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Antimicrobial Activity of Ceftazidime Avibactam (formerly NXL104) Tested Against Gram-Negative Organisms Causing Infections in Medical Centers from Europe, Latin America and the Asia-Pacific Region

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Abstract

Background: Avibactam (NXL104) is a novel non-β-lactam β-lactamase inhibitor (BLI) that inhibits Ambler class A, C and some D enzymes. Ceftazidime avibactam (CAZ104) is in development for treatment of hospital infections, including those caused by antimicrobial-resistant (R) Gram-negative bacilli (GNB).

Methods: CAZ104 and various comparators were tested by CLSI broth microdilution methods against 3,233 GN pathogens cultured from 92 medical centers located in Europe (EU; 2,092 isolates/56 centers), Latin America (LA; 509/13) and Asia-Pacific region (APAC; 632/23) in 2010. The collection included: *E. coli* (EC; n=934; 26.2% ESBL-phenotype), *Klebsiella* spp. (KSP; n=1003; 35.7% ESBL- phenotype and 4.0% meropenem [MER]-non-susceptible [NS]), *Enterobacter* spp. (ESP; n=361; 33.2% CAZ-NS), *Citrobacter* spp. (n=312; 23.4% CAZ-NS), *S. marcescens* (n=325; 6.5% CAZ-NS) and *M. morganii* (n=298; 9.4% CAZ-NS).

Results: ESBL-phenotype among EC/KSP was highest in APAC (33.8/39.3%), followed by LA (26.6/37.0%) and EU (24.3/34.2%), while 39.3, 37.0 and 34.2% of ESP were CAZ-NS in APAC, LA and EU, respectively. CAZ104 was active against all Enterobacteriaceae (ENT) species (MIC_{50} ranging from ≤0.06–0.25 µg/mL; MIC_{90} from 0.12–0.5 µg/mL), and retained activity against ESBL-phenotype (MIC_{90}, ranging from 0.25–1 µg/mL), CAZ-NS (MIC_{90}, 1–2 µg/mL) and MER-NS KSP (MIC_{90}, 4 µg/mL) strains. Overall, 99.2% of strains had CAZ104 MIC of ≤2 mg/mL.

Conclusion: CAZ104 was very active against ENT, including ESBL, KPC, and AmpC producers. NXL104, a broad-spectrum BLI, in combination with a GN β-lactam, such as CAZ, appears to offer a useful option for treatment of infections caused by multidrug-R GNB.

Introduction

Gram-negative bacteria resistant to currently approved agents continue to present a challenge to successful treatment of serious infections. β-lactamase-mediated resistance, in particular, represents a significant clinical threat because it is widespread in nature and many of the genes encoding the enzymes are mobile. An approach to restore the utility of a β-lactam compound is to combine it with novel agents that inhibit β-lactamases, thereby allowing the β-lactam to retain target concentrations.

Avibactam (NXL104) is a non-β-lactam β-lactamase inhibitor with promising activity against class A, C and some D β-lactamases. β-lactamase enzymes are inactivated very efficiently by avibactam, with low IC_{50} (concentration resulting in 50% inhibition) values and low turnover numbers. Avibactam protects β-lactams from hydrolysis by a variety of enzymes.

Avibactam combined with ceftazidime (ceftazidime avibactam [CAZ104]) is currently undergoing clinical development for treatment of complicated urinary tract and intra-abdominal infections (including hospital infections and resistant infections, in each case), including those caused by antimicrobial-resistant Gram-negative bacteria. In this study, we evaluated the activity of ceftazidime avibactam against a contemporary (2010) collection of Gram-negative pathogens collected from 92 medical centers located in Europe (EU), Latin America (LA), and the Asia Pacific (APAC) region.

