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In Vitro Susceptibility to Ceftazidime-Avibactam of Carbapenem-Nonsusceptible *Enterobacteriaceae* Isolates Collected during the INFORM Global Surveillance Study (2012 to 2014)

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The activity of ceftazidime-avibactam was assessed against 961 isolates of meropenem-nonsusceptible *Enterobacteriaceae*. Most meropenem-nonsusceptible metallo-β-lactamase (MBL)-negative isolates (97.7%) were susceptible to ceftazidime-avibactam. Isolates that carried KPC or OXA-48-like β-lactamases, both alone and in combination with extended-spectrum β-lactamases (ESBLs) and/or AmpC β-lactamases, were 98.7% and 98.5% susceptible to ceftazidime-avibactam, respectively. Meropenem-nonsusceptible, carbapenemase-negative isolates demonstrated 94.7% susceptibility to ceftazidime-avibactam. Ceftazidime-avibactam activity was compromised only in isolates for which carbapenem resistance was mediated through metallo-β-lactamases.

Carbapenems are bactericidal β-lactam antibiotics that are recommended for therapy against infections caused by extended-spectrum β-lactamase (ESBL)- and/or AmpC-cephalosporinase-producing *Enterobacteriaceae* (1–4). Two clinically important mechanisms of resistance to carbapenems among *Enterobacteriaceae* have been identified. One is the production of carbapenemases, such as serine carbapenemases (KPC and OXA) and metallo-β-lactamases (VIM, IMP, and NDM) (5), and the other is the production of ESBLs or Ambler class C β-lactamases coupled with reduced expression or loss of function of one or more outer membrane pore-forming proteins (6–8).

Avibactam is a non-β-lactam–β-lactamase inhibitor that inhibits the activities of Ambler class A β-lactamases, including ESBLs and *Klebsiella pneumoniae* carbapenemase (KPC), class C β-lactamases, and some class D β-lactamases (9). Ceftazidime-avibactam displays antibacterial activity *in vitro* against KPC-producing clinical isolates of *Enterobacteriaceae* (10), including isolates carrying *ompK36* mutations (11), and against AmpC-producing *Enterobacter* spp. and ESBL-producing *K. pneumoniae* strains with impaired permeability (12). Ceftazidime-avibactam also displayed low MICs (≤8 μg/ml) against noncarbapenemase-producing, carbapenem-nonsusceptible (NS) *Enterobacteriaceae* isolated from patients in France (13). Moreover, while recognizing that ceftazidime is not hydrolyzed significantly by OXA-48, but that bla_{OXA-48}-containing isolates of *Enterobacteriaceae* commonly also carry genes encoding ESBLs that do hydrolyze ceftazidime, ceftazidime-avibactam was found to be active against carbapenem-resistant, bla_{OXA-48}-positive *Enterobacteriaceae* (12, 14). In contrast, metallo-β-lactamase (MBL)-producing *Enterobacteriaceae* are generally not susceptible to carbapenems, nor are they susceptible to ceftazidime-avibactam (9, 12), because avibactam does not inhibit MBLs (15).

The aim of the present study was to characterize the *in vitro* activity of ceftazidime-avibactam against contemporary carbapenem-nonsusceptible, *bla* (β-lactamase gene)-characterized clinical isolates of *Enterobacteriaceae* collected from hospitalized patients over a 3-year time period in a global surveillance program (International Network for Optimal Resistance Monitoring [INFORM]). In the years 2012 to 2014, inclusive, the INFORM program received 34,062 isolates of *Enterobacteriaceae* collected by medical center laboratories in Europe (19 countries from 93 laboratories), Asia/Pacific (9 countries from 41 laboratories), Latin America (6 countries from 26 laboratories), and the Middle East/Africa (5 countries from 16 laboratories). Of the 34,062 isolates of *Enterobacteriaceae*, 961 (2.8%) isolates were meropenem nonsusceptible (used as a marker of nonsusceptibility to carbapenems), and these were the focus of this study.

All study isolates were shipped to a central reference laboratory at International Health Management Associates, Inc. (IHMA; Schaumburg, IL, USA), where their identities were confirmed using a Bruker Biotyper matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry instrument (Bruker Daltonics, Billerica, MA, USA). All antimicrobial susceptibility testing was performed by using in-house-prepared 96-well broth microdilution panels, according to Clinical and Laboratory Standards Institute (CLSI) standards (16, 17). Avibactam was tested at a fixed concentration of 4 μg/ml in combination with doubling dilutions of ceftazidime (16). MICs were interpreted using CLSI breakpoints (16), where available. Ceftazidime-avibactam MICs were interpreted using U.S. FDA MIC breakpoints for *Enterobacteriaceae*, with susceptibility at an MIC of ≤8 μg/ml and resistance at an MIC of ≥16 μg/ml (18). U.S. FDA MIC interpretative breakpoints were also used for tigecycline (19). For colistin,

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EUCAST MIC interpretative breakpoints against *Enterobacteriaceae* were used (20).

