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Antimicrobial Spectrum and Potency of Ceftaroline-Avibactam Tested Against ESBL-Phenotype and Carbapenem-Resistant Enterobacteriaceae Collected from USA Hospitals (2009-2011)

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Amended Abstract

Background: Ceftaroline is a new broad-spectrum cephalosporin with bactericidal activity against Gram-positive bacteria (including MRSA) and Enterobacteriaceae (ENT). Avibactam is a novel non-β-lactam β-lactamase (BL) inhibitor that inhibits Ambler class A, C, and some D enzymes (eg, ESBL, KPC, and AmpC).

Methods: Ceftaroline-avibactam and comparators were tested for susceptibility (S) by CLSI broth microdilution methods against 7789 ENT, including ESBL-phenotype *E. coli* (285) and *Klebsiella* spp. (KSP; 411), AmpC derepressed *Enterobacter* spp. (ESP; 155) and meropenem (MER)-non-S KSP (most KPC-producing; 115) and ESP (14), among other resistance (R) phenotypes. The strains were consecutively collected in 2009-2011 from 72 USA medical centers.

Results: 97.9% of strains were inhibited at ceftaroline-avibactam MIC of ≤0.5 μg/mL(S breakpoint for ceftaroline alone). Ceftaroline-avibactam was very active against ESBL-phenotype *E. coli* ($MIC_{50/90}$, 0.06/0.25 μg/mL) and KSP ($MIC_{50/90}$, 0.12/1 μg/mL), MER-non-S KSP ($MIC_{50/90}$, 0.5/1 μg/mL) and ESP ($MIC_{50/90}$, 0.5/2 μg/mL), and ceftazidime (CAZ)-non-S ESP ($MIC_{50/90}$, 0.25/1 μg/mL). ESBL-phenotype strains showed low S to gentamicin (GEN; 62.0-69.1%) and levofloxacin (20.4-39.3%). Only 72.0 and 74.3% of ESBL-phenotype KSP were S to MER and amikacin, respectively. MER-non-S *Klebsiella* spp. strains exhibited low S to all agents, except tigecycline ($MIC_{50/90}$, 0.5/2 μg/mL; 95.7% S by CLSI criteria). 78.7% of CAZ-non-S ESP were S to GEN.

Conclusions: Avibactam can effectively lower ceftaroline MIC values for ENT producing the most clinically significant BLs found in USA hospitals. Ceftaroline-avibactam was highly active against ENT producing KPC, various ESBL types, and AmpC (chromosomally derepressed or plasmid-mediated) enzymes. Ceftaroline-avibactam shows potent *in vitro* activity against pathogens associated with infections caused by multidrug-R ENT.

Introduction

Ceftaroline fosamil is the parenterally-administered prodrug form of ceftaroline, a new cephalosporin with potent activity against Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant (MDR) *Streptococcus pneumoniae*. In Phase 3 trials (NCT00424190 [CANVAS 1], NCT00423657 [CANVAS 2], NCT00621504 [FOCUS 1] and NCT00509106 [FOCUS 2]), ceftaroline fosamil was shown to be non-inferior to comparator agents for the treatment of patients with acute bacterial skin and skin-structure infections (ABSSSIs) and community-acquired bacterial pneumonia (CABP) requiring hospitalization. Ceftaroline fosamil has been approved by the United States Food and Drug Administration (USA-FDA) for treatment of ABSSSIs and CABP.

Ceftaroline is also active against most Enterobacteriaceae species but, like other cephalosporins, has limited activity against isolates producing extended-spectrum β-lactamases (ESBL), cephalosporinases and carbapenemases. Avibactam (formerly, NXL104) is a novel 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 ESBL and KPC enzymes (carbapenemases), as well as some class D β-lactamases. We report the *in vitro* activity of ceftaroline combined with avibactam (fixed concentration of 4 μg/mL) when tested against ESBL-phenotype and carbapenem-resistant Enterobacteriaceae collected from USA hospitals (2009-2011).

Methods

Organisms collection: A total of 7789 Enterobacteriaceae isolates were tested, including ESBL-phenotype *E. coli* (285) and *Klebsiella* spp. (411), AmpC stably derepressed *Enterobacter* spp. (155), meropenem-non-susceptible *Klebsiella* spp. (mostly KPC-producing; 115), and *Enterobacter* spp. (14). The strains were consecutively collected in 2009-2011 from 72 USA medical centers. Isolates were sent to the coordinating laboratory (JMI Laboratories, North Liberty, Iowa, USA) for reference susceptibility testing. Only one strain per patient infection episode was included in the surveillance program.

