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Antimicrobial Activity of Ceftazidime-Avibactam against Gram-Negative Organisms Collected from U.S. Medical Centers in 2012

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The activities of the novel β-lactam–β-lactamase inhibitor combination ceftazidime-avibactam and comparator agents were evaluated against a contemporary collection of clinically significant Gram-negative bacilli. Avibactam is a novel non-β-lactam β-lactamase inhibitor that inhibits Ambler class A, C, and some D enzymes. A total of 10,928 Gram-negative bacilli—8,640 *Enterobacteriaceae*, 1,967 *Pseudomonas aeruginosa*, and 321 *Acinetobacter* sp. isolates—were collected from 73 U.S. hospitals and tested for susceptibility by reference broth microdilution methods in a central monitoring laboratory (JMI Laboratories, North Liberty, IA, USA). Ceftazidime was combined with avibactam at a fixed concentration of 4 μg/ml. Overall, 99.8% of *Enterobacteriaceae* strains were inhibited at a ceftazidime-avibactam MIC of ≤4 μg/ml. Ceftazidime-avibactam was active against extended-spectrum β-lactamase (ESBL)-phenotype *Escherichia coli* and *Klebsiella pneumoniae*, meropenem-nonsusceptible (MIC ≥ 2 μg/ml) *K. pneumoniae*, and ceftazidime-nonsusceptible *Enterobacter cloacae*. Among ESBL-phenotype *K. pneumoniae* strains, 61.1% were meropenem susceptible and 99.3% were inhibited at a ceftazidime-avibactam MIC of ≤4 μg/ml. Among *P. aeruginosa* strains, 96.9% were inhibited at a ceftazidime-avibactam MIC of ≤8 μg/ml, and susceptibility rates for meropenem, ceftazidime, and piperacillin-tazobactam were 82.0, 83.2, and 78.3%, respectively. Ceftazidime-avibactam was the most active compound tested against meropenem-nonsusceptible *P. aeruginosa* (MIC_{50}/MIC_{90}, 4/16 μg/ml; 87.3% inhibited at ≤8 μg/ml). *Acinetobacter* spp. (ceftazidime-avibactam MIC_{50}/MIC_{90}, 16/>32 μg/ml) showed high rates of resistance to most tested agents. In summary, ceftazidime-avibactam demonstrated potent activity against a large collection of contemporary Gram-negative bacilli isolated from patients in U.S. hospitals in 2012, including organisms that are resistant to most currently available agents, such as *K. pneumoniae* carbapenemase (KPC)-producing *Enterobacteriaceae* and meropenem-nonsusceptible *P. aeruginosa*.

Bacterial isolates resistant to clinically available β-lactams represent an important challenge to successful treatment of serious infections (1). 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) (2).

The most recent β-lactamase inhibitor approved for clinical use in the United States was tazobactam in 1993 (3). Since then, the occurrence of Gram-negative bacteria expressing higher levels of β-lactamase production, multiple enzymes, inhibitor-resistant enzymes, and enzymes that are not inhibited by tazobactam and earlier inhibitors has increased substantially (4). Tazobactam, clavulanic acid, and sulbactam are essentially specific for certain class A β-lactamases; these inhibitors have negligible activity against class C enzymes and the class A carbapenemases, especially the *Klebsiella pneumoniae* carbapenemases (KPCs), which have become a major problem due to antimicrobial resistance in some geographic regions (5–7).

Avibactam (formerly NXL-104) is a member of a novel class of non-β-lactam β-lactamase inhibitors, the diazabicyclooctanes (DBOs) (8). Compared to current inhibitors available for clinical use, DBOs are more potent and have a broader spectrum and a different mechanism of action (2, 8). Avibactam effectively inactivates class A (including KPC), class C, and some class D β-lactamases, with low IC_{50} (the concentration resulting in 50% inhibition) values and low turnover numbers. Thus, avibactam protects β-lactams from hydrolysis by a variety of clinically relevant enzymes. Ceftazidime-avibactam is currently in phase 3 clinical trials for treatment of complicated intra-abdominal infections, urinary tract infections, and nosocomial pneumonia (identifiers NCT01499290, NCT01500239, NCT 01599806, NCT01595438, and NCT01808092 [http://clinicaltrials.gov]). 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 during 2012.

