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Antimicrobial Activity of Ceftaroline/NXL104 (Ceftaroline/Avibactam) Tested Against Contemporary (2010) Clinical Isolates from USA Medical Centers

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Abstract

Background: Ceftaroline (CPT), the active form of CPT fosamil, is a broad-spectrum, bactericidal cephalosporin active against Gram-positive (including MRSA and multidrug-resistant [R] *S. pneumoniae* [SPN]) and common Gram-negative organisms. Avibactam (previously NXL104 [AVI]) is a novel non-β-lactam β-lactamase inhibitor of Ambler class A, C, and some D enzymes. We evaluated the activity and potency of CPT/AVI (CPA) against recent clinical isolates.

Methods: Isolates were consecutively collected in 2010 from 65 USA medical centers from all 9 CDC Census Regions (5-10/region). Susceptibility (S) testing for CPA (AVI at fixed 4 μg/mL), CPT and comparators was performed by CLSI broth microdilution on 8434 strains.

Results: For MSSA and MRSA, all strains were inhibited at ≤0.5 and ≤2 μg/mL of CPA, respectively (Table 1), and CPT MICs were not impacted by the addition of AVI. Penicillin (PEN)-R ($MIC_{50/90}$, 0.25/0.25 μg/mL) and levofloxacin-non-S ($MIC_{50/90}$, ≤0.03/0.25 μg/mL) SPN were CPA-S. CPA was 8- to 16-fold more active than ceftriaxone against MSSA and PEN-R SPN; the highest CPA MIC value was only 0.5 μg/mL for both organisms. Against *H. influenzae*, the highest CPA MIC value was 0.06 μg/mL (MIC_{90}, ≤0.03 μg/mL). β-haemolytic and viridans group streptococci were CPA-S with MIC_{90}s of 0.015 and 0.12 μg/mL, respectively. All *E. coli*, including ESBL-producing strains, were inhibited at CPA MIC values of ≤0.5 μg/mL. CPA was also active against *H. influenzae* (MIC_{90} ≤0.03 μg/mL), *Klebsiella* spp. (MIC_{90}, 0.12 μg/mL), including ESBL-phenotype and meropenem-non-S strains (MIC_{90}, 1 μg/mL for both subsets) and *M. morganii* (MIC_{90} 0.12 μg/mL).

Conclusions: CPA and CPT were the most potent β-lactam agents tested against staphylococci and streptococci collected from USA hospitals. MRSA and PEN-R-SPN were particularly S to CPA and CPT (data not shown). CPA was also highly active against Enterobacteriaceae producing KPC, various ESBL types, and AmpC (chromosomal or plasmid mediated) enzymes. CPA represents a potential therapeutic option for infections caused by these R organisms.

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 (ABSSSI), including multidrug-resistant *Streptococcus pneumoniae*, methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA), and most Enterobacteriaceae species, as well as common gram-negative pathogens. In 2 phase 3 trials, ceftaroline fosamil was shown to be noninferior to ceftriaxone for the treatment of patients with CABP requiring hospitalization. Similarly, noninferiority of ceftaroline fosamil compared with vancomycin plus aztreonam for the treatment of ABSSSI requiring hospitalization was demonstrated in 2 phase 3 trials. Ceftaroline fosamil was approved by the United States Food and Drug Administration (USA-FDA) for CABP and ABSSSI.

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 and class C enzymes, including extended-spectrum β-lactamase (ESBL) and KPC enzymes (carbapenemases), as well as some class D β-lactamases.

We report the in vitro activity of ceftaroline combined with avibactam (CPA; fixed concentration of 4 μg/mL) against bacterial organisms isolated in USA medical centers in 2010 as part of a worldwide surveillance program.

Methods

Organisms collection: A total of 8434 bacterial isolates were tested. Sixty-five medical centers distributed across all 9 USA Census Regions (5 to 10 medical centers per region) contributed clinical isolates for this surveillance program in 2010. 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) for reference susceptibility testing. Only 1 strain per patient-infection episode was included in the surveillance.