Materials and methods

Bacterial isolates: A total of 3233 non-duplicate, consecutive Gram-negative strains were collected during 2010 from 92 medical centers located in the EU (2092 isolates/56 centers), LA (509/13) and APAC (632/23). These isolates were collected from bloodstream, respiratory tract, and skin and soft tissue infections, according to defined protocols. Only clinically significant isolates were included in the study (one per patient episode). Species identification was confirmed by standard biochemical tests and/or use of the Vitek 2 System (bioMérieux; Hazelwood, Missouri, USA), as necessary. The collection included: *Escherichia coli* (n=934; 26.2% extended spectrum β-lactamases [ESBL]-phenotype), *Klebsiella* spp. (n=1003; 35.7% ESBL-phenotype and 4.0% meropenem-non-susceptible [NS]), *Enterobacter* spp. (n=361; 33.2% ceftazidime-non-susceptible [CAZ-NS]), *Citrobacter* spp. (n=312; 23.4% CAZ-NS), *Serratia marcescens* (n=325; 6.5% CAZ-NS) and *Morganella morganii* (n=298; 9.4% CAZ-NS).

Susceptibility testing: Susceptibility testing was performed by a reference broth microdilution procedure (Clinical and Laboratory Standards Institute [CLSI], 2009) using validated microdilution panels manufactured by TREK Diagnostics (Cleveland, Ohio, USA). The concentration of avibactam was maintained at 4 µg/mL for all test concentrations of ceftazidime. Susceptibility testing results were interpreted according to CLSI (2011) or EUCAST (2011) criteria. As there are currently no established susceptibility criteria for ceftazidime avibactam, interpretation was based on either the CLSI or EUCAST susceptible breakpoint criteria for ceftazidime alone (CLSI, S at ≤4 µg/mL and EUCAST, S at ≤1 µg/mL). *E. coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were concurrently tested for quality assurance; all results were within the published ranges.

E. coli and *Klebsiella* spp. isolates for which the MIC results of ceftriaxone, ceftazidime, or aztreonam were ≥2 µg/mL were considered to be phenotype-positive for ESBL production (CLSI, 2011).

Table 1. *Cumulative frequency distribution of ceftazidime avibactam MIC values for Gram-negative pathogens from EU, LA, and APAC regions (2010)[a]*

Organism/region (no. tested)	Cumulative % inhibited at ceftazidime avibactam MIC (µg/mL) of:							
	≤0.06	0.12	0.25	0.5	1	2	4	8
E. coli (934)	58.0	88.7	97.2	99.9	100.0	–	–	–
ESBL-phenotype (245)	29.0	69.4	91.0	99.6	100.0	–	–	–
Klebsiella spp. (1003)	36.3	70.1	83.6	94.3	97.8	98.9	99.2	99.2
ESBL-phenotype (358)	8.4	32.4	57.5	84.1	93.9	96.9	97.8	97.8
Meropenem-NS (40)	5.0	10.0	27.5	60.0	75.0	87.5	90.0	90.0
Enterobacter spp. (361)	10.5	40.4	74.8	91.1	95.6	98.9	99.7	99.7
CAZ-NS (120)	4.2	10.8	37.5	75.0	87.5	97.5	99.2	99.2
Citrobacter spp. (312)	27.2	63.1	88.1	95.8	99.0	99.4	100.0	–
CAZ-NS (73)	1.4	16.4	58.9	83.6	95.9	97.3	100.0	–
M. morganii (298)	79.5	93.3	96.3	98.3	98.7	98.7	99.3	100.0
S. marcescens (325)	6.2	45.5	79.4	96.0	97.9	98.8	99.1	99.7

[a]As there are currently no established susceptibility criteria for ceftazidime avibactam, interpretation was based on either the CLSI or EUCAST susceptible breakpoint criteria for ceftazidime alone (CLSI, S at ≤4 µg/mL and EUCAST, S at ≤1 µg/mL)

Table 2. *Activity of ceftazidime avibactam and comparator agents tested against 3233 Gram-negative clinical isolates collected from 92 medical centers in EU, LA, and APAC regions (2010)*