All 961 meropenem-nonsusceptible isolates were screened, using a combination of the microarray-based assay Check-MDR CT101 kit (Check-Points, Wageningen, the Netherlands) and published multiplex PCR assays, to detect and identify genes encoding carbapenemases (KPC, OXA-48, GES, IMP, VIM, NDM, and SPM), ESBLs (TEM, SHV, CTX-M, VEB, PER, and GES), original-spectrum β-lactamases (OSBLs) (TEM and SHV that did not contain substitutions at amino acid positions 104, 164, or 238 [TEM] or 146, 238, or 240 [SHV] associated with ESBL activity), and plasmid-mediated AmpC β-lactamases (ACC, ACT, CMY, DHA, FOX, MIR, and MOX), as previously described (21). Enzyme variants were identified by amplification of full-length β-lactamase genes, followed by DNA sequencing, and these were compared against the National Center for Biotechnology Information database (www.ncbi.nlm.nih.gov) and the Lahey Clinic website (www.lahey.org/studies). The distributions of KPC and MBLs in these isolates were described recently in great detail (reference 22 and K. M. Kazmierczak, D. J. Biedenbach, M. Hackel, S. Rabine, B. L. M. de Jonge, S. K. Bouchillon, D. F. Sahm, and P. A. Bradford, unpublished data).

Of the 34,062 isolates of *Enterobacteriaceae* that were tested, 99.5% (33,877 isolates) were susceptible to ceftazidime-avibactam (MIC, ≤8 μg/ml), and 2.8% were meropenem nonsusceptible (Table 1). The considerably lower percentage of susceptibility to imipenem (85.1%) compared to that to doripenem (97.3%) and meropenem (97.2%) was attributable to the presence of 4,572 isolates of *Proteeae* species (13.4% of all isolates tested) in this set, as these species demonstrated intrinsic elevated MICs for imipenem (data not shown) (16). Meropenem-nonsusceptible isolates were more susceptible to ceftazidime-avibactam (83.5% susceptible) than to all other β-lactams tested, which showed rates of susceptibility of ≤12% (Table 1).

Of the 961 meropenem-nonsusceptible isolates identified, 754 isolates (78.5%) possessed one ($n = 738$) or more ($n = 16$) carbapenemase genes, whereas in 207 (21.5%) isolates, no carbapenemase gene could be identified (Table 2). Of the 754 carbapenemase-positive isolates, 132 isolates possessed only a metallo-β-lactamase (MBL), 13 carried an MBL and a KPC or OXA-48-like gene, and 609 harbored one or more serine carbapenemase genes (KPC, OXA-48-like, or GES), with 548 of the 609 (90%) isolates being *K. pneumoniae*. Against carbapenemase-positive, metallo-β-lactamase-negative isolates ($n = 609$), susceptibility to ceftazidime-avibactam was higher (98.7%) than that for any other agent tested, including tigecycline (91.5%) and colistin (81.0%) (Table 1). Ceftazidime-avibactam was very active against KPC-positive (98.7% susceptible), OXA-48-like (98.5% susceptible), and GES (100%) carbapenemase-producing isolates of *Enterobacteriaceae* (Tables 1 and 2). Ceftazidime-avibactam was also active against meropenem-nonsusceptible carbapenemase-negative isolates (94.7% susceptible) but did not demonstrate activity against isolates with metallo-β-lactamases, as expected (Table 1).

Many of the carbapenemase-containing carbapenem-nonsusceptible isolates carried additional β-lactamase genes. Approximately 50% of isolates with a KPC also possessed an ESBL and/or plasmid-encoded AmpC β-lactamase. Similarly, 83%, and 86% of MBL-positive and OXA-48-like-positive isolates, respectively, possessed an ESBL gene, an AmpC gene, or both. The presence of these ESBL and/or AmpC β-lactamases in these carbapenemase-containing isolates did not significantly affect the susceptibility for ceftazidime-avibactam, as shown by the MIC distributions of these subsets of isolates (Table 2). The majority (94%) of the carbapenem-nonsusceptible *Enterobacteriaceae* that did not contain a carbapenemase harbored ESBLs and/or Ambler class C β-lactamases that were encoded by chromosomally located or plasmid-carried genes. The presence of these β-lactamases, coupled with reduced expression or loss of function of one or more outer membrane pore-forming proteins, is most likely the reason for the reduced susceptibility to carbapenems observed among these isolates (6–8). Whereas susceptibility to carbapenems was lost in these isolates, this resistance mechanism did not impact the activity of ceftazidime-avibactam, with 94.7% of the isolates remaining susceptible to this combination.

