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Antimicrobial Activity of Ceftazidime-Avibactam Tested against Contemporary (2012) Gram-negative Organisms Collected from United States (USA) Medical Centers

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Abstract

Background: The activity of the novel β-lactamase (BL) inhibitor combination ceftazidime-avibactam (CAZ-AVI) and comparator agents were evaluated against a contemporary collection of clinically significant gram-negative bacilli (GNB). AVI is a non-β-lactam BL inhibitor that inhibits Ambler class A, C, and some D enzymes (eg, ESBL, KPC, and AmpC).

Methods: 10,928 GNB, including 8,640 Enterobacteriaceae (ENT), 1,967 *P. aeruginosa* (PSA) and 321 *Acinetobacter* spp. (ASP) 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 PCR for genes encoding ESBLs, KPC and selected plasmidic AmpC enzymes.

Results: 99.8% of ENT strains were inhibited at a CAZ-AVI MIC of ≤4 µg/mL (CLSI S breakpoint for CAZ). CAZ-AVI was very active against ESBL-phenotype *E. coli* (11.9% ESBL-phenotype) and *K. pneumoniae* (KPN; 16.0% ESBL-phenotype), meropenem (MER)-non-S (MIC, ≤2 µg/mL) KPN and CAZ-non-S *E. cloacae* (ECL; see Table 1). Among ESBL-phenotype KPN, 61.1% of strains were MER-S and 99.3% were inhibited at CAZ-AVI MIC of ≤4 µg/mL. Among PSA, 96.9% of strains were inhibited at a CAZ-AVI MIC of ≤8 µg/mL, and S rates for MER, CAZ and piperacillin/tazobactam were 82.0, 83.2 and 78.3%, respectively. The most active compounds tested against MER-non-S PSA were CAZ-AVI ($MIC_{50/90}$, 4/16 µg/mL; 87.3% inhibited at ≤8 µg/mL), amikacin (AMK; $MIC_{50/90}$, 4/16 µg/mL; 92.7% S) and colistin (COL; $MIC_{50/90}$, 1/2 µg/mL; 97.7% S). ASP (CAZ-AVI $MIC_{50/90}$, 16/>32 µg/mL) showed high rates of resistance (R) to most tested agents and only COL (96.6% S), AMK (67.9% S) and gentamicin (50.2%) were active against >50% of strains at their S breakpoints.

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

Introduction

Bacterial isolates resistant to clinically available β-lactams represent an important challenge to successful treatment of serious infections. β-lactamase-mediated resistance, in particular, represents a significant clinical threat because of the mobile nature of the genes encoding these enzymes. Two strategies have been used to restore the utility of β-lactam compounds: (i) the design/discovery of novel β-lactam molecules that are refractory to enzymatic inactivation, and (ii) the inhibition of β-lactamases, thereby allowing the β-lactam to retain target concentrations at the sites of inhibition of penicillin-binding proteins (PBPs).

Avibactam (formerly NXL-104) 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. Thus, avibactam protects β-lactams from hydrolysis by a variety of enzymes. In this study, we evaluated the activity of ceftazidime combined with avibactam against a large collection of contemporary gram-negative clinical isolates recovered in hospitals located in the United States (USA) during 2012.

Methods

Bacterial isolates: A total of 10,928 gram-negative organisms, including 8,640 Enterobacteriaceae, 1,967 *Pseudomonas aeruginosa* and 321 *Acinetobacter* spp. were consecutively collected from 73 USA hospitals. 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 (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 CLSI. 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 published ranges as published in CLSI (M100-S23, 2013) documents.

