Antimicrobial Activity of Ceftazidime-Avibactam Tested against Multidrug-Resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* Isolates from United States Medical Centers (2013–2016)

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ABSTRACT

Background: The *in vitro* activity of ceftazidime-avibactam (CAZ-AVI) and many comparator agents were tested against various resistant subsets of organisms selected among 36,380 *Enterobacteriaceae* and 7,868 *Pseudomonas aeruginosa* isolates.

Methods: Isolates were consecutively collected from 94 US hospitals in 2013-2016 and tested for susceptibility by reference broth microdilution methods in a central monitoring laboratory (JMI Laboratories) as part of the International Network for Optimal Resistance Monitoring (INFORM) program. *Enterobacteriaceae* strains with elevated CAZ-AVI MIC values (≥16 µg/mL) were evaluated for the presence of genes encoding extended-spectrum β-lactamases, KPC, NDM, and transferable AmpC enzymes.

Results: CAZ-AVI inhibited 99.9% of all *Enterobacteriaceae* at the susceptible (S) breakpoint of ≤8 µg/mL and was active against multidrug-resistant (MDR; n=2,953; $MIC_{50/90}$, 0.25/1 µg/mL; 99.2%S), extensively drug-resistant (XDR; n=448; $MIC_{50/90}$, 0.5/2 µg/mL; 97.8%S), and carbapenem-resistant isolates (CRE; n=513; $MIC_{50/90}$, 0.5/2 µg/mL; 97.5%S). Only 82.2% of MDR *Enterobacteriaceae* and 64.2% of ceftriaxone-nonsusceptible (NS) *Klebsiella pneumoniae* (n=1,063) were meropenem-S. Among *Enterobacter cloacae* (n=3,740; 22.2% ceftazidime-NS), 99.8% of isolates, including 99.3% of ceftazidime-NS isolates, were CAZ-AVI-S. Only 23 of 36,380 *Enterobacteriaceae* (0.06%) isolates were CAZ-AVI-NS, including 9 MBL-producers (0.02%) and 2 KPC-producing strains with porin alteration; the remaining 12 strains showed negative results for all β-lactamases tested. CAZ-AVI showed potent activity against *P. aeruginosa* (n=7,868; $MIC_{50/90}$, 2/4 µg/mL; 97.1%S), including meropenem-NS (n=1,471; $MIC_{50/90}$, 4/16 µg/mL; 87.2%S) and MDR (n=1,562; $MIC_{50/90}$, 4/16 µg/mL; 86.5%S) isolates, and inhibited 71.8% of isolates NS to meropenem, piperacillin-tazobactam, and ceftazidime (n=628).

Conclusions: CAZ-AVI demonstrated potent activity against a large US collection (n=44,248) of contemporary gram-negative bacilli, including organisms resistant to most currently available agents, such as CRE and meropenem-NS *P. aeruginosa*.

INTRODUCTION

- The wide dissemination of extended-spectrum β-lactamases (ESBLs; such as CTX-M and SHV) and carbapenemases (such as KPC and OXA-48) has left clinicians and patients with very few treatment options for infections caused by multidrug-resistant (MDR) *Enterobacteriaceae*
- Avibactam effectively inactivates class A (ESBLs and KPC), class C (AmpC), and some class D (such as OXA-48) β-lactamases
- Ceftazidime-avibactam is approved by the United States Food and Drug Administration (US FDA) and by the European Medicine Agency (EMA) to treat complicated intra-abdominal infections (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 approved to treat nosocomial pneumonia in Europe and has been studied in pediatric patients (NCT01893346)
- As part of the International Network for Optimal Resistance Monitoring (INFORM) surveillance program, we evaluated the activity of ceftazidime-avibactam against a large collection of contemporary (2013–2016) MDR gram-negative organisms causing infections in patients from US medical centers