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) document, and CLSI interpretations were based on M100-S22 (2012) 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 and concurrent testing of quality control (QC) strains assured proper testing conditions. All QC results were within published ranges.

Results

- Ceftaroline-avibactam was active against non-ESBL strains ($MIC_{50/90}$ of 0.06/0.12 μg/mL; 99.8 and 100.0% inhibited at ≤0.5 and ≤1 μg/mL, respectively) as well as ESBL-phenotype *Klebsiella* spp. ($MIC_{50/90}$ of 0.12/1 μg/mL; 89.1 and 97.1% inhibited at ≤0.5 and ≤1 μg/mL, respectively). Among ESBL-phenotype *Klebsiella* spp., resistance rates to "third-generation" cephalosporins were high (86.6 and 68.6% resistance to ceftriaxone and ceftazidime, respectively, according to CLSI breakpoints), and only 72.0 and 62.0% of strains were susceptible to meropenem and gentamicin, respectively (Tables 1 and 2)
- Ceftaroline-avibactam ($MIC_{50/90}$ of 0.5/1 μg/mL; 97.4% inhibited at ≤2 μg/mL) and tigecycline ($MIC_{50/90}$ of 0.5/2 μg/mL; 95.7% susceptible by USA-FDA breakpoint criteria) were the most active compounds tested against 115 meropenem-non-susceptible (MIC, ≥2 μg/mL) *Klebsiella* spp. isolates (Tables 1 and 2)
- *E. coli* isolates were highly susceptible to ceftaroline-avibactam ($MIC_{50/90,}$ ≤0.03/0.06 μg/mL) with >99.9% of strains inhibited at ceftaroline-avibactam MIC of ≤0.5 μg/mL. The highest ceftaroline-avibactam MIC was only 0.25 μg/mL among non-ESBL-phenotype strains ($MIC_{50/90,}$ ≤0.03/0.06 μg/mL)
- ESBL-phenotype *E. coli* strains exhibited high resistance rates to ceftriaxone (85.6%), ceftazidime (50.9%), gentamicin (30.2%) and levofloxacin (78.9%), but were very susceptible to ceftaroline-avibactam ($MIC_{50/90,}$ 0.06/0.25 μg/mL; highest MIC, 1 μg/mL [one strain]; Tables 1 and 2)
- Among 801 *Enterobacter* spp. strains, 95.9% were inhibited by ceftaroline-avibactam at ≤0.5 μg/mL ($MIC_{50/90,}$ 0.12/0.5 μg/mL). Meropenem ($MIC_{90,}$ ≤0.12 μg/mL; 98.3% susceptible) and tigecycline ($MIC_{50/90,}$ 0.25/1 μg/mL; 98.9% susceptible) were also very active against *Enterobacter* spp. Among ceftazidime-non-susceptible (MIC, ≥8 μg/mL) *Enterobacter* spp. strains, 80.0 and 96.1% of strains were inhibited at ceftaroline-avibactam MIC of ≤0.5 and ≤1 μg/mL, respectively (Tables 1 and 2)
- Overall, 97.9% of Enterobacteriaceae strains were inhibited at ceftaroline-avibactam MIC of ≤0.5 μg/mL, which is the susceptibility breakpoint established for ceftaroline alone by the USA-FDA against indicated Enterobacteriaceae species (Tables 1 and 2); 99.5% at ≤1 μg/mL. Meropenem and tigecycline covered 98.2 and 97.9% of all strains, respectively.

