ICAAC 2015
C-148

Ceftazidime-avibactam Activity Tested against Ceftazidime-non-susceptible *Citrobacter* spp., *Enterobacter* spp., *Serratia marcescens*, and *Pseudomonas aeruginosa* from United States Medical Centers (2011-2014)

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Abstract

Background: Avibactam (AVI) effectively inactivates class C β-lactamases, protecting ceftazidime (CAZ) from hydrolysis by AmpC hyperproducing strains of Enterobacteriaceae (ENT) and *P. aeruginosa* (PSA). AVI also inhibits class A (including KPC) and some D β-lactamases, restoring CAZ activity against Gram-negative (GN) organisms producing a variety of clinically relevant enzymes.

Methods: 6,910 ENT with inducible AmpC β-lactamases and 5,328 PSA were collected from 71 United States hospitals in 2011-2014, and were tested for susceptibility using the reference broth microdilution method against CAZ-AVI (AVI at fixed 4 μg/ml) and numerous comparators.

Results: CAZ-AVI demonstrated potent *in vitro* activity against all three ENT genus groups evaluated, with MIC_{50}/MIC_{90} values of 0.12/0.5 μg/ml for *Enterobacter* spp. and *S. marcescens,* and 0.12/0.25 μg/ml for *Citrobacter* spp. (99.8-99.9% susceptible [S]). Against CAZ-non-S ENT, CAZ-AVI inhibited 99.3% of isolates (1,015 of 1,022) at a MIC of ≤8 μg/ml (MIC_{50}/MIC_{90} of 0.25-0.5/1-2 μg/ml); whereas susceptibility rates for cefepime (CPM) ranged from 45.9% (*Citrobacter* spp.) to 80.0% (*S. marcescens*). CAZ-AVI was also active against PSA (MIC_{50}/MIC_{90}, 2/4 μg/ml; 96.8% S). PSA susceptibility rates to other anti-pseudomonal β-lactams ranged from 79.6% for piperacillin/tazobactam (P/T) to 84.5% for CPM. CAZ-AVI inhibited 67.4% of isolates at ≤8 μg/ml (MIC_{50}/MIC_{90}, 8/32 μg/ml) that were non-S to CAZ, CPM, P/T and meropenem (MER; see Table).

Conclusion: CAZ-AVI demonstrated potent activity against ENT producing derepressed AmpC and remained active against a large proportion of PSA strains resistant to multiple anti-pseudomonal β-lactams. Thus, CAZ-AVI represents a valuable addition to the limited group of antimicrobials currently available for the treatment of serious infections caused by emerging multidrug-resistant GN bacilli.

Abstract Table

	MIC_{50} / % susceptible [CLSI / US-FDA]			
Organism (n)	CAZ-AVI	Cefepime	Meropenem	Gentamicin
CAZ-non-S				
Enterobacter spp. (814)	0.5 / 99.6	2 / 68.3	≤0.06 / 95.7	≤1 / 74.4
S. marcescens (44)	0.5 / 93.2	4 / 45.9	≤0.06 / 86.4	2 / 54.5
Citrobacter spp. (164)	0.25 / 99.4	1 / 80.0	≤0.06 / 95.7	≤1 / 54.4
P. aeruginosa non-S to CAZ, CPM, P/T & MER (396)	8 / 67.4	>16 / 0.0	8 / 0.0	4 / 63.3

Introduction

Ceftazidime-avibactam is a combination agent consisting of the β-lactamase inhibitor avibactam and the broad-spectrum cephalosporin, ceftazidime. Avibactam acts as a reversible, covalent inhibitor and is a member of a novel class of non-β-lactam β-lactamase inhibitors, the diazabicyclooctanes. Avibactam is more potent and has a broader spectrum of enzyme inhibition when compared to current clinically available β-lactamase inhibitors. Importantly, avibactam effectively inactivates class C β-lactamases, protecting companion β-lactams from hydrolysis by AmpC hyperproducing strains of Enterobacteriaceae and *Pseudomonas aeruginosa*. In addition to class C, avibactam also inactivates class A (including ESBLs and KPCs) and some class D β-lactamases, with low IC_{50} (concentration resulting in 50% inhibition) values and low turnover. Thus, avibactam restores ceftazidime *in vitro* activity against Gram-negative organisms producing a variety of clinically relevant enzymes.