Antimicrobial agent (N)	All Regions MIC_{50}	All Regions MIC_{90}	All Regions CLSI[a] %S / %R	All Regions EUCAST[a] %S / %R	EU MIC_{50}	EU MIC_{90}	EU CLSI[a] %S / %R	EU EUCAST[a] %S / %R
E. coli			(934)				(585)	
Ceftazidime avibactam	0.06	0.25	100.0 / 0.0[b]	100.0 / 0.0[b]	0.06	0.25	- / -	- / -
Ceftazidime	0.12	16	80.8 / 14.9	76.9 / 19.2	0.12	16	81.7 / 14.2	77.8 / 18.3
Cefepime	≤0.12	>16	83.8 / 13.2	76.3 / 19.1	≤0.12	>16	84.8 / 12.5	78.3 / 17.3
Ciprofloxacin	≤0.03	>4	63.5 / 36.3	62.7 / 36.5	≤0.03	>4	67.9 / 32.0	67.4 / 32.1
Meropenem	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	16	90.1 / 3.9	83.9 / 9.9	2	32	89.6 / 4.1	82.7 / 10.4
ESBL phenotype			(245)				(142)	
Ceftazidime avibactam	0.12	0.25	100.0 / 0.0[b]	100.0 / 0.0[b]	0.12	0.25	- / -	- / -
Ceftazidime	16	>32	26.9 / 56.7	11.8 / 73.1	16	>32	24.6 / 58.5	8.5 / 75.4
Cefepime	>16	>16	38.4 / 50.2	10.6 / 72.7	>16	>16	37.3 / 51.4	12.0 / 71.1
Ciprofloxacin	>4	>4	19.2 / 80.4	18.0 / 80.8	>4	>4	21.8 / 78.2	20.4 / 78.2
Meropenem	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	8	64	75.9 / 8.2	57.1 / 24.1	8	64	73.2 / 8.5	51.4 / 26.8
Klebsiella spp.			(1003)				(654)	
Ceftazidime avibactam	0.12	0.5	99.2 / 0.8[b]	97.8 / 0.8[b]	0.12	0.5	- / -	- / -
Ceftazidime	0.12	>32	73.3 / 24.3	69.2 / 26.7	0.12	>32	74.6 / 24.2	71.3 / 25.4
Cefepime	≤0.12	>16	77.8 / 19.0	70.8 / 24.7	≤0.12	>16	78.0 / 19.7	72.0 / 23.4
Ciprofloxacin	≤0.03	>4	75.7 / 22.0	73.8 / 24.3	≤0.03	>4	76.6 / 21.3	75.7 / 23.4
Meropenem	≤0.12	≤0.12	96.0 / 3.7	96.3 / 2.6	≤0.12	≤0.12	96.6 / 3.2	96.8 / 2.3
Piperacillin/tazobactam	2	>64	79.5 / 13.2	73.2 / 20.5	2	>64	80.1 / 13.1	74.3 / 19.9
ESBL phenotype			(358)				(224)	
Ceftazidime avibactam	0.25	1	97.8 / 2.2[b]	93.9 / 2.2[b]	0.25	1	- / -	- / -
Ceftazidime	32	>32	25.1 / 68.2	13.7 / 74.9	32	>32	25.9 / 70.5	16.1 / 74.1
Cefepime	>16	>16	37.7 / 53.4	18.4 / 69.3	>16	>16	35.7 / 57.6	18.3 / 68.3
