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Ceftazidime-avibactam Activity Tested Against Contemporary (2012) Gram-negative Organisms Causing Bloodstream Infections in United States (USA) Medical Centers

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Abstract

Background: 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). The activity of the novel BL inhibitor combination ceftazidime-avibactam (CAZ-AVI) and comparator agents were evaluated against gram-negative bacilli (GNB) isolated from patients with bloodstream infections (BSI).

Methods: 1,462 GNB, including 1,269 Enterobacteriaceae (ENT), were collected from 73 USA hospitals and tested for susceptibility (S) by reference broth microdilution methods in a central monitoring laboratory (JMI Laboratories). ENT strains with an ESBL-phenotype were tested by Check MDR-CT 101 for genes encoding ESBLs, KPC and selected plasmidic AmpC enzymes. CAZ-AVI was tested with AVI at fixed 4 μg/mL.

Results: 99.8% of ENT strains were inhibited at a CAZ-AVI MIC of ≤4 μg/mL (CLSI S breakpoint for CAZ). Only 2 ENT strains had CAZ-AVI MIC at >4 μg/mL: a *Providencia* spp. (8 μg/mL) and an *E. aerogenes* (16 μg/mL). 99.0% (1,256/1,269) of ENT strains were meropenem (MER)-S. CAZ-AVI was very active against ESBL-phenotype *E. coli* (12.7%) and *K. pneumoniae* (KPN; 15.1%), MER-non-S (MIC, ≥2 μg/mL) KPN and CAZ-non-S *E. cloacae* (ECL; see Table 1). All ECL strains were inhibited at CAZ-AVI MIC of ≤1 μg/mL. Among ESBL-phenotype KPN, the highest CAZ-AVI MIC was only 2 μg/mL, whereas 24.4% of strains were MER-resistant (R). Among *P. aeruginosa*, 96.5% of strains were inhibited at a CAZ-AVI MIC of ≤8 μg/mL (CLSI S breakpoint for CAZ), and S rates for MER, CAZ and piperacillin/tazobactam were 79.4, 83.0 and 73.6%, respectively. The most active compounds tested against MER-non-S PSA were colistin ($MIC_{50/90}$, 1/2 μg/mL; 100.0% S), amikacin ($MIC_{50/90}$, 4/16 μg/mL; 96.6% S) and CAZ-AVI ($MIC_{50/90}$, 4/>32 μg/mL; 86.2% inhibited at ≤8 μg/mL). CAZ-AVI was also active against *P. mirabilis* (MIC_{90}, 0.06 μg/mL), *K. oxytoca* (MIC_{90}, 0.25 μg/mL), *S. marcescens* (MIC_{90}, 0.5 μg/mL), *E. aerogenes* (MIC_{90}, 0.25 μg/mL), *Citrobacter* spp. (MIC_{90}, 0.5 μg/mL) and *H. influenzae* (MIC_{90}, 0.03 μg/mL).

Conclusions: CAZ-AVI demonstrated potent activity against GNB isolated from patients with BSI in USA hospitals (2012), including organisms R to most currently available agents, such as KPC-producing ENT and MER-non-S PSA.

Introduction

Infections caused by gram-negative bacteria are of great concern. These organisms are very efficient at up-regulating or acquiring antimicrobial resistance genes. Furthermore, they have available to them a wide array of resistance mechanisms, often using multiple mechanisms against the same agent or using a single mechanism to affect multiple antimicrobials. β-lactamase-mediated resistance, in particular, represents a significant clinical threat because of the mobile nature of the genes encoding these enzymes. Inhibition of β-lactamases, thereby allowing the β-lactam to retain target concentrations at the sites of inhibition of penicillin-binding proteins (PBPs), is an important strategy to restore the utility of β-lactam compounds.

Avibactam is a non-β-lactam β-lactamase inhibitor that very effectively inactivates class A, C and some D β-lactamases, with low IC_{50} (concentration resulting in 50% inhibition) values and low turnover numbers. Therefore, avibactam protects β-lactams from hydrolysis by a variety of enzymes. We evaluated the activity of ceftazidime combined with avibactam against a large collection of contemporary gram-negative clinical isolates recovered from patients with bloodstream infections (BSI).