Ceftazidime-avibactam has been approved by the United States (US) Food and Drug Administration (FDA) for treatment of complicated intra-abdominal infections, in combination with metronidazole, and 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 (http://clinicaltrials.gov; NCT01808092). We evaluated the activity of ceftazidime-avibactam and comparator agents against a large collection of Enterobacteriaceae isolates from species that produce inducible chromosomaly-encoded cephalosporinases (AmpC β-lactamase) and *P. aeruginosa* collected over four years (2011-2014) of the International Network for Optimal Resistance Monitoring (INFORM) program in the US.

Methods

Bacterial isolates: A total of 12,238 Gram-negative organisms, including 6,910 Enterobacteriaceae and 5,328 *P. aeruginosa,* were collected from 71 US hospitals from January 2011 to October 2014 as part of the INFORM surveillance program. These isolates were collected from bloodstream, respiratory tract, and skin and skin structure infections, according to defined protocols. Only clinically relevant isolates were included in the study (one 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 tested for susceptibility using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI). Ceftazidime was combined with avibactam at a fixed concentration of 4 μg/ml. Ceftazidime-avibactam breakpoints approved by the US-FDA (≤8 μg/ml for susceptible and ≥16 μg/ml for resistance) were applied for all Enterobacteriaceae species and *P. aeruginosa*. All Enterobacteriaceae isolates displaying ceftazidime-avibactam MIC of >8 μg/ml were screened for the presence of metallo-β-lactamase and serine-carbapenemase encoding gene 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. Categorical interpretations for all comparator agents were those found in CLSI document M100-S25 and EUCAST breakpoint tables, except for tigecycline where the US-FDA breakpoints were applied. Quality control (QC) was performed using *Escherichia coli* ATCC 25922 and 35218, *Klebsiella pneumoniae* 700603 and *P. aeruginosa* ATCC 27853. All QC MIC results were within acceptable ranges as published in CLSI documents.

Results

- Ceftazidime-avibactam demonstrated potent *in vitro* activity against all three Enterobacteriaceae genus groups evaluated, with MIC_{50}/MIC_{90} results at 0.12/0.25-0.5 μg/ml and ≥99.8% susceptible at ≤8 μg/ml (Table 1). When tested against ceftazidime alone, the susceptibility (CLSI criteria) rate was lowest for *Enterobacter* spp. (79.5%), followed by *Citrobacter* spp. (88.3%) and *Serratia* spp. (97.1%; Table 2).
- Against ceftazidime-non-susceptible Enterobacteriaceae, ceftazidime-avibactam inhibited 99.3% of isolates (1,015 of 1,022) at a MIC of ≤8 μg/ml (MIC_{50}/MIC_{90} of 0.25-0.5/1-2 μg/ml); whereas susceptibility rates for cefepime ranged from 45.9% (*Citrobacter* spp.) to 80.0% (*S. marcescens*; Table 2).
- Almost 4,000 *Enterobacter* spp. isolates were tested against ceftazidime-avibactam (MIC_{50}/MIC_{90}, 0.12/0.5 μg/ml) and only three isolates exhibited a MIC at >8 μg/ml (0.08%), one *E. aerogenes* with ceftazidime-avibactam MIC of 16 μg/ml isolated in 2012 and two *E. cloacae* isolates from 2013 and 2014 with ceftazidime-avibactam MIC values of 32 and 16 μg/ml, respectively.
- Ceftazidime-avibactam (MIC_{50}/MIC_{90}, 0.25/1 μg/ml; 99.6% susceptible), meropenem (MIC_{50}/MIC_{90}, ≤0.06/0.12 μg/ml; 95.7% susceptible) and tigecycline (MIC_{50}/MIC_{90}, 0.25/1 μg/ml; 99.4% susceptible) were the most active compounds tested against ceftazidime-non-susceptible *Enterobacter* spp. (n=814), and all other compounds exhibited susceptibility rates at <75.0% (Table 2). Cefepime (MIC_{50}/MIC_{90}, 2/16 μg/ml) was eight- to 16-fold less active than ceftazidime-avibactam against these organisms and inhibited only 68.3% of isolates at the CLSI susceptible breakpoint (Table 2).
- Meropenem was also very active against *Enterobacter* spp. (MIC_{50}/MIC_{90}, ≤0.06/≤0.06 μg/ml; 99.4% susceptible), whereas cefepime (MIC_{50}/MIC_{90}, ≤0.5/2 μg/ml) showed slightly less activity with 93.3% of isolates being susceptible at ≤2 μg/ml (Table 2).
- Ceftazidime-avibactam exhibited potent activity against *S. marcescens* (MIC_{50}/MIC_{90}, 0.12/0.5 μg/ml; 99.8% susceptible), with only three non-susceptible isolates, all with ceftazidime-avibactam MIC values of 16 μg/ml (Tables 1 and 2).
- Only one (0.07%) *Citrobacter* spp. isolate exhibited a ceftazidime-avibactam MIC at >8 μg/ml, a *C. freundii* isolated in 2012 from a patient with pneumonia. Meropenem (MIC_{50}/MIC_{90}, ≤0.06/≤0.06 μg/ml; 99.4% susceptible) and cefepime (MIC_{50}/MIC_{90}, ≤0.5/≤0.5 μg/ml; 97.3% susceptible) were also very active against *Citrobacter* spp. isolates (Tables 1 and 2).
- All seven ceftazidime-avibactam-non-susceptible Enterobacteriaceae strains exhibited negative PCR results for the carbapenemase families tested.
- Ceftazidime-avibactam (MIC_{50}/MIC_{90}, 2/4 μg/ml; 96.8% susceptible at ≤8 μg/ml; Table 1) showed greater *in vitro* activity than ceftazidime tested alone (MIC_{50}/MIC_{90}, 2/32 μg/ml; 83.9% susceptible at ≤8 μg/ml) when tested against *P. aeruginosa* (n=5,328; Table 2).
- Ceftazidime-avibactam inhibited 67.4% of *P. aeruginosa* isolates non-susceptible to ceftazidime (MIC, ≥16 μg/ml), cefepime (MIC, ≥16 μg/ml), piperacillin-tazobactam (MIC, ≥32 μg/ml) and meropenem (MIC, ≥4 μg/ml) at ≤8 μg/ml (Tables 1 and 2).

