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Antimicrobial Activities of Ceftazidime-Avibactam and Comparator Agents against Gram-Negative Organisms Isolated from Patients with Urinary Tract Infections in U.S. Medical Centers, 2012 to 2014

Helio S. Sader, Mariana Castanheira, Robert K. Flamm, Ronald N. Jones

JMI Laboratories, North Liberty, Iowa, USA

A total of 7,272 unique patient clinical isolates were collected from 71 U.S. medical centers from patients with urinary tract infections in 2012 to 2014 and tested for susceptibility to ceftazidime-avibactam and comparators by broth microdilution methods. Ceftazidime-avibactam inhibited >99.9% of all *Enterobacteriaceae* at the susceptible breakpoint of ≤8 μg/ml (there were only three nonsusceptible strains). Ceftazidime-avibactam was also active against *Pseudomonas aeruginosa* isolates (MIC_{50}, 2 μg/ml; MIC_{90}, 4 μg/ml; 97.7% susceptible), including many isolates not susceptible to meropenem, ceftazidime, and/or piperacillin-tazobactam.

Urinary tract infections (UTIs) are among the most frequent health care-associated (HA) infections and represent a major source of Gram-negative bacteremia. *Escherichia coli* is the most common pathogen causing community-associated as well as HA UTIs. Other *Enterobacteriaceae* species, such as *Proteus mirabilis*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Enterobacter cloacae*, and *Serratia marcescens*, also represent important causes of UTIs. In recurrent UTIs, especially in the presence of structural abnormalities of the urinary tract, the relative frequencies increase for *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., and *Pseudomonas aeruginosa*. Since instrumentation and repeat courses of antimicrobial therapy are common in these patients with complicated UTIs, antimicrobial-resistant isolates might be expected (1).

Antimicrobial-resistant strains that produce extended-spectrum β-lactamases (ESBLs), such as the CTX-M and SHV enzymes and/or *K. pneumoniae* carbapenemase (KPC), have emerged among *Enterobacteriaceae*, predominantly among *E. coli* and *K. pneumoniae* strains, and have become endemic in hospitals at various levels of intensity (2, 3). Systemic infections caused by organisms with additional resistances to other antimicrobial classes have become a great therapeutic challenge. *P. aeruginosa* also represents a major cause of UTIs and often demonstrates decreased susceptibility to various antimicrobial agents (1).

Ceftazidime-avibactam is a combination agent consisting of the non-β-lactam β-lactamase inhibitor avibactam and the broad-spectrum cephalosporin ceftazidime (4). Avibactam (formerly NXL-104) is a member of a novel class of β-lactamase inhibitors, the diazabicyclooctanes (DBOs) (5). Compared with current inhibitors available for clinical use, DBOs are more potent, have a broader spectrum of enzyme inhibition, and have a different mechanism of action. Avibactam protects β-lactams from hydrolysis by a wide variety of clinically relevant enzymes (6).

The ceftazidime-avibactam combination has been approved by the U.S. Food and Drug Administration (FDA) for treatment of complicated intra-abdominal infections (IAIs) and complicated UTIs, including pyelonephritis, in patients with limited or no alternative treatment options (4, 7). Ceftazidime-avibactam is also under clinical development for treatment of nosocomial pneumonia (ClinicalTrials.gov registration number NCT01808092). In this investigation, the activity of ceftazidime combined with avibactam was evaluated against a large collection of contemporary Gram-negative organisms isolated from patients with UTIs in U.S. hospitals.

A total of 7,272 unique patient organisms were collected from patients with UTIs in 71 U.S. medical centers in 2012 to 2014 as part of the International Network for Optimal Resistance Monitoring (INFORM) program. Only one isolate per patient episode was included in the surveillance study. Species identification was performed at the participating medical center and was confirmed at the monitoring laboratory (JMI Laboratories, North Liberty, IA, USA) using matrix-assisted laser desorption–ionization time of flight (MALDI-TOF) analysis (Bruker Daltonics, Billerica, MA, USA), as necessary. A strain was defined as having an ESBL screen-positive phenotype when the MIC of ceftazidime, ceftriaxone, and/or aztreonam for it was ≥2 μg/ml (8).

