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Ceftazidime-Avibactam Antimicrobial Activity When Tested against Gram-negative Bacteria Isolated from Intensive Care Unit (ICU) Patients with Pneumonia (2012-2014)

HS SADER, M CASTANHEIRA, RK FLAMM, DJ FARRELL, RN JONES
JMI Laboratories, North Liberty, Iowa, USA

Helio S. Sader, MD, PhD
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
ph. 319.665.3370
fax 319.665.3371
helio-sader@jmilabs.com

Abstract

Introduction: Ceftazidime-avibactam (CAZ-AVI) consists of CAZ combined with the novel non-β-lactam β-lactamase (BL) inhibitor AVI, which inhibits extended-spectrum BLs (ESBLs), KPCs, AmpCs and some OXA enzymes. CAZ-AVI is under clinical development for treatment of nosocomial pneumonia.

Methods: Clinical isolates were consecutively collected from 51 United States (USA) medical centers in 2012-2014 as part of the INFORM Surveillance Program and tested for susceptibility (S) at a central laboratory by reference broth microdilution methods. Results for 1,428 Gram-negative (GN) isolates from ICU patients with pneumonia were evaluated. BL encoding genes were evaluated for all *Klebsiella* spp. (KSP) and *E. coli* (EC) with an ESBL-phenotype (n=98) by microarray-based assay.

Results: The most frequent GN organisms isolated were *P. aeruginosa* (PSA; 28.5% of GN isolates), followed by KSP (23.8%), *Enterobacter* spp. (EBS; 12.0%) and EC (11.7%). CAZ-AVI was the most active agent against PSA (96.1% S) and the only agent showing good activity against multidrug-resistant (MDR; 82.3% S) and extensively drug-resistant (XDR; 76.3% S) PSA (Table). All Enterobacteriaceae (ENT) strains were S to CAZ-AVI except for one EBS with a CAZ-AVI MIC of 16 μg/mL (99.9% S) which had negative results for all BLs tested. ENT S rates for piperacillin/tazobactam (P/T) and meropenem (MEM) were 84.9% and 96.4%, respectively. MEM exhibited limited activity against ESBL-phenotype KSP (59.2% S) and MDR-ENT (63.5% S), whereas CAZ-AVI was very active against these resistant subsets (98.8%-100.0% S). CAZ-AVI, colistin and tigecycline were the only agents active against XDR-ENT and carbapenem-resistant ENT (CRE). *Acinetobacter* spp. showed low S rates for all agents except colistin (94.7% S).

Conclusions: CAZ-AVI demonstrated potent activity against a large collection of GN isolates from ICU patients with pneumonia. These *in vitro* results support further development of CAZ-AVI for treatment of nosocomial pneumonia in the USA.

Organism (no. tested)	$MIC_{50/90}$ in μg/mL (% susceptible [CLSI and USA-FDA])				
	CAZ-AVI	P/T	Meropenem	Gentamicin	Levofloxacin
P. aeruginosa (407)	2/4 (96.1)	8/>64 (76.7)	0.5/8 (78.1)	2/>8 (87.7)	0.5/>4 (74.9)
MDR (79)	4/16 (82.3)	64/>64 (1.7)	8/>8 (20.3)	8/>8 (48.1)	>4/>4 (19.0)
XDR (38)	4/>32 (76.3)	>64/>64 (2.6)	8/>8 (7.9)	>8/>8 (34.2)	>4/>4 (0.0)
Enterobacteriaceae (851)	0.12/0.5 (99.9)	2/64 (84.9)	≤0.06/≤0.06 (96.4)	≤1/2 (91.8)	≤0.12/>4 (82.7)
Klebsiella spp. (340)	0.12/0.5 (100.0)	4/>64 (84.7)	≤0.06/≤0.06 (91.5)	≤1/2 (91.5)	≤0.12/>4 (85.9)
ESBL-phenotype KSP (71)	0.5/1 (100.0)	>64/>64 (26.8)	≤0.06/>8 (59.2)	2/>8 (60.6)	>4/>4 (36.6)
Enterobacter spp. (171)	0.12/0.5 (99.4)	4/64 (74.7)	≤0.06/≤0.06 (98.8)	≤1/≤1 (100.0)	≤0.12/0.25 (98.2)
CAZ-non-S EBS (49)	0.25/1 (98.0)	64/>64 (12.2)	≤0.06/0.25 (95.9)	≤1/≤1 (100.0)	≤0.12/0.25 (93.9)
MDR ENT (85)	0.5/2 (98.8)	>64/>64 (21.4)	≤0.06/>8 (63.5)	8/>8 (49.4)	>4/>4 (11.8)
XDR ENT (11)	0.5/1 (100.0)	>64/>64 (0.0)	>8/>8 (0.0)	>8/>8 (0.0)	>4/>4 (0.0)
CRE (29)	1/2 (100.0)	>64/>64 (0.0)	>8/>8 (0.0)	2/>8 (62.1)	>4/>4 (13.8)