MATERIALS AND METHODS

Bacterial isolates

- 36,380 *Enterobacteriaceae* and 7,868 *Pseudomonas aeruginosa* isolates were collected from 94 medical centers among 39 states from all 9 US census divisions in 2013-2016 as part of the INFORM program
- These isolates were collected from patients with pneumonia (n=11,666; 26.4%), bloodstream infections (n=6,110; 13.8%), skin and skin structure infections (n=9,728; 22.0%), urinary tract infections (n=12,688; 28.7%), intra-abdominal infections (n=2,038; 4.6%), and other infection types (n=2,018; 4.6%) according to defined protocols
- Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the program

Resistant subsets

- Carbapenem-resistant *Enterobacteriaceae* (CRE) were defined as isolates displaying imipenem, meropenem, and/or doripenem MIC values at ≥4 µg/mL (CLSI, 2017)
 - Imipenem was not applied to *Proteus mirabilis* and indole-positive Proteeae due to the intrinsically elevated MIC values
- MDR, extensively drug-resistant (XDR), and pan-drug-resistant (PDR) *Enterobacteriaceae* strains were classified according to recommended guidelines (Magiorakos et al., 2012) and were based on the following recommended parameters:
 - MDR = nonsusceptible (NS; CLSI breakpoints) to at least 3 antimicrobial classes
 - XDR = susceptible (S) to 2 or fewer antimicrobial classes
- *Enterobacteriaceae* analysis included the following antimicrobial classes and drug representatives:
 - Broad-spectrum cephalosporins (ceftriaxone, ceftazidime, and cefepime), carbapenems (imipenem, meropenem, and doripenem), broad-spectrum penicillin combined with β-lactamase-inhibitor (piperacillin-tazobactam), fluoroquinolones (ciprofloxacin and levofloxacin), aminoglycosides (gentamicin, tobramycin, and amikacin), glycylcyclines (tigecycline), and the polymyxins (colistin)
- *P. aeruginosa* analysis included the following antimicrobial classes and drug representatives:
 - Antipseudomonal cephalosporins (ceftazidime and cefepime), carbapenems (imipenem, meropenem, and doripenem), broad-spectrum penicillins combined with β-lactamase-inhibitor (piperacillin-tazobactam), fluoroquinolones (ciprofloxacin and levofloxacin), aminoglycosides (gentamicin, tobramycin, and amikacin), and the polymyxins (colistin)

Susceptibility testing

- Broth microdilution test method was conducted according to CLSI, and ceftazidime-avibactam was tested with avibactam at fixed concentration of 4 µg/mL
- CLSI susceptibility interpretive criteria were applied for comparator agents, and the US FDA breakpoint criteria were applied for ceftazidime-avibactam (susceptible at ≤8 µg/mL and resistant at ≥16 µg/mL when testing *Enterobacteriaceae* and *P. aeruginosa*)