Broth microdilution tests conducted according to the methods of the Clinical and Laboratory Standards Institute (CLSI) were performed to determine the antimicrobial susceptibilities of ceftazidime-avibactam (an inhibitor tested at a fixed concentration of 4 μg/ml) and comparator agents (7–11). Validated MIC panels were manufactured by Thermo Fisher Scientific Inc. (Cleveland, OH, USA). Ceftazidime-avibactam breakpoints approved by the U.S. FDA and CLSI (≤8/4 μg/ml for ceftazidime/avibactam for susceptibility and ≥16/4 μg/ml for ceftazidime/avibactam for resistance) were applied for all *Enterobacteriaceae* species and *P. aeruginosa* (7, 8). Susceptibility interpretations for comparator agents were those found in CLSI document M100-S26 (8), EUCAST breakpoint documentation (10), and/or a U.S. FDA package insert (11). Concurrent quality control (QC) testing was performed on the following strains: *E. coli* ATCC 25922 and

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Address correspondence to Helio S. Sader, helio-sader@jmilabs.com.

ATCC 35218, *K. pneumoniae* ATCC 700603 and BAA 1705, and *P. aeruginosa* ATCC 27853. All QC results were within published ranges.

Enterobacteriaceae isolates showing an ESBL phenotype, as well as those strains for which ceftazidime-avibactam MIC values were >8 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 as previously described (3). This kit has the abilities to detect CTX-M groups 1, 2, 8 plus 25, and 9, wild-type (WT) TEM and ESBL, WT SHV and ESBL, ACC, ACT/MIR, CMYII, DHA, FOX, KPC, and NDM-1.

Ceftazidime-avibactam inhibited >99.9% of all *Enterobacteriaceae* isolates (including all *E. coli* isolates [MIC_{50}, 0.06 μg/ml; MIC_{90}, 0.12 μg/ml], all *P. mirabilis* isolates [MIC_{50}, 0.03 μg/ml; MIC_{90}, 0.06 μg/ml], and 99.93% of *Klebsiella* species isolates [MIC_{50}, 0.12 μg/ml; MIC_{90}, 0.25 μg/ml]) at the susceptibility breakpoint of ≤8 μg/ml (Table 1). Overall, only 3 of 6,773 *Enterobacteriaceae* isolates (0.04%) were nonsusceptible to ceftazidime-avibactam (MIC, ≥16 μg/ml): (i) one *K. pneumoniae* isolate from New York, NY, with VIM-4, KPC-2, and CMY-2 and a ceftazidime-avibactam MIC of >32 μg/ml; (ii) one *Enterobacter cloacae* isolate also isolated in New York City but at a different medical center, for which the ceftazidime-avibactam MIC was 32 μg/ml and results for all β-lactamases tested were negative; and (iii) one *Providencia stuartii* isolate from Winston-Salem, NC, for which the ceftazidime-avibactam MIC was 16 μg/ml and results for all β-lactamases tested were negative. Meropenem (MIC_{50}, ≤0.06 μg/ml; MIC_{90}, ≤0.06 μg/ml; 98.6% susceptible) was also highly active against *Enterobacteriaceae* (Table 2). An ESBL phenotype was observed among 11.5% of *E. coli* isolates, 13.9% of *Klebsiella* species isolates, and 4.7% of *P. mirabilis* isolates tested (Tables 1 and 2).

A total of 2,876 *E. coli* isolates were processed, and the most-active compounds tested against these organisms were ceftazidime-avibactam (MIC_{50}, 0.06 μg/ml; MIC_{90}, 0.12 μg/ml; 100.0% susceptible), meropenem (MIC_{50}, ≤0.06 μg/ml; MIC_{90}, ≤0.06 μg/ml; 99.7% susceptible), colistin (MIC_{50}, 0.05 μg/ml; MIC_{90}, 0.5 μg/ml; 99.4% susceptible [EUCAST]), and piperacillin-tazobactam (MIC_{50}, 2 μg/ml; MIC_{90}, 8 μg/ml; 96.9% susceptible) (Table 2).

Ceftazidime-avibactam was also active against *Klebsiella* spp. (n = 1,484; MIC_{50}, 0.12 μg/ml; MIC_{90}, 0.25 μg/ml; 99.9% susceptible), including those with an ESBL phenotype (n = 207; MIC_{50}, 0.25 μg/ml; MIC_{90}, 1 μg/ml; 99.5% susceptible) and non-meropenem-susceptible *K. pneumoniae* isolates (n = 74; MIC_{50}, 0.5 μg/ml; MIC_{90}, 2 μg/ml; 98.6% susceptible) (Tables 1 and 2). Only ceftazidime-avibactam showed good activity against ESBL phenotype *Klebsiella* spp. and non-meropenem-susceptible *K. pneumoniae* isolates (Table 2). Meropenem was active against only 63.3% of ESBL phenotype *Klebsiella* species isolates, and colistin inhibited only 68.0% of non-meropenem-susceptible *K. pneumoniae* isolates at the EUCAST susceptibility breakpoint of ≤2 μg/ml (Table 2).

