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Activity of Ceftaroline Combined with Avibactam (NXL104) Tested Against Bacterial Isolates from Patients with Respiratory Tract Infections from United States (USA) Medical Centers

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Amended Abstract

Background: Ceftaroline (CPT) is a new broad-spectrum cephalosporin with activity against Gram-positive (including MRSA and *S. pneumoniae* [SPN]) and -negative organisms. Avibactam (previously, NXL104) is a novel non-β-lactam β-lactamase (BL) inhibitor that inhibits Ambler class A, C, and D enzymes. We evaluated the activity of CPT/avibactam (CPA; fixed concentration of 4 μg/mL) against respiratory tract infection (RTI) pathogens.

Methods: Isolates were consecutively collected from 65 USA medical centers in 2008-2010. Susceptibility (S) testing for CPA, CPT, and comparators was performed by CLSI broth microdilution method (M07-A8, 2009) on a total of 4462 strains, including 1708 SPN (22.8% penicillin[PEN]-resistant [R; MIC, ≥2 μg/mL]), 1027 *H. influenzae* (HI; 26.4% BL-positive), 580 *S. aureus* (SA; 48.8%; MRSA), 411 *M. catarrhalis* (MC); 288 *Klebsiella* spp. (KSP; 15.6% ESBL-phenotype and 4.2% meropenem [MER]-R) others.

Results: CPA was 16-fold more active than ceftriaxone (CRO) against PEN-R SPN (highest CPA MIC, 0.5 μg/mL). HI (MIC_{100}, 0.06 μg/mL) and MC (MIC_{100}, 0.12 μg/mL) were very S to CPA, independent of BL production. All MRSA strains were inhibited at ≤2 μg/mL of CPA. Against oxacillin-S SA, CPA inhibited 99.7% of strains at MIC ≤0.5 μg/mL. CPA was active against ($MIC_{50/90}$ in μg/mL): ESBL-phenotype KSP (0.12/0.5), MER-R KSP (KPC strains; 0.5/2), ceftazidime-R *Enterobacter* (0.5/1) and other R subsets of Enterobacteriaceae (ENT; highest CPA MIC, 4 μg/mL; Table).

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. CPA was very active against ENT, including strains producing ESBL, KPC and/or derepressed AmpC enzymes. CPA represents a potential therapeutic option for RTI.

Cumulative % inhibited at CPA MIC (μg/mL) of[a,b]:

Organism (no. tested)	≤0.03	0.06	0.12	0.25	0.5	1	2	4
S. pneumoniae (1708)	64.6	73.3	84.5	98.0	100.0	-	-	-
Pen-R (390)	0.0	0.5	33.1	91.0	100.0			
H. influenzae (1027)	99.7	100.0	-	-	-	-	-	-
S. aureus (580)	0.2	0.3	2.9	44.8	72.2	94.8	100.0	-
MSSA (297)	0.3	0.7	5.7	85.9	99.7	100.0	-	-
MRSA (283)	0.0	0.0	0.0	1.8	43.5	89.4	100.0	-
M. catarrhalis (411)	99.0	99.8	100.0	-	-	-	-	-
Klebsiella spp. (288)	11.5	56.9	84.0	94.1	98.3	99.3	99.7	100.0
ESBL phenotype (45)	6.7	22.2	53.3	77.8	91.1	95.6	97.8	100.0
Meropenem-R (12)[b]	8.3	25.0	25.0	41.7	75.0	83.3	91.7	100.0
E. coli (117)	41.9	83.8	92.3	99.2	100.0			
Enterobacter spp. (60)	3.3	33.3	58.3	85.0	95.0	98.3	100.0	
Ceftazidime-R (13)	0.0	7.7	15.3	46.2	76.9	92.3	100.0	

a. Concentrations reported in the table for ceftaroline/avibactam (CPA) refer to the concentration of ceftaroline tested with fixed 4 μg/mL of avibactam concentration.
b. Probable KPC carbapenemase producer.