Susceptibility testing: Isolates were tested for susceptibility to ceftaroline/avibactam and comparator agents by reference broth microdilution methods as described by Clinical and Laboratory Standards Institute (CLSI) M07-A8 (2009) and CLSI interpretations were based on M100-S21 and M45-A breakpoints. Ceftaroline was combined with avibactam at a fixed concentration of 4 μg/mL. *S. pneumoniae* isolates were tested in Mueller-Hinton broth supplemented with 3-5% lysed horse blood, and *Haemophilus influenzae* isolates 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

- 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 4-fold more active than linezolid (MIC_{50} and MIC_{90}, 1 μg/mL) when tested against methicillin- (oxacillin)-susceptible *S. aureus* (MSSA). The highest ceftaroline/avibactam MIC value among MSSA strains was 0.5 μg/mL and 94.3% of strains were inhibited at a ceftaroline/avibactam MIC of ≤0.25 μg/mL (Tables 1 and 2)
- Against MRSA, ceftaroline/avibactam MIC values ranged from 0.25 to 2 μg/mL (MIC_{50}, 0.5 μg/mL and MIC_{90}, 1 μg/mL). 95.2% and 100.0% of MRSA strains were inhibited at ceftaroline/avibactam MIC values of ≤1 μg/mL and ≤2 μg/mL, respectively (Tables 1 and 2). Ceftaroline and ceftaroline/avibactam exhibited similar activities against MRSA strains (data not shown)
- Ceftaroline/avibactam was potent against β-haemolytic streptococci, with the MIC_{90} at ≤0.03 μg/mL for all subsets evaluated. The highest ceftaroline/avibactam MIC among β-haemolytic streptococci was 0.12 μg/mL (Tables 1 and 2)
- Ceftaroline/avibactam (MIC_{50}, ≤0.03 μg/mL and MIC_{90}, 0.25 μg/mL) and ceftaroline (data not shown) were the most potent β-lactams tested against *S. pneumoniae*. The highest ceftaroline/avibactam MIC value observed was 0.5 μg/mL (14 strains [1.2%]; Tables 1 and 2)
- Against penicillin-resistant (MIC, ≥2 μg/mL) pneumococci, ceftaroline/avibactam (MIC_{50} and MIC_{90}, 0.25 μg/mL) was 4- to 8-fold more active than ceftriaxone (MIC_{50}, 1 μg/mL and MIC_{90}, 2 μg/mL) and 32-fold more potent than amoxicillin/clavulanic acid (MIC_{50} and MIC_{90}, 8 μg/mL; Table 2)
- Ceftaroline/avibactam was also active against *S. pneumoniae* strains with penicillin MIC of ≥8 μg/mL (12 isolates tested; MIC range, 0.06 - 0.5 μg/mL). These isolates were categorized as nonsusceptible for other β-lactam agents tested, except for 1 isolate (8.3%) that was susceptible only to ceftriaxone (Table 2)
- Ceftaroline/avibactam was active against *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Moraxella catarrhalis* (MIC_{50} and MIC_{90}, ≤0.03 μg/mL for all 3 organisms; Tables 1 and 2)
- Using the USA-FDA breakpoint for ceftaroline susceptibility (≤0.5 μg/mL), ceftaroline/avibactam was among the most active agents tested against Enterobacteriaceae (Table 2)
- All *Escherichia coli* isolates were susceptible to ceftaroline/avibactam (MIC_{50} ≤0.03 and MIC_{90}, 0.06 μg/mL) when breakpoints established by the USA-FDA for ceftaroline were applied. Furthermore, ceftaroline/avibactam exhibited potent activity against *E. coli* strains with an ESBL phenotype (MIC_{50}, 0.06 and MIC_{90}, 0.12 μg/mL; Tables 1 and 2)
- Ceftaroline/avibactam was active against *Klebsiella* spp., including strains with an ESBL phenotype (MIC_{50}, 0.12 μg/mL and MIC_{90}, 1 μg/mL) and those with reduced susceptibility to carbapenems (MIC_{50}, 0.5 μg/mL and MIC_{90}, 1 μg/mL; Table 1).

Table 1. Summary of Ceftaroline/Avibactam (previously ceftaroline/NXL104) Activity Tested Against the Main Pathogen Groups Isolated in USA Hospitals in 2010