All *P. mirabilis* strains were susceptible to ceftazidime-avibactam (MIC_{50}, 0.03 μg/ml; MIC_{90}, 0.06 μg/ml) and meropenem (MIC_{50}, ≤0.06 μg/ml; MIC_{90}, 0.12 μg/ml), and ≥99.6% were susceptible to ceftazidime (MIC_{50}, 0.06 μg/ml; MIC_{90}, 0.12 μg/ml) and piperacillin-tazobactam (MIC_{50}, ≤0.5 μg/ml; MIC_{90}, 1 μg/ml) according to the CLSI breakpoint criteria (Table 2). Among *E. cloacae* isolates (ceftazidime-avibactam MIC_{50}, 0.25 μg/ml; MIC_{90}, 0.5 μg/ml; 23.3% were not ceftazidime susceptible), 99.7% of them, including 98.8% of non-ceftazidime-susceptible strains (MIC_{50}, 0.5 μg/ml; MIC_{90}, 1 μg/ml), were susceptible to ceftazidime-avibactam (Table 1). Meropenem (98.6% susceptible) was also highly active against *E. cloacae* (Table 2).

Ceftazidime-avibactam was also very active against *P. aeruginosa* isolates (MIC_{50}, 2 μg/ml; MIC_{90}, 4 μg/ml; 97.7% susceptible), including the majority of isolates not susceptible to meropenem (90.5% susceptible to ceftazidime-avibactam), ceftazidime (82.7% susceptible), or piperacillin-tazobactam (89.3% susceptible) (Table 2). Further, ceftazidime-avibactam inhibited 77.8% (21/27) of isolates at ≤8 μg/ml that were nonsusceptible to meropenem, ceftazidime, and piperacillin-tazobactam (Table 1). Among *P. aeruginosa* isolates, the rate of susceptibility to ceftazidime-avibactam (MIC_{50}, 2 μg/ml; MIC_{90}, 4 μg/ml) was 9.5% higher (97.7 versus 88.2%) than that to ceftazidime tested alone (MIC_{50}, 2 μg/ml; MIC_{90}, 16 μg/ml). Cefepime (MIC_{50}, 2 μg/ml; MIC_{90}, 16 μg/ml), meropenem (MIC_{50}, 0.5 μg/ml; MIC_{90}, 8 μg/ml), and piperacillin-tazobactam (MIC_{50}, 8 μg/ml; MIC_{90}, 32 μg/ml) were active against 87.1, 80.9, and 83.0% of *P. aeruginosa* strains, respectively (Table 2). *Acinetobacter* spp. (57 isolates), which comprised only 0.8% of the UTI organism collection, exhibited decreased susceptibility to ceftazidime-avibactam (MIC_{50}, 16 μg/ml; MIC_{90}, >32 μg/ml) and all other β-lactam compounds tested (Table 2).

Treatment of UTIs has been the subject of many studies as rates of antimicrobial resistance have evolved (2, 12, 13). When dealing with complicated UTIs, common measures include obtaining a urine culture, starting broad-spectrum antimicrobial coverage, and then refining the drug selection after receipt of susceptibility testing results. The major challenge for clinicians is to combine local susceptibility patterns with the agents that are most likely to be effective. Variability in the antimicrobial susceptibility profiles between institutions can be substantial, but susceptibility test results from a large, well-monitored surveillance network can provide very useful data by highlighting prevalences and trends of clinically relevant antimicrobial resistance phenotypes (14–16).

Ceftazidime-avibactam has demonstrated clinical efficacy similar to that of carbapenem therapy in phase II studies of complicated IAIs and complicated UTIs, including acute pyelonephritis, and it was approved by the U.S. FDA in late 2014 for treatment of these infections in patients with limited or no alternative treatment options (4, 7). The addition of avibactam restores the activity of ceftazidime against Gram-negative bacilli that achieve β-lactam resistance through production of the Ambler class A ESBLs, chromosomal or mobile class C β-lactamases, serine carbapenemases (such as KPC), and some class D β-lactamases (5, 17). Production of metallo-β-lactamases (MBLs) represents the most common mechanism of resistance to ceftazidime-avibactam observed among *Enterobacteriaceae*, but the MBL-producing strains remain very uncommon in U.S. hospitals (6, 18). Furthermore, selection of ceftazidime-avibactam resistance among Gram-negative organisms, including *P. aeruginosa*, is limited when this combination is used as the selecting agent (19, 20).