Table 1. Summary of Ceftaroline-Avibactam Activity Tested Against Organisms Collected from Patients Hospitalized in USA Medical Centers (2011)

Organism (no. tested)	No. of isolates (cumulative %) inhibited at ceftaroline-avibactam MIC (μg/mL) of:							
	≤0.03	0.06	0.12	0.25	0.5	1	2	≥4
Klebsiella spp. (2,928)	710 (24.3)	1297 (68.6)	571 (88.1)	212 (95.3)	87 (98.3)	39 (99.6)	9 (99.9)	3 (100.0)
Non-ESBL-phenotype (2517)	673 (26.7)	1226 (75.5)	458 (93.6)	125 (98.6)	29 (99.8)	6 (100.0)	-	-
ESBL-phenotype (411)	37 (9.0)	71 (26.3)	113 (53.8)	87 (74.9)	58 (89.1)	33 (97.1)	9 (99.3)	3 (100.0)
Meropenem-non-S (115)	7 (6.1)	6 (11.3)	14 (23.5)	19 (40.0)	31 (67.0)	28 (91.3)	8 (98.3)	2 (100.0)
E. coli (2517)	1531 (60.8)	783 (91.9)	158 (98.2)	38 (99.7)	6 (>99.9)	1 (100.0)	-	-
Non-ESBL-phenotype (2,232)	1443 (64.7)	676 (94.9)	97 (99.3)	16 (100.0)	-	-	-	-
ESBL-phenotype (285)	88 (30.9)	107 (68.4)	61 (89.8)	22 (97.5)	6 (99.7)	1 (100.0)	-	-
Enterobacter spp. (801)	116 (14.5)	212 (41.0)	249 (72.0)	139 (89.4)	52 (95.9)	27 (99.3)	5 (99.9)	1 (100.0)
Ceftazidime-S (646)	114 (17.7)	193 (47.5)	227 (82.7)	93 (97.1)	17 (99.7)	2 (100.0)	-	-
Ceftazidime-non-S (155)	2 (1.3)	19 (13.6)	22 (27.7)	46 (57.4)	35 (80.0)	25 (96.1)	5 (99.4)	1 (100.0)
Meropenem-non-S (14)	-	-	1 (7.1)	3 (28.6)	3 (50.0)	4 (78.6)	2 (92.9)	1 (100.0)
All Enterobacteraceae	2666 (34.2)	2759 (69.7)	1300 (86.3)	593 (94.0)	308 (97.9)	124 (99.5)	26 (99.8)	13 (100.0)

Abbreviations: ESBL = extended-spectrum β-lactamase; S = susceptible.

Table 2. Activity of Ceftaroline-Avibactam, Ceftaroline and Comparator Antimicrobial Agents When Tested against Enterobacteriaceae Collected from USA Hospitals (2009-2011)