Introduction

Pneumonia represents the second most common infection in hospitalized patients and the importance of Gram-negative organisms, such as *Pseudomonas aeruginosa*, *Klebsiella* spp. and *Enterobacter* spp., has increased substantially in recent years. Antimicrobial resistance is also increasing for each of these pathogens with limited advancement in terms of novel antimicrobials for treatment of multidrug-resistant (MDR) organisms. Thus, antimicrobial resistance has become an important determinant of clinical outcome and higher rates of antimicrobial resistance are expected in the intensive care unit (ICU) due to multiple factors, including high occurrence of invasive procedures, increased use of broad-spectrum antimicrobials and increased chance of transmission of resistant bacteria among patients. Furthermore, Gram-negative bacteria can be highly efficient at up-regulating or acquiring genes that code for antimicrobial resistance, especially in the presence of antimicrobial selection pressure.

Avibactam is a novel broad-spectrum non-β-lactam β-lactamase inhibitor with activity against common serine β-lactamase enzymes, including Ambler class A (e.g., ESBL and KPC), class C (Amp C) and some class D (OXA-48) enzymes. The addition of avibactam to ceftazidime restores ceftazidime *in vitro* activity against common Gram-negative pathogens, including most of those that are resistant to carbapenem agents (e.g. meropenem) due to the production of β-lactamase enzymes. Ceftazidime-avibactam is approved by the United States Food and Drug Administration (US-FDA) in combination with metronidazole for the treatment of complicated intra-abdominal infections as well as complicated urinary tract infections, including pyelonephritis, in patients with limited or no alternative treatment options. Ceftazidime-avibactam is also under clinical development for treatment of nosocomial pneumonia (NCT01808092). We evaluated the activity of ceftazidime-avibactam against contemporary (2012-2014) Gram-negative isolates from patients with pneumonia hospitalized in an ICU.

Methods

Bacterial isolates: Clinical isolates were consecutively collected from 51 United States (USA) medical centers in 2012-2014 as part of the International Network for Optimal Resistance Monitoring (INFORM) program and the results for 1,428 Gram-negative isolates from ICU patients with pneumonia were evaluated. Only bacterial isolates determined to be significant by local criteria as the likely cause of the infection were included in this investigation. 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, US) by following manufacturer instructions.

Resistant subsets: An ESBL-screen-positive phenotype was defined according to the Clinical and Laboratory Standards Institute (CLSI), i.e. a MIC of ≥2 μg/mL for ceftazidime and/or ceftriaxone and/or aztreonam. Carbapenem-resistant Enterobacteriaceae (CRE) was defined as resistant (MIC, ≥4 μg/mL [CLSI]) to imipenem (excluding *Proteus mirabilis* and indole-positive Proteeae), meropenem or doripenem. Further, isolates were categorized as multidrug-resistant (MDR), extensively drug-resistant (XDR) or pan drug-resistant (PDR) according to criteria published by Magiorakos *et al.* (2012); i.e. MDR = nonsusceptible to ≥1 agent in ≥3 antimicrobial classes, XDR = nonsusceptible to ≥1 agent in all but ≤2 antimicrobial classes and PDR = nonsusceptible (CLSI criteria) to all antimicrobial classes tested. Class representatives used in the analysis were: ceftriaxone, meropenem, piperacillin-tazobactam, levofloxacin, gentamicin, tigecycline and colistin for Enterobacteriaceae; and ceftazidime, meropenem, piperacillin-tazobactam, levofloxacin, gentamicin and colistin for *P. aeruginosa*.