MATERIALS AND METHODS

Bacterial isolates. A total of 10,928 Gram-negative organisms, including 8,640 *Enterobacteriaceae*, 1,967 *Pseudomonas aeruginosa*, and 321 *Acinetobacter* sp. isolates, were consecutively collected from 73 U.S. hospitals from January to December 2012. These isolates were collected from bloodstream, respiratory tract, skin, and soft tissue infections according to defined protocols (9). 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 (Billerica, MA, USA) MALDI Biotyper following the manufacturer's instructions.

Antimicrobial susceptibility testing. All isolates were susceptibility tested using the reference broth microdilution method as described by the

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CLSI (10). Ceftazidime was combined with avibactam at a fixed concentration of 4 μg/ml. *Escherichia coli* and *Klebsiella* sp. isolates were grouped as "extended-spectrum β-lactamase (ESBL) phenotype" and "non-ESBL phenotype" based on the CLSI screening criteria for ESBL production (11). Those isolates with positive ESBL screening tests, i.e., a MIC of >1 μg/ml for ceftazidime and/or ceftriaxone and/or aztreonam, were categorized as "ESBL phenotype" for the purpose of susceptibility-testing result analysis. Although other β-lactamases, such as AmpC and KPC, may also produce an ESBL phenotype, these strains were grouped together because they usually demonstrate resistance to various broad-spectrum β-lactam compounds. Categorical interpretations for all antimicrobials were those found in CLSI document M100-S23 (11) and EUCAST breakpoint tables (12). CLSI and EUCAST breakpoint criteria for ceftazidime alone were applied to ceftazidime-avibactam for comparison purposes only. Quality control (QC) was performed using *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853. All QC results were within acceptable ranges as published in CLSI documents (11).

Screening for β-lactamases. *E. coli*, *Klebsiella* spp., and *Proteus mirabilis* strains displaying the CLSI criteria for the ESBL phenotype (a MIC of >1 μg/ml for aztreonam and/or ceftazidime and/or ceftriaxone [11]), as well as all *Enterobacteriaceae* strains with ceftazidime-avibactam MICs of ≥16 μg/ml, were tested for β-lactamase-encoding genes using the microarray-based assay Check-MDR CT101 kit (Check-Points, Wageningen, Netherlands). The assay was performed according to the manufacturer's instructions. The kit has the capability to detect genes encoding CTX-M groups 1, 2, 8, 25, and 9; TEM wild-type (WT) and ESBL; SHV WT and ESBL; ACC; ACT/MIR; CMY-2-like variants (designated CMYII in the checkpoint kit); DHA; FOX; KPC; and NDM-1 (13). Reference PCR and/or sequencing were performed on strains with negative results with the Check-MDR CT101 kit (13).

RESULTS

Enterobacteriaceae. Applying CLSI and EUCAST breakpoints for ceftazidime alone (≤4 and ≤1 μg/ml, respectively), ceftazidime-avibactam was the most active agent tested against *Enterobacteriaceae* (MIC_{50}/MIC_{90}, 0.12/0.25 μg/ml), with 99.8 and 99.3% inhibition at ≤4 and ≤1 μg/ml, respectively (Tables 1 and 2). The breakpoints for ceftazidime alone were applied to ceftazidime-avibactam for comparison purposes, since ceftazidime-avibactam breakpoints have not been established by the U.S. FDA, CLSI, or EUCAST. It is important to note, however, that ceftazidime-avibactam breakpoints could be higher than those established by ceftazidime, since ceftazidime breakpoints are based on the 1 g every 8 h (q8h), 30-min infusion dose (11) and ceftazidime-avibactam is dosed at 2 g q8h with 2 h infusion (identifiers NCT01499290, NCT01500239, NCT01599806, NCT01595438, and NCT01808092 [http://clinicaltrials.gov]).