Organism/subgroup (n)	No. of isolates (cumulative %) inhibited at ceftaroline/avibactam MIC (μg/mL)											
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	MIC_{50}	MIC_{90}
S. aureus (2146)	1 (0.0)	5 (0.3)	59 (3.0)	962 (47.9)	703 (80.6)	365 (97.6)	51 (100.0)	-	-	-	0.5	1
MSSA (1074)	1 (0.1)	5 (0.6)	59 (6.1)	948 (94.3)	61 (100.0)	-	-	-	-	-	0.25	0.25
MRSA (1072)	0 (0.0)	0 (0.0)	0 (0.0)	14 (1.3)	642 (61.2)	365 (95.2)	51 (100.0)	-	-	-	0.5	1
CoNS (486)	12 (2.5)	79 (18.7)	100 (39.3)	144 (68.9)	135 (96.7)	11 (99.0)	5 (100.0)	-	-	-	0.25	0.5
MSCoNS (188)	12 (6.4)	78 (47.9)	81 (91.0)	17 (100.0)	-	-	-	-	-	-	0.12	0.12
MRCoNS (298)	0 (0.0)	1 (0.3)	19 (6.7)	127 (49.3)	135 (94.6)	11 (98.3)	5 (100.0)	-	-	-	0.5	0.5
E. faecalis (195)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	3 (2.1)	25 (14.9)	110 (71.3)	27 (85.1)	20 (95.4)	9 (100.0)	2	8
S. pneumoniae (1200)	810 (67.5)	102 (76.0)	139 (87.6)	135 (98.8)	14 (100.0)	-	-	-	-	-	≤0.03	0.25
PEN-S (678)	668 (98.5)	9 (99.9)	1 (100.0)	-	-	-	-	-	-	-	≤0.03	≤0.03
PEN-I (266)	142 (53.4)	91 (87.6)	32 (99.6)	1 (100.0)	-	-	-	-	-	-	≤0.03	0.12
PEN-R (256)	0 (0.0)	2 (0.8)	106 (42.2)	134 (94.5)	14 (100.0)	-	-	-	-	-	0.25	0.25
Viridans gr. strep. (492)	358 (72.8)	70 (87.0)	22 (91.5)	17 (94.9)	18 (98.6)	7 (100.0)	-	-	-	-	≤0.03	0.12
β-haemolytic strep. (1201)	1181 (98.3)	19 (99.9)	1 (100.0)	-	-	-	-	-	-	-	≤0.03	≤0.03
Group A (422)	418 (99.1)	3 (99.8)	1 (100.0)	-	-	-	-	-	-	-	≤0.03	≤0.03
Group B (576)	572 (99.3)	4 (100.0)	-	-	-	-	-	-	-	-	≤0.03	≤0.03
E. coli (657)	446 (67.9)	178 (95.0)	25 (98.8)	7 (99.8)	1 (100.0)	-	-	-	-	-	≤0.03	0.06
non ESBL (579)	419 (72.4)	140 (96.5)	17 (99.5)	3 (100.0)	-	-	-	-	-	-	≤0.03	0.06
ESBL phenotype[a] (78)	27 (34.6)	38 (83.3)	8 (93.6)	4 (98.7)	1 (100.0)	-	-	-	-	-	0.06	0.12
Klebsiella spp. (903)	220 (24.4)	446 (73.8)	160 (91.5)	49 (96.9)	16 (98.7)	10 (99.8)	1 (99.9)	1 (100.0)	-	-	0.06	0.12
non ESBL (791)	208 (26.3)	427 (80.3)	125 (96.1)	27 (99.5)	4 (100.0)	-	-	-	-	-	0.06	0.12
ESBL phenotype[a] (112)	12 (10.7)	19 (27.7)	35 (58.9)	22 (78.6)	12 (89.3)	10 (98.2)	1 (99.1)	1 (100.0)	-	-	0.12	1
Meropenem-non-S[b] (29)	2 (6.9)	1 (10.3)	4 (24.1)	4 (37.9)	8 (65.5)	9 (96.6)	1 (100.0)	-	-	-	0.5	1
K. pneumoniae (653)	127 (19.4)	337 (71.1)	131 (91.1)	35 (96.5)	13 (98.5)	9 (99.8)	1 (100.0)	-	-	-	0.06	0.12
K. oxytoca (250)	93 (37.2)	109 (80.8)	29 (92.4)	14 (98.0)	3 (99.2)	1 (99.6)	0 (99.6)	1 (100.0)	-	-	0.06	0.12
M. morganii (116)	49 (42.2)	43 (79.3)	17 (94.0)	5 (98.3)	2 (100.0)	-	-	-	-	-	0.06	0.12
H. influenzae (770)	768 (99.7)	2 (100.0)	-	-	-	-	-	-	-	-	≤0.03	≤0.03
β-lactamase-negative (556)	555 (99.8)	1 (100.0)	-	-	-	-	-	-	-	-	≤0.03	≤0.03
β-lactamase-positive (214)	213 (99.5)	1 (100.0)	-	-	-	-	-	-	-	-	≤0.03	≤0.03
H. parainfluenzae (68)	68 (100.0)	-	-	-	-	-	-	-	-	-	≤0.03	≤0.03
M. catarrhalis (200)	198 (99.0)	1 (99.5)	1 (100.0)	-	-	-	-	-	-	-	≤0.03	≤0.03