Ciprofloxacin	>4	>4	38.8 / 55.9	34.4 / 61.2	>4	>4	38.4 / 56.7	37.1 / 61.6
Meropenem	≤0.12	4	88.8 / 10.3	89.7 / 7.3	≤0.12	1	90.2 / 9.4	90.6 / 6.7
Piperacillin/tazobactam	32	>64	46.1 / 34.9	31.8 / 53.9	32	>64	46.4 / 35.7	33.0 / 53.6
Meropenem-non-susceptible			(40)				(22)	
Ceftazidime avibactam	0.5	4	90.0 / 10.0[b]	75.0 / 10.0[b]	0.5	4	- / -	- / -
Ceftazidime	>32	>32	2.5 / 92.5	0.0 / 97.5	>32	>32	4.5 / 95.5	0.0 / 95.5
Cefepime	>16	>16	5.0 / 90.0	0.0 / 100.0	>16	>16	0.0 / 95.5	0.0 / 100.0
Ciprofloxacin	>4	>4	5.0 / 92.5	5.0 / 95.0	>4	>4	0.0 / 100.0	0.0 / 100.0
Meropenem	>8	>8	0.0 / 92.5	7.5 / 65.0	>8	>8	0.0 / 95.5	4.5 / 68.2
Piperacillin/tazobactam	>64	>64	2.5 / 92.5	2.5 / 97.5	>64	>64	0.0 / 100.0	0.0 / 100.0
Enterobacter spp.			(361)				(247)	
Ceftazidime avibactam	0.25	0.5	99.7 / 0.3[b]	95.6 / 0.3[b]	0.25	0.5	- / -	- / -
Ceftazidime	0.25	>32	66.8 / 30.5	64.3 / 33.2	0.5	>32	66.0 / 31.2	63.6 / 34.0
Cefepime	≤0.12	8	90.6 / 6.6	78.7 / 11.9	≤0.12	4	93.1 / 4.0	81.0 / 8.9
Ciprofloxacin	≤0.03	4	85.3 / 11.6	82.5 / 14.7	≤0.03	2	86.6 / 9.7	83.4 / 13.4
Meropenem	≤0.12	≤0.12	98.1 / 1.7	98.3 / 0.8	≤0.12	≤0.12	98.4 / 1.2	98.8 / 0.8
Piperacillin/tazobactam	4	>64	73.7 / 10.2	70.1 / 26.3	4	64	74.1 / 8.9	70.4 / 25.9
Ceftazidime-non-susceptible			(120)				(84)	
Ceftazidime avibactam	0.5	2	99.2 / 0.8[b]	87.5 / 0.8[b]	0.5	1	- / -	- / -
Ceftazidime	>32	>32	0.0 / 91.7	0.0 / 100.0	>32	>32	0.0 / 91.7	0.0 / 100.0
Cefepime	2	>16	75.0 / 18.3	42.5 / 31.7	2	>16	81.0 / 11.9	48.8 / 25.0
Ciprofloxacin	0.25	>4	66.7 / 27.5	60.0 / 33.3	0.25	>4	69.0 / 25.0	61.9 / 31.0
Meropenem	≤0.12	0.5	94.2 / 5.0	95.0 / 2.5	≤0.12	0.5	95.2 / 3.6	96.4 / 2.4
Piperacillin/tazobactam	64	>64	26.7 / 27.5	20.0 / 73.3	64	>64	27.4 / 25.0	20.2 / 72.6
Citrobacter spp.			(312)				(198)	
Ceftazidime avibactam	0.12	0.5	100.0 / 0.0[b]	99.0 / 0.0[b]	0.12	0.25	- / -	- / -