Results

- 99.8% of Enterobacteriaceae strains were inhibited at a ceftazidime-avibactam MIC of 4 µg/mL or less, which is the susceptibility breakpoint established by the CLSI for ceftazidime tested alone (Table 1)
- The highest ceftazidime-avibactam MIC among *E. coli* (2,767 strains) was only 2 µg/mL (one isolate). The ESBL screen (+) phenotype strains were very susceptible to ceftazidime-avibactam ($MIC_{50/90}$, 0.12/0.25 µg/mL). All non-ESBL strains were inhibited at a ceftazidime-avibactam MIC of ≤0.5 µg/mL (Tables 1 and 2)
- Ceftazidime-avibactam was very active against *Klebsiella pneumoniae* (1,847 strains tested; $MIC_{50/90}$, 0.12/0.5 µg/mL) and 442 *K. oxytoca* ($MIC_{50/90}$, 0.06/0.25 µg/mL), including ESBL-phenotype strains (MIC_{90}, 1 µg/mL for both organisms; Table 2). Among meropenem-non-susceptible (MIC, ≥2 µg/mL) *K. pneumoniae* (115 isolates tested), ceftazidime-avibactam inhibited 98.3% of isolates at ≤4 µg/mL (Table 1)
- An ESBL-phenotype was noted among 701 (12.2%) isolates and included 328 *E. coli* (11.9% of the overall samples for this species), 296 *K. pneumoniae* (16.0%), 44 *K. oxytoca* (10.0%) and 33 *Proteus mirabilis* (4.8%)
- CTX-M Group 1 (CTX-M-15-like) was the most common β-lactamase detected among ESBL-phenotype strains (303/701; 43.2%), followed by SHV ESBL (176/701; 25.1%), KPC (118/701; 16.8%), CTX-M-14-like (72/701; 10.3%) and CMY-2-like (64/701; 9.1%; see Poster #C2-1634)
- Only two *K. pneumoniae* strains had ceftazidime-avibactam MIC >4 µg/mL, both at >32 µg/mL. These strains were isolated in a unique medical center in Denver, Colorado and further evaluation showed that they produce NDM-1 and were clonally related [CDC, 2013]; (Table 1)
- Ceftazidime-avibactam exhibited potent activity against *P. mirabilis*, with a MIC_{90} of 0.06 µg/mL and the highest MIC at 0.5 µg/mL (Tables 1 and 2)
- Ceftazidime-avibactam was highly active against *Enterobacter cloacae* ($MIC_{50/90}$, 0.12/0.5 µg/mL), including ceftazidime-non-susceptible strains ($MIC_{50/90}$, 0.5/1 µg/mL). The highest ceftazidime-avibactam MIC value among *E. cloacae* was 4 µg/mL (Tables 1 and 2)
- Ceftazidime-avibactam ($MIC_{50/90}$, 0.12/0.25-0.5 µg/mL) was much more active than ceftazidime ($MIC_{50/90}$, 0.25/32->32 µg/mL) when tested against *E. aerogenes* and *E. cloacae* (Table 2)
- Ceftazidime-avibactam exhibited potent activity against *Morganella morganii* ($MIC_{50/90}$, 0.06/0.12 µg/mL), *Citrobacter koseri* ($MIC_{50/90}$, 0.06/0.12 µg/mL), *C. freundii* ($MIC_{50/90}$, 0.12/0.5 µg/mL), *Serratia marcescens* ($MIC_{50/90}$, 0.12/0.5 µg/mL), *Proteus vulgaris* ($MIC_{50/90}$, 0.06/0.06 µg/mL) and *Providencia* spp. ($MIC_{50/90}$, 0.12/0.5 µg/mL; Tables 1 and 2)
- Against *P. aeruginosa*, the activity of ceftazidime-avibactam ($MIC_{50/90}$, 2/4 µg/mL; 96.9% inhibited at ≤8 µg/mL) was greater than that of ceftazidime alone ($MIC_{50/90}$, 2/32 µg/mL; 83.2% susceptible at ≤8 µg/mL; Table 2)
- Ceftazidime-avibactam inhibited 87.3% of meropenem-non-susceptible (meropenem MIC, ≥4 µg/mL; 354 isolates tested) and 82.1% of ceftazidime-non-susceptible *P. aeruginosa* isolates (ceftazidime MIC, ≥16 µg/mL; 330 isolates tested) at ≤8 µg/mL (Table 1)
- Ceftazidime-avibactam exhibited modest activity against *Acinetobacter* spp. with $MIC_{50/90}$ of 16/>32 µg/mL and 31.2% of strains inhibited at ≤8 µg/mL (Tables 1 and 2).

Table 1. Summary of ceftazidime-avibactam activity tested against the organisms and resistant subsets included in this 2012 report (USA)

