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Antimicrobial Activity of Ceftazidime-Avibactam and Comparator Agents When Tested against Bacterial Isolates Causing Infection in Cancer Patients (2012-2014)

HS SADER, DJ FARRELL, RK FLAMM, M CASTANHEIRA, 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: Avibactam (AVI) inhibits classes A (including ESBLs and KPCs), C (AmpC) and some D β-lactamases (BL), restoring ceftazidime (CAZ) activity against Gram-negative (GN) organisms producing these enzymes.

Methods: A total of 623 Gram-negative (GN) isolates were collected from 52 medical centers over three years (2012-2014) from patients with cancer as part of the International Network for Optimal Resistance Monitoring (INFORM) program in the United States. Isolates were tested for susceptibility (S) against CAZ-AVI (AVI at fixed 4 μg/mL) and comparator agents at a central laboratory by a reference broth microdilution method. BL encoding genes were evaluated for all *E. coli* (EC) and *Klebsiella* spp. (KSP) with an extended-spectrum BL (ESBL) phenotype by microarray-based assay.

Results: The isolates were predominantly from bloodstream (33.2%) and skin/soft tissue (26.0%), and the most frequent GN organisms were EC (31.5%), KSP (20.9%), *P. aeruginosa* (PSA; 14.1%) and *Enterobacter* spp. (EBS; 12.7%). ESBL-phenotype was observed among 17.3 and 11.2% of EC and KSP, respectively; and 21.5% of EBS were ceftazidime (CAZ)-non-S. All Enterobacteriaceae (ENT; n=486) were S to CAZ-AVI with the highest MIC value at 1 μg/mL. Meropenem (MEM) was also very active against ENT overall (99.6% S); but showed more limited activity against ESBL-phenotype KSP (84.6% S) and multidrug-resistant (MDR) ENT (93.3% S). ESBL-phenotype KSP and MDR-ENT exhibited low S to piperacillin-tazobactam (PT; 46.2 and 51.7%, respectively), gentamicin (GEN; 46.2 and 26.7%), levofloxacin (LEV; 53.8 and 10.0%) and colistin (83.3 and 86.4%). The most active agents tested against PSA were colistin (100.0% S), amikacin (97.7% S) and CAZ-AVI (96.6% S).

Conclusions: GN organisms isolated from cancer patients hospitalized in USA medical centers were highly S to CAZ-AVI, including PSA and MDR and/or carbapenem-resistant ENT. The role of CAZ-AVI for treatment of cancer patients should be further evaluated.

Organism (no. tested)	$MIC_{50/90}$ in μg/mL (% susceptible [US-FDA and CLSI])				
	CAZ-AVI	PT	MEM	GEN	LEV
Enterobacteriaceae (486)	0.12/0.25 (100.0)	2/16 (93.6)	≤0.06/≤0.0 6 (99.6)	≤1/2 (90.9)	≤0.12/>4 (81.3)
E. coli (196)	0.06/0.12 (100.0)	2/8 (94.9)	≤0.06/≤0.0 6 (100.0)	≤1/>8 (85.7)	≤0.12/>4 (63.3)
ESBL phenotype (34)	0.12/0.25 (100.0)	8/32 (82.4)	≤0.06/≤0.0 6 (100.0)	≤1/>8 (58.8)	>4/>4 (8.8)
Klebsiella spp. (129)	0.06/0.25 (100.0)	2/16 (92.9)	≤0.06/≤0.0 6 (98.4)	≤1/≤1 (94.6)	≤0.12/0.5 (95.3)
ESBL-phenotype (13)	0.25/1 (100.0)	32/>64 (46.2)	≤0.06/4 (84.6)	8/>8 (46.2)	1/>4 (53.8)
Enterobacter spp. (79)	0.25/0.5 (100.0)	4/32 (87.2)	≤0.06/≤0.0 6 (100.0)	≤1/≤1 (97.5)	≤0.12/0.5 (92.4)
CAZ-non-S EBS (17)	0.5/1 (100.0)	32/>64 (37.5)	≤0.06/0.25 (100.0)	≤1/>8 (88.2)	≤0.12/>4 (70.6)
MDR ENT (30)	0.12/0.5 (100.0)	16/>64 (51.7)	≤0.06/0.12 (93.3)	>8/>8 (26.7)	>4/>4 (10.0)
P. aeruginosa (88)	2/8 (96.6)	4/64 (84.1)	0.5/8 (79.5)	≤1/4 (93.2)	0.5/>4 (73.9)
MDR (12)	8/>32 (75.0)	>64/>64 (0.0)	>8/>8 (0.0)	4/>8 (50.0)	>4/>4 (16.7)