In the present study, we evaluated a large collection (7,272) of contemporary UTI Gram-negative organisms from U.S. medical centers, and ceftazidime-avibactam was active (MIC, ≤8 μg/ml) against 99.3% of these organisms overall. Interestingly, *Acineto-*

TABLE 1 Summary of ceftazidime-avibactam activities against Gram-negative organisms isolated from patients with UTIs in U.S. hospitals in 2012 to 2014

Organism(s) (no. of isolates) or phenotype[a]	No. of isolates (cumulative %) inhibited at a ceftazidime-avibactam MIC (μg/ml) of:												MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32		
Enterobacteriaceae (6,773)	1,307 (19.3)	2,382 (54.5)	2,115 (85.7)	616 (94.8)	247 (98.4)	72 (99.5)	23 (99.8)	7 (99.9)	1 (>99.9)	1 (>99.9)	1 (>99.9)	1 (100.0)	0.06	0.25
E. coli (2,876)	508 (17.7)	1,169 (58.3)	995 (92.9)	172 (98.9)	27 (99.8)	1 (99.9)	2 (99.9)	2 (100.0)					0.06	0.12
With ESBL phenotype (330)	24 (7.3)	53 (23.3)	159 (71.5)	74 (93.9)	15 (98.5)	1 (98.8)	2 (99.4)	2 (100.0)					0.12	0.25
Klebsiella spp. (1,484)	116 (7.8)	561 (45.6)	544 (82.3)	145 (92.0)	77 (97.2)	29 (99.2)	10 (99.9)	1 (99.9)	0 (99.9)	0 (99.9)	0 (99.9)	1 (100.0)	0.12	0.25
With ESBL phenotype (207)	12 (5.8)	12 (11.6)	45 (33.3)	38 (51.7)	61 (81.2)	27 (94.2)	10 (99.0)	1 (99.5)	0 (99.5)	0 (99.5)	0 (99.5)	1 (100.0)	0.25	1
Non-MEM-susceptible *K. pneumoniae* (74)	6 (8.1)	1 (9.5)	4 (14.9)	8 (25.7)	30 (66.2)	14 (85.1)	9 (97.3)	1 (98.6)	0 (98.6)	0 (98.6)	0 (98.6)	1 (100.0)	0.5	2
P. mirabilis (493)	320 (64.9)	160 (97.4)	9 (99.2)	3 (99.8)	0 (99.8)	1 (100.0)							0.03	0.06
Providencia spp. (373)	92 (24.7)	90 (48.8)	97 (74.8)	53 (89.0)	26 (96.0)	5 (97.3)	6 (98.9)	2 (99.5)	1 (99.7)	1 (100.0)			0.12	0.5
E. cloacae (356)	6 (1.7)	24 (8.4)	147 (49.7)	102 (78.4)	48 (91.9)	23 (98.3)	3 (99.2)	2 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	1 (100.0)	0.25	0.5
Non-CAZ susceptible (83)		1 (1.2)	5 (7.2)	25 (37.3)	28 (71.1)	19 (94.0)	2 (96.4)	2 (98.8)	0 (98.8)	0 (98.8)	0 (98.8)	1 (100.0)	0.5	1
Morganella morganii (305)	132 (43.3)	113 (80.3)	32 (90.8)	16 (96.1)	7 (98.4)	5 (100.0)							0.06	0.12
Proteus vulgaris (219)	104 (47.5)	97 (91.8)	12 (97.3)	2 (98.2)	4 (100.0)								0.06	0.06
Citrobacter freundii (204)	6 (2.9)	28 (16.7)	111 (71.1)	38 (89.7)	17 (98.0)	3 (99.5)	1 (100.0)						0.12	0.5
Enterobacter aerogenes (189)	8 (4.2)	58 (34.9)	72 (73.0)	30 (88.9)	19 (98.9)	2 (100.0)							0.12	0.5
Citrobacter koseri (150)	15 (10.0)	78 (62.0)	39 (88.0)	15 (98.0)	2 (99.3)	1 (100.0)							0.06	0.25
S. marcescens (124)		4 (3.2)	57 (49.2)	40 (81.5)	20 (97.6)	2 (99.2)	1 (100.0)						0.25	0.5
P. aeruginosa (442)				2 (0.5)	20 (5.0)	165 (42.3)	148 (75.8)	65 (90.5)	32 (97.7)	6 (99.1)	2 (99.5)	2 (100.0)	2	4
Non-CAZ susceptible (52)						3 (5.8)	12 (28.8)	11 (50.0)	17 (82.7)	5 (92.3)	2 (96.2)	2 (100.0)	4	16
Non-MEM susceptible (84)						5 (6.0)	18 (27.4)	31 (64.3)	22 (90.5)	4 (95.2)	2 (97.6)	2 (100.0)	4	8
Non-P-T susceptible (75)						4 (5.3)	14 (24.0)	23 (54.7)	26 (89.3)	5 (96.0)	2 (98.7)	1 (100.0)	4	16
Non-CAZ, -MEM, or -P-T susceptible (27)						1 (3.7)	0 (3.7)	6 (25.9)	14 (77.8)	3 (88.9)	2 (96.3)	1 (100.0)	8	32
Acinetobacter spp. (57)						3 (5.3)	3 (10.5)	14 (35.1)	8 (49.1)	9 (64.9)	10 (82.5)	10 (100.0)	16	>32