Organism/resistant subset	No. of Isolates	No. of isolates (cumulative %) inhibited at MIC (µg/mL) of: ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16
Enterobacteriaceae	8,640	185 (2.1)	1,043 (14.2)	2,748 (46.0)	3,052 (81.3)	1,043 (93.4)	373 (97.7)	139 (99.3)	30 (99.7)	9 (99.8)	12 (99.9)	4 (>99.9)	2 (100.0)
E. coli	2,767	131 (4.7)	210 (12.3)	1,171 (54.6)	1,050 (92.6)	167 (98.6)	28 (99.6)	9 (>99.9)	1 (100.0)	--	--	--	--
ESBL-phenotype	328	5 (1.5)	6 (3.4)	56 (20.4)	168 (71.6)	61 (90.2)	22 (97.0)	9 (99.7)	1 (100.0)	--	--	--	--
K. pneumoniae	1,847	22 (1.2)	67 (4.8)	625 (38.7)	725 (77.9)	217 (89.7)	121 (96.2)	49 (98.9)	16 (99.7)	3 (99.9)	0 (99.9)	0 (99.9)	2 (100.0)
ESBL-phenotype	296	5 (1.7)	0 (1.7)	14 (6.4)	58 (26.0)	60 (46.3)	89 (76.4)	49 (92.9)	16 (98.3)	3 (99.3)	0 (99.3)	0 (99.3)	2 (100.0)
meropenem-non-susc.[a]	115	--	--	2 (1.7)	10 (10.4)	14 (22.6)	43 (60.0)	29 (85.2)	12 (95.7)	3 (98.3)	0 (98.3)	0 (98.3)	2 (100.0)
K. oxytoca	442	--	29 (6.6)	205 (52.9)	148 (86.4)	41 (95.7)	10 (98.0)	9 (100.0)	--	--	--	--	--
ESBL-phenotype	44	--	--	2 (4.5)	18 (45.5)	10 (68.2)	7 (84.1)	7 (100.0)	--	--	--	--	--
P. mirabilis	683	12 (1.8)	437 (65.7)	206 (95.9)	23 (99.3)	4 (99.9)	1 (100.0)	--	--	--	--	--	--
ESBL-phenotype	33	--	11 (33.3)	16 (81.8)	5 (97.0)	1 (100.0)	--	--	--	--	--	--	--
E. cloacae	951	7 (0.7)	11 (1.9)	47 (6.8)	453 (54.5)	274 (83.3)	109 (94.7)	41 (99.1)	6 (99.7)	3 (100.0)	--	--	--
ceftazidime-non-susc.[b]	200	3 (1.5)	1 (2.0)	3 (3.5)	18 (12.5)	49 (37.0)	82 (78.0)	35 (95.5)	6 (98.5)	3 (100.0)	--	--	--
E. aerogenes	357	2 (0.6)	11 (3.6)	98 (31.1)	155 (74.5)	64 (92.4)	24 (99.2)	2 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	1 (100.0)	--
ceftazidime-non-susc.[b]	82	2 (2.4)	1 (3.7)	2 (6.1)	23 (34.1)	37 (79.3)	14 (96.3)	2 (98.8)	0 (98.8)	0 (98.8)	0 (98.8)	1 (100.0)	--
M. morganii	295	3 (1.0)	141 (48.8)	94 (80.7)	33 (91.9)	16 (97.3)	5 (99.0)	2 (99.7)	0 (99.7)	0 (99.7)	1 (100.0)	--	--
C. koseri	186	2 (1.1)	9 (5.9)	101 (60.2)	57 (90.9)	12 (97.3)	1 (97.8)	4 (100.0)	--	--	--	--	--
C. freundii	185	--	2 (1.1)	29 (16.8)	84 (62.2)	46 (87.0)	13 (94.1)	8 (98.4)	2 (99.5)	0 (99.5)	0 (99.5)	1 (100.0)	--
S. marcescens	506	--	2 (0.4)	48 (9.9)	250 (59.3)	142 (87.4)	49 (97.0)	10 (99.0)	2 (99.4)	1 (99.6)	1 (99.8)	1 (100.0)	--
P. vulgaris	153	--	70 (45.8)	74 (94.1)	8 (99.3)	0 (99.3)	1 (100.0)	--	--	--	--	--	--
Providencia spp.	268	6 (2.2)	54 (22.4)	50 (41.0)	66 (65.7)	60 (88.1)	11 (92.2)	5 (94.0)	3 (95.1)	2 (95.9)	10 (99.6)	1 (100.0)	--
P. aeruginosa	1,967	--	--	3 (0.2)	2 (0.3)	18 (1.2)	105 (6.5)	779 (46.1)	608 (77.0)	273 (90.9)	119 (96.9)	38 (98.9)	22 (100.0)
meropenem-non-susc.[c]	354	--	--	--	--	--	4 (1.1)	39 (12.1)	84 (35.9)	104 (65.3)	78 (87.3)	28 (95.2)	17 (100.0)
ceftazidime-non-susc.[d]	330	--	--	--	--	--	1 (0.3)	26 (8.2)	76 (31.2)	86 (57.3)	82 (82.1)	37 (93.3)	22 (100.0)
Acinetobacter spp.	321	--	--	--	--	2 (0.6)	0 (0.6)	7 (2.8)	8 (5.3)	43 (18.7)	40 (31.2)	70 (53.0)	151 (100.0)

a. MIC, ≥2 µg/mL; b. MIC, ≥8 µg/mL; c. MIC, ≥4 µg/mL; and d. MIC, ≥16 µg/mL.