Introduction

Ceftaroline fosamil is the prodrug form of ceftaroline (CPT), a broad-spectrum cephalosporin with *in vitro* bactericidal activity against pathogens causing community-acquired bacterial pneumonia (CABP), including multidrug-resistant *Streptococcus pneumoniae*, methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA) and most Enterobacteriaceae species. However, like all cephalosporins, ceftaroline has limited activity against extended-spectrum β-lactamase (ESBL)- and AmpC-hyperproducing strains. In two phase 3 trials, ceftaroline was shown to be non-inferior to ceftriaxone for the treatment of patients with CABP requiring hospitalization and was approved by the United States Food and Drug Administration (USA-FDA) for CABP and acute bacterial skin and skin structure infections (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 class A and class C enzymes, including ESBL and KPC enzymes (carbapenemases).

We report the *in vitro* activity of ceftaroline combined with avibactam (fixed concentration of 4 μg/mL) against bacterial organisms responsible for respiratory tract infections.

Methods

Organisms collection: A total of 4,462 bacterial isolates were tested, including: 1,708 *S. pneumoniae* (22.8% penicillin-resistant [MIC, ≥2 μg/mL]), 1,027 *H. influenzae* (26.4% β-lactamase-positive), 580 *S. aureus* (48.8%; MRSA), 411 *M. catarrhalis;* 288 *Klebsiella* spp. (15.6% ESBL-phenotype and 4.2% meropenem-resistant), 117 *E. coli*, 103 *S. pyogenes*, 65 viridans group streptococci, 60 *Enterobacter* spp., 38 *Serratia* spp., 35 *H. parainfluenzae*, and 30 *P. mirabilis.* Isolates were consecutively collected from 65 USA medical centers in 2008-2010.

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-A8 (2009) and CLSI interpretations were based on M100-S21 and M45-A breakpoints. *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. These QC strains included: *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619, and *H. influenzae* ATCC 49247 and 49766.