Ceftazidime	0.25	>32	76.6 / 21.5	72.1 / 23.4	0.25	>32	80.3 / 17.2	76.3 / 19.7
Cefepime	≤0.12	4	94.2 / 3.9	86.8 / 9.0	≤0.12	2	93.9 / 4.6	88.3 / 8.6
Ciprofloxacin	≤0.03	4	84.3 / 13.1	82.7 / 15.7	≤0.03	4	88.4 / 11.1	86.9 / 11.6
Meropenem	≤0.12	≤0.12	99.4 / 0.6	99.4 / 0.0	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	64	83.7 / 6.7	78.2 / 16.3	2	32	87.4 / 4.5	81.8 / 12.6
Ceftazidime-non-susceptible			(73)				(39)	
Ceftazidime avibactam	0.25	1	100.0 / 0.0[b]	95.9 / 0.0[b]	0.25	1	- / -	- / -
Ceftazidime	32	>32	0.0 / 91.8	0.0 / 100.0	>32	>32	0.0 / 87.2	0.0 / 100.0
Cefepime	1	>16	79.5 / 13.7	58.9 / 27.4	1	>16	76.9 / 17.9	61.5 / 28.2
Ciprofloxacin	0.25	>4	63.0 / 30.1	57.5 / 37.0	0.25	>4	61.5 / 35.9	56.4 / 38.5
Meropenem	≤0.12	≤0.12	97.3 / 2.7	97.3 / 0.0	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	32	>64	41.1 / 23.3	26.0 / 58.9	32	>64	46.2 / 15.4	25.6 / 53.8
M. morganii			(298)				(193)	
Ceftazidime avibactam	0.06	0.12	99.3 / 0.0[b]	98.7 / 0.7[b]	0.06	0.12	- / -	- / -
Ceftazidime	0.12	8	87.2 / 9.4	76.5 / 12.8	0.25	8	86.0 / 9.8	74.6 / 14.0
Cefepime	≤0.12	0.25	96.6 / 3.0	93.6 / 4.0	≤0.12	≤0.12	96.4 / 3.6	93.8 / 4.1
Ciprofloxacin	≤0.03	>4	76.8 / 17.1	68.8 / 23.2	≤0.03	>4	78.2 / 16.1	72.0 / 21.8
Meropenem	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	≤0.5	2	98.0 / 0.7	96.6 / 2.0	≤0.5	2	98.4 / 1.0	96.9 / 1.6
S. marcescens			(325)				(215)	
Ceftazidime avibactam	0.25	0.5	99.1 / 0.3[b]	97.9 / 0.3[b]	0.25	0.5	- / -	- / -
Ceftazidime	0.12	2	93.5 / 4.9	88.0 / 6.5	0.12	2	94.0 / 4.7	89.8 / 6.0
Cefepime	≤0.12	2	92.0 / 7.1	88.6 / 8.3	≤0.12	1	94.4 / 5.1	90.7 / 5.6
Ciprofloxacin	0.06	2	88.0 / 5.5	83.7 / 12.0	0.06	2	87.4 / 6.0	83.3 / 12.6
Meropenem	≤0.12	≤0.12	99.7 / 0.3	99.7 / 0.0	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	16	92.3 / 3.1	89.5 / 7.7	2	16	92.1 / 1.9	89.3 / 7.9