Table 1. Summary of ceftazidime-avibactam activity tested against *Enterobacter* spp., *Serratia marcescens*, *Citrobacter* spp. and *Pseudomonas aeruginosa* isolates collected from United States hospitals (2011-2014).

	Number of isolates (cumulative %) inhibited at ceftazidime-avibactam MIC (μg/ml) of:											MIC (μg/ml)	
Organism	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	50%	90%
Enterobacter spp. (3,970)	565 (14.2)	1836 (60.5)	1023 (86.2)	405 (96.4)	111 (99.2)	17 (99.7)	10 (>99.9)	0 (>99.9)[a]	2 (>99.9)	1 (100.0)	--	0.12	0.5
CAZ-S[b] (3,156)	536 (17.0)	1727 (71.7)	766 (96.0)	112 (99.5)	14 (100.0)	1 (100.0)	--	--	--	--	--	0.12	0.25
CAZ-NS[b] (814)	29 (3.6)	109 (17.0)	257 (48.5)	293 (84.5)	97 (96.4)	16 (98.4)	10 (99.6)	0 (99.6)	2 (99.9)	1 (100.0)	--	0.5	1
Serratia marcescens (1,541)	99 (6.4)	691 (51.3)	544 (86.6)	171 (97.7)	23 (99.2)	8 (99.7)	1 (99.7)	1 (99.8)[a]	3 (100.0)	--	--	0.12	0.5
CAZ-S[b] (1,497)	99 (6.6)	685 (52.4)	536 (88.2)	156 (98.6)	16 (99.7)	4 (99.9)	1 (100.0)	--	--	--	--	0.12	0.5
CAZ-NS[b] (44)	--	6 (13.6)	8 (31.8)	15 (65.9)	7 (81.8)	4 (90.9)	0 (90.9)	1 (93.2)	3 (100.0)	--	--	0.5	2
Citrobacter spp. (1,399)	534 (38.2)	538 (76.6)	220 (92.4)	75 (97.7)	24 (99.4)	6 (99.9)	1 (99.9)	0 (99.9)[a]	1 (100.0)	--	--	0.12	0.25
CAZ-S[b] (1,235)	530 (42.9)	511 (84.3)	165 (97.7)	25 (99.7)	4 (100.0)	--	--	--	--	--	--	0.12	0.25
CAZ-NS[b] (164)	4 (2.4)	27 (18.9)	55 (52.4)	50 (82.9)	20 (95.1)	6 (98.8)	1 (99.4)	0 (99.4)	1 (100.0)	--	--	0.25	1
Pseudomonas aeruginosa (5,328)	10 (0.2)	21 (0.6)	48 (1.5)	266 (6.5)	2067 (45.3)	1681 (76.8)	758 (91.0)	308 (96.8)[a]	105 (98.8)	31 (99.4)	33 (100.0)	2	4
CAZ, CPM, P/T and MER-NS (396)[c]	--	--	--	1 (0.3)	2 (0.8)	42 (11.4)	102 (37.1)	120 (67.4)	77 (86.9)	25 (93.2)	27 (100.0)	8	32