Results

- Ceftaroline/avibactam and ceftaroline alone were equally active and very potent against *S. pneumoniae*. MIC_{90} values were 0.25 μg/mL for both compounds and all isolates were inhibited at ≤0.5 μg/mL (Tables 1 and 2). In contrast, relatively low susceptibility rates were observed for ceftriaxone (87.9% and 77.0% by CLSI and EUCAST criteria, respectively), amoxicillin/clavulanate (81.3% [CLSI]) and cefuroxime (71.4% and 70.4% by CLSI and EUCAST criteria, respectively; Table 2)
- Against *S. pneumoniae,* ceftaroline/avibactam (MIC_{90}, 0.25 μg/mL) was 8-, 16-, 32-, and 32-fold more active than ceftriaxone (MIC_{90}, 2 μg/mL), penicillin (MIC_{90}, 4 μg/mL), amoxicillin/clavulanate (MIC_{90}, 8 μg/mL), and cefuroxime (MIC_{90}, 8 μg/mL; Table 2), respectively. Among non-β-lactam comparator agents, only levofloxacin (MIC_{90}, 1 μg/mL; 98.8% susceptible) showed a >80% susceptibility rate
- Ceftaroline/avibactam maintained low MIC values for penicillin-resistant (MIC, ≥2 μg/mL) isolates of *S. pneumoniae* (MIC_{90}, 0.25 μg/mL; Table 1). In contrast, very low susceptibility rates were observed for ceftriaxone (47.2% [CLSI]; MIC_{50}, 2 μg/mL), cefuroxime (0.3%; MIC_{50}, 8 μg/mL), and amoxicillin/clavulanate (18.2% [CLSI]; MIC_{50}, 8 μg/mL) among these organisms (data not shown)
- Ceftaroline/avibactam was highly active against *H. influenzae* strains, including β-lactamase producers (MIC_{90}, ≤0.03 μg/mL; Tables 1 and 2). Comparators with the highest susceptibility rates were ceftaroline, ceftriaxone, levofloxacin, amoxicillin/clavulanate, cefuroxime, azithromycin, and tetracycline (≥98.4% susceptible; Table 2)
- Ceftaroline/avibactam and ceftaroline were equally active against *S. aureus* with 100.0% of strains inhibited at ≤2 μg/mL (Tables 1 and 2). When tested against MSSA strains, ceftaroline/avibactam (MIC_{50}, 0.25 μg/mL and MIC_{90}, 0.5 μg/mL; Table 1) was 8- to 16-fold more active than ceftriaxone (MIC_{50} and MIC_{90}, 4 μg/mL) and exhibited potency comparable to that of daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL) and greater than that of linezolid ($MIC_{50/90}$, 1/2 μg/mL) or vancomycin (MIC_{50} and MIC_{90}, 1 μg/mL; data not shown)
- Ceftaroline/avibactam was also very active against MRSA ($MIC_{50/90}$, 1/2 μg/mL; Table 1) from respiratory tract infections with 89.7% and 100.0% of strains being inhibited at ≤1 μg/mL and ≤2 μg/mL, respectively. Ceftaroline/avibactam potency was comparable to those of linezolid ($MIC_{50/90}$, 1/2 μg/mL) and vancomycin (MIC_{50} and MIC_{90}, 1 μg/mL; data not shown)