If future clinical results confirm the *in vitro* data described here, ceftazidime-avibactam might be useful in the chemotherapy of infections caused by carbapenem-nonsusceptible *Enterobacteriaceae*. To understand this potential, it is helpful to summarize susceptibility to ceftazidime-avibactam by the carbapenem resistance mechanism. In general, only the presence of an MBL gene was associated with resistance to ceftazidime-avibactam (this study and references 12, 23, and 24). Isolates nonsusceptible to carbapenems by other mechanisms, such as KPC (this study and references 10, 12, and 23–28) and OXA-48 (this study and references 12, 14, and 24) carbapenemases were susceptible to ceftazidime-avibactam. Additionally, carbapenem-nonsusceptible *Enterobacteriaceae* that carried noncarbapenemase β-lactamase genes, such as those encoding an ESBL or AmpC enzyme, were susceptible to ceftazidime-avibactam (this study and reference 12). This is in agreement with a recent surveillance analysis of *Enterobacteriaceae* isolates from the United States (25). A further noteworthy point is that intrinsic imipenem resistance among *Proteeae* species (16) did not affect susceptibility to ceftazidime-avibactam (Table 1).

This study identified only a few isolates ($n = 19$; <0.1% of *Enterobacteriaceae*) for which the reduced ceftazidime-avibactam susceptibility could not be explained by the presence of avibactam-insensitive β-lactamases, i.e., MBLs. The mechanisms of reduced susceptibility in those isolates remain to be investigated but might be attributable to target modifications (29). Additionally, the presence of avibactam-insensitive β-lactamases (e.g., other MBLs) that were not detected with the PCR assays cannot be excluded. Upregulated efflux is a less-likely mechanism, as it was not implicated in reduced susceptibility to ceftazidime-avibactam in a direct test of that hypothesis (30). Interestingly, a carbapenem-resistant clinical isolate of *K. pneumoniae* carrying bla_{KPC-3} was recently described that was resistant to ceftazidime-avibactam (31). The inferred amino acid sequence encoded by the bla_{KPC-3} in that isolate was unaltered, similarly implying a non-β-lactamase-mediated mechanism of ceftazidime-avibactam resistance.

A noteworthy feature of the study reported here was that a substantial proportion of the meropenem-nonsusceptible isolates did not contain any gene related to currently known carbapenemases but rather contained an ESBL gene, AmpC gene, or both. Ceftazidime-avibactam showed good activity against these isolates (96.4% susceptible [188 of the 195 isolates]). The proportion of noncarbapenemase-mediated meropenem-nonsusceptible isolates of *Enterobacteriaceae* (207/961) should not be taken as an estimate of prevalence, because INFORM is not a prevalence-based surveillance program. However, prevalence-based studies

TABLE 1 *In vitro* activities of ceftazidime-avibactam and comparative antimicrobial agents tested against *Enterobacteriaceae* collected by the INFORM global surveillance program from 2012 to 2014

