Activity of Ceftaroline-Avibactam Tested Against Multidrug-Resistant Enterobacteriaceae and Methicillin-Resistant *Staphylococcus aureus* Collected from USA Hospitals in 2011

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HS SADER, RK FLAMM, M CASTANHEIRA, RN JONES
JMI Laboratories, North Liberty, Iowa, USA

Helio S. Sader, M.D., Ph.D.
JMI Laboratories
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) combined with avibactam (formerly NXL-104) tested against resistant subsets of Enterobacteriaceae (ENT) and MRSA strains. CPT is a broad-spectrum cephalosporin with activity against Gram-negative and -positive (including MRSA and multidrug-resistant [R] *S. pneumoniae*) organisms. Avibactam is a novel non-beta-lactam β-lactamase (BL) inhibitor that inhibits Ambler class A, C, and D enzymes (eg, ESBL, KPC, and AmpC).

Methods: CPT-avibactam (CPA; avibactam at fixed 4 mg/L) and various comparators were tested for susceptibility (S) by CLSI broth microdilution methods against 1,800 ENT, including ESBL-phenotype *E. coli* (43) and *Klebsiella* spp. (KSP; 67), AmpC derepressed *Enterobacter* spp. (ESP; 60), carbapenem (CB)-non-S (most were KPC-producing), KSP (13) and ESP (2), ciprofloxacin-R ENT (224) and gentamicin-R ENT (120), among other R phenotypes. 1496 *S. aureus*, including 738 MRSA strains were also tested. The strains were consecutively collected in 2011 from 52 medical centres located in the 9 USA Census Regions.

Results: 99.7% of ENT and 99.1% of MRSA strains were inhibited at CPA MIC of ≤1 mg/L (see Table 1). Highest CPA MIC was only 4 mg/L (2 *S. marcescens* strains; 0.1% of ENT). The most active compounds tested against the ESBL-phenotype and CB-non-S KSP were CPA (95.5% and 76.9% inhibited at ≤0.5 mg/L [USA-FDA S breakpoint for CPT], respectively), tigecycline (95.5/85.1% and 100.0/92.3% S by CLSI/EUCAST criteria, respectively) and gentamicin (65.7/61.2% and 69.2/69.2% S by CLSI/EUCAST criteria, respectively). All MRSA strains were inhibited at ≤2 mg/L of CPA, and CPT MIC results were not affected by the addition of avibactam. Against methicillin-S *S. aureus*, CPA inhibited all at MIC ≤0.5 mg/L and was 16-fold more active than ceftriaxone.

Conclusions: Avibactam can effectively lower CPT MIC values for ENT strains producing the most clinically significant BLs found in USA hospitals. CPA was highly active against ENT-producing KPC, various ESBL types, and AmpC (chromosomally derepressed or plasmid mediated), and MRSA. CPA represents a promising therapeutic option for treatment of infections caused by multidrug-R ENT and MRSA.

Introduction

Ceftaroline fosamil is the parenteral prodrug form of ceftaroline, a new cephalosporin with activity against Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Streptococcus pneumoniae*. Ceftaroline fosamil has been approved by the United States Food and Drug Administration (USA-FDA) for acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP).

Ceftaroline is also active against most Enterobacteriaceae species but, like other cephalosporins, has limited activity against isolates producing extended-spectrum β-lactamase (ESBL), cephalosporinases and carbapenemases. However, the spectrum of activity of ceftaroline is expanded when combined with avibactam (formerly NXL-104), a potent non-β-lactam β-lactamase inhibitor against Ambler classes A (eg, ESBL, KPC), C (AmpC), and D (OXA-like) enzymes.

In the present study, we evaluated the activity of ceftaroline combined with avibactam tested against Enterobacteriaceae and *S. aureus* strains isolated in United States hospitals in 2011.

Methods

Bacterial isolates. 1,800 Enterobacteriaceae and 1,496 *S. aureus* were collected from 52 medical centres located in the nine USA Census Regions. The isolates were collected between January and September of 2011 and only one isolate per patient from documented infections were included in this prevalence design study. Species identification was confirmed by standard biochemical tests, the Vitek System (bioMerieux, Hazelwood, Missouri, USA) or 16S rRNA sequencing, when necessary.