- Ceftaroline/avibactam activity against *M. catarrhalis* (MIC_{90}, ≤0.03 μg/mL) was at least 16- and 64-fold greater than ceftriaxone (MIC_{90}, 0.5 μg/mL) and cefuroxime (MIC_{90}, 2 μg/mL), respectively (Tables 1 and 2)
- Ceftaroline/avibactam ($MIC_{50/90}$, 0.06/0.25 μg/mL) was the most active compound tested against *Klebsiella* spp. with 99.3% of strains inhibited at ≤1 μg/mL (Table 1). Ceftaroline/avibactam was very active against *Klebsiella* spp. displaying an ESBL-phenotype ($MIC_{50/90}$, 0.12/0.5 μg/mL) and those showing decreased susceptibility to meropenem ($MIC_{50/90}$, 0.5/2 μg/mL; Abstract Table). Meropenem (MIC_{50} and MIC_{90}, ≤0.12 μg/mL) inhibited 95.5% of strains at the CLSI susceptible breakpoint of ≤1 μg/mL (Table 2)

Table 1. Summary of ceftaroline/avibactam activity tested against organisms collected from patients with respiratory tract infections hospitalized in USA medical centers (2010)

	Cumulative % inhibited at avibactam (μg/mL)[a] of:									
Organisms/subgroup	0.03	0.06	0.12	0.25	0.5	1	2	4	MIC_{50}	MIC_{90}
Streptococcus pneumoniae (1,708)	64.6	73.3	85.5	98.0	100.0	-	-	-	≤0.03	0.25
penicillin-susceptible (939)	98.1	99.5	99.9	100.0	-	-	-	-	≤0.03	≤0.03
penicillin-intermediate (379)	48.3	83.4	99.5	100.0	-	-	-	-	0.06	0.12
penicillin-resistant (390)	-	0.5	33.1	91.0	100.0	-	-	-	0.25	0.25
Haemophilus influenzae (1,027)	99.7	100.0	-	-	-	-	-	-	≤0.03	≤0.03
β-lactamase positive (756)	99.7	100.0	-	-	-	-	-	-	≤0.03	≤0.03
β-lactamase negative (271)	99.6	100.0	-	-	-	-	-	-	≤0.03	≤0.03
Staphylococcus aureus (580)	0.2	0.3	2.9	44.8	72.2	94.8	100.0	-	0.5	1
MSSA (297)	0.3	0.7	5.7	85.9	99.7	100.0	-	-	0.25	0.5
MRSA (283)	-	-	-	1.8	43.5	89.4	100.0	-	1	2
Moraxella catarrhalis (411)	99.0	99.8	100.0	-	-	-	-	-	≤0.03	≤0.03
Klebsiella spp. (288)	11.5	56.9	84.0	94.1	98.3	99.3	99.7	100.0	0.06	0.25
Escherichia coli (117)	41.9	83.8	92.3	99.2	100.0	-	-	-	0.06	0.12
S. pyogenes (103)	98.1	100.0	-	-	-	-	-	-	≤0.03	≤0.03
Viridans group streptococci (65)	52.3	76.9	84.6	98.2	95.4	100.0	-	-	≤0.03	0.25
Enterobacter spp. (60)	3.3	33.3	58.3	85.0	95.0	98.3	100.0	-	0.12	0.5
Serratia spp. (38)	-	-	2.6	26.3	60.5	89.5	97.4	100.0	0.5	2
Haemophilus parainfluenzae (35)	100.0	-	-	-	-	-	-	-	≤0.03	≤0.03
P. mirabilis (30)	3.3	36.7	93.3	-	100.0	-	-	-	0.12	0.12