Methods

Bacterial isolates: A total of 1,462 gram-negative organisms, including 1,269 Enterobacteriaceae, 141 *Pseudomonas aeruginosa*, 27 *Acinetobacter* spp. and 25 *Haemophilus influenzae* were consecutively collected from 73 USA hospitals in 2012. Only clinically significant isolates were included in the study (1 per patient episode). Species identification was confirmed when necessary by Matrix-Assisted Laser Desorption Ionization-Time Of Flight Mass Spectrometry (MALDI-TOF MS) using the Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, USA) by following manufacturer instructions.

Antimicrobial susceptibility testing: All isolates were susceptibility tested using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI). Ceftazidime-avibactam was tested with avibactam at a fixed concentration of 4 μg/mL. Categorical interpretations for all antimicrobials were those found in M100-S23 (2013) and quality control (QC) was performed using *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853. All QC results were within ranges as published in CLSI (M100-S23, 2013) documents.

Screening for β-lactamases: Isolates displaying the CLSI criteria for ESBL phenotype (MIC >1 μg/mL for aztreonam and/or ceftazidime and/or ceftriaxone; M100-S23), as well as any Enterobacteriaceae with ceftazidime-avibactam MIC >4 μg/mL, were tested for β-lactamase-encoding genes using the microarray based assay Check-MDR CT101 kit (Check-Points, Wageningen, Netherlands). The assay was performed according to the manufacturer's instructions. This kit has the capabilities to detect genes encoding CTX-M Groups 1 (referred as CTX-M-15-like), 2, 8+25 and 9 (referred as CTX-M-14-like), TEM wild-type (WT) and ESBL, SHV WT and ESBL, ACC, ACT/MIR, CMYII (which has the ability to detect the majority of the non-intrinsic genes encoding CMY-2-like variants), DHA, FOX, KPC and NDM-1.