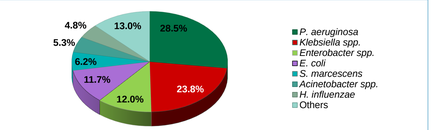
Antimicrobial susceptibility testing. All isolates were tested for susceptibility using the reference broth microdilution method as described by the CLSI. Ceftazidime was combined with a fixed concentration of avibactam at 4 μg/mL. Ceftazidime-avibactam breakpoints approved by the US-FDA (≤8/4 μg/mL for susceptible and ≥16/4 μg/mL for resistant) were applied for all Enterobacteriaceae species and *P. aeruginosa*. Susceptibility interpretations for comparator agents were those found in CLSI document M100-S26, EUCAST breakpoints and/or US-FDA package insert. Quality control (QC) was performed using *Escherichia coli* ATCC 25922 and 35218, *Klebsiella pneumoniae* ATCC 700603 and *P. aeruginosa* ATCC 27853. All QC MIC results were within acceptable ranges as published in CLSI documents.

Screening for β-lactamases. Isolates displaying an ESBL-phenotype (MIC, ≥2 μg/mL for aztreonam and/or ceftazidime and/or ceftriaxone) were tested for β-lactamase-encoding genes using a 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 capability to detect CTX-M Groups 1, 2, 8+25 and 9, TEM wild-type (WT) and ESBL, SHV WT and ESBL, ACC, ACT/MIR, CMYI/MOX, CMYII, DHA, FOX, KPC and NDM. The most common mutations that expand the spectrum of TEM and SHV enzymes are detected by this assay and these mutations include E104K, R164S/H or G238S for TEM and G238A/S and E240K for SHV. Validation of the assay against US isolates was previously performed. Additionally, all isolates displaying a ceftazidime-avibactam MIC of >4 μg/mL were screened for the presence of metallo-β-lactamase and serine-carbapenemase encoding genes families (bla_{IMP}, bla_{VIM}, bla_{NDM}, bla_{KPC}, bla_{OXA-48}, bla_{GES}, bla_{IMI}, bla_{NMC-A}, and bla_{SME}) by PCR as previously described. Amplicons were sequenced on both strands and results were analyzed using the Lasergene software package (DNASTAR, Madison, Wisconsin, USA). Amino acid sequences were compared with those available through the internet using NCBI/BLAST.