Organism group (*n*)	Antimicrobial agent	MIC values (μg/ml)			MIC interpretation (%)[a]		
		MIC_{50}	MIC_{90}	MIC range	Susceptible	Intermediate	Resistant
All *Enterobacteriaceae* (34,062)[b]	Ceftazidime-avibactam	0.12	0.5	≤0.015 to >128	99.5		0.5
	Ceftazidime	0.25	64	≤0.015 to >128	75.6	1.9	22.5
	Cefepime[c]	≤0.12	>16	≤0.12 to >16	77.3	4.9	17.8
	Aztreonam	0.12	64	≤0.015 to >128	74.3	1.9	23.8
	Piperacillin-tazobactam	2	128	≤0.25 to >128	84.0	5.9	10.1
	Doripenem	0.06	0.25	≤0.008 to >4	97.3	0.5	2.2
	Ertapenem (n = 20,885)[d]	0.015	0.25	≤0.002 to >1	94.5	1.6	3.9
	Imipenem	0.25	2	≤0.03 to >8	85.1	7.6	7.3
	Meropenem	0.03	0.12	≤0.004 to >8	97.2	0.4	2.4
	Amikacin	2	8	≤0.25 to >32	96.3	1.5	2.2
	Colistin[e]	≤0.12	>4	≤0.015 to >4	83.1		16.9
	Tigecycline	0.5	2	≤0.015 to >8	92.9	5.7	1.4
	Levofloxacin	0.06	>4	≤0.03 to >4	75.0	2.5	22.5
Meropenem nonsusceptible (961)	Ceftazidime-avibactam	1	>128	≤0.015 to >128	83.5		16.5
	Ceftazidime	>128	>128	0.06 to >128	5.3	2.3	92.4
	Cefepime	>16	>16	≤0.12 to >16	5.4	9.0	85.6
	Aztreonam	>128	>128	≤0.015 to >128	8.9	0.8	90.3
	Piperacillin-tazobactam	>128	>128	0.5 to >128	3.2	3.7	93.1
	Doripenem	>4	>4	0.03 to >4	9.6	13.2	77.2
	Ertapenem (n = 534)	>1	>1	0.015 to >1	2.8	0.8	96.4
	Imipenem	>8	>8	0.06 to >8	12.2	5.2	82.6
	Meropenem	>8	>8	2 to >8	0.0	16.2	83.8
	Amikacin	16	>32	≤0.25 to >32	58.1	22.0	19.9
	Colistin	≤0.12	>4	≤0.015 to >4	81.4		18.6
	Tigecycline	1	2	0.06 to >8	91.0	7.5	1.5
	Levofloxacin	>4	>4	≤0.03 to >4	18.6	4.3	77.1
Meropenem nonsusceptible, MBL negative (816)	Ceftazidime-avibactam	1	4	≤0.015 to >128	97.7		2.3[f]
	Ceftazidime	128	>128	0.06 to >128	5.9	2.7	91.4
	Cefepime	>16	>16	≤0.12 to >16	5.6	9.4	85.0
	Aztreonam	>128	>128	≤0.015 to >128	4.7	0.6	94.7
	Piperacillin-tazobactam	>128	>128	0.5 to >128	2.6	3.8	93.6
	Doripenem	>4	>4	0.03 to >4	11.2	15.0	73.8
	Ertapenem (n = 452)	>1	>1	0.015 to >1	2.4	0.4	97.2
	Imipenem	>8	>8	0.06 to >8	14.1	5.5	80.4
	Meropenem	>8	>8	2 to >8	0.0	17.4	82.6
	Amikacin	16	>32	≤0.25 to >32	57.9	25.2	16.9
	Colistin	≤0.12	>4	≤0.015 to >4	81.5		18.5
	Tigecycline	1	2	0.06 to 8	91.4	7.4	1.2
	Levofloxacin	>4	>4	≤0.03 to >4	16.5	3.7	79.8
Meropenem nonsusceptible, carbapenemase positive, MBL negative (609)	Ceftazidime-avibactam	1	4	≤0.015 to >128	98.7		1.3
	Ceftazidime	128	>128	0.06 to >128	5.6	2.9	91.5
	Cefepime	>16	>16	≤0.12 to >16	5.1	9.4	85.5
	Aztreonam	>128	>128	≤0.015 to >128	3.6	0.3	96.1
	Piperacillin-tazobactam	>128	>128	2 to >128	0.5	2.0	97.5
	Doripenem	>4	>4	0.5 to >4	4.8	10.2	85.0
	Ertapenem (n = 329)	>1	>1	0.25 to >1	0.9	0.3	98.8
	Imipenem	>8	>8	0.5 to >8	0.8	3.5	95.7
	Meropenem	>8	>8	2 to >8	0.0	8.4	91.6
	Amikacin	16	>32	≤0.25 to >32	52.1	32.0	15.9
	Colistin	≤0.12	>4	≤0.015 to >4	81.0		19.0
	Tigecycline	1	2	0.06 to 8	91.5	7.7	0.8
	Levofloxacin	>4	>4	≤0.03 to >4	14.8	3.9	81.3
KPC positive, MBL negative (476)[g]	Ceftazidime-avibactam	1	4	≤0.015 to 128	98.7		1.3
	Ceftazidime	>128	>128	1 to >128	2.1	3.4	94.5
	Cefepime	>16	>16	≤0.12 to >16	2.9	10.7	86.4
	Aztreonam	>128	>128	2 to >128	0.4	0.2	99.4
	Piperacillin-tazobactam	>128	>128	2 to >128	0.6	2.1	97.3
	Doripenem	>4	>4	0.5 to >4	2.1	8.4	89.5
	Ertapenem (n = 269)	>1	>1	0.25 to >1	1.1	0.4	98.5
	Imipenem	>8	>8	0.5 to >8	0.4	1.1	98.5
	Meropenem	>8	>8	2 to >8	0.0	3.6	96.4