Introduction

Infection remains a significant cause of excess morbidity and premature mortality among cancer patients. The spectrum of infection continues to change, and it is influenced by various factors, including local epidemiology, the use of chemoprophylaxis, and the use of central venous catheters and other medical devices. Empirical antimicrobial treatment using broad spectrum agents must be started immediately in neutropenic patients with severe infection. Rapid introduction of effective antimicrobial therapy is decisive and knowledge of local microbiology is crucial for the selection of an empirical antimicrobial agent.

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 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 has recently been approved by the US Food and Drug Administration (FDA) for the treatment of complicated intra-abdominal infection (cIAI), in combination with metronidazole, 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) isolates causing infection in patients with cancer in US medical centers.

Methods

Bacterial isolates: A total of 623 Gram-negative organisms, including 486 Enterobacteriaceae and 88 *Pseudomonas aeruginosa* isolates, were collected from 52 US hospitals between January 2012 and December 2014 as part of the International Network for Optimal Resistance Monitoring (INFORM) program. Bacterial isolates determined to be significant by local criteria as the reported probable cause of the infection were consecutively collected (one per patient episode), and aerobic Gram-negative isolates from patients with cancer 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 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) or meropenem or doripenem. Further, isolates were categorized as multidrug-resistant (MDR), extensively drug-resistant (XDR) and 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 *Pseudomonas aeruginosa*.