Table 2. Activity of ceftazidime-avibactam and comparator antimicrobial agents

Organism (no. tested) / Antimicrobial agent	MIC (µg/mL) 50%	90%	%S / %I / %R CLSI[a]	EUCAST[a]
Enterobacteriaceae (8,640)				
Ceftazidime-avibactam	0.12	0.25	- / - / -	- / - / -
Ceftazidime	0.12	8	89.3 / 1.3 / 9.4	87.0 / 2.3 / 10.7
Ceftriaxone	≤0.06	>8	86.2 / 1.0 / 12.8	86.2 / 1.0 / 12.8
Ampicillin/sulbactam	8	>32	54.5 / 16.8 / 28.7	54.5 / 0.0 / 45.5
Piperacillin/tazobactam	2	16	91.8 / 3.2 / 5.1	88.4 / 3.3 / 8.2
Meropenem	≤0.06	≤0.06	98.4 / 0.1 / 1.5	98.5 / 0.4 / 1.1
Levofloxacin	≤0.12	>4	81.6 / 2.3 / 16.1	80.0 / 1.6 / 18.4
Gentamicin	≤1	4	90.5 / 1.6 / 7.9	88.4 / 2.1 / 9.5
Tigecycline[b]	0.25	1	97.9 / 2.1 / <0.1	91.7 / 6.2 / 2.1
Escherichia coli (2,767)				
Ceftazidime-avibactam	0.06	0.12	- / - / -	- / - / -
Ceftazidime	0.12	2	91.8 / 1.5 / 6.7	89.2 / 2.6 / 8.2
Ceftriaxone	≤0.06	>8	89.1 / 0.2 / 10.8	89.1 / 0.2 / 10.8
Ampicillin/sulbactam	8	>32	51.1 / 20.2 / 28.7	51.1 / 0.0 / 48.9
Piperacillin/tazobactam	2	8	95.2 / 2.0 / 2.8	92.4 / 2.8 / 4.8
Meropenem	≤0.06	≤0.06	99.9 / 0.0 / 0.1	99.9 / 0.1 / 0.0
Levofloxacin	≤0.12	>4	70.7 / 0.5 / 28.8	70.3 / 0.4 / 29.3
Gentamicin	≤1	>8	87.3 / 0.5 / 12.2	86.3 / 1.0 / 12.7
Tigecycline[b]	0.12	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
ESBL-phenotype (328)				
Ceftazidime-avibactam	0.12	0.25	- / - / -	- / - / -
Ceftazidime	16	>32	30.8 / 12.8 / 56.4	9.1 / 21.7 / 69.2
Ceftriaxone	>8	>8	7.6 / 0.9 / 91.5	7.6 / 0.9 / 91.5
Ampicillin/sulbactam	32	>32	11.9 / 16.5 / 71.6	11.9 / 0.0 / 88.1
Piperacillin/tazobactam	8	>64	76.8 / 10.4 / 12.8	61.9 / 14.9 / 23.2
Meropenem	≤0.06	≤0.06	98.8 / 0.7 / 0.6	99.4 / 0.6 / 0.0
Levofloxacin	>4	>4	23.8 / 1.5 / 74.7	22.6 / 1.2 / 76.2
Gentamicin	2	>8	64.8 / 0.3 / 34.9	62.7 / 2.1 / 35.2
Tigecycline[b]	0.12	0.25	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Klebsiella pneumoniae (1,847)				
Ceftazidime-avibactam	0.12	0.5	- / - / -	- / - / -
Ceftazidime	0.12	32	85.4 / 1.3 / 13.3	84.1 / 1.4 / 14.6
Ceftriaxone	≤0.06	>8	85.4 / 0.1 / 14.4	85.4 / 0.1 / 14.4
Ampicillin/sulbactam	8	>32	73.9 / 6.3 / 19.8	73.9 / 0.0 / 26.1
Piperacillin/tazobactam	4	>64	86.6 / 2.7 / 10.8	80.7 / 5.8 / 13.4
Meropenem	≤0.06	≤0.06	93.8 / 0.1 / 6.1	93.9 / 1.5 / 4.6
Levofloxacin	≤0.12	>4	86.1 / 1.5 / 12.4	85.0 / 1.1 / 13.9
Gentamicin	≤1	2	91.7 / 1.7 / 6.6	90.1 / 1.7 / 8.3
Tigecycline[b]	0.25	1	99.2 / 0.7 / 0.1	95.3 / 3.9 / 0.8
ESBL-phenotype (296)				
Ceftazidime-avibactam	0.5	1	- / - / -	- / - / -
Ceftazidime	>32	>32	8.8 / 8.1 / 83.1	1.0 / 7.8 / 91.2
Ceftriaxone	>8	>8	8.8 / 1.4 / 89.8	8.8 / 1.4 / 89.8
Ampicillin/sulbactam	>32	>32	2.7 / 4.7 / 92.6	2.7 / 0.0 / 97.3
Piperacillin/tazobactam	>64	>64	24.4 / 11.9 / 63.7	17.3 / 7.1 / 75.6
Meropenem	≤0.06	>8	61.1 / 1.1 / 37.8	62.2 / 9.1 / 28.7
Levofloxacin	>4	>4	24.3 / 5.1 / 70.6	22.6 / 1.7 / 75.7
Gentamicin	4	>8	51.4 / 10.8 / 37.8	42.6 / 8.8 / 48.6
Tigecycline[b]	0.5	1	98.0 / 1.7 / 0.3	91.2 / 6.8 / 2.0