a. ESBL phenotype indicates isolates with an MIC value of ≥2 μg/mL for ceftazidime or ceftriaxone or aztreonam [CLSI, 2011].
b. Meropenem-non-S = meropenem-non-susceptible strains (MIC, ≥2 μg/mL).
CoNS = coagulase-negative staphylococci; ESBL = extended-spectrum β-lactamase; MIC = minimum inhibitory concentration; MRCoNS = methicillin (oxacillin)-resistant coagulase negative staphylococci; MRSA = methicillin (oxacillin)-resistant *S. aureus*; MSCoNS = methicillin (oxacillin)-susceptible coagulase negative staphylococci; MSSA = methicillin (oxacillin)-susceptible *S. aureus*; PEN-I = penicillin-intermediate; PEN-R = penicillin-resistant; PEN-S = penicillin-susceptible; S = susceptible.

Table 2. Activity of Ceftaroline/Avibactam (CPA; previously ceftaroline/NXL104) and Comparator Agents Tested Against Bacterial Isolates Collected in USA Hospitals in 2010

Antimicrobial agent	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	Range (μg/mL)	CLSI[a] %S / %R	EUCAST %S / %R
S. aureus (2146)					
CPA	0.5	1	≤0.03 – 2	- / -	- / -
Oxacillin	2	>2	≤0.25 – >2	50.0 / 50.0	50.0 / 50.0
Cefuroxime	4	>16	≤0.25 – >16	50.0 / 50.0	50.0 / 50.0
Ceftriaxone[b]	8	>8	≤0.06 – >8	49.2 / 50.0	50.0 / 50.0
Clindamycin	≤0.25	>2	≤0.25 – >2	82.8 / 17.1	82.2 / 17.2
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Linezolid	1	1	≤0.12 – 4	100.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.5	>4	≤0.5 – >4	60.4 / 38.2	60.4 / 38.2
TMP/SMX	≤0.5	≤0.5	≤0.5 – >4	98.1 / 1.9	98.1 / 1.7
Daptomycin	0.25	0.5	≤0.06 – 2	99.9 / -	99.9 / 0.1
MSSA (1074)					
CPA	0.25	0.25	≤0.03 – 0.5	- / -	- / -
Cefuroxime	1	4	≤0.25 – >16	91.5 / 7.4	100.0 / 0.0
Ceftriaxone[b]	4	4	≤0.06 – >8	98.0 / 0.2	100.0 / 0.0
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	94.1 / 5.5	93.6 / 5.9
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Linezolid	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.5	4	≤0.5 – >4	88.4 / 11.0	88.4 / 11.0
TMP/SMX	≤0.5	≤0.5	≤0.5 – >4	98.8 / 1.2	98.8 / 1.2
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
MRSA (1072)					
CPA	0.5	1	0.25 – 2	- / -	- / -
Penicillin	>4	>4	0.06 – >4	0.0 / 100.0	0.0 / 100.0
Cefuroxime	>16	>16	≤0.25 – >16	0.0 / 100.0	0.0 / 100.0
Ceftriaxone	>8	>8	4 – >8	0.0 / 100.0	0.0 / 100.0
Clindamycin	≤0.25	>2	≤0.25 – >2	71.4 / 28.6	70.9 / 28.6
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Linezolid	1	1	≤0.12 – 4	100.0 / 0.0	100.0 / 0.0
Levofloxacin	4	>4	≤0.5 – >4	32.4 / 65.5	32.4 / 65.5
TMP/SMX	≤0.5	≤0.5	≤0.5 – >4	97.5 / 2.5	97.5 / 2.2
Daptomycin	0.25	0.5	0.12 – 2	99.7 / -	99.7 / 0.3
CoNS (486)[c]					
CPA	0.25	0.5	≤0.03 – 2	- / -	- / -
Oxacillin	1	>2	≤0.25 – >2	38.7 / 61.3	38.7 / 61.3
Penicillin	2	>4	≤0.03 – >4	19.3 / 80.7	19.3 / 80.7
Cefuroxime	2	16	≤0.25 – >16	38.7 / 61.3	38.7 / 61.3
Ceftriaxone	8	>8	0.25 – >8	38.7 / 61.3	38.7 / 61.3
Clindamycin	≤0.25	>2	≤0.25 – >2	71.0 / 25.3	68.7 / 29.0
Vancomycin	1	2	0.25 – 4	100.0 / 0.0	99.8 / 0.2
Linezolid	0.5	1	≤0.12 – >8	97.9 / 2.1	97.9 / 2.1
Levofloxacin	≤0.5	>4	≤0.5 – >4	50.8 / 47.3	50.8 / 47.3
TMP/SMX	≤0.5	>4	≤0.5 – >4	64.8 / 35.2	64.8 / 18.1
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
E. faecalis (195)					
CPA	2	8	0.25 – 16	- / -	- / -
Ampicillin	≤1	2	≤1 – 4	100.0 / 0.0	100.0 / 0.0
Ceftriaxone	>8	>8	2 – >8	- / -	- / -
Q/D	>4	>4	≤0.5 – >4	0.5 / 94.4	0.5 / 75.9
Vancomycin	1	2	0.5 – >16	96.4 / 3.6	96.4 / 3.6
Teicoplanin	≤1	≤1	≤1 – >8	96.9 / 3.1	96.9 / 3.1
Linezolid	1	1	0.5 – >8	99.5 / 0.5	99.5 / 0.5
Levofloxacin	1	>4	≤0.5 – >4	69.7 / 29.2	- / -
Daptomycin	1	1	≤0.06 – 2	100.0 / -	- / -