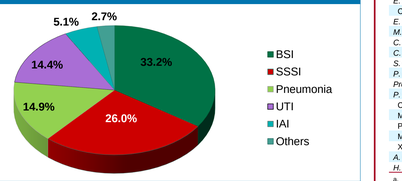
Antimicrobial susceptibility testing: All isolates were tested for susceptibility using the reference broth microdilution method as described by the CLSI. Ceftazidime was combined with avibactam at a fixed concentration of 4 μg/mL. Ceftazidime-avibactam breakpoints approved by the US-FDA (≤8/4 μg/mL 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, >1 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 capabilities to detect CTX-M Groups 1, 2, 8+25 and 9, TEM wild-type (WT) and ESBL, SHV WT and ESBL, ACC, ACT/MIR, CMYII, DHA, FOX, KPC and NDM-1. 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 IS 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 isolates were predominantly from bloodstream (33.2%) and skin/soft tissue (26.0%; Figure 1), and the most frequently isolated Gram-negative organisms were *E. coli* (31.5%), *Klebsiella* spp. (20.9%), *P. aeruginosa* (PSA; 14.1%) and *Enterobacter* spp. (12.7%; Figure 2).
- ESBL-phenotype was observed among 17.3 and 9.9% of *E. coli* and *K. pneumoniae*, respectively; and 25.0% of *Enterobacter cloacae* were not ceftazidime-susceptible (Tables 1 and 2).
- All Enterobacteriaceae (n=486) were categorized as susceptible to ceftazidime-avibactam, with the highest MIC value at 1 μg/mL (Tables 1 and 2 and Figure 3).
- Ceftazidime-avibactam was particularly active against multidrug-resistant Enterobacteriaceae (n=30; $MIC_{50/90}$, 0.12/0.5 μg/mL; highest MIC, 1 μg/mL), ESBL-phenotype *E. coli* (n=34; $MIC_{50/90}$, 0.12/0.25 μg/mL) and ESBL-phenotype *K. pneumoniae* (n=11; $MIC_{50/90}$, 0.25/1 μg/mL; highest MIC, 1 μg/mL; Tables 1 and 2 and Figure 3).
- Meropenem was also very active against Enterobacteriaceae overall ($MIC_{50/90}$, ≤0.06/≤0.06 μg/mL; 99.6% susceptible), but showed more limited activity against ESBL-phenotype *K. pneumoniae* ($MIC_{50/90}$, ≤0.06/4 μg/mL; 81.8% susceptible; data not shown) and multidrug-resistant strains ($MIC_{50/90}$, ≤0.06/0.12 μg/mL; 93.3% susceptible; Table 2).
- Ceftazidime-avibactam was very active against two CRE and XDR isolates of *K. pneumoniae*, with MIC values of 0.5 and 1 μg/mL (Table 1 and Figure 3).
- ESBL-phenotype *K. pneumoniae* and MDR Enterobacteriaceae exhibited low susceptibility rates for piperacillin-tazobactam (54.5 and 51.7% susceptible, respectively), gentamicin (36.4 and 26.7% susceptible, respectively), levofloxacin (45.5 and 10.0% susceptible, respectively) and colistin (75.0 and 86.4% susceptible [EUCAST], respectively; Table 2).
- The most common ESBL observed among *E. coli* was CTX-M-15-like (22 strains [64.7%], including two strains with CTX-M-15-like plus CMY-2-like and one strain with CTX-M-15-like plus DHA-like) and CTX-M-14-like (six strains; 17.6%). The highest ceftazidime-avibactam MIC value among isolates producing either CTX-M-15-like or CTX-M-14-like was only 0.5 μg/mL (MIC_{50}, 0.12 μg/mL; Table).
- CTX-M-15-like was also the most common β-lactamase detected among *K. pneumoniae* (four strains; 36.4%), and bla_{KPC-2} was identified in one strain only, which exhibited a ceftazidime-avibactam MIC of 0.5 μg/mL (Table 3).
- Ceftazidime-avibactam inhibited 96.6% of *P. aeruginosa* isolates at the US-FDA susceptible breakpoint of ≤8 μg/mL, and MIC_{50} and MIC_{90} values were 2 and 8 μg/mL, respectively. Susceptibility rates for ceftazidime ($MIC_{50/90}$, 2/32 μg/mL), cefepime ($MIC_{50/90}$, 2/16 μg/mL), piperacillin-tazobactam ($MIC_{50/90}$, 4/64 μg/mL) and meropenem ($MIC_{50/90}$, 0.5/8 μg/mL) were 86.4, 88.6, 84.1 and 79.5%, respectively (Table 2 and Figure 3).
- The addition of avibactam to ceftazidime increased the percentage of susceptible *P. aeruginosa* isolates from 86.4% to 96.6% (Table 2).
- Among non-β-lactam agents, colistin ($MIC_{50/90}$, 2/2 μg/mL; 100.0% susceptible) and amikacin ($MIC_{50/90}$, 2/4 μg/mL; 97.7% susceptible) were the most active compounds tested against *P. aeruginosa* (Table 2).
- Ceftazidime-avibactam exhibited good activity against *P. aeruginosa* isolates non-susceptible to ceftazidime (75.0% susceptible), meropenem (83.3% susceptible) and piperacillin-tazobactam (78.6% susceptible; Table 1).
- MDR and XDR phenotypes were observed in 13.6 and 11.4% of *P. aeruginosa* isolates, respectively. Among MDR and XDR *P. aeruginosa*, 75.0 and 70.0% were susceptible to ceftazidime-avibactam, respectively (Table 1); while all isolates were non-susceptible to ceftazidime, piperacillin-tazobactam (Figure 3) and meropenem (Figure 3) and 80.0-83.3% of isolates were susceptible to amikacin.
- Ceftazidime-avibactam was highly active against *Haemophilus influenzae* (n=28; highest MIC, 0.03 μg/mL), but showed limited activity against *Acinetobacter* spp. (n=5; MIC_{50}, >32 μg/mL; Table 1).

Figure 1. Distribution of isolates by site of infection.



Conclusions

- Gram-negative organisms, including *P. aeruginosa* and MDR and/or carbapenem-resistant Enterobacteriaceae, isolated from cancer patients hospitalized in USA medical centers were highly susceptible to ceftazidime-avibactam.
- The role of ceftazidime-avibactam for treatment of Gram-negative infections in cancer patients should be further evaluated.