meropenem-non-susceptible (MIC, ≥2 µg/mL; 115)				
Ceftazidime-avibactam	0.5	2	- / - / -	- / - / -
Ceftazidime	>32	>32	0.0 / 0.0 / 100.0	0.0 / 0.0 / 100.0
Ceftriaxone	>8	>8	0.0 / 0.0 / 100.0	0.0 / 0.0 / 100.0
Ampicillin/sulbactam	>32	>32	0.0 / 0.0 / 100.0	0.0 / 0.0 / 100.0
Piperacillin/tazobactam	>64	>64	0.0 / 0.0 / 100.0	0.0 / 0.0 / 100.0
Meropenem	>8	>8	0.0 / 2.6 / 97.4	2.6 / 23.5 / 73.9
Levofloxacin	>4	>4	7.0 / 1.7 / 91.3	5.2 / 1.8 / 93.0
Gentamicin	8	>8	48.7 / 17.4 / 33.9	33.0 / 15.7 / 51.3
Tigecycline[b]	0.5	1	98.2 / 0.8 / 0.9	92.1 / 6.2 / 1.8
K. oxytoca (442)				
Ceftazidime-avibactam	0.06	0.25	- / - / -	- / - / -
Ceftazidime	0.12	0.5	96.8 / 0.5 / 2.7	95.2 / 1.6 / 3.2
Ceftriaxone	≤0.06	0.5	90.5 / 0.7 / 8.8	90.5 / 0.7 / 8.8
Ampicillin/sulbactam	8	32	61.5 / 27.2 / 11.3	61.5 / 0.0 / 38.5
Piperacillin/tazobactam	2	8	92.5 / 0.2 / 7.3	90.7 / 1.8 / 7.5
Meropenem	≤0.06	≤0.06	99.3 / 0.5 / 0.2	99.8 / 0.0 / 0.2
Levofloxacin	≤0.12	0.25	97.7 / 0.3 / 2.0	96.4 / 1.3 / 2.3
Gentamicin	≤1	≤1	96.6 / 1.7 / 1.8	96.4 / 0.1 / 3.4
Tigecycline[b]	0.12	0.25	99.8 / 0.2 / 0.0	98.2 / 1.6 / 0.2
ESBL-phenotype (44)				
Ceftazidime-avibactam	0.25	1	- / - / -	- / - / -
Ceftazidime	1	>32	68.2 / 4.5 / 27.3	52.3 / 15.9 / 31.8
Ceftriaxone	8	>8	4.5 / 6.9 / 88.6	4.5 / 6.9 / 88.6
Ampicillin/sulbactam	>32	>32	4.5 / 4.6 / 90.9	4.5 / 0.0 / 95.5
Piperacillin/tazobactam	>64	>64	25.0 / 2.3 / 72.7	20.5 / 4.5 / 75.0
Meropenem	≤0.06	≤0.06	93.2 / 4.5 / 2.3	97.7 / 0.0 / 2.3
Levofloxacin	≤0.12	>4	77.3 / 2.2 / 20.5	68.2 / 9.1 / 22.7
Gentamicin	≤1	>8	72.7 / 13.7 / 13.6	70.5 / 2.2 / 27.3
Tigecycline[b]	0.25	1	97.7 / 2.3 / 0.0	95.5 / 2.2 / 2.3
P. mirabilis (683)				
Ceftazidime-avibactam	0.03	0.06	- / - / -	- / - / -
Ceftazidime	0.06	0.12	99.1 / 0.9 / 0.0	97.4 / 1.6 / 0.9
Ceftriaxone	≤0.06	≤0.06	95.3 / 1.2 / 3.5	95.3 / 1.2 / 3.5
Ampicillin/sulbactam	1	16	88.4 / 6.8 / 4.7	88.4 / 0.0 / 11.6
Piperacillin/tazobactam	≤0.5	1	99.7 / 0.2 / 0.1	99.6 / 0.2 / 0.3
Meropenem	≤0.06	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	>4	75.5 / 5.4 / 19.1	71.4 / 4.1 / 24.5
Gentamicin	≤1	8	88.7 / 2.6 / 8.7	84.6 / 4.2 / 11.3
Tigecycline[b]	2	4	82.9 / 16.8 / 0.3	42.3 / 40.6 / 17.1
ESBL-phenotype (33)				
Ceftazidime-avibactam	0.06	0.12	- / - / -	- / - / -
Ceftazidime	2	8	81.8 / 18.2 / 0.0	45.5 / 36.3 / 18.2
Ceftriaxone	>8	>8	3.0 / 24.3 / 72.7	3.0 / 24.3 / 72.7
Ampicillin/sulbactam	16	32	30.3 / 24.2 / 45.5	30.3 / 0.0 / 69.7
Piperacillin/tazobactam	1	4	100.0 / 0.0 / 0.0	97.0 / 3.0 / 0.0
Meropenem	≤0.06	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	>4	>4	33.3 / 15.2 / 51.5	21.2 / 12.1 / 66.7
Gentamicin	2	>8	60.6 / 6.1 / 33.3	60.6 / 0.0 / 39.4
Tigecycline[b]	2	4	81.8 / 18.2 / 0.0	48.5 / 33.3 / 18.2
Enterobacter cloacae (951)				
Ceftazidime-avibactam	0.12	0.5	- / - / -	- / - / -
Ceftazidime	0.25	>32	79.0 / 1.0 / 20.0	76.9 / 2.1 / 21.0
Ceftriaxone	0.25	>8	74.4 / 1.8 / 23.8	74.4 / 1.8 / 23.8
Ampicillin/sulbactam	16	>32	32.5 / 20.9 / 46.6	32.5 / 0.0 / 67.5