Results

- Overall, 99.8% of Enterobacteriaceae strains were inhibited at a ceftazidime-avibactam MIC of ≤4 μg/mL ($MIC_{50/90}$, 0.12/0.25 μg/mL), which is the susceptibility breakpoint established by the CLSI for ceftazidime tested alone (Table 1 and Figure 1). Only 2 Enterobacteriaceae strains had ceftazidime-avibactam MIC values at >4 μg/mL: a *Providencia* spp. (8 μg/mL) and an *Enterobacter aerogenes* (16 μg/mL; Table 1), and none of the tested β-lactamase-encoding genes was detected in these strains
- The most active agents tested against Enterobacteriaceae were ceftazidime-avibactam ($MIC_{50/90}$, 0.12/0.25 μg/mL, 99.8% inhibited at ≤4 μg/mL), meropenem ($MIC_{50/90}$, ≤0.06/≤0.06 μg/mL, 99.0% susceptible) and tigecycline ($MIC_{50/90}$, 0.25/1 μg/mL, 98.6% susceptible; Table 2)
- Ceftazidime-avibactam was very active against ESBL-phenotype *E. coli* (12.7%; $MIC_{50/90}$, 0.12/0.5 μg/mL, 100.0% inhibited at ≤2 μg/mL), *Klebsiella pneumoniae* (15.1%; $MIC_{50/90}$, 0.25/0.5 μg/mL, 100.0% inhibited at ≤2 μg/mL), meropenem-non-susceptible (MIC, ≥2 μg/mL) *K. pneumoniae* (3.7%; $MIC_{50/90}$, 0.5/2 μg/mL, 100.0% inhibited at ≤2 μg/mL), and ceftazidime-non-susceptible (MIC, ≥8 μg/mL) *E. cloacae* (26.6%; $MIC_{50/90}$, 0.25/0.5 μg/mL, 100.0% inhibited at ≤1 μg/mL; Table 1)
- Among 72 ESBL-phenotype *E. coli* strains tested for β-lactamase-encoding genes, 56 (77.8%) carried $bla_{CTX\text{-}M\text{-}15\text{-}like}$ and/or $bla_{CTX\text{-}M\text{-}14\text{-}like}$, 16 (22.2%) harbored bla_{CMY}, three (4.2%) strains carried both $bla_{CTX\text{-}M\text{-}15\text{-}like}$ and bla_{CMY}, two (2.8%) strains were positive for bla_{SHV} (ESBL) and one (1.4%) strain harbored a bla_{TEM} (ESBL; data not shown)
- Only 75.6% of ESBL-phenotype *K. pneumoniae* strains were susceptible to meropenem, 55.6% were susceptible to gentamicin and 33.3% were susceptible to levofloxacin. Tigecycline was active against 97.8% of strains at the CLSI susceptible breakpoint and the highest ceftazidime-avibactam MIC was only 2 μg/mL (Tables 1 and 2)
- The most frequent β-lactamase-encoding genes among ESBL-phenotype *K. pneumoniae* were $bla_{CTX\text{-}M\text{-}15\text{-}like}$ (25 strains, 55.6%), bla_{SHV} (ESBL; 22 strains, 48.9%) and bla_{KPC} (11 strains, 24.4%). Furthermore, eight (17.8%) strains carried both $bla_{CTX\text{-}M\text{-}15}$ and bla_{SHV}, six (13.3%) strains harbored both bla_{SHV} and bla_{KPC}, two (4.4%) strains had both $bla_{CTX\text{-}M\text{-}15}$ and bla_{KPC} and one (2.2%) strain had $bla_{CTX\text{-}M\text{-}15}$, bla_{SHV} and bla_{KPC} (data not shown)
- Ceftazidime-avibactam was also active against *Proteus mirabilis* ($MIC_{50/90}$, 0.03/0.06 μg/mL; highest MIC, 0.12 μg/mL), *K. oxytoca* ($MIC_{50/90}$, 0.06/0.25 μg/mL; highest MIC, 1 μg/mL), *Serratia marcescens* ($MIC_{50/90}$, 0.12/0.5 μg/mL; highest MIC, 1 μg/mL), *E. aerogenes* ($MIC_{50/90}$, 0.12/0.25 μg/mL; 97.6% [40/41] inhibited at ≤0.5 μg/ml and one strain with ceftazidime-avibactam MIC of 16 μg/mL) and *Citrobacter* spp. ($MIC_{50/90}$, 0.12/0.5 μg/mL; highest MIC of 0.5 μg/ml; Tables 1 and 2)
- Against *P. aeruginosa*, the activity of ceftazidime-avibactam ($MIC_{50/90}$, 2/8 μg/mL; 96.5% inhibited at ≤8 μg/mL) was greater than that of ceftazidime alone ($MIC_{50/90}$, 2/>32 μg/mL; 83.0% susceptible at ≤8 μg/mL; Tables 1 and 2 and Figure 2). Susceptibility rates for meropenem and piperacillin/tazobactam were 79.4 and 73.6%, respectively
- The most active compounds tested against meropenem-non-susceptible *P. aeruginosa* (MIC, ≥4 μg/mL) were colistin ($MIC_{50/90}$, 1/2 μg/mL; 100.0% susceptible), amikacin ($MIC_{50/90}$, 4/16 μg/mL; 96.6% susceptible) and ceftazidime-avibactam ($MIC_{50/90}$, 4/>32 μg/mL; 86.2% inhibited at ≤8 μg/mL; Tables 1 and 2). Furthermore, ceftazidime-avibactam inhibited 79.2% of ceftazidime-non-susceptible *P. aeruginosa* at MICs of ≤8 μg/mL; Table 1)
- Ceftazidime-avibactam exhibited modest activity against *Acinetobacter baumannii* with $MIC_{50/90}$ of 16/>32 μg/mL and 33.3% of strains inhibited at ≤8 μg/mL (Table 1)
- Ceftazidime-avibactam was very active against *H. influenzae* ($MIC_{50/90}$, ≤0.015/0.03 μg/mL) with the highest MIC value at 0.25 μg/mL; Table 1).

Figure 1. MIC distributions for ceftazidime-avibactam and ceftazidime when testing 1,269 Enterobacteriaceae isolates from bloodstream infections

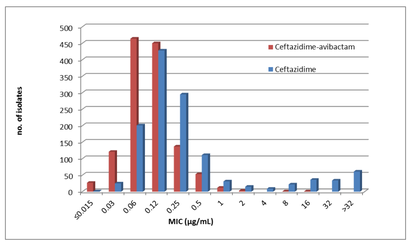

Figure 2. MIC distributions for ceftazidime-avibactam and ceftazidime when testing 141 *P. aeruginosa* isolates from bloodstream infections