Antimicrobial agent (N)	LA MIC_{50}	LA MIC_{90}	LA CLSI[a] %S / %R	LA EUCAST[a] %S / %R	APAC MIC_{50}	APAC MIC_{90}	APAC CLSI[a] %S / %R	APAC EUCAST[a] %S / %R
E. coli			(207)				(142)	
Ceftazidime avibactam	0.06	0.25	- / -	- / -	0.06	0.25	- / -	- / -
Ceftazidime	0.25	32	77.8 / 18.8	75.4 / 22.2	0.25	16	81.7 / 12.0	75.4 / 18.3
Cefepime	≤0.12	>16	83.1 / 12.6	76.3 / 21.3	≤0.12	>16	81.0 / 16.9	68.3 / 23.2
Ciprofloxacin	0.12	>4	56.0 / 44.0	55.6 / 44.0	0.25	>4	56.3 / 43.0	54.2 / 43.7
Meropenem	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	32	88.4 / 2.9	81.6 / 11.6	2	4	95.1 / 4.2	92.3 / 4.9
ESBL phenotype			(55)				(48)	
Ceftazidime avibactam	0.12	0.5	- / -	- / -	0.12	0.25	- / -	- / -
Ceftazidime	16	>32	16.4 / 70.9	7.3 / 83.6	8	>32	45.8 / 35.4	27.1 / 54.2
Cefepime	16	>16	36.4 / 47.3	10.9 / 80.0	16	>16	43.8 / 50.0	6.3 / 68.8
Ciprofloxacin	>4	>4	10.9 / 89.1	10.9 / 89.1	>4	>4	20.8 / 77.1	18.8 / 79.2
Meropenem	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	16	64	67.3 / 9.1	47.3 / 32.7	2	16	93.8 / 6.3	85.4 / 6.3
Klebsiella spp.			(135)				(214)	
Ceftazidime avibactam	0.12	0.5	- / -	- / -	0.12	0.5	- / -	- / -
Ceftazidime	0.25	>32	72.6 / 24.4	66.7 / 27.4	0.25	>32	69.6 / 24.8	64.5 / 30.4
Cefepime	≤0.12	>16	80.0 / 16.3	69.6 / 24.4	≤0.12	>16	75.7 / 18.7	67.8 / 29.0
Ciprofloxacin	≤0.03	>4	72.6 / 23.7	68.9 / 27.4	≤0.03	>4	74.8 / 23.4	71.0 / 25.2
Meropenem	≤0.12	0.25	93.3 / 5.9	94.1 / 3.7	≤0.12	≤0.12	95.8 / 3.7	96.3 / 2.8
Piperacillin/tazobactam	2	>64	74.1 / 19.3	70.4 / 25.9	4	64	80.8 / 9.3	71.5 / 19.2
ESBL phenotype			(50)				(84)	
Ceftazidime avibactam	0.25	1	- / -	- / -	0.25	1	- / -	- / -
Ceftazidime	32	>32	26.0 / 66.0	10.0 / 74.0	32	>32	22.6 / 63.1	9.5 / 77.4
Cefepime	16	>16	46.0 / 44.0	18.0 / 66.0	16	>16	38.1 / 47.6	19.0 / 73.8
Ciprofloxacin	4	>4	40.0 / 52.0	30.0 / 60.0	>4	>4	39.3 / 56.0	29.8 / 60.7
Meropenem	≤0.12	4	82.0 / 16.0	84.0 / 10.0	≤0.12	2	89.3 / 9.5	90.5 / 7.1
Piperacillin/tazobactam	64	>64	32.0 / 50.0	22.0 / 68.0	16	>64	53.6 / 23.8	34.5 / 46.4
Meropenem-non-susceptible			(9)				(9)	
Ceftazidime avibactam	0.5	-	- / -	- / -	2	-	- / -	- / -
Ceftazidime	>32	-	0.0 / 88.9	0.0 / 100.0	>32	-	0.0 / 88.9	0.0 / 100.0
Cefepime	>16	-	11.1 / 77.8	0.0 / 100.0	>16	-	11.1 / 88.9	0.0 / 100.0
Ciprofloxacin	>4	-	11.1 / 77.8	11.1 / 88.9	>4	-	11.1 / 88.9	11.1 / 88.9
Meropenem	>8	-	0.0 / 88.9	11.1 / 55.6	>8	-	0.0 / 88.9	11.1 / 66.7
Piperacillin/tazobactam	>64	-	0.0 / 88.9	0.0 / 100.0	>64	-	11.1 / 77.8	11.1 / 88.9
Enterobacter spp.			(46)				(68)	
Ceftazidime avibactam	0.25	0.5	- / -	- / -	0.25	1	- / -	- / -
Ceftazidime	0.25	>32	78.3 / 21.7	73.9 / 21.7	0.5	>32	61.8 / 33.8	60.3 / 38.2