Antimicrobial susceptibility testing. All isolates were tested for antimicrobial susceptibility using the broth microdilution method (BMD) as described by the Clinical and Laboratory Standards Institute (CLSI; M07-A9, 2012). Cation-adjusted Mueller-Hinton broth was used in validated BMD panels. Ceftaroline-avibactam was tested in a fixed 4 mg/L concentration of avibactam. Categorical interpretations were those found in CLSI document M100-S22. In the absence of CLSI breakpoints, USA-FDA breakpoints were used when available. Quality control (QC) was performed using *Escherichia coli* ATCC 25922, *S. aureus* ATCC 29213 and *Pseudomonas aeruginosa* ATCC 27853. All QC results were within specified ranges as published in CLSI documents. *E. coli* and *Klebsiella* spp. isolates for which ceftriaxone or ceftazidime were ≥2 mg/L were considered to be phenotype-positive for ESBL production (CLSI, 2012).

Results

- Among Enterobacteriaceae, 98.4% of strains would be categorized as susceptible to ceftaroline-avibactam when the susceptible breakpoint established by the USA-FDA for ceftaroline (≤0.5 mg/L) was applied. Among the 28 non-susceptible strains, 23 had a ceftaroline-avibactam MIC of 1 mg/L (intermediate category by USA-FDA breakpoint criteria for ceftaroline) and 15 (55.6%) were *S. marcescens* (Table 1)
- Ceftaroline-avibactam was active against non-ESBL strains ($MIC_{50/90}$ of 0.06/0.12 mg/L; 100.0% inhibited at ≤0.5 mg/L) as well as ESBL-phenotype *Klebsiella* spp. ($MIC_{50/90}$ of 0.12/0.5 mg/L; 95.5 and 98.5% inhibited at ≤0.5 and ≤1 mg/L, respectively). Resistance rates to "third-generation" cephalosporins were high among ESBL-phenotype *Klebsiella* spp. (80.6 and 59.7% resistance to ceftriaxone and ceftazidime, respectively, according to CLSI breakpoints; Table 2)
- All *E. coli* isolates were inhibited at ceftaroline-avibactam MIC of ≤0.25 mg/L ($MIC_{50/90,}$ 0.03/0.06 mg/L). Among non-ESBL-phenotype strains ($MIC_{50/90,}$ 0.03/0.06 mg/L), the highest ceftaroline-avibactam MIC was only 0.12 mg/L, and ESBL-phenotype strains also were very susceptible to ceftaroline-avibactam ($MIC_{50/90,}$ 0.03/0.12 mg/L; highest MIC, 0.25 mg/L; Tables 1 and 2)
- Among 337 *Enterobacter* spp. strains, 97.3% were inhibited by ceftaroline-avibactam at ≤0.5 mg/L. Meropenem ($MIC_{90,}$ ≤0.06 mg/L; 99.4% susceptible) and tigecycline ($MIC_{50/90,}$ 0.25/0.5 mg/L; 98.5/95.3% susceptible by CLSI/EUCAST breakpoint criteria) were also very active against *Enterobacter* spp. (Table 2). Among ceftazidime-non-susceptible (MIC, ≥8 mg/L) *Enterobacter* spp. strains, 85.0 and 96.7% of strains were inhibited at ceftaroline-avibactam MIC of ≤0.5 and ≤1 mg/L, respectively (Tables 1 and 2)
- Ceftaroline-avibactam inhibited all 150 *P. mirabilis* strains at ≤0.25 mg/L ($MIC_{50/90,}$ 0.06/0.12 mg/L). Ceftaroline-avibactam was also active against *Serratia marcescens* ($MIC_{50/90}$, 0.5/1 mg/L), with 89.9 and 98.7% of strains being inhibited at MIC of ≤0.5 and ≤1 mg/L, respectively (Tables 1 and 2)
- Applying the ceftaroline susceptible breakpoint established by the USA-FDA for some Enterobacteriaceae species (≤0.5 mg/L; E. *coli, K. pneumoniae* and *K. oxytoca*), 99.0% of *Citrobacter* spp. strains were considered susceptible to ceftaroline-avibactam ($MIC_{50/90}$, 0.06/0.12 mg/L). Ceftaroline-avibactam was also very active against indole-positive *Proteae* ($MIC_{50/90}$, 0.03/0.06 mg/L), with the highest MIC value being only 0.25 mg/L (Tables 1 and 2)
- *S. aureus* was very susceptible to ceftaroline and ceftaroline-avibactam ($MIC_{50/90}$, 0.25/1 mg/L for both compounds; Tables 1 and 3). All isolates were inhibited at a ceftaroline-avibactam MIC of ≤2 mg/L and 99.5% were inhibited at a ceftaroline-avibactam MIC of ≤1 mg/L, which is the susceptible breakpoint established by the USA-FDA for ceftaroline
- Ceftaroline and ceftaroline-avibactam exhibited very similar activities against MRSA strains, and 99.1% of strains were inhibited at a ceftaroline-avibactam MIC of ≤1 mg/L. Furthermore, ceftaroline-avibactam ($MIC_{50/90}$, 0.5/1 mg/L) was slightly more potent than linezolid (MIC_{50} and MIC_{90}, 1 mg/L) and vancomycin (MIC_{50} and MIC_{90}, 1 mg/L) when tested against MRSA (Table 3)
- The overall MRSA rate was 49.3% and these strains exhibited high rates of resistance to erythromycin (88.6/89.7% [CLSI/EUCAST]), clindamycin (26.8%) and levofloxacin (64.5%; Table 3).