RESULTS

- Ceftazidime-avibactam inhibited 99.9% of all *Enterobacteriaceae* isolates (n=36,380) at the susceptible breakpoint of ≤8 µg/mL (Tables 1 and 2 and Figure 1) and was highly active against:
 - MDR: n=2,953; $MIC_{50/90}$, 0.25/1 µg/mL; 99.2%S
 - XDR: n=448; $MIC_{50/90}$, 0.5/2 µg/mL; 97.8%S
 - CRE: n=513; $MIC_{50/90}$, 0.5/2 µg/mL; 97.5%S
- Amikacin (99.2%S), tigecycline (98.0%S [US FDA]), and meropenem (98.5%S) were also very active against the entire collection of *Enterobacteriaceae* isolates, but these antimicrobial agents exhibited limited activity against MDR, XDR, and CRE isolates (Table 2 and Figure 2)
- The most active compound tested against MDR (Figure 2) and XDR *Enterobacteriaceae* isolates was ceftazidime-avibactam, followed by tigecycline, amikacin, and meropenem (Table 2)
- Among CRE, 97.5% of isolates were susceptible to ceftazidime-avibactam, 98.8% of isolates were susceptible (US FDA criteria) to tigecycline, 68.2% were susceptible to amikacin, and 79.1% were susceptible to colistin at ≤2 µg/mL (Table 2)
- Only 23 of 36,380 *Enterobacteriaceae* (0.06%) were ceftazidime-avibactam-nonsusceptible, including:
 - 6 NDM-1-producing strains (3 *Escherichia coli*, 2 *Klebsiella pneumoniae,* and 1 *Enterobacter cloacae* with MIC of >32 µg/mL)
 - 1 VIM-4-producing *K. pneumoniae* (MIC, >32 µg/mL)
 - 1 IMP-64-producing *P. mirabilis* (MIC, >32 µg/mL)
 - 1 IMP-27-producing *Morganella morganii* (MIC, 16 µg/mL)
 - 2 KPC-producing isolates with porin alterations, a *K. pneumoniae* and an *E. cloacae* (MIC, 16 µg/mL)
 - 12 isolates (4 *E. cloacae*, 1 *E. aerogenes*, 5 *Providencia stuartii,* and 2 *Serratia marcescens*) with negative results for all β-lactamases tested
- Ceftazidime-avibactam was also active against colistin-resistant *K. pneumoniae* (99.5%S) and ceftazidime-nonsusceptible *E. cloacae* (99.3%S; Table 1)
- Ceftazidime-avibactam exhibited potent activity against *P. aeruginosa* (97.1%S), including most MDR (86.5%S) and XDR (75.9%S) isolates (Tables 1 and 2 and Figures 1 and 2)

Table 1 Antimicrobial activity of ceftazidime-avibactam tested against antimicrobial resistant *Enterobacteriaceae* and *P. aeruginosa* from US hospitals (2013–2016)

Organism (no. of isolates)	No. of isolates at MIC (µg/mL; cumulative %)													MIC_{50}	MIC_{90}
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32		
Enterobacteriaceae (36,380)	1334 3.7	4428 15.8	11139 46.5	12342 80.4	4815 93.6	1631 98.1	448 99.3	142 99.7	63 99.9	15 99.9	13 >99.9	1 >99.9	9 100.0	0.12	0.25
CRE (513)	16 3.1	5 4.1	13 6.6	35 13.5	76 28.3	137 55.0	138 81.9	59 93.4	20 97.3	1 97.5	4 98.2	0 98.2	9 100.0	0.5	2
MDR (2,953)	98 3.3	217 10.7	428 25.2	597 45.4	587 65.3	525 83.0	296 93.1	116 97.0	53 98.8	13 99.2	13 99.7	1 99.7	9 100.0	0.25	1
XDR (448)	16 3.6	9 5.6	20 10.0	25 15.6	53 27.5	126 55.6	117 81.7	44 91.5	23 96.7	5 97.8	4 98.7	0 98.7	6 100.0	0.5	2
Colistin-NS *K. pneumoniae* (205)	9 4.4	4 6.3	22 17.1	49 41.0	30 55.6	36 73.2	32 88.8	13 95.1	9 99.5	0 99.5	0 99.5	0 99.5	1 100.0	0.25	2
CAZ-NS *E. cloacae* (831)	13 1.6	3 1.9	7 2.8	44 8.1	229 35.6	345 77.1	146 94.7	30 98.3	8 99.3	0 99.3	3 99.6	1 99.8	2 100.0	0.5	1
P. aeruginosa (7,868)					141 1.8	388 6.7	2771 41.9	2779 77.3	1137 91.7	426 97.1	134 98.8	43 99.4	49 100.0	2	4
CAZ-NS (1,204)				1 0.1	1 0.2	7 0.7	93 8.5	317 34.8	344 63.4	216 81.3	133 92.4	43 95.9	49 100.0	4	16
MEM-NS (1,471)					4 0.3	8 0.8	121 9.0	382 35.0	485 68.0	282 87.2	107 94.4	37 96.9	45 100.0	4	16
P-T-NS (1,497)				2 0.1	1 0.2	15 1.2	108 8.4	360 32.5	467 63.7	336 86.1	125 94.5	39 97.1	44 100.0	4	16
CAZ, MEM, and P-T-NS (628)							22 3.5	106 20.4	174 48.1	149 71.8	101 87.9	35 93.5	41 100.0	8	32
MDR (1,562)					8 0.5	18 1.7	129 9.9	384 34.5	498 66.4	314 86.5	122 94.3	42 97.0	47 100.0	4	16
XDR (717)				1 0.1	0 0.1	1 0.3	32 4.7	126 22.3	190 48.8	194 75.9	93 88.8	36 93.9	44 100.0	8	32