Cefepime	≤0.12	>16	89.1 / 10.9	78.3 / 17.4	≤0.12	>16	82.4 / 13.2	70.6 / 19.1
Ciprofloxacin	≤0.03	>4	84.8 / 15.2	80.4 / 15.2	≤0.03	>4	80.9 / 16.2	80.9 / 19.1
Meropenem	≤0.12	≤0.12	93.5 / 6.5	93.5 / 2.2	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	64	80.4 / 8.7	80.4 / 19.6	4	>64	67.6 / 16.2	61.8 / 32.4
Ceftazidime-non-susceptible			(10)				(26)	
Ceftazidime avibactam	0.5	2	- / -	- / -	0.5	2	- / -	- / -
Ceftazidime	>32	>32	0.0 / 100.0	0.0 / 100.0	>32	>32	0.0 / 88.5	0.0 / 100.0
Cefepime	2	>16	70.0 / 30.0	30.0 / 50.0	4	>16	57.7 / 34.6	26.9 / 46.2
Ciprofloxacin	1	>4	60.0 / 40.0	40.0 / 40.0	0.25	>4	61.5 / 30.8	61.5 / 38.5
Meropenem	≤0.12	8	70.0 / 30.0	70.0 / 10.0	≤0.12	0.25	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	64	>64	30.0 / 30.0	30.0 / 70.0	64	>64	23.1 / 34.6	15.4 / 76.9
Citrobacter spp.			(37)				(77)	
Ceftazidime avibactam	0.12	0.25	- / -	- / -	0.25	0.5	- / -	- / -
Ceftazidime	0.25	32	70.3 / 29.7	64.9 / 29.7	0.5	>32	70.1 / 28.6	64.9 / 29.9
Cefepime	≤0.12	4	97.3 / 2.7	86.5 / 8.1	≤0.12	8	93.5 / 2.6	83.1 / 10.4
Ciprofloxacin	≤0.03	2	89.2 / 5.4	86.5 / 10.8	0.12	>4	71.4 / 22.1	70.1 / 28.6
Meropenem	≤0.12	≤0.12	94.6 / 5.4	94.6 / 0.0	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	64	75.7 / 8.1	70.3 / 24.3	4	>64	77.9 / 11.7	72.7 / 22.1
Ceftazidime-non-susceptible			(11)				(23)	
Ceftazidime avibactam	0.25	0.5	- / -	- / -	0.5	2	- / -	- / -
Ceftazidime	32	>32	0.0 / 100.0	0.0 / 100.0	32	>32	0.0 / 95.7	0.0 / 100.0
Cefepime	1	8	90.9 / 9.1	54.5 / 27.3	1	16	78.3 / 8.7	56.5 / 26.1
Ciprofloxacin	≤0.03	2	81.8 / 9.1	72.7 / 18.2	0.5	>4	56.5 / 30.4	52.2 / 43.5
Meropenem	≤0.12	4	81.8 / 18.2	81.8 / 0.0	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	32	>64	18.2 / 27.3	9.1 / 81.8	64	>64	43.5 / 34.8	34.8 / 56.5
M. morganii			(35)				(70)	
Ceftazidime avibactam	0.06	0.25	- / -	- / -	0.06	0.12	- / -	- / -
Ceftazidime	0.12	16	82.9 / 11.4	71.4 / 17.1	0.12	2	92.9 / 7.1	84.3 / 7.1
Cefepime	≤0.12	2	97.1 / 2.9	88.6 / 5.7	≤0.12	≤0.12	97.1 / 1.4	95.7 / 2.9
Ciprofloxacin	0.5	>4	65.7 / 31.4	51.4 / 34.3	≤0.03	4	78.6 / 12.9	68.6 / 21.4
Meropenem	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	≤0.5	4	94.3 / 0.0	94.3 / 5.7	≤0.5	1	98.6 / 0.0	97.1 / 1.4
S. marcescens			(49)				(61)	
Ceftazidime avibactam	0.25	0.5	- / -	- / -	0.25	0.5	- / -	- / -
Ceftazidime	0.25	4	91.8 / 4.1	79.6 / 8.2	0.12	2	93.4 / 6.6	88.5 / 6.6
Cefepime	≤0.12	>16	81.6 / 14.3	79.6 / 18.4	≤0.12	2	91.8 / 8.2	88.5 / 9.8
Ciprofloxacin	0.12	2	87.8 / 6.1	85.7 / 12.2	0.06	1	90.2 / 3.3	83.6 / 9.8
Meropenem	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0	≤0.12	≤0.12	98.4 / 1.6	98.4 / 0.0
Piperacillin/tazobactam	2	>64	85.7 / 12.2	83.7 / 14.3	2	8	98.4 / 0.0	95.1 / 1.6