Antimicrobial agent	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	Range (μg/mL)	CLSI[a] %S / %R	EUCAST %S / %R
S. pneumoniae (1200)					
CPA	≤0.03	0.25	≤0.03 – 0.5	- / -	- / -
Penicillin[d]	≤0.03	4	≤0.03 – >4	85.4 / 1.0	- / -
Penicillin[e]	≤0.03	4	≤0.03 – >4	56.5 / 21.3	56.5 / 14.6
A/C	≤1	8	≤1 – >8	83.1 / 14.1	- / -
Ceftriaxone	≤0.06	2	≤0.06 – 8	89.8 / 1.7	78.9 / 1.7
Cefuroxime	≤0.12	8	≤0.12 – >16	72.8 / 23.4	71.5 / 27.2
Tetracycline	0.5	>8	≤0.25 – >8	74.6 / 25.4	74.6 / 25.4
TMP/SMX	≤0.5	>4	≤0.5 – >4	66.7 / 25.0	71.9 / 25.0
Clindamycin	≤0.25	>1	≤0.25 – >1	77.4 / 22.2	77.8 / 22.2
Erythromycin	≤0.06	>8	≤0.06 – >8	58.3 / 41.2	58.3 / 41.2
Levofloxacin	1	1	≤0.5 – >4	99.0 / 0.9	99.0 / 1.0
Linezolid	1	1	≤0.12 – 4	99.9 / -	100.0 / 0.0
PEN-S (MIC, ≤0.06 μg/mL; 678)					
CPA	≤0.03	≤0.03	≤0.03 – 0.12	- / -	- / -
A/C	≤1	≤1	≤1 – 2	100.0 / 0.0	- / -
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.5	100.0 / 0.0	100.0 / 0.0
Cefuroxime	≤0.12	≤0.12	≤0.12 – 1	100.0 / 0.0	99.6 / 0.0
Tetracycline	0.5	0.5	≤0.25 – >8	96.8 / 3.2	96.8 / 3.2
Clindamycin	≤0.25	≤0.25	≤0.25 – >1	97.2 / 2.5	97.5 / 2.5
Erythromycin	≤0.06	4	≤0.06 – >8	86.4 / 13.0	86.4 / 13.0
Levofloxacin	1	1	≤0.5 – >4	99.3 / 0.7	99.3 / 0.7
Linezolid	1	1	≤0.12 – 4	99.9 / -	100.0 / 0.0
PEN-I (MIC, 0.12-1 μg/mL; 266)					
CPA	≤0.03	0.12	≤0.03 – 0.25	- / -	- / -
A/C	≤1	≤1	≤1 – 4	99.2 / 0.0	- / -
Ceftriaxone	0.12	0.5	≤0.06 – 4	99.6 / 0.4	94.4 / 0.4
Cefuroxime	0.5	4	≤0.12 – 4	73.7 / 10.2	68.8 / 26.3
Tetracycline	0.5	>8	≤0.25 – >8	60.8 / 38.9	60.8 / 39.2
Clindamycin	≤0.25	>1	≤0.25 – >1	68.8 / 30.5	69.5 / 30.5
Erythromycin	4	>8	≤0.06 – >8	34.2 / 65.4	34.2 / 65.4
Levofloxacin	1	1	≤0.5 – >4	98.5 / 1.5	98.5 / 1.5
Linezolid	1	1	≤0.12 – 1	100.0 / -	100.0 / 0.0
PEN-R (MIC, ≥2 μg/mL; 256)					
CPA	0.25	0.25	0.06 – 0.5	- / -	- / -
A/C	8	8	≤1 – >8	21.6 / 66.3	- / -
Ceftriaxone	1	2	0.25 – 8	52.7 / 7.4	7.0 / 7.4
Cefuroxime	8	16	2 – >16	0.0 / 99.2	0.0 / 100.0
Tetracycline	>8	>8	≤0.25 – >8	30.1 / 69.9	30.1 / 69.9
Clindamycin	>1	>1	≤0.25 – >1	34.0 / 65.6	34.4 / 65.6
Erythromycin	>8	>8	≤0.06 – >8	9.0 / 90.6	9.0 / 90.6
Levofloxacin	1	1	≤0.5 – >4	98.8 / 0.8	98.8 / 1.2
Linezolid	0.5	1	0.25 – 2	100.0 / -	100.0 / 0.0
PEN-R (high-level; MIC, ≥8 μg/mL; 12)					
CPA	0.25	0.5	0.06 – 0.5	- / -	- / -
A/C	>8	>8	8 – >8	0.0 / 100.0	- / -
Ceftriaxone	2	8	0.5 – 8	8.3 / 41.7	8.3 / 41.7
Cefuroxime	16	>16	4 – >16	0.0 / 100.0	0.0 / 100.0
Tetracycline	>8	>8	>8	0.0 / 100.0	0.0 / 100.0
Clindamycin	>1	>1	>1	0.0 / 100.0	0.0 / 100.0
Erythromycin	>8	>8	>8	0.0 / 100.0	0.0 / 100.0
Levofloxacin	1	1	≤0.5 – 2	100.0 / 0.0	100.0 / 0.0
Linezolid	0.5	1	0.5 – 1	100.0 / -	100.0 / 0.0