(Continued on following page)

TABLE 1 (Continued)

Organism group (*n*)	Antimicrobial agent	MIC values (μg/ml)			MIC interpretation (%)[a]		
		MIC_{50}	MIC_{90}	MIC range	Susceptible	Intermediate	Resistant
	Amikacin	32	>32	≤0.25 to >32	44.6	40.1	15.3
	Colistin	≤0.12	>4	≤0.015 to >4	82.6		17.4
	Tigecycline	1	2	0.06 to 8	91.6	7.4	1.0
	Levofloxacin	>4	>4	≤0.03 to >4	12.8	3.2	84.0
OXA-48-like positive, MBL negative (134)[h]	Ceftazidime-avibactam	0.5	2	0.03 to 64	98.5		1.5
	Ceftazidime	64	>128	0.06 to >128	17.9	1.5	80.6
	Cefepime	>16	>16	≤0.12 to >16	12.7	4.5	82.8
	Aztreonam	128	>128	≤0.015 to >128	14.9	0.8	84.3
	Piperacillin-tazobactam	>128	>128	32 to >128	0.0	1.5	98.5
	Doripenem	>4	>4	0.5 to >4	14.9	16.4	68.7
	Ertapenem (*n* = 62)	>1	>1	>1	0.0	0.0	100
	Imipenem	8	>8	1 to >8	2.2	12.0	85.8
	Meropenem	>8	>8	2 to >8	0.0	26.1	73.9
	Amikacin	8	>32	0.5 to >32	78.4	3.0	18.6
	Colistin	≤0.12	>4	≤0.015 to >4	75.4		24.6
	Tigecycline	1	2	0.12 to 4	91.0	9.0	0.0
	Levofloxacin	>4	>4	≤0.03 to >4	20.9	6.7	72.4
Meropenem nonsusceptible, MBL negative, carbapenemase negative (207)	Ceftazidime-avibactam	2	4	0.06 to >128	94.7		5.3
	Ceftazidime	128	>128	0.12 to >128	6.8	1.9	91.3
	Cefepime	>16	>16	≤0.12 to >16	7.2	9.7	83.1
	Aztreonam	128	>128	0.03 to >128	7.7	1.5	90.8
	Piperacillin-tazobactam	>128	>128	0.5 to >128	8.7	9.2	82.1
	Doripenem	2	>4	0.03 to >4	30.4	29.0	40.6
	Ertapenem (*n* = 123)	>1	>1	0.015 to >1	6.5	0.8	92.7
	Imipenem	1	>8	0.06 to >8	53.1	11.6	35.3
	Meropenem	4	>8	2 to >8	0.0	44.0	56.0
	Amikacin	8	>32	≤0.25 to >32	74.9	5.3	19.8
	Colistin	≤0.12	>4	≤0.015 to >4	83.1		16.9
	Tigecycline	1	2	0.06 to 8	91.3	6.3	2.4
	Levofloxacin	>4	>4	≤0.03 to >4	21.7	2.9	75.4
MBL positive (145)[i]	Ceftazidime-avibactam	>128	>128	0.5 to >128	3.4		96.6
	Ceftazidime	>128	>128	0.5 to >128	2.1	0.0	97.9
	Cefepime	>16	>16	≤0.12 to >16	4.1	6.2	89.7
	Aztreonam	64	>128	≤0.015 to >128	32.4	2.1	65.5
	Piperacillin-tazobactam	>128	>128	0.5 to >128	6.9	2.8	90.3
	Doripenem	>4	>4	2 to >4	0.0	3.4	96.6
	Ertapenem (*n* = 82)	>1	>1	0.12 to >1	4.9	2.4	92.7
	Imipenem	>8	>8	0.5 to >8	1.4	3.4	95.2
	Meropenem	>8	>8	2 to >8	0.0	9.7	90.3
	Amikacin	16	>32	1 to >32	59.3	4.1	36.6
	Colistin	≤0.12	>4	≤0.015 to >4	80.7		19.3
	Tigecycline	1	4	0.06 to >8	88.3	8.3	3.4
	Levofloxacin	>4	>4	0.06 to >4	30.3	7.6	62.1

[a] MICs were interpreted according to CLSI breakpoints (16), with the exception of the following: ceftazidime-avibactam, for which MICs were interpreted using the MIC interpretative criteria according to the FDA (18); tigecycline, for which MICs were interpreted using the MIC interpretative criteria according to the FDA (19); and colistin, for which EUCAST breakpoints were applied (20).