[a]Criteria as published by the CLSI (2011) and EUCAST (2011). [b]As there are currently no established susceptibility criteria for ceftazidime avibactam, interpretation was based on either the CLSI or EUCAST susceptible breakpoint criteria for ceftazidime alone (CLSI, S at ≤4 µg/mL and EUCAST, S at ≤1 µg/mL).

Results

- All 934 *E. coli* were inhibited at ≤1 µg/mL by ceftazidime avibactam (100.0% susceptible) using either the CLSI or EUCAST susceptible breakpoint criteria for ceftazidime (Table 1).
- For *E. coli* with the ESBL phenotype, ceftazidime avibactam and meropenem were the most potent compounds and provided the best coverage (100.0%) using either the CLSI or EUCAST susceptible breakpoint (Tables 1 and 2).
- Nearly all *Klebsiella* spp. (99.2%) were categorized as susceptible to ceftazidime avibactam using the CLSI susceptible breakpoint for ceftazidime and 97.8% when applying the EUCAST susceptible breakpoint for ceftazidime. Ceftazidime avibactam showed the highest susceptibility rate followed by meropenem at 96.0% and 96.3% (CLSI and EUCAST susceptibility criteria, respectively, see Tables 1 and 2).
- A total of 90.0% and 75.0% of the meropenem-non-susceptible isolates were susceptible to ceftazidime avibactam using the CLSI and the EUCAST susceptible breakpoints for ceftazidime, respectively (Table 1).
- The presence of carbapenemases was evaluated by polymerase chain reaction (PCR) analysis on eight isolates with both meropenem and ceftazidime avibactam MIC values ≥4 µg/mL, six *Klebsiella* spp., one *Serratia marcescens*, and one *Enterobacter aerogenes*. Two isolates contained a VIM-like metallo-β-lactamase (one isolate from Romania and one from Mexico). One isolate from Italy contained the serine carbapenemase KPC-3. Five isolates, which included the *S. marcescens* and *E. aerogenes*, were negative for KPC, IMP, VIM, NDM, SIM, DIM, GIM, AIM, SPM, and KHM-like β-lactamases.
- For *Enterobacter* spp., 99.7% of the isolates were susceptible to ceftazidime avibactam at ≤4 µg/mL and 95.6% at ≤1 µg/mL. The agent with the next highest susceptibility was meropenem at 98.1% and 98.3%, respectively (Tables 1 and 2).
- Ceftazidime avibactam inhibited all (100.0%) *Citrobacter* spp., 99.3% of *M. morganii*, and 99.1% of *S. marcescens* strains at ≤4 µg/mL (Table 1).

Conclusions

- The ESBL-phenotype isolates among *E. coli* and *Klebsiella* spp. and ceftazidime-non-susceptible *Enterobacter* spp. were prevalent across all regions and most prevalent in the APAC region.
- Ceftazidime avibactam was very active against these resistant Enterobacteriaceae, including ESBL, KPC, and AmpC producers with 99.2% of all isolates having a ceftazidime avibactam MIC of ≤2 µg/mL.
- Ceftazidime avibactam provided the highest overall susceptibility when tested against this contemporary collection of Gram-negative pathogens from EU, LA, and APAC medical centers.
- The use of avibactam, a broad-spectrum non-β-lactam β-lactamase inhibitor, in combination with the well-known β-lactam, ceftazidime, may offer a useful therapeutic alternative for treatment of multidrug-resistant Gram-negative bacteria worldwide.

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Antimicrobial Activity of Ceftazidime Avibactam (formerly NXL104) Tested Against Gram-Negative Organisms Causing Infections in Medical Centers from Europe, Latin America and the Asia-Pacific Region

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