[a] Abbreviations: ESBL, extended-spectrum β-lactamase; CAZ, ceftazidime; MEM, meropenem; P-T, piperacillin-tazobactam.

TABLE 2 Activities of ceftazidime-avibactam and comparator antimicrobial agents tested against Gram-negative organisms isolated from patients with UTIs from U.S. hospitals in 2012 to 2014

Organism(s) (no. of isolates), phenotype, or antimicrobial	MIC_{50}	MIC_{90}	%S[a]	%R[a]
Enterobacteriaceae (6,773)				
Ceftazidime-avibactam	0.06	0.25	>99.9	<0.1[b]
Ceftazidime	0.12	4	90.3	8.3
Ceftriaxone	≤0.06	8	87.2	11.8
Ampicillin-sulbactam	8	>32	59.0	23.8
Piperacillin-tazobactam	2	8	94.2	3.3
Meropenem	≤0.06	≤0.06	98.6	1.3
Levofloxacin	≤0.12	>4	80.8	17.0
Gentamicin	≤1	8	89.9	8.7
Colistin[b]	0.5	>8	75.4	24.6
Escherichia coli (2,876)				
Ceftazidime-avibactam	0.06	0.12	100.0	0.0[b]
Ceftazidime	0.12	2	91.9	6.4
Ceftriaxone	≤0.06	>8	89.3	10.6
Ampicillin-sulbactam	8	32	56.4	24.0
Piperacillin-tazobactam	2	8	96.9	1.2
Meropenem	≤0.06	≤0.06	99.7	0.2
Levofloxacin	≤0.12	>4	74.5	24.8
Gentamicin	≤1	>8	88.2	11.4
Colistin[b]	0.5	0.5	99.4	0.6
With ESBL phenotype (330)				
Ceftazidime-avibactam	0.12	0.25	100.0	0.0[b]
Ceftazidime	16	>32	29.7	55.5
Ceftriaxone	>8	>8	6.7	92.4
Ampicillin-sulbactam	32	>32	15.5	67.3
Piperacillin-tazobactam	4	32	83.6	6.7
Meropenem	≤0.06	≤0.06	97.0	2.1
Levofloxacin	>4	>4	20.9	76.4
Gentamicin	2	>8	57.9	42.1
Colistin[b]	0.5	0.5	100.0	0.0
Klebsiella spp. (1,484)[c]				
Ceftazidime-avibactam	0.12	0.25	99.9	0.1[b]
Ceftazidime	0.12	16	88.5	10.6
Ceftriaxone	≤0.06	>8	87.0	12.7
Ampicillin-sulbactam	8	>32	75.9	16.6
Piperacillin-tazobactam	2	32	89.6	8.6
Meropenem	≤0.06	≤0.06	94.9	5.0
Levofloxacin	≤0.12	4	88.6	9.7
Gentamicin	≤1	2	91.9	6.9
Colistin[b]	0.5	0.5	97.4	2.6
With ESBL phenotype (207)				
Ceftazidime-avibactam	0.25	1	99.5	0.5[b]
Ceftazidime	>32	>32	17.4	75.8
Ceftriaxone	>8	>8	6.8	91.3
Ampicillin-sulbactam	>32	>32	2.4	89.9
Piperacillin-tazobactam	>64	>64	31.4	58.9
Meropenem	≤0.06	>8	63.3	35.7
Levofloxacin	>4	>4	28.5	63.3
Gentamicin	8	>8	45.9	45.9
Colistin[b]	0.5	4	88.6	11.4