Results

- The most frequent Gram-negative organism isolated was *P. aeruginosa* (28.5% of Gram-negative isolates), followed by *Klebsiella* spp. (23.8%), *Enterobacter* spp. (12.0%), *E. coli* (11.7%), *S. marcescens* (6.2%), *Acinetobacter* spp. (5.3%) and *H. influenzae* (4.8%; Figure 1).
- Ceftazidime-avibactam was the most active β-lactam agent against *P. aeruginosa* ($MIC_{50/90}$, 2/4 μg/mL; 96.1% susceptible). Further, ceftazidime-avibactam retained potent activity against meropenem-non-susceptible ($MIC_{50/90}$, 4/16 μg/mL; 86.5% susceptible) and ceftazidime-non-susceptible isolates ($MIC_{50/90}$, 4/16 μg/mL; 78.9% susceptible; Table 1).
- Amikacin (99.5% susceptible) and colistin (99.8% susceptible) were also very active against *P. aeruginosa*, whereas susceptibility rates for the comparator β-lactam agents ranged from 76.7% for piperacillin-tazobactam to 82.8% for cefepime (Table 2).
- Ceftazidime-avibactam was the only β-lactam agent showing good activity against MDR ($MIC_{50/90}$, 4/16 μg/mL; 82.3% susceptible) and XDR ($MIC_{50/90}$, 4/>32 μg/mL; 76.3% susceptible) *P. aeruginosa* isolates (Tables 1, 2 and Figure 2).
- All Enterobacteriaceae isolates were susceptible to ceftazidime-avibactam, except for one *Enterobacter* spp. isolate with a ceftazidime-avibactam MIC value of 16 μg/mL (99.9% susceptible) which had negative results for all β-lactamases tested.
- Enterobacteriaceae susceptibility rates for comparator β-lactam agents were 83.9% for ceftazidime, 79.2% for ceftriaxone, 84.9% for piperacillin/tazobactam and 96.4% for meropenem (Table 2).
- ESBL-phenotype was observed among 16.2% and 22.2% of *E. coli* and *K. pneumoniae*, respectively; 28.3% of *Enterobacter cloacae* were not ceftazidime-susceptible (Tables 1 and 2).
- Ceftazidime-avibactam was particularly active against CRE ($MIC_{50/90}$, 1/2 μg/mL; 100.0% susceptible), MDR ($MIC_{50/90}$, 0.5/2 μg/mL; 98.8% susceptible) and XDR ($MIC_{50/90}$, 0.5/1 μg/mL; 100.0% susceptible) Enterobacteriaceae (Table 1 and Figure 2).
- ESBL-phenotype ($MIC_{50/90}$, 0.5/2 μg/mL; 100.0% susceptible) and meropenem-non-susceptible *K. pneumoniae* ($MIC_{50/90}$, 1/2 μg/mL; 100.0% susceptible), as well as ceftazidime-non-susceptible *E. cloacae* ($MIC_{50/90}$, 0.5/1 μg/mL; 100.0% susceptible) isolates, were very susceptible to ceftazidime-avibactam (Table 1 and Figure 2).
- Meropenem was also very active against Enterobacteriaceae overall ($MIC_{50/90}$, ≤0.06/≤0.06 μg/mL; 96.4% susceptible), but exhibited limited activity against ESBL-phenotype *K. pneumoniae* ($MIC_{50/90}$, 0.12/>8 μg/mL; 50.0% susceptible; data not shown) and MDR Enterobacteriaceae ($MIC_{50/90}$, ≤0.06/>8 μg/mL; 63.5% susceptible; Table 2 and Figure 2).
- Ceftazidime-avibactam demonstrated potent *in vitro* activity against *H. influenzae* ($MIC_{50/90}$, ≤0.015/0.03 μg/mL; highest MIC, 0.12 μg/mL), but like all other β-lactam agents tested, showed limited activity against *A. baumannii* ($MIC_{50/90}$, 32/>32 μg/mL; Table 1).
- The most common ESBL observed among *K. pneumoniae* was KPC-like (26 strains; 44.8%) and CTX-M-15-like (15 strains; 25.9%). The highest ceftazidime-avibactam MIC value among isolates producing KPC-like enzymes was only 2 μg/mL ($MIC_{50/90}$, 0.5/2 μg/mL; 100.0% susceptible) and all ESBL-producing *K. pneumoniae* isolates were inhibited at ≤1 μg/mL of ceftazidime-avibactam (Table 3).
- CTX-M-15-like was the most common β-lactamase detected among *E. coli* (15 strains; 55.6%), followed by CMY-2-like (five isolates; 18.5%) and CTX-M-14-like (four isolates; 14.8%). The highest ceftazidime-avibactam MIC value among ESBL-producing *E. coli* was only 1 μg/mL (100.0% susceptible; Table 3).
- Among the entire collection of Gram-negative organisms evaluated in this investigation, 94.8% of isolates (1,354/1,428) were inhibited at a ceftazidime-avibactam MIC of ≤8 μg/mL, whereas 88.2% of isolates were susceptible to meropenem and 80.3% to piperacillin/tazobactam (Figure 2).