Organism/antimicrobial agent (no. tested)	MIC (μg/mL)			%S / %R[a]	
	MIC_{50}	MIC_{90}	Range	CLSI[a]	EUCAST[a]
***Klebsiella* spp.[b] (2,928)**					
Ceftaroline-avibactam	0.06	0.25	≤0.03 – 16	- / -	- / -
Ceftaroline[c]	0.12	>16	≤0.015 – >16	82.6 / 14.3	- / -
Ceftriaxone	≤0.25	>8	≤0.25 – >8	87.3 / 12.2	87.3 / 12.2
Ceftazidime	≤1	8	≤1 – >16	89.5 / 9.6	87.8 / 10.5
Ampicillin/sulbactam	8	>16	≤2 – >16	73.2 / 16.3	- / 26.8
Piperacillin/tazobactam	2	32	≤0.5 – >64	89.3 / 8.7	84.1 / 10.7
Tigecycline[d]	0.25	1	0.06 – >4	98.5 / 0.2	95.0 / 1.5
Cefuroxime	≤2	>16	≤2 – >16	81.0 / 14.5	81.0 / 19.0
Gentamicin	≤2	≤2	≤2 – >8	93.6 / 4.9	92.9 / 6.4
Levofloxacin	≤0.5	4	≤0.5 – >4	89.7 / 9.2	88.2 / 10.3
Meropenem	≤0.12	≤0.12	≤0.12 – >8	96.1 / 3.7	96.3 / 2.8
non-ESBL phenotype (2,517)					
Ceftaroline-avibactam	0.06	0.12	≤0.03 – 1	- / -	- / -
Ceftaroline[c]	0.12	0.5	≤0.015 – >16	95.7 / 1.1	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 1	100.0 / 0.0	100.0 / 0.0
Ceftazidime	≤1	≤1	≤1 – 1	100.0 / 0.0	100.0 / 0.0
Ampicillin/sulbactam	4	16	≤2 – >16	84.2 / 5.0	- / 15.8
Piperacillin/tazobactam	2	8	≤0.5 – >64	98.7 / 0.6	94.1 / 1.3
Tigecycline[d]	0.25	0.5	0.06 – >4	98.8 / 0.1	96.0 / 1.2
Gentamicin	≤2	≤2	≤2 – >8	98.7 / 1.1	98.7 / 1.3
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	97.9 / 1.4	96.9 / 2.1
Meropenem	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / 0.0	100.0 / 0.0
ESBL phenotype (411)					
Ceftaroline-avibactam	0.12	1	≤0.03 – 16	- / -	- / -
Ceftaroline[c]	>16	>16	0.06 – >16	2.4 / 95.6	- / -
Ceftriaxone	>8	>8	≤0.25 – >8	9.5 / 86.6	9.5 / 86.6
Ceftazidime	>16	>16	≤1 – >16	25.5 / 68.6	13.1 / 74.5
Ampicillin/sulbactam	>16	>16	2 – >16	5.6 / 84.9	- / 94.4
Piperacillin/tazobactam	>64	>64	1 – >64	31.4 / 58.4	22.6 / 68.6
Tigecycline[d]	0.5	2	0.06 – >4	96.4 / 0.5	89.1 / 3.6
Gentamicin	≤2	>8	≤2 – >8	62.0 / 28.2	56.9 / 38.0
Levofloxacin	>4	>4	≤0.5 – >4	39.3 / 57.3	34.6 / 60.7
Meropenem	≤0.12	>8	≤0.12 – >8	72.0 / 26.0	74.0 / 20.0
meropenem-non-susceptible (115)					
Ceftaroline-avibactam	0.5	1	≤0.03 – 16	- / -	- / -
Ceftaroline[c]	>16	>16	4 – >16	0.0 / 100.0	- / -
Ceftriaxone	>8	>8	8 – >8	0.0 / 100.0	0.0 / 100.0
Ceftazidime	>16	>16	2 – >16	1.7 / 93.9	0.0 / 98.3
Ampicillin/sulbactam	>16	>16	>16	0.0 / 100.0	- / 100.0
Piperacillin/tazobactam	>64	>64	8 – >64	0.9 / 98.3	0.9 / 99.1
Tigecycline[d]	0.5	2	0.06 – >4	95.7 / 0.9	88.7 / 4.3
Gentamicin	8	>8	≤2 – >8	49.6 / 34.8	42.6 / 50.4
Levofloxacin	>4	>4	≤0.5 – >4	9.6 / 90.4	7.8 / 90.4
Meropenem	>8	>8	2 – >8	0.0 / 93.0	7.0 / 71.3
***Escherichia coli* (2,517)**					
Ceftaroline-avibactam	≤0.03	0.06	≤0.03 – 1	- / -	- / -
Ceftaroline[c]	0.12	8	≤0.015 – >16	84.3 / 12.8	- / -
Ceftriaxone	≤0.25	1	≤0.25 – >8	90.0 / 9.7	90.0 / 9.7
Ceftazidime	≤1	≤1	≤1 – >16	92.9 / 5.8	90.2 / 7.1
Ampicillin/sulbactam	8	>16	≤2 – >16	51.2 / 26.6	- / 48.8
Piperacillin/tazobactam	2	8	≤0.5 – >64	94.2 / 3.0	91.6 / 5.8
Tigecycline[d]	0.12	0.25	≤0.03 – 2	100.0 / 0.0	99.9 / 0.0
Gentamicin	≤2	>8	≤2 – >8	87.6 / 11.8	86.7 / 12.4
Levofloxacin	≤0.5	>4	≤0.5 – >4	69.4 / 30.0	69.3 / 30.6
Meropenem	≤0.12	≤0.12	≤0.12 – 4	>99.9 / <0.1	>99.9 / 0.0
non-ESBL phenotype (2,232)					
Ceftaroline-avibactam	≤0.03	0.06	≤0.03 – 0.25	- / -	- / -
Ceftaroline[c]	0.12	0.5	≤0.015 – >16	94.1 / 2.9	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 1	100.0 / 0.0	100.0 / 0.0
Ceftazidime	≤1	≤1	≤1 – 1	100.0 / 0.0	100.0 / 0.0
Ampicillin/sulbactam	8	>16	≤2 – >16	56.3 / 21.2	- / 43.7
Piperacillin/tazobactam	2	4	≤0.5 – >64	96.8 / 2.0	95.7 / 3.2
Tigecycline[d]	0.12	0.25	≤0.03 – 2	100.0 / 0.0	99.9 / 0.0
Gentamicin	≤2	4	≤2 – >8	90.0 / 9.5	89.1 / 10.0
Levofloxacin	≤0.5	>4	≤0.5 – >4	75.7 / 23.7	75.6 / 24.3