Only 6 of 8,640 strains (0.07%) had a ceftazidime-avibactam MIC at ≥16 μg/ml (Table 1) (11). The highest ceftazidime-avibactam MIC among *E. coli* strains (2,767 strains) was only 2 μg/ml (one isolate). The ESBL screen-positive phenotype strains were very susceptible to ceftazidime-avibactam (MIC_{50}/MIC_{90}, 0.12/0.25 μg/ml), and all non-ESBL-phenotype strains were inhibited at a ceftazidime-avibactam MIC of ≤0.5 μg/ml (Tables 1 and 2). Ceftazidime-avibactam was also active against *K. pneumoniae* (1,847 strains; MIC_{50}/MIC_{90}, 0.12/0.5 μg/ml) and *Klebsiella oxytoca* (442 strains; MIC_{50}/MIC_{90}, 0.06/0.25 μg/ml), including ESBL-phenotype strains (MIC_{90}, 1 μg/ml for both species) (Table 2). Among meropenem-nonsusceptible (MIC, ≥2 μg/ml) *K. pneumoniae* strains (115 strains; MIC_{50}/MIC_{90}, 0.5/2 μg/ml), ceftazidime-avibactam inhibited 98.3% of the isolates at ≤4 μg/ml (Table 1). Only two *K. pneumoniae* strains had ceftazidime-avibactam MICs of >4 μg/ml, both at >32 μg/ml. These strains were isolated in a single medical center in Denver, CO, and further evaluation showed that they produced NDM-1 and were clonally related (14). Furthermore, 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).

An ESBL phenotype was noted among 701 (12.2%) *Enterobacteriaceae* 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 *P. mirabilis* (4.8%) isolates; a complete analysis of the molecular characterization of these strains has been previously reported by Castanheira et al. (15). In summary, 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). Among *E. coli* strains, CTX-M type was the most common β-lactamase identified (75.9% of strains), followed by non-ESBL TEM type (41.2%) and CMY type (15.2%), whereas among *K. pneumoniae* strains, SHV type (53.4%) and CTX-M type (33.8%) were the most common ESBLs and KPC was identified among 37.8% of the strains. Other enzymes were also detected in a small number of strains (15).

When tested against *Enterobacter cloacae*, ceftazidime-avibactam (MIC_{50}/MIC_{90}, 0.12/0.5 μg/ml) inhibited 100.0% of the strains at MICs of 4 μg/ml or less, including ceftazidime-nonsusceptible strains (200 strains tested; ceftazidime-avibactam MIC_{50}/MIC_{90}, 0.5/1 μg/ml) (Tables 1 and 2). Ceftazidime-avibactam inhibited 99.7% (356 of 357) of *Enterobacter aerogenes* strains (MIC_{50}/MIC_{90}, 0.12/0.25 μg/ml) at ≤1 μg/ml; one strain had a ceftazidime-avibactam MIC of 16 μg/ml (Table 1).

Ceftazidime-avibactam exhibited potent activity against *Morganella morganii* (MIC_{50}/MIC_{90}, 0.06/0.12 μg/ml; 99.7% inhibited at ≤1 μg/ml), *Citrobacter koseri* (MIC_{50}/MIC_{90}, 0.06/0.12 μg/ml; 100.0% inhibited at ≤1 μg/ml), *Citrobacter freundii* (MIC_{50}/MIC_{90}, 0.12/0.5 μg/ml; 98.4 and 99.5% inhibited at ≤1 and ≤4 μg/ml, respectively), *Serratia marcescens* (MIC_{50}/MIC_{90}, 0.12/0.5 μg/ml; 99.0 and 99.6% inhibited at ≤1 and ≤4 μg/ml, respectively), *Proteus vulgaris* (MIC_{50}/MIC_{90}, 0.06/0.06 μg/ml; 100.0% inhibited at ≤0.5 μg/ml), and *Providencia* spp. (MIC_{50}/MIC_{90}, 0.12/0.5 μg/ml; 94.0 and 95.9% inhibited at ≤1 and ≤4 μg/ml, respectively) (Tables 1 and 2).

Six *Enterobacteriaceae* strains (0.07%) exhibited ceftazidime-avibactam MICs of ≥16 μg/ml, including two NDM-1-producing *K. pneumoniae* strains with ceftazidime-avibactam MICs of >16 μg/ml and four organisms (*C. freundii*, *E. aerogenes*, *Providencia stuartii*, and *S. marcescens*) with ceftazidime-avibactam MICs of 16 μg/ml that were susceptible to meropenem and had negative results for all ESBL- and carbapenemase-encoding genes tested. Twelve additional *Enterobacteriaceae* strains exhibited a ceftazidime-avibactam MICs of 8 μg/ml: 10 *Providencia* spp., 1 *S. marcescens* strain, and one *M. morganii* strain.