References

1. Avycaz (2015). Avycaz (ceftazidime-avibactam) package insert. United States Food and Drug Administration. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206494s000lbl.pdf. Accessed March 2016.
2. Bush K (2015). A resurgence of beta-lactamase inhibitor combinations effective against multidrug-resistant Gram-negative pathogens. *Int J Antimicrob Agents* 46: 483-493.
3. Clinical and Laboratory Standards Institute (2015). *M07-A10. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard- tenth edition*. Wayne, PA: CLSI.
4. Clinical and Laboratory Standards Institute (2016). *M100-S26. Performance standards for antimicrobial susceptibility testing: 26th informational supplement.* Wayne, PA: CLSI.
5. EUCAST (2016). Breakpoint tables for interpretation of MICs and zone diameters. Version 6.0, January 2016. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 2016.
6. Legrand M, Max A, Peigne V, Mariotte E, Canet E, Debrumetz A, Lemiale V, Seguin A, Darmon M, Schlemmer B, Azoulay E (2012). Survival in neutropenic patients with severe sepsis or septic shock. *Crit Care Med* 40: 43-49.
7. Li H, Estabrook M, Jacoby GA, Nichols WW, Testa RT, Bush K (2015). In vitro susceptibility of characterized beta-lactamase-producing strains tested with avibactam combinations. *Antimicrob Agents Chemother* 59: 1788-1793.
8. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL (2012). Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 18: 268-281.
9. Nesher L, Rolston KV (2014). The current spectrum of infection in cancer patients with chemotherapy related neutropenia. *Infection* 42: 5-13.
10. Penack O, Becker C, Buchheidt D, Christopeit M, Kiehl M, von Lilienfeld-Toal M, Hentrich M, Reinwald M, Salwender H, Schalk E, Schmidt-Hieber M, Weber T, Ostermann H (2014). Management of sepsis in neutropenic patients: 2014 updated guidelines from the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (AGIHO). *Ann Hematol* 93: 1083-1095.
11. Zhanel GG, Lawson CD, Adam H, Schweizer F, Zelenitsky S, Lagace-Wiens PR, Denisuik A, Rubinstein E, Gin AS, Hoban DJ, Lynch JP, 3rd, Karlowsky JA (2013). Ceftazidime-avibactam: a novel cephalosporin/β-lactamase inhibitor combination. *Drugs* 73: 159-177.

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Table 1. Summary of ceftazidime-avibactam activity tested against Gram-negative bacterial isolates causing infections in patients with cancer (USA, 2012-2014).

Organism	No.	No. of isolates (cumulative %) inhibited at ceftazidime-avibactam MIC (μg/mL) of[a]:									MIC_{50}	MIC_{90}
		≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32		
Enterobacteriaceae	486	60 (12.3)	170 (47.3)	160 (80.2)	66 (93.8)	23 (98.6)	7 (**100.0**)	--	--	--	--	--	--	0.12	0.25
CRE	2	--	--	--	--	1 (50.0)	1 (**100.0**)	--	--	--	--	--	--	0.5	--
MDR	30	1 (3.3)	2 (10.0)	12 (50.0)	7 (73.3)	5 (90.0)	3 (**100.0**)	--	--	--	--	--	--	0.12	0.5
XDR	2	--	--	--	--	1 (50.0)	1 (**100.0**)	--	--	--	--	--	--	0.5	--
E. coli	196	28 (14.3)	81 (55.6)	72 (92.3)	13 (99.0)	1 (99.5)	1 (**100.0**)	--	--	--	--	--	--	0.06	0.12
ESBL-phenotype	34	2 (5.9)	3 (14.7)	19 (70.6)	8 (94.1)	1 (97.1)	1 (**100.0**)	--	--	--	--	--	--	0.12	0.25
K. pneumoniae	111	6 (5.4)	51 (51.4)	32 (80.2)	14 (92.8)	6 (98.2)	2 (**100.0**)	--	--	--	--	--	--	0.06	0.25
ESBL-phenotype	11	--	--	5 (45.5)	2 (63.6)	2 (81.8)	2 (**100.0**)	--	--	--	--	--	--	0.25	1
MEM-NS	2	--	--	--	--	1 (50.0)	1 (**100.0**)	--	--	--	--	--	--	0.5	--
K. oxytoca	18	2 (11.1)	8 (55.6)	7 (94.4)	0 (94.4)	0 (94.4)	1 (**100.0**)	--	--	--	--	--	--	0.06	0.12
P. mirabilis	28	17 (60.7)	10 (96.4)	1 (**100.0**)	--	--	--	--	--	--	--	--	--	0.03	0.06
E. cloacae	64	--	5 (7.8)	24 (45.3)	24 (82.8)	9 (96.9)	2 (**100.0**)	--	--	--	--	--	--	0.25	0.5
CAZ-NS	16	--	--	1 (6.2)	5 (37.5)	8 (87.5)	2 (**100.0**)	--	--	--	--	--	--	0.5	1
E. aerogenes	15	--	3 (20.0)	9 (80.0)	1 (86.7)	2 (**100.0**)	--	--	--	--	--	--	--	0.12	0.5
M. morganii	7	3 (42.9)	2 (71.4)	1 (85.7)	1 (**100.0**)	--	--	--	--	--	--	--	--	0.06	--
C. koseri	4	1 (25.0)	2 (75.0)	1 (**100.0**)	--	--	--	--	--	--	--	--	--	0.06	--
C. freundii	10	--	1 (10.0)	6 (70.0)	3 (**100.0**)	--	--	--	--	--	--	--	--	0.12	0.25
S. marcescens	23	--	2 (8.7)	6 (34.8)	9 (73.9)	5 (95.7)	1 (**100.0**)	--	--	--	--	--	--	0.25	0.5
P. vulgaris	6	2 (33.3)	4 (**100.0**)	--	--	--	--	--	--	--	--	--	--	0.06	--
Providencia spp.	4	1 (25.0)	1 (50.0)	1 (75.0)	1 (**100.0**)	--	--	--	--	--	--	--	--	0.06	--
P. aeruginosa	88	--	--	1 (1.1)	0 (1.1)	4 (5.7)	32 (42.0)	27 (72.7)	12 (86.4)	9 (**96.6**)	1 (97.7)	0 (97.7)	2 (100.0)	2	8
CAZ-NS	12	--	--	--	--	--	--	2 (16.7)	1 (25.0)	6 (**75.0**)	1 (83.3)	0 (83.3)	2 (100.0)	8	>32
MEM-NS	18	--	--	--	--	--	--	3 (16.7)	4 (38.9)	8 (**83.3**)	1 (88.9)	0 (88.9)	2 (100.0)	8	>32
PT-NS	14	--	--	--	--	--	--	3 (21.4)	1 (28.6)	7 (**78.6**)	1 (85.7)	0 (85.7)	2 (100.0)	8	>32
MDR	12	--	--	--	--	--	--	2 (16.7)	1 (25.0)	6 (**75.0**)	1 (83.3)	0 (83.3)	2 (100.0)	8	>32
XDR	10	--	--	--	--	--	--	2 (20.0)	0 (20.0)	5 (**70.0**)	1 (80.0)	0 (80.0)	2 (100.0)	8	>32
A. baumannii	5	--	--	--	--	--	--	--	1 (20.0)	0 (20.0)	1 (40.0)	0 (40.0)	3 (100.0)	>32	--
H. influenzae	28	28 (**100.0**)	--	--	--	--	--	--	--	--	--	--	--	≤0.015	0.03