[b] The 34,062 *Enterobacteriaceae* isolates were composed of the following: *Citrobacter amalonaticus* (*n* = 21), *Citrobacter braakii* (*n* = 109), *Citrobacter diversus* (*n* = 1), *Citrobacter farmeri* (*n* = 4), *Citrobacter freundii* (*n* = 1,033), *Citrobacter gillenii* (*n* = 1), *Citrobacter koseri* (*n* = 707), *Citrobacter murliniae* (*n* = 5), *Citrobacter sedlakii* (*n* = 3), *Citrobacter youngae* (*n* = 1), *Citrobacter*, species not determined (*n* = 4), *Enterobacter aerogenes* (*n* = 1,350), *Enterobacter amnigenus* (*n* = 1), *Enterobacter asburiae* (*n* = 250), *Enterobacter cancerogenus* (*n* = 1), *Enterobacter cloacae* (*n* = 2,207), *Enterobacter gergoviae* (*n* = 4), *Enterobacter hormaechei* (*n* = 1), *Enterobacter kobei* (*n* = 93), *Enterobacter ludwigii* (*n* = 24), *Escherichia coli* (*n* = 11,770), *Escherichia fergusonii* (*n* = 1), *Escherichia hermannii* (*n* = 2), *Escherichia vulneris* (*n* = 1), *Hafnia alvei* (*n* = 4), *Klebsiella oxytoca* (*n* = 1,900), *Klebsiella ozaenae* (*n* = 1), *Klebsiella pneumoniae* (*n* = 9,098), *Klebsiella variicola* (*n* = 7), *Kluyvera ascorbata* (*n* = 2), *Morganella morganii* (*n* = 979), *Pantoea agglomerans* (*n* = 2), *Proteus hauseri* (*n* = 3), *Proteus mirabilis* (*n* = 2,235), *Proteus penneri* (*n* = 42), *Proteus rettgeri* (*n* = 2), *Proteus vulgaris* (*n* = 995), *Providencia alcalifaciens* (*n* = 14), *Providencia rettgeri* (*n* = 141), *Providencia stuartii* (*n* = 161), *Raoultella ornithinolytica* (*n* = 57), *Raoultella planticola* (*n* = 13), *Raoultella terrigena* (*n* = 2), *Serratia liquefaciens* (*n* = 16), *Serratia marcescens* (*n* = 785), *Serratia odorifera* (*n* = 1), *Serratia rubidaea* (*n* = 1), and *Serratia ureilytica* (*n* = 7).

[c] For cefepime, the susceptible-dose-dependent (SDD) interpretive category replaced the intermediate category in 2014.

[d] Ertapenem was not tested against isolates collected in 2014.

[e] Colistin was tested with a final concentration of 0.002% polysorbate-80 in each panel well.

[f] The 19 MBL-negative isolates that were resistant to ceftazidime-avibactam (MIC, >8 μg/ml) were composed of the following: *C. braakii* (*n* = 1), *E. aerogenes* (*n* = 1), *E. coli* (*n* = 2), *K. oxytoca* (*n* = 2), *K. pneumoniae* (*n* = 11), *P. vulgaris* (*n* = 1), and *S. marcescens* (*n* = 1).

[g] Includes two isolates carrying KPC-2 and OXA-163 and one isolate carrying KPC-2 and GES-6; does not include 6 isolates carrying KPC and MBL.

[h] Includes isolates carrying OXA-48 (*n* = 116), OXA-244 (*n* = 9), OXA-181 (*n* = 4), and OXA-163 (*n* = 5); two of these carry both OXA-163 and KPC-2. Does not include 7 isolates carrying OXA-48-like and MBL.

[i] The 145 isolates that were MBL positive were composed of the following: *C. freundii* (*n* = 8), *E. asburiae* (*n* = 4), *E. cloacae* (*n* = 31), *E. coli* (*n* = 5), *K. oxytoca* (*n* = 7), *K. pneumoniae* (*n* = 73), *P. mirabilis* (*n* = 8), *P. rettgeri* (*n* = 1), *P. stuartii* (*n* = 3), and *S. marcescens* (*n* = 5). Also included are 13 isolates carrying MBLs and serine carbapenemases: VIM-1 and KPC-2 (*n* = 4), IMP-4 and KPC-2 (*n* = 2), VIM-4 and OXA-48 (*n* = 2), VIM-31 and OXA-48 (*n* = 1), NDM-1 and OXA-48 (*n* = 3), and NDM-1 and OXA-232 (*n* = 1).