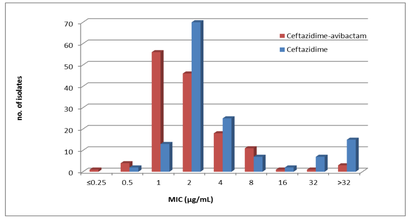

Table 1. Summary of ceftazidime-avibactam activity tested against the organisms causing bloodstream infections in USA medical centers (2012)

Organism/subset (no. tested)	No. of isolates (cumulative %) inhibited at MIC (μg/mL): ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}
Enterobacteriaceae (1,269)	27 (2.1)	121 (11.7)	464 (48.2)	450 (83.7)	137 (94.5)	53 (98.7)	12 (99.6)	3 (99.8)	0 (99.8)	1 (99.9)	1 (100.0)	--	--	0.12	0.25
E. coli (568)	24 (4.2)	50 (13.0)	249 (56.9)	207 (93.3)	26 (97.9)	6 (98.9)	5 (99.8)	1 (100.0)	--	--	--	--	--	0.06	0.12
ESBL-phenotype (72)	--	2 (2.8)	15 (23.6)	34 (70.8)	10 (84.7)	5 (91.7)	5 (98.6)	1 (100.0)	--	--	--	--	--	0.12	0.5
Klebsiella spp. (353)	1 (0.3)	13 (4.0)	148 (45.9)	121 (80.2)	46 (93.2)	19 (98.6)	3 (99.4)	2 (100.0)	--	--	--	--	--	0.12	0.25
K. pneumoniae (298)	1 (0.3)	8 (3.0)	122 (44.0)	106 (79.5)	38 (92.3)	19 (98.7)	2 (99.3)	2 (100.0)	--	--	--	--	--	0.12	0.25
ESBL-phenotype (45)	--	--	3 (6.7)	11 (31.1)	14 (62.2)	13 (91.1)	2 (95.6)	2 (100.0)	--	--	--	--	--	0.25	0.5
meropenem-non-susc (MIC, ≥2 μg/mL; 11)	--	--	--	--	4 (36.4)	4 (72.7)	1 (81.8)	2 (100.0)	--	--	--	--	--	0.5	2
K. oxytoca (55)	--	5 (9.1)	26 (56.4)	15 (83.6)	8 (98.2)	0 (98.2)	1 (100.0)	--	--	--	--	--	--	0.06	0.25
P. mirabilis (70)	2 (2.9)	36 (54.3)	27 (92.9)	5 (100.0)	--	--	--	--	--	--	--	--	--	0.03	0.06
E. cloacae (109)	--	--	6 (5.5)	54 (55.0)	33 (85.3)	13 (97.2)	3 (100.0)	--	--	--	--	--	--	0.12	0.5
ceftazidime-non-susc (MIC, ≥8 μg/mL; 29)	--	--	1 (3.4)	5 (20.7)	10 (55.2)	11 (93.1)	2 (100.0)	--	--	--	--	--	--	0.25	0.5
E. aerogenes (41)	--	1 (2.4)	7 (19.5)	20 (68.3)	9 (90.2)	3 (97.6)	0 (97.6)	0 (97.6)	0 (97.6)	0 (97.6)	1 (100.0)	--	--	0.12	0.25
M. morganii (23)	--	13 (56.5)	6 (82.6)	3 (95.7)	0 (95.7)	1 (100.0)	--	--	--	--	--	--	--	0.03	0.12
Citrobacter koseri (11)	--	--	5 (45.5)	4 (81.8)	2 (100.0)	--	--	--	--	--	--	--	--	0.12	0.25
C. freundii (14)	--	--	--	6 (42.9)	4 (71.4)	4 (100.0)	--	--	--	--	--	--	--	0.25	0.5
S. marcescens (55)	--	--	6 (10.9)	28 (61.8)	13 (85.5)	7 (98.2)	1 (100.0)	--	--	--	--	--	--	0.12	0.5
P. vulgaris (5)	--	2 (40.0)	3 (100.0)	--	--	--	--	--	--	--	--	--	--	0.06	--
Providencia spp. (20)	--	6 (30.0)	7 (65.0)	2 (75.0)	4 (95.0)	0 (95.0)	0 (95.0)	0 (95.0)	0 (95.0)	1 (100.0)	--	--	--	0.06	0.25
P. aeruginosa (141)	--	--	--	--	1 (0.7)	4 (3.5)	56 (43.3)	46 (75.9)	18 (88.7)	11 (96.5)	1 (97.2)	1 (97.9)	3 (100.0)	2	8
meropenem-non-susc (MIC, ≥4 μg/mL; 29)	--	--	--	--	--	--	1 (3.4)	4 (17.2)	13 (62.1)	7 (86.2)	1 (89.7)	0 (89.7)	3 (100.0)	4	>32
ceftazidime-non-susc (MIC, ≥16 μg/mL; 24)	--	--	--	--	--	--	2 (8.3)	4 (25.0)	4 (41.7)	9 (79.2)	1 (83.3)	1 (87.5)	3 (100.0)	8	>32
A. baumannii (27)	--	--	--	--	--	--	1 (3.7)	2 (11.1)	5 (29.6)	1 (33.3)	8 (63.0)	5 (81.5)	5 (100.0)	16	>32
H. influenzae (25)	17 (68.0)	6 (92.0)	1 (96.0)	0 (96.0)	1 (100.0)	--	--	--	--	--	--	--	--	≤0.015	0.03