***P. aeruginosa* and *Acinetobacter* spp.** Ceftazidime-avibactam (MIC_{50}/MIC_{90}, 2/4 μg/ml; 96.9% inhibited at ≤8 μg/ml) exhibited greater *in vitro* activity than ceftazidime alone (MIC_{50}/MIC_{90}, 2/32 μg/ml; 83.2% susceptible at ≤8 μg/ml) when tested against *P. aeruginosa* (Tables 1 and 2). Moreover, ceftazidime-avibactam inhibited 82.1% of ceftazidime-nonsusceptible *P. aeruginosa* isolates (ceftazidime MIC, ≥16 μg/ml; 330 isolates tested) at ≤8 μg/ml (Table 1). Ceftazidime-avibactam also showed potent activity against meropenem-nonsusceptible *P.*

TABLE 1 Summary of ceftazidime-avibactam activities tested against the organisms and resistant subsets included in this report (United States, 2012)

Organism/resistant subset	No. of isolates	No. of isolates (cumulative %) inhibited at a MIC (μg/ml) of[a]: ≤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 nonsusceptible[b]	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 nonsusceptible[c]	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 nonsusceptible[c]	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 nonsusceptible[d]	354						4 (1.1)	39 (12.1)	84 (35.9)	104 (65.3)	78 (87.3)	28 (95.2)	17 (100.0)
Ceftazidime nonsusceptible[e]	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] Underlined values represent the percentages inhibited at the CLSI susceptible breakpoint for ceftazidime alone (11).
[b] Defined according to the CLSI nonsusceptibility breakpoint of ≥2 μg/ml (11).
[c] Defined according to the CLSI nonsusceptibility breakpoint of ≥8 μg/ml (11).
[d] Defined according to the CLSI nonsusceptibility breakpoint of ≥4 μg/ml (11).
[e] Defined according to the CLSI nonsusceptibility breakpoint of ≥16 μg/ml (11).

TABLE 2 Activities of ceftazidime-avibactam and comparator antimicrobial agents

Organism (no. tested)/antimicrobial agent	MIC (μg/ml)		% S/% I/% R[a]	
	50	90	CLSI	EUCAST
Enterobacteriaceae (8,640)				
Ceftazidime-avibactam	0.12	0.25	(99.8)[b]	(99.3)[c]
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[d]	0.25	1	97.9/2.1/<0.1	91.7/6.2/2.1
E. coli (2,767)				
Ceftazidime-avibactam	0.06	0.12	(100.0)[b]	(>99.9)[c]
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[d]	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	(100.0)[b]	(99.7)[c]
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[d]	0.12	0.25	100.0/0.0/0.0	100.0/0.0/0.0
K. pneumoniae (1,847)				
Ceftazidime-avibactam	0.12	0.5	(99.9)[b]	(98.9)[c]
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[d]	0.25	1	99.2/0.7/0.1	95.3/3.9/0.8
ESBL phenotype (296)				
Ceftazidime-avibactam	0.5	1	(99.3)[b]	(92.9)[c]
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[d]	0.5	1	98.0/1.7/0.3	91.2/6.8/2.0
Meropenem nonsusceptible (MIC ≥ 2 μg/ml; 115)				
Ceftazidime-avibactam	0.5	2	(98.3)[b]	(85.2)[c]
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[d]	0.5	1	98.2/0.8/0.9	92.1/6.2/1.8

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TABLE 2 (Continued)

Organism (no. tested)/antimicrobial agent	MIC (μg/ml)		% S/% I/% R[a]	
	50	90	CLSI	EUCAST
K. oxytoca (442)				
Ceftazidime-avibactam	0.06	0.25	(100.0)[b]	(100.0)[c]
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[d]	0.12	0.25	99.8/0.2/0.0	98.2/1.6/0.2
ESBL phenotype (44)				
Ceftazidime-avibactam	0.25	1	(100.0)[b]	(100.0)[c]
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[d]	0.25	1	97.7/2.3/0.0	95.5/2.2/2.3
P. mirabilis (683)				
Ceftazidime-avibactam	0.03	0.06	(100.0)[b]	(100.0)[c]
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[d]	2	4	82.9/16.8/0.3	42.3/40.6/17.1
ESBL phenotype (33)				
Ceftazidime-avibactam	0.06	0.12	(100.0)[b]	(100.0)[c]
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[d]	2	4	81.8/18.2/0.0	48.5/33.3/18.2
E. cloacae (951)				
Ceftazidime-avibactam	0.12	0.5	(100.0)[b]	(99.1)[c]
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[d]	0.25	1	98.5/1.5/0.0	94.4/4.1/1.5
Ceftazidime nonsusceptible (MIC ≥ 8 μg/ml; 200)				
Ceftazidime-avibactam	0.5	1	(100.0)[b]	(95.5)[c]
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[d]	0.25	2	94.5/5.5/0.0	85.0/9.5/5.5