a. avibactam at fixed concentration of 4 μg/mL.

Table 2. Antimicrobial activity of ceftaroline/avibactam, ceftaroline and comparator agents tested against bacterial isolates from respiratory tract infections

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[b] %S / %R	EUCAST[a] %S / %R
S. pneumoniae (1,708)					
Ceftaroline/avibactam	≤0.03	0.25	≤0.03 – 0.5	- / -	- / -
Ceftaroline	0.015	0.25	≤0.008 – 0.5	98.4[h] / -	- / -
Ceftriaxone	≤0.25	2	≤0.25 – 8	87.9 / 2.3	77.0 / 2.3
Cefuroxime	≤1	8	≤1 – >8	71.4 / 25.0	70.4 / 28.6
Amoxicillin/clavulanate	≤1	8	≤1 – >8	81.3 / 15.7	- / -
Penicillin	≤0.03	4	≤0.03 – >4	55.0[c] (83.5)[d] / 22.8[c] (1.8)[d]	55.0 / 16.5
Tetracycline	≤2	>8	≤2 – >8	73.4 / 26.1	73.4 / 26.6
TMP/SMX[e]	≤0.5	>2	≤0.5 – >2	64.9 / 27.4	69.5 / 27.4
Erythromycin	≤0.25	>2	≤0.25 – >2	57.2 / 42.3	57.2 / 42.3
Clindamycin	≤0.25	>1	≤0.25 – >1	77.0 / 22.5	77.5 / 22.5
Levofloxacin	1	1	≤0.5 – >4	98.8 / 1.1	98.8 / 1.2
H. influenzae (1,027)					
Ceftaroline/avibactam	≤0.03	≤0.03	≤0.03 – 0.06	- / -	- / -
Ceftaroline	≤0.008	0.03	≤0.008 – 0.25	99.9[h] / -	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / -	99.5 / 0.5
Cefuroxime	≤2	≤2	≤2 – 8	99.4 / 0.0	81.4 / 3.8
Amoxicillin/clavulanate	≤1	≤1	≤1 – 8	99.9 / 0.1	90.8 / 9.2
Azithromycin	1	2	≤0.5 – >4	98.4 / -	2.4 / 1.6
Clarithromycin	8	16	≤0.25 – >32	74.3 / 4.5	1.3 / 1.0
Tetracycline	≤2	≤2	≤2 – >8	98.6 / 1.2	98.4 / 1.4
TMP/SMX[e]	≤0.5	>2	≤0.5 – >2	76.0 / 21.2	76.0 / 23.1
Levofloxacin	≤0.5	≤0.5	≤0.5	100.0 / -	100.0 / 0.0
S. aureus (580)					
Ceftaroline/avibactam	0.5	1	≤0.03 – 2	- / -	- / -
Ceftaroline	0.5	1	0.03 – 2	97.4[g] / -	- / -
Ceftriaxone	4	>8	0.5 – >8	50.1 / 48.8	51.2 / 48.8
Oxacillin	2	>2	≤0.25 – >2	51.2 / 48.8	51.2 / 48.8
Erythromycin	>2	>2	≤0.25 – >2	37.4 / 61.2	37.8 / 62.1
Clindamycin	≤0.25	>2	≤0.25 – >2	74.5 / 25.2	73.4 / 25.5
Levofloxacin	≤0.5	>4	≤0.5 – >4	53.6 / 45.2	53.6 / 45.2
Linezolid	1	2	0.5 – >8	99.3 / 0.7	99.3 / 0.7
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Moraxella catarrhalis (411)					
Ceftaroline/avibactam	≤0.03	≤0.03	≤0.03 – 0.12	- / -	- / -
Ceftaroline	0.06	0.12	≤0.008 – 1	- / -	- / -
Ceftriaxone	≤0.25	0.5	≤0.25 – 8	99.8 / -	99.3 / 0.2
Cefuroxime	≤1	2	≤1 – >8	99.5 / 0.2	77.4 / 1.9
Amoxicillin/clavulanate	≤1	≤1	≤1 – >8	100.0 / 0.0	100.0 / 0.0
Erythromycin	0.12	0.25	≤0.06 – >8	99.5 / -	90.8 / 0.5
Tetracycline	≤2	≤2	≤2 – 8	99.8 / 0.2	99.8 / 0.2
TMP/SMX[e]	≤0.5	≤0.5	≤0.5 – >2	94.2 / 2.7	94.2 / 4.1
Levofloxacin	≤0.5	≤0.5	≤0.5 – 1	100.0 / -	100.0 / 0.0
Klebsiella spp. (288)[f]					
Ceftaroline/avibactam	0.06	0.25	≤0.03 – 4	- / -	- / -
Ceftaroline	0.12	>16	0.03 – >16	78.1 / 17.0[h]	- / -
Ceftriaxone	≤0.25	>8	≤0.25 – >8	84.4 / 15.3	84.4 / 15.3
Ampicillin/sulbactam	8	>16	≤2 – >16	71.9 / 18.1	- / 28.1
Piperacillin/tazobactam	4	32	≤0.5 – >64	88.2 / 9.4	81.6 / 11.8
Meropenem	≤0.12	≤0.12	≤0.12 – >8	95.5 / 4.2	95.8 / 3.5
Gentamicin	≤2	≤2	≤2 – >8	91.3 / 5.2	90.6 / 8.7
Levofloxacin	≤0.5	>4	≤0.5 – >4	87.8 / 10.8	85.8 / 12.2
E. coli (117)					
Ceftaroline/avibactam	0.06	0.12	≤0.03 – 0.5	- / -	- / -
Ceftaroline	0.25	>16	≤0.008 – >16	77.8 / 17.9[h]	- / -
Ceftazidime	0.25	4	0.03 – >16	90.6 / 8.5	83.8 / 9.4
Ceftriaxone	≤0.25	>8	≤0.25 – >8	84.6 / 14.5	84.6 / 14.5
Ampicillin/sulbactam	16	>16	≤2 – >16	38.5 / 38.5	- / 61.5
Piperacillin/tazobactam	2	8	≤0.5 – >64	93.2 / 4.3	90.6 / 6.8
Meropenem	≤0.12	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Gentamicin	≤2	>8	≤2 – >8	84.6 / 13.7	82.9 / 15.4
Levofloxacin	≤0.5	>4	≤0.5 – >4	59.8 / 37.6	59.8 / 40.2