a. Values in bold indicate percentage susceptible.
Abbreviations: CRE: carbapenem-resistant Enterobacteriaceae; MDR = multidrug-resistant, XDR = extensively drug-resistant, ESBL = extended-spectrum β-lactamase, MEM = meropenem, NS = non-susceptible, CAZ = ceftazidime, PT = piperacillin-tazobactam,

Table 2. Activity of ceftazidime-avibactam and comparator antimicrobial agents when tested against bacterial isolates causing infections in patients with cancer (2012-2014).

Antimicrobial Agent	MIC_{50}	MIC_{90}	CLSI[a]		EUCAST[a]	
			%S	%R	%S	%R
Enterobacteriaceae (486)[b]						
Ceftazidime-avibactam	0.12	0.25	100.0[c]	0.0[c]	-	-
Ceftazidime	0.25	16	88.7	10.1	86.4	11.3
Ceftriaxone	≤0.06	>8	84.6	14.4	84.6	14.4
Piperacillin-tazobactam	2	16	93.6	2.7	89.6	6.4
Meropenem	≤0.06	≤0.06	99.6	0.4	99.6	0.2
Levofloxacin	≤0.12	>4	81.3	17.7	80.7	18.7
Gentamicin	≤1	2	90.9	8.2	90.3	9.1
Tigecycline	0.12	1	99.2[c]	0.0[c]	95.1	0.8
Colistin	≤0.5	>8	-	-	87.0	13.0
MDR strains (30)[d]						
Ceftazidime-avibactam	0.12	0.5	100.0[c]	0.0[c]	-	-
Ceftazidime	32	>32	16.7	76.7	10.0	83.3
Ceftriaxone	>8	>8	3.3	93.3	3.3	93.3
Piperacillin-tazobactam	16	>64	51.7	17.2	44.8	48.3
Meropenem	≤0.06	0.12	93.3	6.7	93.3	3.3
Levofloxacin	>4	>4	10.0	80.0	10.0	90.0
Gentamicin	>8	>8	26.7	66.7	20.0	73.3
Tigecycline	0.25	1	100.0	0.0[c]	93.3	0.0
Colistin	≤0.5	>8	-	-	86.4	13.6
P. aeruginosa (88)						
Ceftazidime-avibactam	2	8	96.6	3.4[b]	-	-
Ceftazidime	2	32	86.4	11.4	86.4	13.6
Cefepime	2	16	88.6	6.8	88.6	11.4
Piperacillin-tazobactam	4	64	84.1	9.1	84.1	15.9
Meropenem	0.5	8	79.5	17.0	79.5	9.1
Levofloxacin	0.5	>4	73.9	20.5	68.2	26.1
Gentamicin	≤1	4	93.2	6.8	93.2	6.8
Amikacin	2	4	97.7	2.3	97.7	2.3
Colistin	2	2	100.0	0.0	100.0	0.0