Figure 1. Distribution of pathogens.



Conclusions

- Ceftazidime-avibactam demonstrated potent *in vitro* activity against a large collection of Gram-negative isolates from ICU patients with pneumonia.
- Notably, ceftazidime-avibactam remained highly active against CRE as well as Enterobacteriaceae and *P. aeruginosa* isolates with MDR and XDR phenotypes.
- These *in vitro* results support further development of ceftazidime-avibactam for treatment of nosocomial pneumonia in the USA.

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Table 1. Summary of ceftazidime-avibactam activity tested against Gram-negative organisms isolated from patients with pneumonia hospitalized in an ICU (USA, 2012-2014).

Organism	Total	No. of isolates (cumulative %) inhibited at ceftazidime-avibactam MIC (μg/mL) of:										MIC_{50}	MIC_{90}
		≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32		
P. aeruginosa	407	--	0 (0.0)	1 (0.2)	0 (0.2)	0 (0.2)	13 (3.4)	137 (37.1)	155 (75.2)	64 (90.9)	**21 (96.1)**	10 (98.5)	1 (98.8)	5 (100.0)	2	4
CAZ-NS	76	--	--	--	--	--	0 (0.0)	1 (1.3)	21 (28.9)	27 (64.5)	**11 (78.9)**	10 (92.1)	1 (93.4)	5 (100.0)	4	16
MEM-NS	89	--	--	--	--	--	0 (0.0)	4 (4.5)	27 (34.8)	31 (69.7)	**15 (86.5)**	6 (93.3)	1 (94.4)	5 (100.0)	4	16
MDR	79	--	--	--	--	--	0 (0.0)	3 (3.8)	26 (36.7)	24 (67.1)	**12 (82.3)**	8 (92.4)	1 (93.7)	5 (100.0)	4	16
XDR	38	--	--	--	--	--	0 (0.0)	2 (5.3)	4 (15.8)	16 (57.9)	**7 (76.3)**	4 (86.8)	1 (89.5)	4 (100.0)	4	>32
Enterobacteriaceae	851	14 (1.6)	55 (8.1)	254 (38.0)	284 (71.3)	136 (87.3)	76 (96.2)	20 (98.6)	10 (99.8)	1 (99.9)	**0 (99.9)**	1 (100.0)	--	--	0.12	0.5
CRE	29	0 (0.0)	1 (3.4)	0 (3.4)	1 (6.9)	2 (13.8)	9 (44.8)	9 (75.9)	**7 (100.0)**	--	--	--	--	--	1	2
MDR	85	4 (4.7)	2 (7.1)	5 (12.9)	6 (20.0)	20 (43.5)	27 (75.3)	12 (89.4)	7 (97.6)	1 (98.8)	**0 (98.8)**	1 (100.0)	--	--	0.5	2