a. Underlined values indicate percentage inhibited at ceftazidime-avibactam susceptible breakpoint of ≤8 μg/ml.
b. CAZ-S = ceftazidime-susceptible (≤4 μg/ml) and CAZ-NS = ceftazidime-non-susceptible (≥8 μg/ml).
c. Isolates non-susceptible to ceftazidime (CAZ; MIC, ≥16 μg/ml), cefepime (CPM; MIC, ≥16 μg/ml), piperacillin-tazobactam (P/T; MIC, ≥32 μg/ml) and meropenem (MER; MIC, ≥4 μg/ml) according to the CLSI breakpoint criteria.

Table 2. Activity of ceftazidime-avibactam and comparator antimicrobial agents when tested against *Enterobacter* spp., *Serratia marcescens*, *Citrobacter* spp. and *Pseudomonas aeruginosa* from USA hospitals (2011-2014).

Organism /	MIC (μg/ml)		% S / %I / %R	
Antimicrobial agent	50%	90%	CLSI[a]	EUCAST[a]
Enterobacter spp.[b] (3,970)				
Ceftazidime-avibactam[c]	0.12	0.5	99.9 / 0.0 / 0.1[c]	- / - / -
Ceftazidime	0.25	>32	79.5 / 1.5 / 19.0	77.1 / 2.4 / 20.5
Cefepime	≤0.5	2	93.3 / 4.2 / 2.5	89.5 / 6.9 / 3.6
Ceftriaxone	0.25	>8	75.6 / 2.0 / 22.4	75.6 / 2.0 / 22.4
Piperacillin-tazobactam	2	64	84.0 / 9.4 / 6.6	80.0 / 4.0 / 16.0
Meropenem	≤0.06	≤0.06	99.4 / 0.1 / 0.5	99.5 / 0.4 / 0.1
Levofloxacin	≤0.12	0.5	95.7 / 1.2 / 3.1	94.7 / 1.0 / 4.3
Gentamicin	≤1	≤1	96.4 / 0.6 / 3.0	96.0 / 0.4 / 3.6
Tigecycline[d]	0.25	0.5	99.1 / 0.9 / 0.0[d]	95.7 / 3.4 / 0.9
Colistin	0.5	>8	- / - / -	84.7 / 0.0 / 15.3
Ceftazidime-non-susceptible[e] (814)				
Ceftazidime-avibactam[c]	0.5	1	99.6 / 0.0 / 0.4[c]	- / - / -
Ceftazidime	>32	>32	0.0 / 3.0 / 97.0	0.0 / 0.0 / 100.0
Cefepime	2	16	68.3 / 19.6 / 12.1	49.8 / 32.7 / 17.6
Ceftriaxone	>8	>8	0.0 / 1.8 / 98.2	0.0 / 1.8 / 98.2
Piperacillin-tazobactam	64	>64	27.0 / 35.0 / 38.0	12.9 / 14.1 / 73.0
Meropenem	≤0.06	0.12	95.7 / 1.2 / 3.1	96.9 / 1.9 / 1.2
Levofloxacin	0.5	>4	71.3 / 9.8 / 18.9	61.0 / 10.3 / 28.7
Gentamicin	≤1	>8	74.4 / 1.2 / 24.4	72.0 / 2.4 / 25.6
Tigecycline[d]	0.25	1	99.4 / 0.6 / 0.0[d]	93.9 / 5.5 / 0.6
Colistin	0.5	>8	- / - / -	83.0 / 0.0 / 17.0
S. marcescens (1,541)				
Ceftazidime-avibactam[c]	0.12	0.5	99.8 / 0.0 / 0.2[c]	- / - / -
Ceftazidime	0.25	0.5	97.1 / 0.5 / 2.4	96.2 / 0.9 / 2.9
Cefepime	≤0.5	≤0.5	97.7 / 1.7 / 0.6	97.2 / 1.4 / 1.4
Ceftriaxone	0.25	2	89.6 / 2.5 / 7.9	89.6 / 2.5 / 7.9
Piperacillin-tazobactam	2	8	96.4 / 2.4 / 1.2	94.7 / 1.7 / 3.6
Meropenem	≤0.06	≤0.06	99.2 / 0.2 / 0.6	99.4 / 0.2 / 0.4
Levofloxacin	≤0.12	1	96.0 / 2.0 / 2.0	93.0 / 3.0 / 4.0
Gentamicin	≤1	≤1	97.6 / 0.6 / 1.8	96.7 / 0.9 / 2.4
Tigecycline[d]	0.5	1	99.1 / 0.7 / 0.2[d]	95.5 / 3.6 / 0.9
Colistin	>8	>8	- / - / -	6.0 / 0.0 / 94.0
Ceftazidime-non-susceptible (44)				
Ceftazidime-avibactam[c]	0.5	2	93.2 / 0.0 / 6.8[c]	- / - / -