Antimicrobial agent	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	Range (μg/mL)	CLSI[a] %S / %R	EUCAST %S / %R
Viridans gr. streptococci (492)[f]					
CPA	≤0.03	0.12	≤0.03 – 1	- / -	- / -
Penicillin	0.06	1	≤0.03 – >4	74.6 / 4.3	83.3 / 4.3
Cefuroxime	≤0.25	2	≤0.25 – >16	- / -	80.0 / 20.0
Ceftriaxone	0.12	1	≤0.06 – 8	92.9 / 4.1	88.0 / 12.0
Clindamycin	≤0.25	0.5	≤0.25 – >2	89.0 / 10.0	90.0 / 10.0
Linezolid	1	1	≤0.12 – 2	100.0 / -	- / -
Levofloxacin	1	2	≤0.5 – >4	92.1 / 7.1	- / -
Daptomycin	0.25	0.5	≤0.06 – 4	99.6 / -	- / -
β-haemolytic streptococci (1201)[g]					
CPA	≤0.03	≤0.03	≤0.03 – 0.12	- / -	- / -
Penicillin	≤0.03	0.06	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Cefuroxime	≤0.25	≤0.25	≤0.25 – >1	- / -	100.0 / 0.0
Ceftriaxone	≤0.06	0.12	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	>4	≤0.25 – >4	68.2 / 30.9	68.2 / 30.9
Clindamycin	≤0.25	>2	≤0.25 – >2	84.3 / 15.0	85.0 / 15.0
Linezolid	1	1	≤0.12 – 2	100.0 / -	100.0 / 0.0
Tetracycline	>8	>8	≤0.25 – >8	46.3 / 51.8	45.6 / 53.7
Levofloxacin	≤0.5	1	≤0.5 – >4	99.3 / 0.7	96.2 / 0.7
Daptomycin	0.12	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
E. coli (657)					
Non-ESBL (579)					
CPA	≤0.03	0.06	≤0.03 – 0.25	- / -	- / -
Ceftazidime	0.12	0.25	0.03 – 1	100.0 / 0.0	100.0 / 0.0
Amp/Sulb	4	32	0.5 – >32	63.2 / 18.1	- / 36.8
Pip/Taz	2	4	≤0.5 – >64	98.1 / 1.0	96.7 / 1.9
Ceftriaxone	≤0.06	0.12	≤0.06 – 1	100.0 / 0.0	100.0 / 0.0
Gentamicin	≤1	2	≤1 – >8	91.5 / 7.9	91.0 / 8.5
Levofloxacin	≤0.5	>4	≤0.5 – >4	77.7 / 22.1	77.7 / 22.3
Meropenem	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / 0.0	100.0 / 0.0
ESBL phenotype (78)					
CPA	0.06	0.12	≤0.03 – 0.5	- / -	- / -
Ceftazidime	8	32	0.25 – >32	35.9 / 46.2	7.7 / 64.1
Amp/Sulb	32	>32	4 – >32	16.7 / 59.0	- / 83.3
Pip/Taz	4	64	1 – >64	74.4 / 7.7	62.8 / 25.6
Ceftriaxone	>8	>8	0.12 – >8	9.0 / 88.5	9.0 / 88.5
Gentamicin	≤1	>8	≤1 – >8	73.1 / 26.9	73.1 / 26.9
Levofloxacin	>4	>4	≤0.5 – >4	20.5 / 78.2	20.5 / 79.5
Meropenem	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / 0.0	100.0 / 0.0
Klebsiella spp. (903)					
Non-ESBL (791)[h]					
CPA	0.06	0.12	≤0.03 – 0.5	- / -	- / -
Ceftazidime	0.12	0.25	0.03 – 1	100.0 / 0.0	100.0 / 0.0
Amp/Sulb	4	16	0.5 – >32	85.2 / 4.3	- / 14.8
Pip/Taz	2	4	≤0.5 – >64	98.7 / 0.8	95.7 / 1.3
Ceftriaxone	≤0.06	0.12	≤0.06 – 1	100.0 / 0.0	100.0 / 0.0
Gentamicin	≤1	≤1	≤1 – >8	99.0 / 0.9	99.0 / 1.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	98.6 / 0.9	97.6 / 1.4
Meropenem	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / 0.0	100.0 / 0.0