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TABLE 2 (Continued)

Organism (no. tested)/antimicrobial agent	MIC (μg/ml)		% S/% I/% R[a]	
	50	90	CLSI	EUCAST
E. aerogenes (357)				
Ceftazidime-avibactam	0.12	0.25	(99.7)[b]	(99.7)[c]
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 nonsusceptible (MIC, ≥ 8 μg/ml; 82)				
Ceftazidime-avibactam	0.25	0.5	(98.8)[b]	(98.8)[c]
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[d]	0.25	1	97.6/2.4/0.0	96.3/1.3/2.4
M. morganii (295)				
Ceftazidime-avibactam	0.06	0.12	(99.7)[b]	(99.7)[c]
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[d]	0.5	2	95.9/4.1/0.0	86.1/9.9/4.1
C. koseri (186)				
Ceftazidime-avibactam	0.06	0.12	(100.0)[b]	(100.0)[c]
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	(99.5)[b]	(98.4)[c]
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[d]	0.25	1	98.9/1.1/0.0	92.9/6.0/1.1
S. marcescens (506)				
Ceftazidime-avibactam	0.12	0.5	(99.6)[b]	(99.0)[c]
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[d]	0.5	1	99.0/1.0/0.0	94.3/4.7/1.0

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TABLE 2 (Continued)

Organism (no. tested)/antimicrobial agent	MIC (μg/ml)		% S/% I/% R[a]	
	50	90	CLSI	EUCAST
P. vulgaris (153)				
Ceftazidime-avibactam	0.06	0.06	(100.0)[b]	(100.0)[c]
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[d]	0.5	1	98.7/1.3/0.0	90.9/7.8/1.3
Providencia spp.[e] (268)				
Ceftazidime-avibactam	0.12	0.5	(95.90)[b]	(94.0)[c]
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[d]	1	2	95.1/4.9/0.0	76.0/19.1/4.9
P. aeruginosa (1,967)				
Ceftazidime-avibactam	2	4	(96.9)[b]	(96.9)[c]
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
Meropenem nonsusceptible (MIC ≥ 4 μg/ml; 354)				
Ceftazidime-avibactam	4	16	(87.3)[b]	(87.3)[c]
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
Ceftazidime nonsusceptible (MIC ≥ 16 μg/ml; 330)				
Ceftazidime-avibactam	4	16	(82.1)[b]	(82.1)[c]
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
Acinetobacter spp. (321)				
Ceftazidime-avibactam	16	>32	(31.2)[b]	-/-/-
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

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TABLE 2 (Continued)

Organism (no. tested)/antimicrobial agent	MIC (μg/ml)		% S/% I/% R[a]	
	50	90	CLSI	EUCAST
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 (11) and EUCAST (12). S, susceptible; I, intermediate; R, resistant.
[b] Percentage inhibited at the CLSI susceptible breakpoint for ceftazidime alone; for comparison only (11).
[c] Percentage inhibited at the EUCAST susceptible breakpoint for ceftazidime alone; for comparison only (12).
[d] Due to the lack of CLSI breakpoints, U.S. FDA breakpoints were applied instead (31).
[e] Includes *Providencia alcalifaciens* (3 strains), *Providencia rettgeri* (111 strains), and *Providencia stuartii* (154 strains).

aeruginosa (meropenem MIC, ≥4 μg/ml; 354 isolates tested), inhibiting 87.3% of strains at ≤8 μg/ml (Table 1). The most active antimicrobials tested against meropenem-nonsusceptible *P. aeruginosa* were ceftazidime-avibactam (MIC_{50}/MIC_{90}, 4/16 μg/ml), amikacin (MIC_{50}/MIC_{90}, 4/16 μg/ml; 92.7% susceptible [CLSI criteria]), and colistin (MIC_{50}/MIC_{90}, 1/2 μg/ml, 97.7% susceptible) (Table 2).

Ceftazidime-avibactam exhibited limited activity against *Acinetobacter* spp. (MIC_{50}/MIC_{90}, 16/>32 μg/ml; 31.2% inhibited at ≤8 μg/ml). Colistin (MIC_{50}/MIC_{90}, 1/2 μg/ml; 96.6% susceptible) and amikacin (MIC_{50}/MIC_{90}, 8/>32 μg/ml; 67.9% susceptible) were the most active compounds tested against this organism; all other compounds tested exhibited ≤50% susceptibility (Table 2).