XDR	11	--	--	--	0 (0.0)	1 (9.1)	5 (54.5)	4 (90.9)	**1 (100.0)**	--	--	--	--	--	0.5	1
E. coli	167	8 (4.8)	16 (14.4)	74 (58.7)	50 (88.6)	14 (97.0)	4 (99.4)	1 (**100.0**)	--	--	--	--	--	--	0.06	0.25
Klebsiella spp.	340	4 (1.2)	11 (4.4)	126 (41.5)	118 (76.2)	31 (85.3)	32 (94.7)	11 (97.9)	**7 (100.0)**	--	--	--	--	--	0.12	0.5
K. pneumoniae	261	3 (1.1)	9 (4.6)	98 (42.1)	84 (74.3)	24 (83.5)	27 (93.9)	9 (97.3)	**7 (100.0)**	--	--	--	--	--	0.12	0.5
ESBL-phenotype	58	3 (5.2)	1 (6.9)	3 (12.1)	7 (24.1)	9 (39.7)	19 (72.4)	9 (87.9)	**7 (100.0)**	--	--	--	--	--	0.5	2
MEM-NS	29	0 (0.0)	1 (3.4)	1 (6.9)	1 (10.3)	2 (17.2)	9 (48.3)	8 (75.9)	**7 (100.0)**	--	--	--	--	--	1	2
K. oxytoca	78	0 (0.0)	2 (2.6)	28 (38.5)	34 (82.1)	7 (91.0)	5 (97.4)	2 (100.0)	--	--	--	--	--	--	0.12	0.25
P. mirabilis	34	1 (2.9)	20 (61.8)	11 (94.1)	1 (97.1)	0 (97.1)	1 (**100.0**)	--	--	--	--	--	--	--	0.03	0.06
E. cloacae	99	0 (0.0)	1 (1.0)	3 (4.0)	39 (43.4)	36 (79.8)	16 (96.0)	4 (**100.0**)	--	--	--	--	--	--	0.25	0.5
CAZ-NS	28	--	--	0 (0.0)	2 (7.1)	10 (42.9)	13 (89.3)	3 (**100.0**)	--	--	--	--	--	--	0.5	1
E. aerogenes	72	--	0 (0.0)	23 (31.9)	28 (70.8)	14 (90.3)	5 (97.2)	1 (98.6)	0 (98.6)	0 (98.6)	**0 (98.6)**	1 (100.0)	--	--	0.12	0.25
M. morganii	10	0 (0.0)	5 (50.0)	4 (90.0)	1 (**100.0**)	--	--	--	--	--	--	--	--	--	0.03	0.06
C. koseri	15	0 (0.0)	1 (6.7)	7 (53.3)	4 (80.0)	3 (**100.0**)	--	--	--	--	--	--	--	--	0.06	0.25
C. freundii	15	1 (6.7)	1 (13.3)	3 (33.3)	4 (60.0)	4 (86.7)	1 (93.3)	1 (**100.0**)	--	--	--	--	--	--	0.12	0.5
S. marcescens	86	--	0 (0.0)	2 (2.2)	36 (42.7)	34 (80.9)	15 (97.8)	2 (**100.0**)	--	--	--	--	--	--	0.25	0.5
A. baumannii	76	--	--	--	--	--	0 (0.0)	1 (1.3)	1 (2.6)	7 (11.8)	10 (25.0)	16 (46.1)	11 (60.5)	30 (100.0)	32	>32
H. influenzae	68	45 (66.2)	17 (91.2)	5 (98.5)	1 (100.0)	--	--	--	--	--	--	--	--	--	≤0.015	0.03