Antimicrobial agent	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	Range (μg/mL)	CLSI[a] %S / %R	EUCAST %S / %R
ESBL phenotype (112)[i]					
CPA	0.12	1	≤0.03 – 4	- / -	- / -
Ceftazidime	16	>32	0.12 – >32	35.7 / 58.0	17.0 / 64.3
Amp/Sulb	>32	>32	4 – >32	8.0 / 81.3	- / 92.0
Pip/Taz	64	>64	1 – >64	39.3 / 50.0	25.0 / 60.7
Ceftriaxone	>8	>8	0.12 – >8	8.9 / 89.3	8.9 / 89.3
Gentamicin	≤1	>8	≤1 – >8	67.9 / 19.6	62.5 / 32.1
Levofloxacin	4	>4	≤0.5 – >4	46.4 / 49.1	39.3 / 53.6
Meropenem	≤0.12	>8	≤0.12 – >8	74.1 / 22.3	77.7 / 17.0
M. morganii (116)					
CPA	0.06	0.12	≤0.03 – 0.5	- / -	- / -
Ceftazidime	0.12	16	0.03 – >32	81.0 / 12.9	75.9 / 19.0
Amp/Sulb	16	32	1 – >32	18.1 / 48.3	- / 81.9
Pip/Taz	≤0.5	2	≤0.5 – >64	95.7 / 1.7	95.7 / 4.3
Ceftriaxone	≤0.06	2	≤0.06 – >8	83.6 / 7.8	83.6 / 7.8
Gentamicin	≤1	>8	≤1 – >8	86.2 / 12.1	83.6 / 13.8
Levofloxacin	≤0.5	>4	≤0.5 – >4	80.2 / 15.5	74.1 / 19.8
Meropenem	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / 0.0	100.0 / 0.0
H. influenzae (770)					
CPA	≤0.03	≤0.03	≤0.03 – 0.06	- / -	- / -
A/C	≤1	≤1	≤1 – 4	100.0 / 0.0	90.5 / 9.5
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 1	100.0 / -	99.1 / 0.9
Cefuroxime	0.5	2	≤0.12 – 8	99.5 / 0.0	79.7 / 3.4
Meropenem	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
Tetracycline	0.5	1	≤0.25 – >8	98.7 / 1.2	98.4 / 1.3
Azithromycin	1	2	≤0.25 – >4	98.6 / -	0.3 / 1.4
Clarithromycin	8	16	≤0.25 – >32	78.7 / 3.1	1.2 / 0.7
Levofloxacin	≤0.5	≤0.5	≤0.5 – 1	100.0 / -	100.0 / 0.0
H. parainfluenzae (68)					
CPA	≤0.03	≤0.03	≤0.03	- / -	- / -
A/C	≤1	≤1	≤1 – 2	100.0 / 0.0	- / -
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / -	- / -
Cefuroxime	0.25	1	≤0.12 – 4	100.0 / 0.0	- / -
Tetracycline	0.5	1	≤0.25 – >8	97.1 / 1.5	- / -
Azithromycin	1	2	≤0.25 – >8	98.5 / -	- / -
Clarithromycin	8	16	≤0.25 – >32	76.5 / 2.9	- / -
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	97.1 / -	- / -
M. catarrhalis (200)					
CPA	≤0.03	≤0.03	≤0.03 – 0.12	- / -	- / -
A/C	≤1	≤1	≤1	100.0 / 0.0	100.0 / 0.0
Ceftriaxone	0.25	0.5	≤0.06 – 2	100.0 / -	99.0 / 0.0
Cefuroxime	1	2	≤0.12 – 8	99.5 / 0.0	74.5 / 2.5
Tetracycline	≤0.25	0.5	≤0.25 – 1	100.0 / 0.0	100.0 / 0.0
Erythromycin	0.12	0.25	≤0.06 – 4	99.5 / -	92.0 / 0.5
Levofloxacin	≤0.5	≤0.5	≤0.5 – 1	100.0 / -	100.0 / 0.0