Piperacillin/tazobactam	2	64	85.0 / 7.1 / 7.9	80.9 / 4.1 / 15.0
Meropenem	≤0.06	≤0.06	99.5 / 0.0 / 0.5	99.5 / 0.2 / 0.3
Ciprofloxacin	≤0.03	0.5	92.5 / 2.1 / 5.4	91.5 / 1.0 / 7.5
Levofloxacin	≤0.12	0.5	94.1 / 2.0 / 3.9	92.5 / 1.6 / 5.9
Gentamicin	≤1	≤1	94.5 / 0.9 / 4.6	94.2 / 0.3 / 5.5
Tigecycline[b]	0.25	1	98.5 / 1.5 / 0.0	94.4 / 4.1 / 1.5
ceftazidime-non-susceptible (MIC, ≥8 µg/mL; 200)				
Ceftazidime-avibactam	0.5	1	- / - / -	- / - / -
Ceftazidime	>32	>32	0.0 / 5.0 / 95.0	0.0 / 0.0 / 100.0
Ceftriaxone	>8	>8	0.0 / 0.0 / 100.0	0.0 / 0.0 / 100.0
Ampicillin/sulbactam	>32	>32	1.0 / 2.5 / 96.5	1.0 / 0.0 / 99.0
Piperacillin/tazobactam	64	>64	29.1 / 33.2 / 37.7	17.1 / 12.0 / 70.9
Meropenem	≤0.06	0.25	97.5 / 0.0 / 2.5	97.5 / 1.0 / 1.5
Levofloxacin	≤0.12	>4	76.9 / 8.0 / 15.1	73.4 / 3.5 / 23.1
Gentamicin	≤1	>8	77.4 / 3.5 / 19.1	76.4 / 1.0 / 22.6
Tigecycline[b]	0.25	2	94.5 / 5.5 / 0.0	85.0 / 9.5 / 5.5
E. aerogenes (357)				
Ceftazidime-avibactam	0.12	0.25	- / - / -	- / - / -
Ceftazidime	0.25	32	77.0 / 1.7 / 21.3	74.2 / 2.8 / 23.0
Ceftriaxone	0.12	>8	73.6 / 2.3 / 24.1	73.6 / 2.3 / 24.1
Ampicillin/sulbactam	16	>32	40.3 / 22.2 / 37.5	40.3 / 0.0 / 59.7
Piperacillin/tazobactam	4	64	80.6 / 14.7 / 4.8	73.8 / 6.8 / 19.4
Meropenem	≤0.06	≤0.06	99.4 / 0.3 / 0.3	99.7 / 0.3 / 0.0
Levofloxacin	≤0.12	0.25	96.9 / 1.1 / 2.0	95.5 / 1.4 / 3.1
Gentamicin	≤1	≤1	97.2 / 0.6 / 2.2	96.4 / 0.8 / 2.8
Tigecycline[b]	0.25	0.5	99.2 / 0.8 / 0.0	95.8 / 3.4 / 0.8
ceftazidime-non-susceptible (MIC, ≥8 µg/mL; 82)				
Ceftazidime-avibactam	0.25	0.5	- / - / -	- / - / -
Ceftazidime	32	>32	0.0 / 7.3 / 92.7	0.0 / 0.0 / 100.0
Ceftriaxone	>8	>8	0.0 / 1.2 / 98.8	0.0 / 1.2 / 98.8
Ampicillin/sulbactam	>32	>32	0.0 / 1.2 / 98.8	0.0 / 0.0 / 100.0
Piperacillin/tazobactam	64	>64	22.0 / 57.3 / 20.7	11.0 / 11.0 / 78.0
Meropenem	≤0.06	0.12	97.6 / 1.2 / 1.2	98.8 / 1.2 / 0.0
Levofloxacin	≤0.12	2	90.2 / 3.7 / 6.1	85.4 / 4.8 / 9.8
Gentamicin	≤1	4	91.5 / 2.4 / 6.1	87.8 / 3.7 / 8.5
Tigecycline[b]	0.25	1	97.6 / 2.4 / 0.0	96.3 / 1.3 / 2.4
M. morganii (295)				
Ceftazidime-avibactam	0.06	0.12	- / - / -	- / - / -
Ceftazidime	0.12	16	85.8 / 4.0 / 10.2	77.3 / 8.5 / 14.2
Ceftriaxone	≤0.06	4	86.7 / 2.7 / 10.6	86.7 / 2.7 / 10.6
Ampicillin/sulbactam	16	32	23.5 / 36.7 / 39.8	23.5 / 0.0 / 76.5
Piperacillin/tazobactam	≤0.5	2	96.6 / 1.4 / 2.0	95.9 / 0.6 / 3.4
Meropenem	≤0.06	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	>4	70.4 / 8.5 / 21.1	66.0 / 4.4 / 29.6
Gentamicin	≤1	>8	83.3 / 2.2 / 14.6	79.6 / 3.7 / 16.7
Tigecycline[b]	0.5	2	95.9 / 4.1 / 0.0	86.1 / 9.9 / 4.1
C. koseri (186)				
Ceftazidime-avibactam	0.06	0.12	- / - / -	- / - / -
Ceftazidime	0.12	0.5	98.4 / 0.5 / 1.1	96.2 / 2.2 / 1.6
Ceftriaxone	≤0.06	0.25	98.4 / 0.0 / 1.6	98.4 / 0.0 / 1.6
Ampicillin/sulbactam	2	8	95.7 / 1.6 / 2.7	95.7 / 0.0 / 4.3
Piperacillin/tazobactam	2	8	98.4 / 1.1 / 0.5	94.6 / 3.9 / 1.6
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	≤0.12	99.5 / 0.0 / 0.5	98.4 / 1.1 / 0.5