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[b] %S / %R	EUCAST[a] %S / %R
S. pyogenes (103)					
Ceftaroline/avibactam	≤0.03	≤0.03	≤0.03 – 0.06	- / -	- / -
Ceftaroline	≤0.008	≤0.008	≤0.008 – 0.06	98.1[h] / -	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0 / -	100.0 / 0.0
Penicillin	≤0.03	≤0.03	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	1	≤0.25 – >2	87.4 / 11.7	87.4 / 11.7
Clindamycin	≤0.25	≤0.25	≤0.25 – 0.5	99.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.5	2	≤0.5 – 2	100.0 / 0.0	97.4 / 0.0
Linezolid	1	1	≤0.12 – 1	100.0 / -	100.0 / 0.0
Vancomycin	0.25	0.5	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
Viridans group streptococci (65)[g]					
Ceftaroline/avibactam	≤0.03	0.5	≤0.03 – 1	- / -	- / -
Ceftaroline	0.03	0.5	≤0.008 – 1	- / -	- / -
Ceftriaxone	≤0.25	2	≤0.25 – 8	89.2 / 4.6	80.0 / 20.0
Penicillin	0.06	2	≤0.03 – >4	69.2 / 6.2	73.8 / 6.2
Erythromycin	2	>2	≤0.25 – >2	44.6 / 50.8	- / -
Clindamycin	≤0.25	>2	≤0.25 – >2	81.5 / 18.5	81.5 / 18.5
Levofloxacin	1	4	≤0.5 – >4	89.2 / 9.2	- / -
Linezolid	1	1	≤0.12 – 1	100.0 / -	- / -
Vancomycin	0.5	1	0.25 – 1	100.0 / -	100.0 / 0.0
Enterobacter spp. (60)[h]					
Ceftaroline/avibactam	0.12	0.5	≤0.03 – 2	- / -	- / -
Ceftaroline	0.25	>16	0.06 – >16	68.3[h] / 23.3	- / -
Ceftazidime	≤1	>16	≤1 – >16	78.3 / 21.7	73.3 / 21.7
Ceftriaxone	≤0.25	32	≤0.25 – >32	73.3 / 25.0	73.3 / 25.0
Ampicillin	>16	>16	4 – >16	10.0 / 86.7	- / 90.0
Piperacillin/tazobactam	4	>64	1 – >64	81.7 / 15.0	78.3 / 18.3
Meropenem	≤0.12	≤0.12	≤0.12 – >8	98.3 / 1.7	98.3 / 1.7
Gentamicin	≤2	≤2	≤2 – >8	93.3 / 3.3	91.7 / 6.7
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	96.7 / 1.7	91.7 / 3.3
Serratia spp. (38)[i]					
Ceftaroline/avibactam	0.5	2	0.12 – 4	- / -	- / -
Ceftaroline	1	16	0.25 – >16	31.6[h] / 31.6	- / -
Ceftazidime	0.25	16	0.06 – >16	89.5 / 10.5	89.5 / 10.5
Ceftriaxone	≤0.25	32	≤0.25 – >32	84.2 / 13.2	84.2 / 13.2
Ampicillin/sulbactam	>16	>16	4 – >16	5.3 / 76.3	- / 94.7
Piperacillin/tazobactam	2	4	1 – >64	94.7 / 2.6	94.7 / 5.3
Meropenem	≤0.12	≤0.12	≤0.12 – 8	97.4 / 2.6	97.4 / 0.0
Gentamicin	≤2	>8	≤2 – >8	89.5 / 10.5	89.5 / 10.5
Levofloxacin	≤0.5	2	≤0.5 – >4	94.7 / 5.3	86.8 / 5.3
H. parainfluenzae (35)					
Ceftaroline/avibactam	≤0.03	≤0.03	≤0.03	- / -	- / -
Ceftaroline	≤0.008	0.03	≤0.008 – 0.5	- / -	- / -
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / -	- / -
Cefuroxime	≤0.12	1	≤0.12 – 2	100.0 / 0.0	- / -
Ampicillin	≤1	2	≤1 – >8	88.6 / 8.6	- / -
Amoxicillin/clavulanate	≤1	≤1	≤1 – 2	100.0 / 0.0	- / -
Azithromycin	0.5	2	≤0.25 – >8	97.1 / -	- / -
Clarithromycin	8	16	≤0.25 – >32	80.0 / 2.9	- / -
Tetracycline	0.5	1	≤0.25 – >8	94.3 / 2.9	- / -
TMP/SMX	≤0.5	>4	≤0.5 – >4	82.9 / 17.1	- / -
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	97.1 / -	- / -
Proteus mirabilis (30)					
Ceftaroline/avibactam	0.12	0.12	≤0.03 – 0.25	- / -	- / -
Ceftaroline[g]	0.12	0.25	≤0.03 – >16	96.7 / 3.3	- / -
Ceftazidime	0.06	0.06	0.03 – 0.25	100.0 / 0.0	100.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0 / 0.0	100.0 / 0.0
Ampicillin/sulbactam	≤2	16	≤2 – >16	86.7 / 3.3	- / 13.3
Piperacillin/tazobactam	≤0.5	≤0.5	≤0.5 – >64	96.7 / 3.3	96.7 / 3.3
Meropenem	≤0.12	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Gentamicin	≤2	≤2	≤2 – >8	93.3 / 6.7	90.0 / 6.7
Levofloxacin	≤0.5	>4	≤0.5 – >4	83.3 / 13.3	76.7 / 16.7