Abbreviations: CRE, carbapenem-resistant *Enterobacteriaceae*; MDR, multidrug-resistant; XDR, extensively drug-resistant; NS, nonsusceptible; MEM, meropenem; CAZ, ceftazidime; and P-T, piperacillin-tazobactam

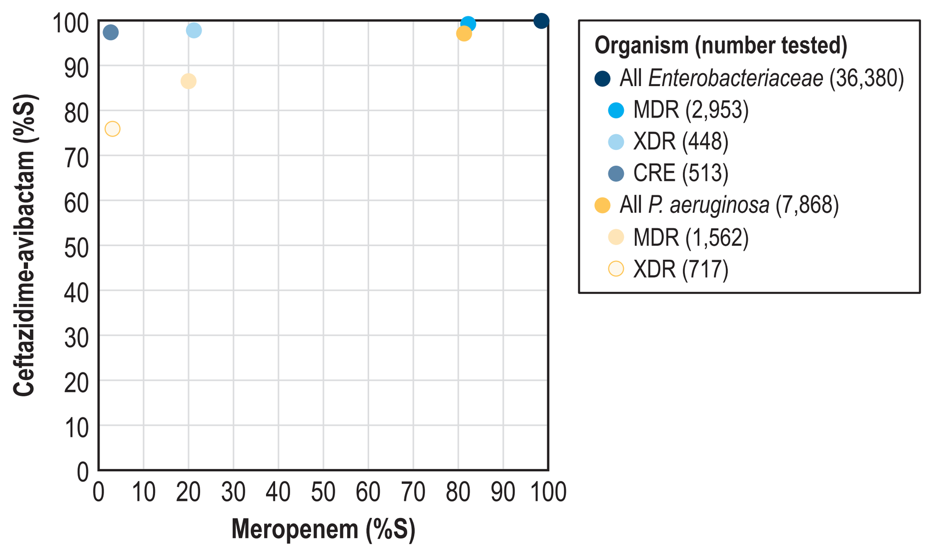
- Ceftazidime-avibactam retained *in vitro* activity against *P. aeruginosa* isolates nonsusceptible to meropenem (87.2%S), piperacillin-tazobactam (86.1%S), or ceftazidime (81.3%S), as well as isolates nonsusceptible to meropenem, piperacillin-tazobactam, and ceftazidime (71.8%S; Table 1)
- When tested against *P. aeruginosa*, amikacin was active against 87.1% of MDR; 80.8% of XDR; and 83.0% of isolates nonsusceptible to ceftazidime, meropenem, and piperacillin-tazobactam at the CLSI susceptible breakpoint of ≤16 µg/mL (Table 2 and Figure 2)

Table 2 Activity of ceftazidime-avibactam and comparator antimicrobial agents when tested against *Enterobacteriaceae*, *P. aeruginosa*, and selected resistant subsets