a. Criteria as published by the CLSI [2011] and EUCAST [2011], β-lactam susceptibility should be directed by the oxacillin test results.
b. USA-FDA breakpoints were applied when available [Rocephin Product Insert, 2010].
c. Includes: *Staphylococcus auricularis* (3 strains), *S. capitis* (5 strains), *S. epidermidis* (93 strains), *S. haemolyticus* (11 strains), *S. hominis* (10 strains), *S. intermedius* (2 strains), *S. lugdunensis* (18 strains), *S. saccharolyticus* (1 strain), *S. saprophyticus* (7 strains), *S. sciuri* (1 strain), *S. warneri* (3 strains), *Staphylococcus xylosus* (1 strain), and unspeciated coagulase-negative staphylococci (331 strains).
d. Criteria as published by the CLSI [2011] for 'Penicillin parenteral (non-meningitis)'.
e. Criteria as published by the CLSI [2011] for 'Penicillin (oral penicillin V)'.
f. Includes: *Streptococcus anginosus* (41 strains), *S. bovis* (12 strains), *S. canis* (1 strain), *S. constellatus* (21 strains), *S. crista* (1 strain), *S. gallolyticus* (8 strains), *S. gordonii* (3 strains), *S. infantarius* (2 strains), *S. intermedius* (12 strains), *S. milleri* (5 strains), *S. mitis* (56 strains), *S. mutans* (3 strains), *S. oralis* (5 strains), *S. parasanguinis* (9 strains), *S. salivarius* (9 strains), *S. sanguinis* (13 strains), *S. vestibularis* (2 strains), unspeciated α-haemolytic streptococci (8 strains), and unspeciated viridans group streptococci (281 strains).
g. Includes: *Streptococcus dysgalactiae* (12 strains), *S. equisimilis* (1 strain), Group A *Streptococcus* (422 strains), Group B *Streptococcus* (576 strains), Group C *Streptococcus* (67 strains), Group F *Streptococcus* (21 strains), and Group G *Streptococcus* (102 strains).
h. Includes: *Klebsiella oxytoca* (218 strains) and *K. pneumoniae* (573 strains).
i. Includes: *Klebsiella oxytoca* (32 strains) and *K. pneumoniae* (80 strains).

A/C = amoxicillin/clavulanate; Amp/Sulb = ampicillin/sulbactam; CLSI = Clinical and Laboratory Standards Institute; CoNS = coagulase-negative staphylococci; CPA = ceftaroline/avibactam; ESBL = extended-spectrum β-lactamase; EUCAST = European Committee on Antimicrobial Susceptibility Testing; MIC = minimum inhibitory concentration; MRSA = methicillin (oxacillin)-resistant *Staphylococcus aureus*; MSSA = methicillin (oxacillin)-susceptible *S. aureus*; PEN-I = penicillin-intermediate; PEN-R = penicillin-resistant; PEN-S = penicillin-susceptible; Pip/taz = piperacillin/tazobactam; Q/D = quinupristin/dalfopristin; R = resistant; S = susceptible; TMP/SMX = trimethoprim/sulfamethoxazole.

Conclusions

- Ceftaroline/avibactam and ceftaroline were the most potent β-lactam agents tested against staphylococci and streptococci collected from hospitals in the United States
- When breakpoints established by the USA-FDA for ceftaroline were applied, MRSA and penicillin-resistant *S. pneumoniae* were particularly susceptible to ceftaroline/avibactam
- Ceftaroline/avibactam was also highly active against Enterobacteriaceae, including strains producing KPC, various ESBL types, and AmpC (chromosomal- or plasmid-mediated) enzymes
- Ceftaroline/avibactam represents a potential therapeutic option for infections caused by resistant organisms.

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