a. Criteria as published by the CLSI [2011] and EUCAST [2011]. β-lactam susceptibility should be directed by the oxacillin test results.
b. US-FDA breakpoints were applied when available [Teflaro® Product Insert, 2010].
c. Criteria as published by the CLSI [2011] for 'Penicillin (oral penicillin V).
d. Criteria as published by the CLSI [2011] for 'Penicillin parenteral (non-meningitis).
e. TMP/SMX = trimethoprim/sulfamethoxazole.
f. Includes: *Klebsiella oxytoca* (57 strains), *K. pneumoniae* (221 strains), and unspecified *Klebsiella* (10 strains).
g. Includes: *Streptococcus anginosus* (8 strains), *S. constellatus* (7 strains), *S. intermedius* (3 strains), *S. mitis* (2 strains), *S. sanguinis* (1 strain), unspecified viridans group streptococci (44 strains).
h. Includes: *Enterobacter aerogenes* (20 strains), *E. cloacae* (38 strains), and unspecified *Enterobacter* (2 strains).
i. Includes: *Serratia liquefaciens* (2 strains), *S. marcescens* (35 strains), and unspecified *Serratia* (1 strain).

- *E. coli* ($MIC_{50/90}$, 0.06/0.12 μg/mL), *Enterobacter* spp. ($MIC_{50/90}$, 0.12/0.5 μg/mL), *Serratia* spp. ($MIC_{50/90}$, 0.5/2 μg/mL) and *P. mirabilis* (MIC_{50} and MIC_{90}, 0.12 μg/mL) strains from respiratory tract were very susceptible to ceftaroline/avibactam (Tables 1 and 2)
- Ceftaroline/avibactam was also very active against *S. pyogenes* (MIC_{50} and MIC_{90}, ≤0.03 μg/mL), viridans group *Streptococcus* spp. ($MIC_{50/90}$, ≤0.03/0.5 μg/mL), and *H. parainfluenzae* (MIC_{50} and MIC_{90}, ≤0.03 μg/mL) strains isolated from respiratory tract infections in USA hospitals (Tables 1 and 2).

Conclusions

- Ceftaroline/avibactam and ceftaroline were the most potent β-lactam agents tested against the *S. pneumoniae* and *S. aureus* strains collected from USA hospitals. MRSA and penicillin-resistant *S. pneumoniae* were particularly susceptible to ceftaroline/avibactam
- Ceftaroline/avibactam was very active against Enterobacteriaceae, including strains producing ESBL, KPC and/or derepressed AmpC enzymes
- Ceftaroline combined with avibactam represents a potential therapeutic option for the treatment of respiratory tract infections caused by *S. pneumoniae*, *H. influenzae* and *S. aureus* in addition to possessing excellent activity against Enterobacteriaceae.

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