Conclusions

- Avibactam can effectively lower ceftaroline MIC values for Enterobacteriaceae strains producing the most clinically significant β-lactamases found in USA hospitals
- Ceftaroline-avibactam demonstrated excellent activity against Enterobacteriaceae-producing KPC, various ESBL types, and AmpC (chromosomally derepressed or plasmid mediated). Using the USA-FDA breakpoint for ceftaroline susceptibility (≤0.5 mg/L), ceftaroline-avibactam was among the most active agents tested
- Ceftaroline-avibactam and ceftaroline were highly active and the most potent β-lactam agents tested against *S. aureus*. Ceftaroline-avibactam exhibited potent activity against MRSA (99.1% of strains inhibited at ≤1 mg/L and highest MIC of only 2 mg/L)
- Ceftaroline-avibactam represents a promising therapeutic option for treatment of infections caused by multidrug-resistant Enterobacteriaceae and MRSA.

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Table 1. Summary of ceftaroline-avibactam activity tested against organisms collected from patients hospitalized in USA medical centres (2011)

Organism (no. tested)	No. of isolates (cumulative %) inhibited at ceftaroline-avibactam MIC (mg/L) of: ≤0.03	0.06	0.12	0.25	0.5	1	2	4
Enterobacteriaceae								
Klebsiella spp. (539)	218 (40.5)	209 (79.2)	72 (92.6)	29 (98.0)	8 (99.4)	2 (99.8)	1 (100.0)	-
Non-ESBL-phenotype (472)	206 (43.6)	194 (84.8)	53 (96.0)	16 (99.4)	3 (100.0)	-	-	-
ESBL-phenotype (67)	12 (17.9)	15 (40.3)	19 (68.7)	13 (88.1)	5 (95.5)	2 (98.5)	1 (100.0)	-
Meropenem-non-S (13)	-	1 (7.7)	2 (23.1)	6 (69.2)	1 (76.9)	2 (92.3)	1 (100.0)	-
E. coli (435)	356 (81.8)	65 (96.8)	11 (99.3)	3 (100.0)	-	-	-	-
Non-ESBL-phenotype (392)	331 (84.4)	57 (99.0)	4 (100.0)	-	-	-	-	-
ESBL-phenotype (43)	25 (58.1)	8 (76.7)	7 (96.0)	3 (100.0)	-	-	-	-
Enterobacter spp. (337)	56 (16.6)	117 (51.3)	91 (78.3)	49 (92.9)	15 (97.3)	7 (99.4)	2 (100.0)	-
Ceftazidime-S (277)	55 (19.9)	106 (58.1)	83 (88.1)	28 (98.2)	5 (100.0)	-	-	-
Ceftazidime-R (60)	1 (1.7)	11 (20.0)	8 (33.3)	21 (68.3)	10 (85.0)	7 (96.7)	2 (100.0)	-
Meropenem-non-S (2)	-	-	1 (50.0)	0 (50.0)	0 (50.0)	0 (50.0)	1 (100.0)	-
P. mirabilis (150)	33 (22.0)	89 (81.3)	25 (98.0)	3 (100.0)	-	-	-	-
S. marcescens (148)	-	1 (0.7)	14 (10.1)	57 (48.7)	61 (89.9)	13 (98.7)	0 (98.7)	2 (100.0)
Citrobacter spp. (100)	29 (29.0)	46 (75.0)	20 (95.0)	3 (98.0)	1 (99.0)	1 (100.0)	-	-
Ceftazidime-S (89)	29 (32.6)	43 (80.9)	13 (95.5)	3 (98.9)	0 (98.9)	1 (100.0)	-	-
Ceftazidime-R (11)	-	3 (27.3)	7 (90.9)	1 (100.0)	-	-	-	-
Indole-positive *Proteae* (91)	58 (63.7)	24 (90.1)	8 (98.9)	1 (100.0)	-	-	-	-
Staphylococcus aureus								
All strains (1496)	1 (0.1)	6 (0.5)	182 (12.6)	601 (52.8)	551 (89.6)	148 (99.5)	7 (100.0)	-
MRSA (738)	1 (0.1)	0 (0.1)	2 (0.4)	40 (5.4)	543 (79.0)	148 (99.1)	7 (100.0)	-