Table 2. Activity of ceftazidime-avibactam and comparator antimicrobial agents tested against gram-negative organisms causing bloodstream infections in USA medical centers (2012)

Organism (no. tested) / Antimicrobial agent	MIC (μg/mL) 50%	MIC (μg/mL) 90%	%S / %I / %R CLSI[b]
Enterobacteriaceae[a] (1,269)			
Ceftazidime-avibactam	0.12	0.25	(99.8)[c]
Ceftazidime	0.12	16	87.9 / 1.8 / 10.3
Ceftriaxone	≤0.06	>8	85.2 / 0.7 / 14.1
Piperacillin/tazobactam	2	16	91.9 / 3.3 / 4.8
Meropenem	≤0.06	≤0.06	99.0 / 0.1 / 0.9
Levofloxacin	≤0.12	>4	80.3 / 1.2 / 18.5
Gentamicin	≤1	8	89.7 / 0.8 / 9.5
Tigecycline[d]	0.25	1	98.6 / 1.4 / 0.0
Escherichia coli (568)			
Ceftazidime-avibactam	0.06	0.12	(100.0)[c]
Ceftazidime	0.12	4	90.3 / 1.4 / 8.3
Ceftriaxone	≤0.06	>8	87.9 / 0.0 / 12.1
Piperacillin/tazobactam	2	8	94.5 / 1.8 / 3.7
Meropenem	≤0.06	≤0.06	99.8 / 0.2 / 0.0
Levofloxacin	≤0.12	>4	70.0 / 0.4 / 29.6
Gentamicin	≤1	>8	85.4 / 0.1 / 14.5
Tigecycline[d]	0.12	0.12	100.0 / 0.0 / 0.0
ESBL-phenotype (72)			
Ceftazidime-avibactam	0.12	0.5	(100.0)[c]
Ceftazidime	16	>32	23.6 / 11.1 / 65.3
Ceftriaxone	>8	>8	4.2 / 0.0 / 95.8
Piperacillin/tazobactam	8	>64	75.0 / 8.3 / 16.7
Meropenem	≤0.06	≤0.06	98.6 / 1.4 / 0.0
Levofloxacin	>4	>4	23.6 / 1.4 / 75.0
Gentamicin	2	>8	57.7 / 1.5 / 40.8
Tigecycline[d]	0.12	0.25	100.0 / 0.0 / 0.0
Klebsiella pneumoniae (298)			
Ceftazidime-avibactam	0.12	0.25	(100.0)[c]
Ceftazidime	0.12	16	86.2 / 1.7 / 12.1
Ceftriaxone	≤0.06	>8	85.9 / 0.0 / 14.1
Piperacillin/tazobactam	4	16	90.3 / 2.7 / 7.0
Meropenem	≤0.06	≤0.06	96.3 / 0.0 / 3.7
Levofloxacin	≤0.12	>4	87.9 / 1.0 / 11.1
Gentamicin	≤1	≤1	93.0 / 1.0 / 6.0
Tigecycline[d]	0.25	1	99.3 / 0.7 / 0.0
ESBL-phenotype (45)			
Ceftazidime-avibactam	0.25	0.5	(100.0)[c]
Ceftazidime	32	>32	8.9 / 11.1 / 80.0
Ceftriaxone	>8	>8	6.7 / 0.0 / 93.3
Piperacillin/tazobactam	64	>64	37.8 / 15.5 / 46.7
Meropenem	≤0.06	>8	75.6 / 0.0 / 24.4
Levofloxacin	>4	>4	33.3 / 2.3 / 64.4
Gentamicin	4	>8	55.6 / 6.6 / 37.8
Tigecycline[d]	0.5	2	97.8 / 2.2 / 0.0
meropenem-non-susceptible (MIC, ≥2 μg/mL; 11)			
Ceftazidime-avibactam	0.5	2	(100.0)[c]
Ceftazidime	>32	>32	0.0 / 0.0 / 100.0
Ceftriaxone	>8	>8	0.0 / 0.0 / 100.0
Piperacillin/tazobactam	>64	>64	0.0 / 0.0 / 100.0
Meropenem	>8	>8	0.0 / 0.0 / 100.0
Levofloxacin	>4	>4	18.2 / 0.0 / 81.8
Gentamicin	4	>8	54.5 / 9.1 / 36.4
Tigecycline[d]	0.5	2	100.0 / 0.0 / 0.0
Klebsiella oxytoca (55)			
Ceftazidime-avibactam	0.06	0.25	(100.0)[c]
Ceftazidime	0.12	0.5	98.2 / 0.0 / 1.8
Ceftriaxone	≤0.06	0.25	92.7 / 0.0 / 7.3
Piperacillin/tazobactam	2	8	94.5 / 0.0 / 5.5
Meropenem	≤0.06	≤0.06	98.2 / 0.0 / 1.8
Levofloxacin	≤0.12	0.25	98.2 / 1.8 / 0.0
Gentamicin	≤1	2	96.4 / 1.8 / 1.8
Tigecycline[d]	0.12	0.5	100.0 / 0.0 / 0.0
Enterobacter cloacae (109)			