TABLE 2 Ceftazidime-avibactam and ceftazidime MIC distributions for meropenem-nonsusceptible *Enterobacteriaceae* that were carbapenemase negative, KPC positive, OXA-48 positive, GES positive, or metallo-β-lactamase positive and ceftazidime-avibactam distributions stratified by the presence or absence of an ESBL or AmpC β-lactamase gene

Genotype/organism (*n*)	Antimicrobial agent	No. (%) of isolates inhibited at MIC (μg/ml) of[a]:														
		≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Carbapenemase negative																
All (207)	Ceftazidime				4 (1.9)	2 (2.9)	4 (4.8)	1 (5.3)	1 (5.8)	2 (6.8)	4 (8.7)	6 (11.6)	19 (20.8)	34 (37.2)	43 (58.0)	**87 (100)**
	Ceftazidime-avibactam			4 (1.9)	15 (9.2)	17 (17.4)	24 (29.0)	36 (46.4)	60 (75.4)	**36 (92.8)**	4 (94.7)	4 (96.6)	1 (97.1)	0 (97.1)	1 (97.6)	5 (100)
AmpC positive,[b] ESBL positive[c] (16)	Ceftazidime-avibactam				1 (6.3)	1 (12.5)	2 (25.0)	3 (43.8)	5 (75.0)	2 (87.5)	**1 (93.8)**	0 (93.8)	0 (93.8)	0 (93.8)	1 (100)	
AmpC positive, ESBL negative (32)	Ceftazidime-avibactam			2 (6.3)	2 (12.5)	5 (28.1)	3 (37.5)	8 (62.5)	5 (78.1)	**5 (93.8)**	0 (93.8)	2 (100)				
AmpC negative, ESBL positive (147)	Ceftazidime-avibactam			1 (0.7)	9 (6.8)	10 (13.6)	17 (25.2)	24 (41.5)	50 (75.5)	**29 (95.2)**	3 (97.3)	0 (97.3)	0 (97.3)	0 (97.3)	0 (97.3)	4 (100)
AmpC negative, ESBL negative (12)	Ceftazidime-avibactam			1 (8.3)	3 (33.3)	1 (41.7)	2 (58.3)	1 (66.7)	0 (66.7)	0 (66.7)	0 (66.7)	2 (83.3)	**1 (91.7)**	0 (91.7)	0 (91.7)	1 (100)
KPC positive, MBL negative																
All (476)[d]	Ceftazidime							1 (0.2)	5 (1.3)	4 (2.1)	16 (5.5)	37 (13.2)	38 (21.2)	70 (35.9)	54 (47.3)	**251 (100)**
	Ceftazidime-avibactam	2 (0.4)	12 (2.9)	12 (5.5)	17 (9.0)	34 (16.2)	83 (33.6)	150 (65.1)	109 (88.0)	**41 (96.6)**	10 (98.7)	4 (99.6)	1 (99.8)	0 (99.8)	1 (100)	
AmpC positive, ESBL positive (11)	Ceftazidime-avibactam					1 (9.1)	3 (36.4)	5 (81.8)	**1 (90.9)**	1 (100)						
AmpC positive, ESBL negative (19)	Ceftazidime-avibactam			1 (5.3)	2 (15.8)	0 (15.8)	5 (42.1)	9 (89.5)	**2 (100)**							
AmpC negative, ESBL positive (205)	Ceftazidime-avibactam	1 (0.5)	5 (2.9)	6 (5.9)	6 (8.8)	13 (15.1)	30 (29.8)	73 (65.4)	50 (89.8)	**18 (98.5)**	1 (99.0)	2 (100)				
AmpC negative, ESBL negative (241)	Ceftazidime-avibactam	1 (0.4)	7 (3.3)	5 (5.4)	9 (9.1)	20 (17.4)	45 (36.1)	63 (62.2)	56 (85.5)	**22 (94.6)**	9 (98.3)	2 (99.2)	1 (99.6)	0 (99.6)	1 (100)	
OXA-48-like positive, MBL negative																
All (134)[e]	Ceftazidime			1 (0.7)	0 (0.7)	3 (3.0)	6 (7.5)	4 (10.4)	3 (12.7)	7 (17.9)	2 (19.4)	6 (23.9)	11 (32.1)	26 (51.5)	28 (72.4)	**37 (100)**
	Ceftazidime-avibactam		1 (0.7)	1 (1.5)	6 (6.0)	25 (24.6)	46 (59.0)	37 (86.6)	**12 (95.5)**	3 (97.8)	1 (98.5)	1 (99.3)	0 (99.3)	1 (100)		
AmpC positive, ESBL positive (4)	Ceftazidime-avibactam						2 (50.0)	1 (75.0)	0 (75.0)	0 (75.0)	0 (75.0)	0 (75.0)	0 (75.0)	1 (100)		
AmpC positive, ESBL negative (6)	Ceftazidime-avibactam					2 (33.3)	2 (66.7)	2 (100)								
AmpC negative, ESBL positive (105)	Ceftazidime-avibactam				3 (2.9)	19 (21.0)	37 (56.2)	31 (85.7)	**11 (96.2)**	3 (99.0)	1 (100)					
AmpC negative, ESBL negative (19)	Ceftazidime-avibactam		1 (5.3)	1 (10.5)	3 (26.3)	4 (47.4)	5 (73.7)	3 (89.5)	**1 (94.7)**	0 (94.7)	0 (94.7)	1 (100)				
GES positive, MBL negative																
All (2)[f]	Ceftazidime													1 (50.0)	0 (50.0)	1 (100)
	Ceftazidime-avibactam					1 (50.0)	0 (50.0)	1 (100)								
AmpC negative, ESBL positive (1)	Ceftazidime-avibactam							1 (100)								
AmpC negative, ESBL negative (1)	Ceftazidime-avibactam					1 (100)										
MBL positive																
All (145)[g]	Ceftazidime						3 (2.1)	0 (2.1)	0 (2.1)	0 (2.1)	0 (2.1)	1 (2.8)	4 (5.5)	4 (8.3)	9 (14.5)	**124 (100)**
	Ceftazidime-avibactam						4 (2.8)	0 (2.8)	0 (2.8)	0 (2.8)	1 (3.4)	2 (4.8)	8 (10.3)	8 (15.9)	10 (22.8)	**112 (100)**
AmpC positive, ESBL positive (28)	Ceftazidime-avibactam												2 (7.1)	2 (14.3)	2 (21.4)	**22 (100)**
AmpC positive, ESBL negative (37)	Ceftazidime-avibactam										1 (2.7)	1 (5.4)	4 (16.2)	4 (27.0)	2 (32.4)	**25 (100)**
AmpC negative, ESBL positive (56)	Ceftazidime-avibactam											1 (1.8)	2 (5.4)	1 (7.1)	4 (14.3)	**48 (100)**
AmpC negative, ESBL negative (24)	Ceftazidime-avibactam						4 (16.7)	0 (16.7)	0 (16.7)	0 (16.7)	0 (16.7)	0 (16.7)	0 (16.7)	1 (20.8)	2 (29.2)	**17 (100)**