Abbreviations: ESBL = extended-spectrum β-lactamase; S = susceptible; R = resistant; MRSA = methicillin- (oxacillin)-resistant *Staphylococcus aureus*.

Table 2. Antimicrobial activity of ceftaroline-avibactam and comparator agents tested against Enterobacteriaceae isolates from USA medical centres (2011)

Antimicrobial agent (no. tested)	MIC (mg/L) MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Klebsiella spp. (539)					
Ceftaroline-avibactam	0.06	0.12	≤0.015 – 2	-[a] / -	- / -
Ceftazidime	0.12	2	0.03 – >32	91.8 / 7.4	89.8 / 8.2
Ceftriaxone	≤0.06	4	≤0.06 – >8	88.9 / 10.0	88.9 / 10.0
Meropenem	≤0.06	≤0.06	≤0.06 – >8	97.6 / 2.2	97.8 / 1.7
Piperacillin/tazobactam	2	16	≤0.5 – >64	90.7 / 7.8	85.5 / 9.3
Gentamicin	≤1	≤1	≤1 – >8	95.0 / 3.7	94.4 / 5.0
Levofloxacin	≤0.12	1	≤0.12 – >4	92.0 / 6.7	91.3 / 8.0
Tigecycline[b]	0.25	1	0.06 – >4	98.5 / 0.2	94.8 / 1.5
ESBL-phenotype[c] (67)					
Ceftaroline-avibactam	0.12	0.5	≤0.015 – 2	- / -	- / -
Ceftazidime	32	>32	0.12 – >32	34.3 / 59.7	17.9 / 65.7
Ceftriaxone	>8	>8	0.12 – >8	10.4 / 80.6	10.4 / 80.6
Meropenem	≤0.06	>8	≤0.06 – >8	80.6 / 17.9	82.1 / 13.4
Piperacillin/tazobactam	>64	>64	1 – >64	32.8 / 58.2	23.9 / 67.2
Gentamicin	2	>8	≤1 – >8	65.7 / 25.4	61.2 / 34.3
Levofloxacin	>4	>4	≤0.12 – >4	44.8 / 50.7	43.3 / 55.2
Tigecycline[b]	0.5	2	0.06 – 4	95.5 / 0.0	85.1 / 4.5
Meropenem-non-susceptible[d] (13)					
Ceftaroline-avibactam	0.25	1	0.06 – 2	- / -	- / -
Ceftazidime	>32	>32	2 – >32	7.7 / 92.3	0.0 / 92.3
Ceftriaxone	>8	>8	>8	0.0 / 100.0	0.0 / 100.0
Piperacillin/tazobactam	>64	>64	>64	0.0 / 100.0	0.0 / 100.0
Gentamicin	2	>8	≤1 – >8	69.2 / 23.1	69.2 / 30.8
Levofloxacin	>4	>4	0.25 – >4	7.7 / 92.3	7.7 / 92.3
Tigecycline[b]	0.5	1	0.25 – 2	100.0 / 0.0	92.3 / 0.0
Escherichia coli (435)					
Ceftaroline-avibactam	0.03	0.06	≤0.015 – 0.25	- / -	- / -
Ceftazidime	0.12	1	≤0.015 – >32	94.0 / 5.3	91.5 / 6.0
Ceftriaxone	≤0.06	0.25	≤0.06 – >8	91.3 / 8.5	91.3 / 8.5
Meropenem	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	8	≤0.5 – >64	94.3 / 3.9	92.2 / 5.7
Gentamicin	≤1	>8	≤1 – >8	86.0 / 13.3	85.1 / 14.0
Levofloxacin	≤0.12	>4	≤0.12 – >4	69.9 / 29.7	69.7 / 30.1
Tigecycline[b]	0.12	0.25	≤0.03 – 0.5	100.0 / 0.0	100.0 / 0.0
ESBL-phenotype[c] (43)					
Ceftaroline-avibactam	0.03	0.12	≤0.015 – 0.25	- / -	- / -
Ceftazidime	16	>32	1 – >32	39.5 / 53.5	14.0 / 60.5
Ceftriaxone	>8	>8	0.25 – >8	11.6 / 86.0	11.6 / 86.0
Meropenem	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	8	>64	1 – >64	79.1 / 14.0	62.8 / 20.9
Gentamicin	≤1	>8	≤1 – >8	65.1 / 34.9	62.8 / 34.9
Levofloxacin	>4	>4	≤0.12 – >4	16.3 / 83.7	16.3 / 83.7
Tigecycline[b]	0.12	0.25	0.06 – 0.25	100.0 / 0.0	100.0 / 0.0
Enterobacter (337)					
Ceftaroline-avibactam	0.06	0.25	≤0.015 – 2	- / -	- / -