Ceftazidime-avibactam	0.12	0.5	(100.0)[c]
Ceftazidime	0.5	>32	73.4 / 3.7 / 22.9
Ceftriaxone	0.5	>8	67.9 / 2.7 / 29.4
Piperacillin/tazobactam	4	64	81.7 / 10.0 / 8.3
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	0.5	99.1 / 0.9 / 0.0
Gentamicin	≤1	≤1	96.3 / 0.0 / 3.7
Tigecycline[d]	0.25	1	97.2 / 2.8 / 0.0
ceftazidime-non-susceptible (MIC, ≥8 μg/mL; 29)			
Ceftazidime-avibactam	0.25	0.5	(100.0)[c]
Ceftazidime	>8	>8	0.0 / 0.0 / 100.0
Piperacillin/tazobactam	64	>64	31.0 / 38.0 / 31.0
Meropenem	≤0.06	0.12	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	0.5	100.0 / 0.0 / 0.0
Gentamicin	≤1	4	93.1 / 0.0 / 6.9
Tigecycline[d]	0.25	1	96.6 / 3.4 / 0.0
Enterobacter aerogenes (41)			
Ceftazidime-avibactam	0.12	0.25	(97.6)[c]
Ceftazidime	0.25	32	61.0 / 7.3 / 31.7
Ceftriaxone	0.25	>8	56.1 / 4.9 / 39.0
Piperacillin/tazobactam	4	64	70.7 / 19.5 / 9.8
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	1	92.7 / 2.3 / 4.9
Gentamicin	≤1	≤1	100.0 / 0.0 / 0.0
Tigecycline[d]	0.25	1	97.6 / 2.4 / 0.0
Proteus mirabilis (70)			
Ceftazidime-avibactam	0.03	0.06	(100.0)[c]
Ceftazidime	0.06	0.12	98.6 / 1.4 / 0.0
Ceftriaxone	≤0.06	≤0.06	94.3 / 1.4 / 4.3
Piperacillin/tazobactam	≤0.5	1	100.0 / 0.0 / 0.0
Meropenem	≤0.06	0.12	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	>4	65.7 / 7.2 / 27.1
Gentamicin	≤1	>8	84.3 / 2.8 / 12.9
Tigecycline[d]	2	4	87.1 / 12.9 / 0.0
Serratia marcescens (55)			
Ceftazidime-avibactam	0.12	0.5	(100.0)[c]
Ceftazidime	0.25	0.5	100.0 / 0.0 / 0.0
Ceftriaxone	0.25	1	90.9 / 0.0 / 9.1
Piperacillin/tazobactam	2	4	98.2 / 1.8 / 0.0
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	0.25	100.0 / 0.0 / 0.0
Gentamicin	≤1	2	94.5 / 0.0 / 5.5
Tigecycline[d]	0.5	1	100.0 / 0.0 / 0.0
Pseudomonas aeruginosa (141)			
Ceftazidime-avibactam	2	8	(96.5)[e]
Ceftazidime	2	>32	83.0 / 1.4 / 15.6
Cefepime	2	>16	83.7 / 5.7 / 10.6
Piperacillin/tazobactam	8	>64	73.6 / 11.4 / 15.0
Meropenem	0.5	8	79.4 / 5.0 / 15.6
Levofloxacin	0.5	>4	79.4 / 2.9 / 17.7
Gentamicin	≤1	4	90.8 / 2.2 / 7.1
Amikacin	2	8	99.3 / 0.0 / 0.7
Colistin	1	2	99.3 / 0.7 / 0.0
meropenem-non-susceptible (MIC, ≥4 μg/mL; 29)			
Ceftazidime-avibactam	4	>32	(86.2)[e]
Ceftazidime	8	>32	51.7 / 3.5 / 44.8
Cefepime	16	>16	48.3 / 17.2 / 34.5
Piperacillin/tazobactam	64	>64	31.0 / 24.2 / 44.8
Levofloxacin	>4	>4	37.9 / 6.9 / 55.2
Gentamicin	2	>8	58.6 / 6.9 / 34.5
Amikacin	4	16	96.6 / 0.0 / 3.4
Colistin	1	2	100.0 / 0.0 / 0.0
Acinetobacter baumannii (27)			
Ceftazidime-avibactam	16	>32	(33.3)[e]
Ceftazidime	8	>32	63.0 / 0.0 / 37.0
Cefepime	8	>16	59.3 / 7.4 / 33.3
Piperacillin/tazobactam	16	>64	63.0 / 0.0 / 37.0
Meropenem	1	>8	63.0 / 3.7 / 33.3
Levofloxacin	0.25	>4	59.3 / 0.0 / 40.7
Gentamicin	2	>8	70.4 / 0.0 / 29.6
Amikacin	4	>32	77.8 / 0.0 / 22.2
Colistin	1	2	96.3 / 0.0 / 3.7