Gentamicin	≤1	≤1	99.5 / 0.0 / 0.5	99.5 / 0.0 / 0.5
Tigecycline[b]	0.12	0.25	100.0 / 0.0 / 0.0	99.5 / 0.5 / 0.0
C. freundii (185)				
Ceftazidime-avibactam	0.12	0.5	- / - / -	- / - / -
Ceftazidime	0.5	>32	76.8 / 1.0 / 22.2	73.5 / 3.3 / 23.2
Ceftriaxone	0.25	>8	75.0 / 1.1 / 23.9	75.0 / 1.1 / 23.9
Ampicillin/sulbactam	8	>32	60.3 / 9.3 / 30.4	60.3 / 0.0 / 39.7
Piperacillin/tazobactam	4	64	82.1 / 9.2 / 8.7	74.5 / 7.6 / 17.9
Meropenem	≤0.06	≤0.06	97.8 / 0.7 / 1.6	98.4 / 1.1 / 0.5
Levofloxacin	≤0.12	4	85.4 / 5.3 / 9.2	80.5 / 4.9 / 14.6
Gentamicin	≤1	>8	87.6 / 0.5 / 11.9	87.0 / 0.6 / 12.4
Tigecycline[b]	0.25	1	98.9 / 1.1 / 0.0	92.9 / 6.0 / 1.1
S. marcescens (506)				
Ceftazidime-avibactam	0.12	0.5	- / - / -	- / - / -
Ceftazidime	0.25	0.5	97.4 / 0.1 / 2.4	96.6 / 0.9 / 2.6
Ceftriaxone	0.25	2	89.8 / 2.4 / 7.8	89.8 / 2.4 / 7.8
Ampicillin/sulbactam	32	>32	9.1 / 15.0 / 75.9	9.1 / 0.0 / 90.9
Piperacillin/tazobactam	2	4	96.6 / 2.4 / 1.0	94.4 / 2.1 / 3.4
Meropenem	≤0.06	≤0.06	99.2 / 0.3 / 0.4	99.6 / 0.2 / 0.2
Levofloxacin	≤0.12	1	94.7 / 2.8 / 2.4	91.3 / 3.4 / 5.3
Gentamicin	≤1	2	97.0 / 0.8 / 2.2	95.1 / 1.9 / 3.0
Tigecycline[b]	0.5	1	99.0 / 1.0 / 0.0	94.3 / 4.7 / 1.0
Proteus vulgaris (153)				
Ceftazidime-avibactam	0.06	0.06	- / - / -	- / - / -
Ceftazidime	0.06	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Ceftriaxone	0.12	4	72.8 / 9.3 / 17.9	72.8 / 9.3 / 17.9
Ampicillin/sulbactam	8	16	65.4 / 32.0 / 2.6	65.4 / 0.0 / 34.6
Piperacillin/tazobactam	≤0.5	1	99.3 / 0.0 / 0.7	99.3 / 0.0 / 0.7
Meropenem	≤0.06	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	≤0.12	98.7 / 0.6 / 0.7	98.7 / 0.0 / 1.3
Gentamicin	≤1	2	98.7 / 1.3 / 0.0	94.7 / 4.0 / 1.3
Tigecycline[b]	0.5	1	98.7 / 1.3 / 0.0	90.9 / 7.8 / 1.3
Providencia spp.[c] (268)				
Ceftazidime-avibactam	0.12	0.5	- / - / -	- / - / -
Ceftazidime	0.12	4	90.7 / 1.8 / 7.5	85.1 / 5.7 / 9.3
Ceftriaxone	≤0.06	1	90.3 / 2.2 / 7.5	90.3 / 2.2 / 7.5
Ampicillin/sulbactam	16	32	36.0 / 29.9 / 34.1	36.0 / 0.0 / 64.0
Piperacillin/tazobactam	1	8	94.4 / 1.5 / 4.1	92.2 / 2.2 / 5.6
Meropenem	≤0.06	0.12	99.2 / 0.3 / 0.4	99.6 / 0.0 / 0.4
Levofloxacin	2	>4	51.5 / 13.8 / 34.7	45.9 / 5.6 / 48.5
Gentamicin	4	>8	72.1 / 16.2 / 11.7	49.8 / 22.3 / 27.9
Tigecycline[b]	1	2	95.1 / 4.9 / 0.0	76.0 / 19.1 / 4.9
P. aeruginosa (1,967)				
Ceftazidime-avibactam	2	4	- / - / -	- / - / -
Ceftazidime	2	32	83.2 / 3.8 / 13.0	83.2 / 0.0 / 16.8
Cefepime	2	16	83.8 / 8.2 / 8.0	83.8 / 0.0 / 16.2
Piperacillin/tazobactam	8	>64	78.3 / 8.9 / 12.8	78.3 / 0.0 / 21.7
Meropenem	0.5	8	82.0 / 5.6 / 12.4	82.0 / 11.4 / 6.6
Ciprofloxacin	0.12	>4	77.5 / 5.0 / 17.5	72.1 / 5.4 / 22.5
Levofloxacin	0.5	>4	75.3 / 6.5 / 18.2	66.7 / 8.6 / 24.7
Gentamicin	≤1	8	88.8 / 3.4 / 7.8	88.8 / 0.0 / 11.2
Amikacin	2	8	97.5 / 1.3 / 1.2	94.0 / 3.5 / 2.5
Colistin	1	2	98.6 / 1.4 / 0.1	98.6 / 0.0 / 1.4
ceftazidime-non-susceptible (MIC, ≥16 µg/mL; 330)				
Ceftazidime-avibactam	4	16	- / - / -	- / - / -