Non-meropenem susceptible (74)				
Ceftazidime-avibactam	0.5	2	98.6	1.4[b]
Ceftazidime	>32	>32	0.0	98.6
Ceftriaxone	>8	>8	0.0	100.0
Ampicillin-sulbactam	>32	>32	0.0	100.0
Piperacillin-tazobactam	>64	>64	0.0	98.6
Meropenem	>8	>8	0.0	97.3
Levofloxacin	>4	>4	2.7	93.2
Gentamicin	4	>8	51.4	41.9
Colistin[b]	0.5	>8	68.0	32.0
Proteus mirabilis (493)				
Ceftazidime-avibactam	0.03	0.06	100.0	0.0[b]
Ceftazidime	0.06	0.12	99.6	0.0
Ceftriaxone	≤0.06	≤0.06	96.1	3.0
Ampicillin-sulbactam	1	8	91.1	3.0
Piperacillin-tazobactam	≤0.5	1	99.8	0.0
Meropenem	≤0.06	0.12	100.0	0.0
Levofloxacin	≤0.12	>4	76.9	18.5
Gentamicin	≤1	4	91.0	6.1
Colistin[b]	>8	>8	0.0	100.0
Enterobacter cloacae (356)				
Ceftazidime-avibactam	0.25	0.5	99.7	0.3[b]
Ceftazidime	0.5	>32	76.7	22.8
Ceftriaxone	0.25	>8	69.3	27.3
Ampicillin-sulbactam	32	>32	30.5	50.6
Piperacillin-tazobactam	2	64	83.1	7.9
Meropenem	≤0.06	≤0.06	98.6	1.4
Levofloxacin	≤0.12	1	91.3	7.3
Gentamicin	≤1	≤1	92.1	7.0
Colistin[b]	0.5	>8	84.6	15.4
Non-ceftazidime susceptible (83)				
Ceftazidime-avibactam	0.5	1	98.8	1.2[b]
Piperacillin-tazobactam	64	>64	29.3	32.9
Meropenem	≤0.06	0.12	95.2	4.8
Levofloxacin	0.5	>4	71.1	24.1
Gentamicin	≤1	>8	72.3	24.1
Colistin[c]	0.5	>8	78.8	21.2
Pseudomonas aeruginosa (442)				
Ceftazidime-avibactam	2	4	97.7	2.3[b]
Ceftazidime	2	16	88.2	8.1
Cefepime	2	16	87.1	4.3
Piperacillin-tazobactam	8	32	83.0	6.3
Meropenem	0.5	8	80.9	13.6
Levofloxacin	0.5	>4	69.0	26.9
Gentamicin	≤1	8	89.4	8.4
Amikacin	2	8	98.9	0.5
Colistin	1	2	100.0	0.0
Non-ceftazidime susceptible (52)				
Ceftazidime-avibactam	4	16	82.7	17.3[b]
Cefepime	16	>16	26.9	26.9
Piperacillin-tazobactam	64	>64	13.5	38.5
Meropenem	8	>8	36.5	57.7
Levofloxacin	>4	>4	25.0	69.2
Gentamicin	4	>8	75.0	23.1
Amikacin	4	8	98.1	0.0
Non-meropenem susceptible (84)				
Ceftazidime-avibactam	4	8	90.5	9.5[b]
Ceftazidime	8	>32	60.7	29.8
Cefepime	8	>16	56.0	17.9
Piperacillin-tazobactam	16	>64	50.0	25.0
Levofloxacin	>4	>4	19.0	75.0
Gentamicin	4	>8	60.7	33.3
Amikacin	4	8	95.2	2.4

(Continued on following page)

TABLE 2 (Continued)