[a] The MIC_{90} is in bold type for each MIC distribution. The MIC_{90} was not calculated for <10 isolates.

[b] AmpC-positive isolates include organisms that carry a plasmid-mediated AmpC or are presumed to harbor an intrinsic AmpC (*Citrobacter* spp., *Enterobacter* spp., *Providencia* spp., and *S. marcescens*).

[c] ESBL-positive isolates include organisms that carry a plasmid-mediated ESBL or are presumed to harbor an intrinsic ESBL (*K. oxytoca*).

[d] Includes two isolates carrying KPC-2 and OXA-163 and one isolate carrying KPC-2 and GES-6; does not include six isolates carrying KPC and MBL.

[e] Includes two isolates carrying OXA-163 and KPC-2; does not include seven isolates carrying OXA-48-like β-lactamases and MBL.

[f] Includes one isolate carrying KPC-2 and GES-6.

[g] Includes 13 isolates carrying MBLs and serine carbapenemases.

have been performed, and the frequency of noncarbapenemase-mediated mechanisms among carbapenem-nonsusceptible *Enterobacteriaceae* has been found to be 77.2 to 98.6% (13, 32–34). These estimates exceeded the proportion observed here, but that is likely because those collections included ertapenem-nonsusceptible isolates, against which meropenem can retain some activity, whereas that was not the case in the present work (35). In one of these examples, consisting of carbapenem-nonsusceptible but carbapenemase-negative isolates collected in France (13), the ceftazidime-avibactam MICs were ≤4 μg/ml (MIC_{90}, 1 μg/ml), in good agreement with the global surveillance data reported here.

In conclusion, the analyses presented here of global surveillance data for ceftazidime-avibactam and comparator agents tested against carbapenem-nonsusceptible *Enterobacteriaceae* should prove helpful in identifying potential anti-*Enterobacteriaceae* therapies when therapeutic options are limited through reduced susceptibility to currently available agents. Ceftazidime-avibactam is a potent agent *in vitro* against meropenem-nonsusceptible *Enterobacteriaceae*, except for isolates in which carbapenem resistance is mediated through MBLs.

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