Ceftazidime	0.25	>32	0.03 – >32	82.2 / 16.6	78.9 / 17.8
Ceftriaxone	0.25	>8	≤0.06 – >8	78.9 / 19.6	78.9 / 19.6
Meropenem	≤0.06	≤0.06	≤0.06 – 8	99.4 / 0.6	99.4 / 0.0
Piperacillin/tazobactam	2	64	≤0.5 – >64	84.6 / 6.5	82.5 / 15.4
Gentamicin	≤1	≤1	≤1 – >8	96.4 / 3.6	95.8 / 3.6
Levofloxacin	≤0.12	0.5	≤0.12 – >4	96.1 / 3.3	96.1 / 3.9
Tigecycline[b]	0.25	0.5	0.12 – 4	98.5 / 0.0	95.3 / 1.5
Ceftazidime-non-susceptible[e] (60)					
Ceftaroline-avibactam	0.25	1	0.03 – 2	- / -	- / -
Ceftazidime	>32	>32	8 – >32	0.0 / 93.3	0.0 / 100.0
Ceftriaxone	>8	>8	2 – >8	0.0 / 96.7	0.0 / 96.7
Meropenem	≤0.06	0.25	≤0.06 – 8	96.7 / 3.3	96.7 / 0.0
Piperacillin/tazobactam	64	>64	1 – >64	16.7 / 36.7	11.7 / 83.3
Gentamicin	≤1	>8	≤1 – >8	83.3 / 16.7	81.7 / 16.7
Levofloxacin	≤0.12	>4	≤0.12 – >4	83.3 / 16.7	83.3 / 16.7
Tigecycline[b]	0.25	2	0.12 – 4	95.0 / 0.0	85.0 / 5.0
Proteus mirabilis (150)					
Ceftaroline-avibactam	0.06	0.12	0.03 – 0.25	- / -	- / -
Ceftazidime	0.06	0.06	0.03 – 4	100.0 / 0.0	96.7 / 0.0
Ceftriaxone	≤0.06	≤0.06	≤0.06 – >8	97.3 / 2.0	97.3 / 2.0
Meropenem	≤0.06	≤0.06	≤0.06 – 0.5	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	≤0.5	1	≤0.5 – >64	98.7 / 0.7	98.7 / 1.3
Gentamicin	≤1	4	≤1 – >8	91.3 / 5.3	89.3 / 8.7
Levofloxacin	≤0.12	>4	≤0.12 – >4	77.3 / 18.7	76.0 / 22.7
Tigecycline[b]	2	4	0.25 – >4	81.2 / 1.3	44.3 / 18.8
Serratia marcescens (148)					
Ceftaroline-avibactam	0.5	1	0.06 – 4	- / -	- / -
Ceftazidime	0.25	0.5	0.03 – 32	98.0 / 1.4	97.3 / 2.0
Ceftriaxone	0.25	1	≤0.06 – >8	93.9 / 5.4	93.9 / 5.4
Meropenem	≤0.06	≤0.06	≤0.06 – 2	99.3 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	4	≤0.5 – >64	99.3 / 0.7	98.6 / 0.7
Gentamicin	≤1	≤1	≤1 – >8	98.0 / 2.0	98.0 / 2.0
Levofloxacin	≤0.12	0.5	≤0.12 – >4	96.6 / 0.7	95.3 / 3.4
Tigecycline[b]	0.5	1	0.25 – >4	98.6 / 1.4	95.9 / 1.4
Citrobacter spp. (100)					
Ceftaroline-avibactam	0.06	0.12	≤0.015 – 1	- / -	- / -
Ceftazidime	0.25	16	0.06 – >32	89.0 / 11.0	89.0 / 11.0
Ceftriaxone	0.12	1	≤0.06 – >8	90.0 / 10.0	90.0 / 10.0
Meropenem	≤0.06	≤0.06	≤0.06	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	16	≤0.5 – >64	94.0 / 2.0	87.0 / 6.0
Gentamicin	≤1	≤1	≤1 – >8	99.0 / 1.0	99.0 / 1.0
Levofloxacin	≤0.12	0.25	≤0.12 – >4	99.0 / 1.0	96.0 / 1.0
Tigecycline[b]	0.12	0.25	0.06 – 1	100.0 / 0.0	100.0 / 0.0
Indole-positive Proteae (91)					
Ceftaroline-avibactam	0.03	0.06	≤0.015 – 0.25	- / -	- / -
Ceftazidime	0.12	16	0.03 – >32	84.6 / 11.0	80.2 / 15.4
Ceftriaxone	≤0.06	2	≤0.06 – >8	84.6 / 9.9	84.6 / 9.9
Meropenem	≤0.06	0.12	≤0.06 – 0.25	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	≤0.5	2	≤0.5 – >64	95.6 / 3.3	95.6 / 4.4
Gentamicin	≤1	>8	≤1 – >8	84.6 / 12.1	80.2 / 15.4
Levofloxacin	≤0.12	>4	≤0.12 – >4	82.4 / 13.2	79.1 / 17.6
Tigecycline[b]	0.5	2	0.12 – >4	93.4 / 1.1	87.9 / 6.6