Organism / antimicrobial agent (no. tested)	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %R
***Enterobacteriaceae* (36,380)**				
Ceftazidime-avibactam[b]	0.12	0.25	99.9	0.1[b]
Ceftazidime	0.25	8	88.8	9.9
Piperacillin-tazobactam	2	16	92.7	4.1
Meropenem	≤0.06	≤0.06	98.5	1.3
Levofloxacin	≤0.12	>4	82.6	15.6
Gentamicin	≤1	2	91.2	7.6
Amikacin	2	4	99.2	0.2
Tigecycline	0.25	1	98.0	0.1[b]
Colistin[c]	≤0.5	>8	78.2	21.8
MDR (2,953)[d]				
Ceftazidime-avibactam[b]	0.25	1	99.2	0.8[b]
Piperacillin-tazobactam	16	>64	52.7	29.8
Meropenem	≤0.06	8	82.2	15.3
Amikacin	4	16	91.1	2.2
Tigecycline	0.5	4	88.9	0.3[b]
Colistin[c]	≤0.5	>8	60.7	39.3
XDR (448)[e]				
Ceftazidime-avibactam[b]	0.5	2	97.8	2.2[b]
Piperacillin-tazobactam	>64	>64	7.1	83.7
Meropenem	8	>8	21.2	72.5
Amikacin	16	32	60.2	9.6
Tigecycline	0.5	4	90.0	0.2[b]
Colistin[c]	≤0.5	>8	61.3	38.7
CRE (513)[f]				
Ceftazidime-avibactam[b]	0.5	2	97.5	2.5[b]
Piperacillin-tazobactam	>64	>64	3.1	91.2
Meropenem	>8	>8	2.7	89.7
Amikacin	8	32	68.2	7.0
Tigecycline	0.5	1	98.8	0.0[b]
Colistin[c]	≤0.5	>8	79.1	20.9
***P. aeruginosa* (7,868)**				
Ceftazidime-avibactam[b]	2	4	97.1	2.9[b]
Ceftazidime	2	32	84.7	10.9
Piperacillin-tazobactam	4	64	81.0	9.4
Meropenem	0.5	8	81.3	12.8
Levofloxacin	0.5	>4	74.5	18.6
Gentamicin	2	8	87.0	8.4
Amikacin	4	8	96.5	1.9
Colistin	1	2	99.6	0.4
MDR (1,562)				
Ceftazidime-avibactam[b]	4	16	86.5	13.5[b]
Ceftazidime	16	>32	43.6	41.6
Piperacillin-tazobactam	64	>64	31.2	36.2
Meropenem	8	>8	20.0	58.2
Amikacin	8	32	87.1	7.6
Colistin	1	2	99.2	0.8
XDR (717)				
Ceftazidime-avibactam[b]	8	32	75.9	24.1[b]
Ceftazidime	32	>32	21.5	60.0
Piperacillin-tazobactam	>64	>64	7.7	52.6
Meropenem	>8	>8	3.1	79.6
Amikacin	8	>32	80.8	11.6
Colistin	1	2	99.3	0.7
Ceftazidime, meropenem, and piperacillin-tazobactam-nonsusceptible (628)				
Ceftazidime-avibactam[b]	8	32	71.8	28.2[b]
Levofloxacin	>4	>4	21.9	66.2
Gentamicin	4	>8	54.0	37.4
Amikacin	8	>32	83.0	10.7
Colistin	1	2	99.5	0.5