Ceftazidime	32	>32	0.0 / 22.7 / 77.3	0.0 / 0.0 / 100.0
Cefepime	16	>16	20.0 / 36.1 / 43.9	20.0 / 0.0 / 80.0
Piperacillin/tazobactam	>64	>64	4.5 / 22.8 / 72.7	4.5 / 0.0 / 95.5
Meropenem	4	>8	45.3 / 9.4 / 45.3	45.3 / 28.6 / 26.1
Ciprofloxacin	2	>4	42.4 / 8.2 / 49.4	36.7 / 5.7 / 57.6
Levofloxacin	>4	>4	39.4 / 9.7 / 50.9	30.3 / 9.1 / 60.6
Gentamicin	2	>8	67.3 / 6.3 / 26.4	67.3 / 0.0 / 32.7
Amikacin	4	16	93.0 / 3.4 / 3.6	85.8 / 7.2 / 7.0
Colistin	1	2	99.1 / 0.7 / 0.3	99.1 / 0.0 / 0.9
meropenem-non-susceptible (MIC, ≥4 µg/mL; 354)				
Ceftazidime-avibactam	4	16	- / - / -	- / - / -
Ceftazidime	16	>32	49.2 / 10.7 / 40.1	49.2 / 0.0 / 50.8
Cefepime	16	>16	46.6 / 24.0 / 29.4	46.6 / 0.0 / 53.4
Piperacillin/tazobactam	64	>64	36.4 / 23.2 / 40.4	36.4 / 0.0 / 63.6
Meropenem	8	>8	0.0 / 31.4 / 68.6	0.0 / 63.3 / 36.7
Ciprofloxacin	4	>4	37.6 / 6.7 / 55.7	30.5 / 7.1 / 62.4
Levofloxacin	>4	>4	33.6 / 8.2 / 58.2	21.8 / 11.8 / 66.4
Gentamicin	4	>8	64.7 / 7.6 / 27.7	64.7 / 0.0 / 35.3
Amikacin	4	16	92.7 / 4.2 / 3.1	84.2 / 8.5 / 7.3
Colistin	1	2	97.7 / 1.7 / 0.6	97.7 / 0.0 / 2.3
Acinetobacter spp. (321)				
Ceftazidime-avibactam	16	>32	- / - / -	- / - / -
Ceftazidime	32	>32	41.7 / 5.3 / 53.0	- / - / -
Cefepime	>16	>16	40.5 / 6.5 / 53.0	- / - / -
Piperacillin/tazobactam	>64	>64	41.3 / 0.1 / 58.8	- / - / -
Ampicillin/sulbactam	16	>32	48.9 / 15.0 / 36.1	- / - / -
Meropenem	8	>8	47.0 / 5.0 / 48.0	45.5 / 6.5 / 48.0
Ciprofloxacin	>4	>4	41.7 / 0.0 / 58.3	41.7 / 0.0 / 58.3
Levofloxacin	>4	>4	42.1 / 2.4 / 55.5	41.7 / 0.4 / 57.9
Gentamicin	4	>8	50.2 / 4.0 / 45.8	50.2 / 0.0 / 49.8
Amikacin	8	>32	67.9 / 4.7 / 27.4	62.3 / 5.6 / 32.1
Colistin	1	2	96.6 / 0.0 / 3.4	96.6 / 0.0 / 3.4

a. Criteria as published by the CLSI [2013] and EUCAST [2013].
b. US-FDA breakpoints were applied when available [Tygacil Product Insert, 2012].
c. Includes: *Providencia alcalifaciens* (3 strains), *P. rettgeri* (111 strains), and *P. stuartii* (154 strains).

Conclusions

- Ceftazidime-avibactam demonstrated potent activity against a large collection of contemporary (2012) gram-negative organisms isolated from patients in USA hospitals, including organisms resistant to most currently available agents, such as KPC-producing Enterobacteriaceae and meropenem-non-susceptible *P. aeruginosa*
- Activity of ceftazidime-avibactam was very limited against *Acinetobacter* spp. and metallo-β-lactamase-producing strains, the latter of which are extremely rare in USA hospitals
- The increase of community and nosocomial infections caused by β-lactamase-producing organisms (often multidrug-resistant) reduces antimicrobial therapy options. The use of avibactam, a broad-spectrum β-lactamase inhibitor, in combination with a well-known β-lactam such as ceftazidime, could become a valuable addition to the limited armamentarium currently available to treat serious gram-negative infections.

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