a. Includes: *Citrobacter freundii* (14 strains), *Citrobacter koseri* (11 strains), *Enterobacter aerogenes* (41 strains), *E. cloacae* (109 strains), *Escherichia coli* (568 strains), *Klebsiella oxytoca* (55 strains), *K. pneumoniae* (298 strains), *Morganella morganii* (23 strains), *Proteus mirabilis* (70 strains), *P. vulgaris* (five strains), *Providencia rettgeri* (12 strains), *P. stuartii* (eight strains), and *Serratia marcescens* (55 strains).
b. Criteria as published by the CLSI [2013].
c. Percentage inhibited at ceftazidime-avibactam MICs of ≤4 μg/mL, which is the breakpoint established by the CLSI [2013] for ceftazidime alone.
d. USA-FDA breakpoints were applied when available [Tygacil Product Insert, 2012].
e. Percentage inhibited at ceftazidime-avibactam MICs of ≤8 μg/mL, which is the breakpoint established by the CLSI [2013] for ceftazidime alone.

Conclusions

- Ceftazidime-avibactam demonstrated potent activity against gram-negative organisms isolated from patients with bloodstream infections in USA hospitals (2012)
- Ceftazidime-avibactam was highly active against KPC-producing *K. pneumoniae,* as well as ESBL-producing *E. coli* and *K. pneumoniae,* and ceftazidime-non-susceptible *Enterobacter* spp.
- Ceftazidime-avibactam was more active than ceftazidime when tested against *P. aeruginosa,* and displayed good activity against meropenem-non-susceptible strains
- The in vitro activity results presented here indicate that ceftazidime-avibactam may provide a valuable therapeutic option for serious infections caused by resistant gram-negative bacteria.

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