Ceftazidime	32	>32	0.0 / 15.9 / 84.1	0.0 / 0.0 / 100.0
Cefepime	4	16	45.9 / 35.1 / 18.9	37.8 / 21.6 / 40.5
Ceftriaxone	>8	>8	4.7 / 0.0 / 95.3	4.7 / 0.0 / 95.3
Piperacillin-tazobactam	16	>64	52.3 / 13.6 / 34.1	47.7 / 4.6 / 47.7
Meropenem	≤0.06	2	86.4 / 4.5 / 9.1	90.9 / 6.8 / 2.3
Levofloxacin	1	>4	68.2 / 13.6 / 18.2	50.0 / 18.2 / 31.8
Gentamicin	2	>8	54.5 / 13.7 / 31.8	52.3 / 2.2 / 45.5
Tigecycline[d]	1	2	97.7 / 2.3 / 0.0[d]	86.4 / 11.3 / 2.3
Colistin	>8	>8	- / - / -	27.8 / 0.0 / 72.2
Citrobacter spp. (1,399)[f]				
Ceftazidime-avibactam[c]	0.12	0.25	99.9 / 0.0 / 0.1[c]	- / - / -
Ceftazidime	0.25	16	88.3 / 0.3 / 11.4	86.7 / 1.6 / 11.7
Cefepime	≤0.5	≤0.5	97.3 / 1.0 / 1.6	95.3 / 2.8 / 1.9
Ceftriaxone	0.12	>8	87.7 / 0.3 / 12.0	87.7 / 0.3 / 12.0
Piperacillin-tazobactam	2	16	90.5 / 4.7 / 4.8	85.6 / 4.9 / 9.5
Meropenem	≤0.06	≤0.06	99.4 / 0.2 / 0.4	99.6 / 0.3 / 0.1
Levofloxacin	≤0.12	1	94.8 / 1.8 / 3.4	92.1 / 2.7 / 5.2
Gentamicin	≤1	≤1	95.0 / 0.1 / 4.9	94.6 / 0.4 / 5.0
Tigecycline[d]	0.12	0.5	99.7 / 0.3 / 0.0[d]	98.2 / 1.5 / 0.3
Colistin	0.5	1	- / - / -	99.8 / 0.0 / 0.2
Ceftazidime-non-susceptible[e] (164)				
Ceftazidime-avibactam[c]	0.25	1	99.4 / 0.0 / 0.6[c]	- / - / -
Ceftazidime	>32	>32	0.0 / 3.0 / 97.0	0.0 / 0.0 / 100.0
Cefepime	1	16	80.0 / 7.2 / 12.8	64.0 / 21.6 / 14.4
Ceftriaxone	>8	>8	0.0 / 1.8 / 98.2	0.0 / 1.8 / 98.2
Piperacillin-tazobactam	64	>64	27.0 / 35.0 / 38.0	12.1 / 2.7 / 73.0
Meropenem	≤0.06	0.12	95.7 / 1.2 / 3.1	96.9 / 1.9 / 1.2
Levofloxacin	0.5	>4	71.3 / 9.8 / 18.9	61.0 / 10.3 / 28.7
Gentamicin	≤1	>8	74.4 / 1.2 / 24.4	72.0 / 2.4 / 25.6
Tigecycline[d]	0.25	1	99.4 / 0.6 / 0.0[d]	93.9 / 5.5 / 0.6
Colistin	0.5	1	- / - / -	100.0 / 0.0 / 0.0
P. aeruginosa (5,328)				
Ceftazidime-avibactam[c]	2	4	96.8 / 0.0 / 3.2[c]	- / - / -
Ceftazidime	2	32	83.9 / 3.8 / 12.3	83.9 / 0.0 / 16.1
Cefepime	2	16	84.5 / 8.2 / 7.3	84.5 / 0.0 / 15.5
Piperacillin-tazobactam	8	>64	79.6 / 9.0 / 11.4	79.6 / 0.0 / 20.4
Meropenem	0.5	8	82.5 / 5.6 / 11.9	82.5 / 11.5 / 6.0
Levofloxacin	0.5	>4	75.0 / 6.4 / 18.6	66.3 / 8.7 / 25.0
Gentamicin	≤1	8	89.1 / 3.2 / 7.7	89.1 / 0.0 / 10.9
Amikacin	2	8	97.4 / 1.1 / 1.5	94.2 / 3.2 / 2.6
Tobramycin	0.5	4	91.7 / 0.2 / 8.1	91.7 / 0.0 / 8.3
Colistin	1	2	>99.9 / 0.0 / <0.1	>99.9 / 0.0 / <0.1
CAZ, CPM, P/T and MER-non-susceptible (396)[g]				
Ceftazidime-avibactam[c]	8	32	67.4 / 0.0 / 32.6[c]	- / - / -
Levofloxacin	>4	>4	17.9 / 8.4 / 73.7	11.9 / 6.0 / 82.1
Gentamicin	4	>8	53.3 / 7.6 / 38.9	53.3 / 0.0 / 46.7
Amikacin	4	32	87.4 / 7.3	77.8 / 9.6 / 12.6
Tobramycin	1	>16	62.6 / 3.8 / 33.6	62.6 / 0.0 / 37.4
Colistin	1	2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0