Meropenem	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / 0.0	100.0 / 0.0
ESBL phenotype (285)					
Ceftaroline-avibactam	0.06	0.25	≤0.03 – 1	- / -	- / -
Ceftaroline[c]	>16	>16	0.06 – >16	7.7 / 89.8	- / -
Ceftriaxone	>8	>8	≤0.25 – >8	11.9 / 85.6	11.9 / 85.6
Ceftazidime	16	>16	≤1 – >16	37.2 / 50.9	13.3 / 62.8
Ampicillin/sulbactam	>16	>16	≤2 – >16	11.6 / 69.1	- / 88.4
Piperacillin/tazobactam	8	>64	≤0.5 – >64	73.7 / 10.5	59.3 / 26.3
Tigecycline[d]	0.12	0.25	0.06 – 1	100.0 / 0.0	100.0 / 0.0
Gentamicin	≤2	>8	≤2 – >8	69.1 / 30.2	68.1 / 30.9
Levofloxacin	>4	>4	≤0.5 – >4	20.4 / 78.9	20.4 / 79.6
Meropenem	≤0.12	≤0.12	≤0.12 – 4	99.6 / 0.4	99.6 / 0.0
***Enterobacter* spp.* (801)**					
Ceftaroline-avibactam	0.12	0.5	≤0.03 – 4	- / -	- / -
Ceftaroline[c]	0.25	>16	≤0.015 – >16	74.2 / 22.3	- / -
Ceftriaxone	≤0.25	>8	≤0.25 – >8	77.3 / 21.2	77.3 / 21.2
Ceftazidime	≤1	>16	≤1 – >16	80.6 / 18.0	77.9 / 19.4
Ampicillin/sulbactam	16	>16	≤2 – >16	37.2 / 39.6	- / 62.8
Piperacillin/tazobactam	2	64	≤0.5 – >64	83.6 / 7.7	79.9 / 16.4
Tigecycline[d]	0.25	1	0.12 – 4	98.9 / 0.0	94.5 / 1.1
Gentamicin	≤2	≤2	≤2 – >8	95.0 / 4.4	94.4 / 5.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	94.8 / 4.1	93.6 / 5.3
Meropenem	≤0.12	≤0.12	≤0.12 – >8	98.3 / 1.4	98.6 / 0.2
ceftazidime-susceptible (646)					
Ceftaroline-avibactam	0.12	0.25	≤0.03 – 1	- / -	- / -
Ceftaroline[c]	0.12	0.5	≤0.015 – >16	92.0 / 4.0	- / -
Ceftriaxone	≤0.25	0.5	≤0.25 – >8	95.8 / 2.8	95.8 / 2.8
Ceftazidime	≤1	≤1	≤1 – 4	100.0 / 0.0	96.6 / 0.0
Ampicillin/sulbactam	16	>16	≤2 – >16	46.1 / 25.9	- / 53.9
Piperacillin/tazobactam	2	4	≤0.5 – 64	99.1 / 0.0	96.7 / 0.9
Tigecycline[d]	0.25	0.5	0.12 – 4	99.2 / 0.0	97.1 / 0.8
Cefuroxime	8	>16	≤2 – >16	68.3 / 15.3	68.3 / 31.7
Gentamicin	≤2	≤2	≤2 – >8	98.9 / 0.9	98.6 / 1.1
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	98.3 / 0.8	98.0 / 1.7
Meropenem	≤0.12	≤0.12	≤0.12 – 2	99.8 / 0.0	100.0 / 0.0
ceftazidime-non-susceptible (155)					
Ceftaroline-avibactam	0.25	1	≤0.03 – 4	- / -	- / -
Ceftaroline[c]	>16	>16	1 – >16	0.0 / 98.7	- / -
Ceftriaxone	>8	>8	2 – >8	0.0 / 98.1	0.0 / 98.1
Ceftazidime	>16	>16	8 – >16	0.0 / 92.9	0.0 / 100.0
Ampicillin/sulbactam	>16	>16	16 – >16	0.0 / 96.8	- / 100.0
Piperacillin/tazobactam	64	>64	1 – >64	19.4 / 40.0	9.7 / 80.6
Tigecycline[d]	0.25	2	0.12 – 4	97.4 / 0.0	83.9 / 2.6
Gentamicin	≤2	>8	≤2 – >8	78.7 / 18.7	76.8 / 21.3
Levofloxacin	≤0.5	>4	≤0.5 – >4	80.0 / 18.1	75.5 / 20.0
Meropenem	≤0.12	0.5	≤0.12 – >8	91.6 / 7.1	92.9 / 1.3
meropenem-non-susceptible (14)					
Ceftaroline-avibactam	0.5	2	0.12 – 4	- / -	- / -
Ceftaroline[c]	>16	>16	>16	0.0 / 100.0	- / -
Ceftriaxone	>8	>8	8 – >8	0.0 / 100.0	0.0 / 100.0
Ceftazidime	>16	>16	4 – >16	7.1 / 92.9	0.0 / 92.9
Ampicillin/sulbactam	>16	>16	>16	0.0 / 100.0	- / 100.0
Piperacillin/tazobactam	>64	>64	32 – >64	0.0 / 78.6	0.0 / 100.0
Tigecycline[d]	1	2	0.25 – 2	100.0 / 0.0	78.6 / 0.0
Gentamicin	8	>8	≤2 – >8	42.9 / 50.0	35.7 / 57.1
Levofloxacin	>4	>4	≤0.5 – >4	35.7 / 57.1	21.4 / 64.3
Meropenem	8	>8	2 – >8	0.0 / 78.6	21.4 / 14.3
Enterobacteriaceae (7,789)					
Ceftaroline-avibactam	0.06	0.25	≤0.03 – 16	- / -	- / -
Ceftaroline[c]	0.12	>16	≤0.015 – >16	80.3 / 14.9	- / -
Ceftriaxone	≤0.25	8	≤0.25 – >8	87.7 / 11.5	87.7 / 11.5
Ceftazidime	≤1	4	≤1 – >16	90.2 / 8.7	88.0 / 9.8
Ampicillin/sulbactam	8	>16	≤2 – >16	58.3 / 25.0	- / 41.7
Piperacillin/tazobactam	2	16	≤0.5 – >64	91.5 / 5.5	88.1 / 8.5
Tigecycline[d]	0.25	1	≤0.03 – 4	97.9 / 0.2	93.2 / 2.1
Gentamicin	≤2	≤2	≤2 – >8	91.5 / 7.4	90.3 / 8.5
Levofloxacin	≤0.5	>4	≤0.5 – >4	82.9 / 15.7	81.4 / 17.1
Meropenem	≤0.12	≤0.12	≤0.12 – >8	98.2 / 1.6	98.4 / 1.1