a. Criteria as published by the CLSI [2012] and EUCAST [2012]. "-" indicates that no breakpoint has been established.
b. USA-FDA breakpoints were applied [Tygacil® Product Insert, 2010].
c. ESBL phenotype defined as an MIC ≥2 mg/L for ceftazidime or ceftriaxone [CLSI, 2012].
d. Meropenem non-susceptible at ≥2 mg/L, as established by the CLSI for Enterobacteriaceae [CLSI, 2012].
e. Ceftazidime non-susceptible at ≥8 mg/L, as established by the CLSI for Enterobacteriaceae [CLSI, 2012].
Abbreviation: ESBL = extended-spectrum β-lactamase.

Table 3. Antimicrobial activity of ceftaroline-avibactam and comparator agents tested against *S. aureus* from USA medical centres (2011)

Antimicrobial agent (no. tested)	MIC (mg/L) MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Staphylococcus aureus (1,496)					
Ceftaroline-avibactam	0.25	1	0.03 – 2	-[a] / -	- / -
Ceftaroline[b]	0.25	1	0.06 – 2	99.4 / -	- / -
Ceftriaxone[c]	8	>8	1 – >8	49.7 / 49.3	50.7 / 49.3
Oxacillin	2	>2	≤0.25 – >2	50.7 / 49.3	50.7 / 49.3
Erythromycin	>16	>16	≤0.12 – >16	37.7 / 60.4	37.9 / 61.7
Clindamycin	≤0.25	>2	≤0.25 – >2	84.4 / 15.6	84.2 / 15.6
Levofloxacin	0.25	>4	≤0.12 – >4	61.1 / 37.0	61.1 / 37.0
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tigecycline[d]	0.06	0.12	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
MRSA (738)					
Ceftaroline-avibactam	0.5	1	0.03 – 2	- / -	- / -
Ceftaroline[b]	0.5	1	0.12 – 2	98.8 / -	- / -
Ceftriaxone[c]	>8	>8	4 – >8	0.0 / 100.0	0.0 / 100.0
Erythromycin	>16	>16	≤0.12 – >16	10.0 / 88.6	10.3 / 89.7
Clindamycin	≤0.25	>2	≤0.25 – >2	73.2 / 26.8	73.2 / 26.8
Levofloxacin	4	>4	≤0.12 – >4	32.5 / 64.5	32.5 / 64.5
Linezolid	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tigecycline[d]	0.06	0.12	≤0.03 – 0.5	100.0 / -	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

a. Criteria as published by the CLSI [2012] and EUCAST [2012]. "-" indicates that no breakpoint has been established.
b. USA-FDA breakpoints were applied [Teflaro® Package Insert, 2010].
c. USA-FDA breakpoints were applied [Rocephin® Package Insert, 2010].
d. USA-FDA breakpoints were applied [Tygacil® Product Insert, 2010].
Abbreviation: MRSA = methicillin-resistant *S. aureus*.