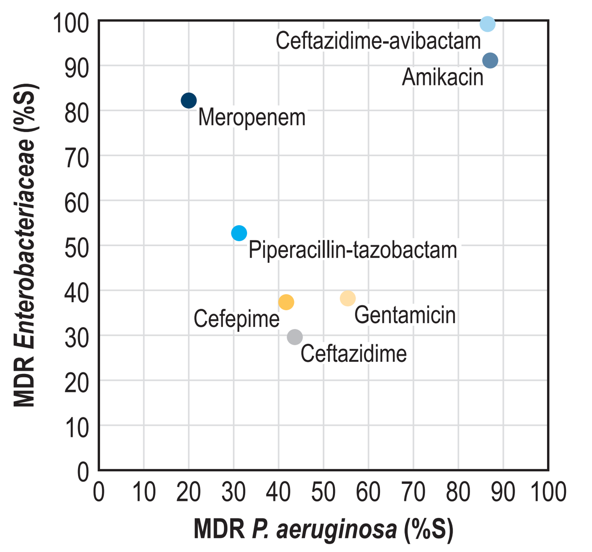
[a] Criteria as published by CLSI
[b] Breakpoints from FDA Package Insert; susceptible at ≤8 µg/mL and resistant at ≥16 µg/mL
[c] EUCAST breakpoints were applied; susceptible at ≤2 µg/mL and resistant at ≥4 µg/mL
[d] Organisms include: *Citrobacter freundii* (59), *C. koseri* (1), *Enterobacter aerogenes* (42), *E. cloacae* (119), *E. cloacae* species complex (153), *Escherichia coli* (797), *Hafnia alvei* (3), *Klebsiella oxytoca* (55), *K. pneumoniae* (793), *Morganella morganii* (174), *Proteus mirabilis* (426), *P. vulgaris* (5), *P. vulgaris* group (1), *Providencia rettgeri* (17), *P. stuartii* (191), *Raoultella ornithinolytica* (1), *Serratia liquefaciens* (1), *S. marcescens* (112), unspeciated *Raoultella* (2), unspeciated *Serratia* (1).
[e] Organisms include: *Citrobacter freundii* (9), *Enterobacter aerogenes* (1), *E. cloacae* (44), *Escherichia coli* (12), *Klebsiella oxytoca* (8), *K. pneumoniae* (297), *Morganella morganii* (17), *Proteus mirabilis* (19), *Providencia stuartii* (18), *Raoultella ornithinolytica* (1), *Serratia marcescens* (21), unspeciated *Raoultella* (1)
[f] Organisms include: *Citrobacter freundii* (6), *Enterobacter aerogenes* (13), *E. cloacae* (5), *E. cloacae* species complex (50), *Escherichia coli* (24), *Klebsiella oxytoca* (16), *K. pneumoniae* (368), *Proteus mirabilis* (4), *Providencia stuartii* (2), *Raoultella ornithinolytica* (1), *Serratia marcescens* (22), unspeciated *Raoultella* (2)

Figure 1. Comparative coverage (susceptibility rates) of ceftazidime-avibactam and meropenem when tested against resistant subsets of *Enterobacteriaceae* and *P. aeruginosa* from US hospitals (2013-2016)



Ceftazidime-avibactam (%S)
Meropenem (%S)
0
10
20
30
40
50
60
70
80
90
100
Organism (number tested)
All Enterobacteriaceae (36,380)
MDR (2,953)
XDR (448)
CRE (513)
All P. aeruginosa (7,868)
MDR (1,562)
XDR (717)

Figure 2. Antimicrobial susceptibility of multidrug-resistant *Entero-bacteriaceae* and multidrug-resistant *P. aeruginosa* from US hospitals



MDR Enterobacteriaceae (%S)
MDR P. aeruginosa (%S)
0
10
20
30
40
50
60
70
80
90
100
Ceftazidime-avibactam
Amikacin
Meropenem
Piperacillin-tazobactam
Cefepime
Gentamicin
Ceftazidime

CONCLUSIONS

- Ceftazidime-avibactam demonstrated potent activity against a large US collection (n=44,248) of contemporary gram-negative bacilli, including organisms resistant to most currently available agents, such as CRE and meropenem-nonsusceptible *P. aeruginosa*
- Only ceftazidime-avibactam and amikacin were active against >85% of MDR *Enterobacteriaceae* and MDR *P. aeruginosa* isolates combined (Figure 2)
- Ceftazidime-avibactam represents a valuable option for treating serious infections caused by antimicrobial resistant gram-negative organisms in US medical centers

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