a. Criteria as published by the CLSI [2012] and EUCAST [2012].
b. Includes: *Klebsiella oxytoca* (633 strains), *K. ozaenae* (2 strains), *K. pneumoniae* (2230 strains), and unspecified *Klebsiella* (63 strains).
c. USA-FDA breakpoints were applied [Teflaro® Prescribing Information, 2012].
d. USA-FDA breakpoints were applied [Tygacil® Prescribing Information, 2011].
e. Includes: *Enterobacter aerogenes* (206 strains), *E. asburiae* (4 strains), *E. cancerogenus* (1 strain), *E. cloacae* (583 strains), *E. gergoviae* (1 strain), *E. hormaechei* (1 strain), *E. intermedius* (1 strain), *E. sakazakii* (1 strain), and unspecified *Enterobacter* (3 strains).

Conclusions

- Avibactam can effectively lower ceftaroline MIC values for Enterobacteriaceae producing clinically significant β-lactamases.
- Ceftaroline-avibactam was highly active against Enterobacteriaceae-producing KPC, various ESBL types, and AmpC (chromosomally derepressed or plasmid-mediated) enzymes.
- In summary, ceftaroline-avibactam shows potent *in vitro* activity against pathogens associated with infections caused by multidrug-resistant Enterobacteriaceae in USA hospitals (2009–2011).

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