Organism(s) (no. of isolates), phenotype, or antimicrobial	MIC_{50}	MIC_{90}	%S[a]	%R[a]
Non-piperacillin-tazobactam susceptible (75)				
Ceftazidime-avibactam	4	16	89.3	10.7[b]
Ceftazidime	16	>32	40.0	42.7
Cefepime	16	>16	34.7	21.3
Meropenem	8	>8	44.0	52.0
Levofloxacin	>4	>4	25.3	68.0
Gentamicin	4	>8	69.3	28.0
Amikacin	4	8	96.0	2.7
Acinetobacter baumannii (57)				
Ceftazidime-avibactam	16	>32		
Ceftazidime	8	>32	52.6	40.4
Cefepime	16	>16	47.4	42.1
Ampicillin-sulbactam	8	>32	56.1	31.6
Piperacillin-tazobactam	32	>64	47.4	42.1
Meropenem	1	>8	59.6	40.4
Levofloxacin	0.5	>4	54.4	42.1
Gentamicin	2	>8	56.1	35.1
Amikacin	4	>32	73.2	23.2
Colistin	1	2	95.2	4.8

[a] %S and %R, percentages of isolates susceptible and resistant, respectively, according to the criteria published by the CLSI (8), unless otherwise noted.
[b] Criteria were as published by the EUCAST (10).
[c] Organisms include *Klebsiella oxytoca* (175 isolates) and *K. pneumoniae* (1,309 isolates).

bacter spp. represented only 0.8% of all isolates collected from patients with UTIs (52 of 7,272) but 75.0% (39 of 52) of non-ceftazidime-avibactam-susceptible isolates. Ceftazidime-avibactam coverage against this large collection of UTI organisms from the United States was greater than that observed for meropenem (97.2% susceptible) and piperacillin-tazobactam (93.2% susceptible). Furthermore, ceftazidime-avibactam demonstrated potent activity against ESBL-producing and carbapenem-resistant *Enterobacteriaceae* (CRE) and also inhibited the vast majority of *P. aeruginosa* strains nonsusceptible to ceftazidime, meropenem, and/or piperacillin-tazobactam.

The main limitation of the study is the lack of clinical and epidemiologic information about the patient population. Analyses of the susceptibility results according to epidemiologic traits, such as HA versus community-acquired infections, recurrent infection versus the first episode, and previous exposure to antimicrobial agents, for example, would provide important additional data. Despite these study limitations, the results presented here provide valuable information on the contemporary antimicrobial susceptibility patterns of Gram-negative pathogens causing UTIs in U.S. medical centers.

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REFERENCES

1. **Lane DR, Takhar SS.** 2011. Diagnosis and management of urinary tract infection and pyelonephritis. Emerg Med Clin North Am **29:**539–552. http://dx.doi.org/10.1016/j.emc.2011.04.001.
2. **Briongos-Figuero LS, Gomez-Traveso T, Bachiller-Luque P, Dominguez-Gil Gonzalez M, Gomez-Nieto A, Palacios-Martin T, Gonzalez-Sagrado M, Duenas-Laita A, Perez-Castrillon JL.** 2012. Epidemiology, risk factors and comorbidity for urinary tract infections caused by extended-spectrum beta-lactamase (ESBL)-producing enterobacteria. Int J Clin Pract **66:**891–896. http://dx.doi.org/10.1111/j.1742-1241.2012.02991.x.
3. **Castanheira M, Farrell SE, Deshpande LM, Mendes RE, Jones RN.** 2013. Prevalence of β-lactamase encoding genes among *Enterobacteriaceae* bacteremia isolates collected in 26 U.S. hospitals: report from the SENTRY Antimicrobial Surveillance Program (2010). Antimicrob Agents Chemother **57:**3012–3020. http://dx.doi.org/10.1128/AAC.02252-12.
4. **Zhanel GG, Lawson CD, Adam H, Schweizer F, Zelenitsky S, Lagace-Wiens PR, Denisuik A, Rubinstein E, Gin AS, Hoban DJ, Lynch JP, III, Karlowsky JA.** 2013. Ceftazidime-avibactam: a novel cephalosporin/β-lactamase inhibitor combination. Drugs **73:**159–177. http://dx.doi.org/10.1007/s40265-013-0013-7.
5. **Coleman K.** 2011. Diazabicyclooctanes: a potent new class of non-β-lactam β-lactamase inhibitors. Curr Opin Microbiol **14:**550–555. http://dx.doi.org/10.1016/j.mib.2011.07.026.
6. **Bush K.** 2015. A resurgence of beta-lactamase inhibitor combinations effective against multidrug-resistant Gram-negative pathogens. Int J Antimicrob Agents **46:**483–493. http://dx.doi.org/10.1016/j.ijantimicag.2015.08.011.
7. **Avycaz.** 2015. Avycaz prescribing information. http://www.avycaz.com. Forest Laboratories, New York, NY. Accessed 29 January 2016.
8. **Clinical and Laboratory Standards Institute.** 2016. Performance standards for antimicrobial susceptibility testing: 26th informational supplement. M100-S26. Clinical and Laboratory Standards Institute, Wayne, PA.
9. **Clinical and Laboratory Standards Institute.** 2015. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard. Tenth edition. M07-A10. Clinical and Laboratory Standards Institute, Wayne, PA.
10. **EUCAST.** 2016. Breakpoint tables for interpretation of MICs and zone diameters, version 6.0, January 2016. http://www.eucast.org/clinical_breakpoints/. Accessed January 2016.
11. **Wyeth Pharmaceuticals.** 2014.Tygacil® package insert. Wyeth Pharmaceuticals, Dallas, TX. http://www.tygacil.com. Accessed 25 January 2016.
12. **Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper DE.** 2011. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis **52:**e103–e120. http://dx.doi.org/10.1093/cid/ciq257.
13. **Wagenlehner FM, Cek M, Naber KG, Kiyota H, Bjerklund-Johansen TE.** 2012. Epidemiology, treatment and prevention of healthcare-associated urinary tract infections. World J Urol **30:**59–67. http://dx.doi.org/10.1007/s00345-011-0757-1.
14. **Koningstein M, van der Bij AK, de Kraker ME, Monen JC, Muilwijk J, de Greeff SC, Geerlings SE, van Hall MA, ISIS-AR Study Group.** 2014. Recommendations for the empirical treatment of complicated urinary tract infections using surveillance data on antimicrobial resistance in the Netherlands. PLoS One **9:**e86634. http://dx.doi.org/10.1371/journal.pone.0086634.