a. Values in bold indicate percentage susceptible according to CLSI and US-FDA susceptible breakpoint of ≤8 μg/mL.
Abbreviations: CAZ = ceftazidime, NS = non-susceptible, MEM = meropenem, MDR = multidrug-resistant, XDR = extensively drug-resistant, CRE = carbapenem-resistant Enterobacteriaceae; ESBL = extended-spectrum β-lactamase.

Table 2. Activity of ceftazidime-avibactam and comparator antimicrobial agents when tested against bacterial isolates from ICU patients with pneumonia.

Organism/antimicrobial	MIC (μg/mL)		CLSI[a]	
	MIC_{50}	MIC_{90}	%S	%R
P. aeruginosa (407)				
Ceftazidime-avibactam[b]	2	4	96.1	3.9
Ceftazidime	2	32	81.3	13.8
Cefepime	4	16	82.8	7.6
Piperacillin-tazobactam	8	>64	76.7	12.3
Meropenem	0.5	8	78.1	15.2
Levofloxacin	0.5	>4	74.9	18.7
Gentamicin	2	>8	87.7	10.3
Amikacin	2	8	99.5	0.5
Colistin	2	2	99.8	0.0
MDR *P. aeruginosa* (79)				
Ceftazidime-avibactam[b]	4	16	82.3	17.7
Ceftazidime	32	>32	27.8	53.2
Cefepime	16	>16	29.1	31.6
Piperacillin-tazobactam	64	>64	17.7	45.6
Meropenem	8	>8	20.3	60.8
Levofloxacin	>4	>4	19.0	69.6
Gentamicin	8	>8	48.1	45.6
Amikacin	4	16	97.5	2.5
Colistin	1	2	100.0	0.0
Enterobacteriaceae (851)				
Ceftazidime-avibactam[b]	0.12	0.5	99.9	0.1
Ceftazidime	0.25	32	83.9	14.5
Ceftriaxone	0.12	>8	79.2	19.1
Piperacillin-tazobactam	2	64	84.9	8.5
Meropenem	≤0.06	≤0.06	96.4	3.3
Imipenem	≤0.12	1	92.9	3.8
Levofloxacin	≤0.12	>4	82.7	15.4
Gentamicin	≤1	2	91.8	7.2
Tigecycline[b]	0.25	1	99.3	0.0
Colistin	≤0.5	>8	-	-
MDR Enterobacteriaceae (85)				
Ceftazidime-avibactam[b]	0.5	2	98.8	1.2[b]
Ceftazidime	>32	>32	18.8	75.3
Ceftriaxone	>8	>8	7.1	92.9
Piperacillin-tazobactam	>64	>64	21.4	52.4
Meropenem	≤0.06	>8	63.5	32.9
Imipenem	1	>8	58.8	32.9
Levofloxacin	>4	>4	11.8	76.5
Gentamicin	8	>8	49.4	43.5
Tigecycline[b]	0.5	1	98.8	0.0[b]
Colistin	≤0.5	>8	-	-

a. Criteria as published by CLSI [2015] and EUCAST [2015]
b. Breakpoints from US-FDA Package Insert

Table 3. Ceftazidime-avibactam activity stratified by organism and β-lactamase production.

Organism / β-lactamase (no.)	No. of isolates (cumulative %) inhibited at ceftazidime-avibactam MIC (μg/mL) of:							MIC (μg/mL)	
	≤0.03	0.06	0.12	0.25	0.5	1	2	50%	90%
***K. pneumoniae* (58)**									
KPC-like (26)	1 (3.8)	1 (7.7)	1 (11.5)	2 (19.2)	8 (50.0)	8 (80.7)	5 (100.0)	0.5	2
CTX-M-15-like (15)		2 (13.3)	1 (20.0)	3 (40.0)	3 (60.0)	3 (93.3)	1 (100.0)	0.25	0.5
SHV ESBL (7)		1 (14.3)	1 (28.6)	0 (28.6)	1 (42.9)	4 (100.0)		0.5	-
FOX-like (2)			1 (50.0)	1 (100.0)				0.12	-
CTX-M-15-like + SHV-5 + OXA-1/30 (1)				1 (100.0)				-	-
Negative (7)[a]			2 (28.6)	3 (42.9)	2 (71.4)	2 (100.0)		0.5	-
***E. coli* (27)**									
CTX-M-15-like (15)	1 (6.7)	2 (20.0)	3 (40.0)	5 (73.3)	3 (93.3)	1 (100.0)		0.25	0.5
CMY-2-like (5)		1 (20.0)	0 (40.0)	3 (40.0)	1 (100.0)			0.25	-
CTX-M-14-like (4)			3 (75.0)	1 (100.0)				0.06	-
SHV ESBL (1)			1 (100.0)					-	-
CTX-M-14-like + TEM ESBL (1)					1 (100.0)			-	-
Negative (1)[a]				1 (100.0)				-	-

a. Negative results by Check-points for the following genes: CTX-M Groups 1, 2, 8+25 and 9, TEM ESBL, SHV ESBL, ACC, ACT/MIR, CMYII, DHA, FOX, KPC and NDM-1.

Figure 2. Antimicrobial susceptibility rates for ceftazidime-avibactam (CAZ-AVI), meropenem (MEM) and piperacillin-tazobactam (PT).