DISCUSSION

The increasing trend of antimicrobial resistance is most troublesome for Gram-negative bacteria, because there has been little successful development of new antimicrobial agents targeting this group of organisms (16, 17). We are now facing infections caused by pandrug-resistant (PDR) or extremely drug-resistant (XDR) organisms, which are resistant to all (PDR) or almost all (XDR) antimicrobial agents currently available for clinical use (18). Thus, the use of second-line and more toxic compounds, such as the polymyxins, is rapidly increasing in some geographic regions, and new antimicrobial agents for treatment of infections caused by resistant Gram-negative organisms are desperately needed (16).

The prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE) remained extremely low for approximately 20 years after the approval of the first carbapenem for clinical use in 1985 (19, 20). However, in the last few years, the occurrence of carbapenemase-producing *Enterobacteriaceae* has increased rapidly in some geographic regions (6). In particular, clonal *K. pneumoniae* strains with KPCs (class A carbapenemases) have disseminated widely in the United States, Israel, and some European countries (5, 7, 13, 20, 21).

P. aeruginosa and *Acinetobacter* spp. represent major causes of hospital-acquired infections, particularly pneumonia, and are often resistant to multiple antimicrobial agents (17). These organisms demonstrate intrinsic decreased susceptibility to a wide variety of antimicrobials because of low outer membrane permeability; this allows secondary adaptive resistance mechanisms to work more efficiently, including β-lactamases and efflux pumps (22).

Ceftazidime is a well-established cephalosporin with an excellent safety profile and broad-spectrum activity against Gram-negative organisms, including *P. aeruginosa* (23). However, similar to other cephalosporins, ceftazidime can be hydrolyzed by some class A enzymes, including ESBLs and KPCs, and class C enzymes. Avibactam is a novel non-β-lactam β-lactamase inhibitor that protects β-lactams from hydrolysis by Ambler class A and C β-lactamases and some class D (OXA) enzymes (8, 24, 25). The results of the present study clearly demonstrate that avibactam restores ceftazidime activity against *Enterobacteriaceae* producing the β-lactamases most commonly found in U.S. hospitals, including ESBLs and KPCs (13). Ceftazidime-avibactam inhibited all ESBL- and KPC-producing *Enterobacteriaceae* strains at MICs of ≤4 μg/ml. Furthermore, ceftazidime-avibactam inhibited all *E. cloacae* and 98.8% (81/82) of *E. aerogenes* strains showing an AmpC-derepressed phenotype (i.e., ceftazidime-nonsusceptible strains). Eleven of 18 (66.7%) *Enterobacteriaceae* isolates with an elevated ceftazidime-avibactam MIC value (>4 μg/ml) were represented by *Providencia* spp. (10 *P. stuartii* and one *P. rettgeri* strains) (Table 1).

Ceftazidime-avibactam was also active against *P. aeruginosa* and inhibited 96.9% of strains at ≤8 μg/ml. Ceftazidime-avibactam (MIC_{50}/MIC_{90}, 2/4 μg/ml) exhibited greater anti-*P. aeruginosa* activity than ceftazidime (MIC_{50}/MIC_{90}, 2/32 μg/ml; 83.2% susceptible) and inhibited 82.1% of ceftazidime-nonsusceptible strains at ≤8 μg/ml. Moreover, ceftazidime-avibactam was highly active against meropenem-nonsusceptible strains (MIC_{50}/MIC_{90}, 4/16 μg/ml; 87.3% inhibited at ≤8 μg/ml). Similar to other β-lactams and to most antimicrobial agents tested, ceftazidime-avibactam showed limited activity against *Acinetobacter* spp. and metallo-β-lactamase-producing strains of *Enterobacteriaceae*; the latter are extremely rare in U.S. hospitals (13, 14).

In summary, ceftazidime-avibactam was active against a large collection of contemporary (2012) Gram-negative organisms isolated from patients in U.S. hospitals, including organisms resistant to most currently available agents, such as KPC-producing *Enterobacteriaceae* and meropenem-nonsusceptible *P. aeruginosa*. The results of this study corroborate other investigations demonstrating potent *in vitro* activity against multidrug-resistant strains of *Enterobacteriaceae* (26–28) and *P. aeruginosa* (29, 30) and indicate that 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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