15. **Sader HS, Flamm RK, Jones RN.** 2014. Frequency of occurrence and antimicrobial susceptibility of gram-negative bacteremia isolates in patients with urinary tract infection: results from United States and European hospitals (2009–2011). J Chemother **26:**133–138. http://dx.doi.org/10.1179/1973947813Y.0000000121.
16. **Sorlozano A, Jimenez-Pacheco A, de Dios Luna Del Castillo J, Sampedro A, Martinez-Brocal A, Miranda-Casas C, Navarro-Mari JM, Gutierrez-Fernandez J.** 2014. Evolution of the resistance to antibiotics of bacteria involved in urinary tract infections: a 7-year surveillance study. Am J Infect Control **42:**1033–1038. http://dx.doi.org/10.1016/j.ajic.2014.06.013.
17. **Castanheira M, Farrell SE, Krause KM, Jones RN, Sader HS.** 2014. Contemporary diversity of β-lactamases among *Enterobacteriaceae* in the nine United States census regions and ceftazidime-avibactam activity tested against isolates producing the most prevalent β-lactamase groups. Antimicrob Agents Chemother **58:**833–838. http://dx.doi.org/10.1128/AAC.01896-13.
18. **Castanheira M, Mills JC, Costello SE, Jones RN, Sader HS.** 2015. Ceftazidime-avibactam activity tested against *Enterobacteriaceae* from United States hospitals (2011–2013) and characterization of beta-lactamase producing strains. Antimicrob Agents Chemother **59:**3509–3517. http://dx.doi.org/10.1128/AAC.00163-15.
19. **Lahiri SD, Walkup GK, Whiteaker JD, Palmer T, McCormack K, Tanudra MA, Nash TJ, Thresher J, Johnstone MR, Hajec L, Livchak S, McLaughlin RE, Alm RA.** 2015. Selection and molecular characterization of ceftazidime/avibactam-resistant mutants in Pseudomonas aeruginosa strains containing derepressed AmpC. J Antimicrob Chemother **70:**1650–1658. http://dx.doi.org/10.1093/jac/dkv004.
20. **Livermore DM, Warner M, Jamrozy D, Mushtaq S, Nichols WW, Mustafa N, Woodford N.** 2015. In vitro selection of ceftazidime-avibactam resistance in *Enterobacteriaceae* with KPC-3 carbapenemase. Antimicrob Agents Chemother **59:**5324–5330. http://dx.doi.org/10.1128/AAC.00678-15.