 15.3	84.5 / 0.1 / 15.4
Levofloxacin	0.25	>4	60.9 / 2.2 / 36.9	60.9 / 2.2 / 36.9
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	98.1 / 0.0 / 1.9	98.1 / 0.3 / 1.6
Linezolid	1	2	>99.9 / 0.0 / <0.1	>99.9 / 0.0 / <0.1
Vancomycin	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Daptomycin	0.25	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
β-hemolytic streptococci[c] (1,144)				
Ceftaroline-avibactam	≤0.015	≤0.015	- / - / -	- / - / -
Ceftaroline[b]	≤0.015	0.03	- / - / -	- / - / -
Ceftriaxone	≤0.06	0.12	99.9 / - / -	100.0 / 0.0 / 0.0
Penicillin	≤0.06	≤0.06	100.0 / - / -	100.0 / 0.0 / 0.0
Erythromycin	≤0.12	>16	66.2 / 1.1 / 32.7	66.2 / 1.1 / 32.7
Clindamycin	≤0.25	>2	81.9 / 0.2 / 17.9	82.1 / 0.0 / 17.9
Levofloxacin	0.5	1	99.5 / 0.1 / 0.4	95.0 / 4.5 / 0.5
Tetracycline	8	>8	49.2 / 0.5 / 50.3	48.0 / 1.2 / 50.8
Linezolid	1	1	100.0 / - / -	100.0 / 0.0 / 0.0
Vancomycin	0.5	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Daptomycin	0.12	0.25	100.0 / - / -	100.0 / 0.0 / 0.0

a. Criteria as published by the CLSI and EUCAST (2012).
b. USA-FDA breakpoints were applied when available [Teflaro® Prescribing Information, 2012].
c. Includes: *Streptococcus dysgalactiae* (7 strains), Group A *Streptococcus* (491 strains), Group B *Streptococcus* (561 strains), and Group C *Streptococcus* (90 strains).

Conclusions

- Ceftaroline-avibactam was the most active agent tested against Enterobacteriaceae strains and exhibited great *in vitro* activity against multidrug-resistant strains having β-lactamase-mediated mechanisms
- Ceftaroline-avibactam and ceftaroline were the most potent β-lactam agents tested against staphylococci and streptococci collected from USA hospitals. MRSA and penicillin-resistant *S. pneumoniae* were particularly susceptible to ceftaroline-avibactam and ceftaroline
- Ceftaroline-avibactam also showed potent activity against Gram-negative pathogens (*H. influenzae, H. parainfluenzae* and *M. catarrhalis*) associated with community-acquired respiratory tract infections.

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