a. Criteria as published by the CLSI or US-FDA when CLSI breakpoints are not available, and EUCAST.
b. Includes: *Enterobacter aerogenes* (1050 strains), *E. cloacae* (2517 strains), and *E. cloacae* species complex (403 strains).
c. Ceftazidime-avibactam breakpoints approved by the US-FDA (≤8 μg/ml for susceptible and ≥16 μg/mlfor resistance) were applied.
d. US-FDA breakpoints were applied when available.
e. Includes: *Enterobacter aerogenes* (215 strains), *E. cloacae* (526 strains), and *E. cloacae* species complex (73 strains).
f. Includes: *Citrobacter freundii* (145 strains), *C. freundii* species complex (10 strains), and *C. koseri* (9 strains).
g. Includes: *Citrobacter freundii* (692 strains), *C. freundii* species complex (59 strains), and *C. koseri* (648 strains).
h. Isolates non-susceptible to ceftazidime (MIC, ≥16 μg/ml), cefepime (MIC, ≥16 μg/ml), piperacillin-tazobactam (MIC, ≥32 μg/ml) and meropenem (MIC, ≥4 μg/ml) according to the CLSI breakpoint criteria.

Conclusions

- Bacterial organisms expressing derepressed AmpC β-lactamases were generally resistant to multiple agents, making the selection of an effective antimicrobial treatment very difficult.
- Ceftazidime-avibactam demonstrated potent activity against Enterobacteriaceae producing derepressed AmpC and remained active (MICs, ≤8 μg/ml) against a large proportion of *P. aeruginosa* strains resistant to multiple anti-pseudomonal β-lactams (96.8-99.9% susceptibility rates).
- Ceftazidime-avibactam represents a valuable addition to the limited group of antimicrobials currently available for the treatment of serious infections caused by emerging multidrug-resistant Gram-negative bacilli.

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Acknowledgment

The authors would like to thank all participants of the International Network for Optimal Resistance Monitoring (INFORM) program for providing bacterial isolates.

This study was supported by Cerexa, Inc., an Allergan affiliate. Forest Laboratories, LLC, an Allergan affiliate provided financial support for the analysis of the data and was involved in the design and decision to present these results. Neither Cerexa, Inc. nor Forest Laboratories, LLC, had any involvement in the collection, analysis, and interpretation of data.