a. Criteria as published by CLSI [2016] and EUCAST [2016].
b. Organisms include: *Citrobacter freundii* (9), *C. koseri/ species complex* (1), *C. koseri* (4), *Enterobacter aerogenes* (15), *Escherichia coli* (196), *E. cloacae* (48), *E. cloacae* species complex (16), *Klebsiella oxytoca* (18), *K. pneumoniae* (111), *Morganella morganii* (7), *Proteus mirabilis* (28), *P. vulgaris* (6), *Providencia rettgeri* (2), *P. stuartii* (2), *Serratia marcescens* (23).
c. Breakpoints from US-FDA Package Insert.
d. Organisms include: *Escherichia coli* (18), *Enterobacter cloacae* (3), *Klebsiella pneumoniae* (6), *Proteus mirabilis* (1), *Providencia stuartii* (1), *Serratia marcescens* (1).

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	50%	90%
***E. coli* (34)**								
CTX-M-15-like (19)	1 (5.3)	1 (10.5)	12 (73.7)	5 (100.0)			0.12	0.25
CTX-M-14-like (6)	1 (16.7)	1 (33.3)	4 (100.0)				0.12	-
CMY-2-like (2)			1 (50.0)	1 (100.0)			0.12	-
CTX-M-15-like + CMY-2-like (2)				1 (50.0)	1 (100.0)		0.25	-
CTX-M-15-like + DHA-like (1)			1 (100.0)				-	-
Negative (4)[a]		1 (25.0)	1 (50.0)	1 (75.0)	0 (75.0)	1 (100.0)	0.12	-
***K. pneumoniae* (11)**								
CTX-M-15-like (4)				1 (25.0)	1 (50.0)	2 (100.0)	0.5	-
SHV ESBL (2)			2 (100.0)				0.12	-
KPC-2 (1)					1 (100.0)		-	-
CTX-M-14-like (1)				1 (100.0)			-	-
FOX-like (1)			1 (100.0)				-	-
CTX-M-15-like + SHV 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. Frequency of occurrence of Gram-negative organisms causing infection in patients with cancer.

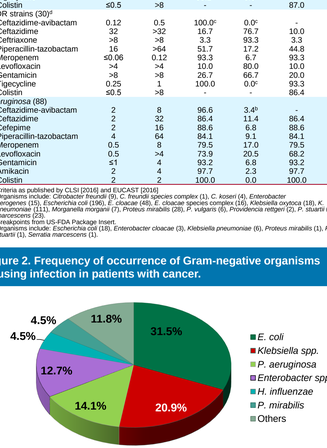
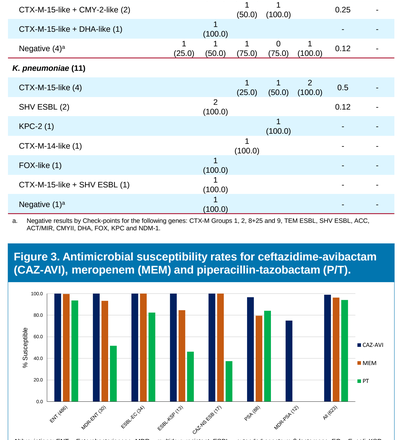


Figure 3. Antimicrobial susceptibility rates for ceftazidime-avibactam (CAZ-AVI), meropenem (MEM) and piperacillin-tazobactam (P/T).



Abbreviations: ENT = Enterobacteriaceae, MDR = multidrug-resistant, ESBL = extended-spectrum β-lactamase, EC = *E. coli*, KSP = *Klebsiella* spp., CAZ-NS ESB = ceftazidime-non-susceptible *Enterobacter* spp. And PSA = *P. aeruginosa*