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In Vitro Activity of Ceftazidime-Avibactam against Contemporary *Pseudomonas aeruginosa* Isolates from U.S. Medical Centers by Census Region, 2014

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The *in vitro* antibacterial activities of ceftazidime-avibactam and comparator agents were evaluated using reference broth microdilution methods against 1,743 *Pseudomonas aeruginosa* isolates collected in 2014 from 69 U.S. medical centers, representing each of the nine census regions. Ceftazidime-avibactam demonstrated potent activity against *P. aeruginosa*, including many isolates not susceptible to ceftazidime, meropenem, and piperacillin-tazobactam. In each of the nine census regions, ceftazidime-avibactam demonstrated the highest percentage of susceptible isolates.

Increasing occurrence of antimicrobial resistance in Gram-negative bacilli, including *Enterobacteriaceae* and *Pseudomonas aeruginosa*, has complicated the treatment of serious nosocomial infections. β-Lactam antibacterials, which were once highly effective against these pathogens, have been compromised by isolates that harbor resistance due to the production of extended-spectrum β-lactamases (ESBLs) and carbapenemases (1–4), along with other resistance mechanisms, including efflux and porin loss (5, 6) and the recent emergence of plasmid-mediated resistance to colistin (7). The spread of β-lactamases is particularly problematic due to the potential for additional mutations that can broaden their spectrum of hydrolysis, as well as their ability to disseminate to other pathogens. Ceftazidime-avibactam is the combination of the established third-generation cephalosporin ceftazidime and the novel non–β-lactam β-lactamase inhibitor avibactam. Avibactam inhibits a broad range of serine β-lactamases, including Ambler class A (ESBL and *Klebsiella pneumoniae* carbapenemase), class C (AmpC), and some class D (OXA-48) enzymes. When used in combination with ceftazidime, avibactam restores the activity of ceftazidime against a number of clinically relevant β-lactamase–producing Gram-negative pathogens that cause serious infections (8). We evaluated the *in vitro* antibacterial activities and susceptibility patterns of ceftazidime-avibactam and comparator compounds against *P. aeruginosa* surveillance isolates obtained in 2014 from a variety of infection types (skin and soft tissue, urinary tract, intra-abdominal, and others) from each of the nine census regions within the United States.

A total of 1,743 *P. aeruginosa* isolates collected in 2014 from 69 medical centers within the nine U.S. census regions were included in the International Network for Optimal Resistance Monitoring (INFORM) surveillance program. Broth microdilution susceptibility testing for ceftazidime-avibactam, ceftazidime, cefepime, meropenem, piperacillin-tazobactam, ciprofloxacin, levofloxacin, amikacin, gentamicin, and colistin was performed according to Clinical and Laboratory Standards Institute (CLSI) guidelines (9) using validated MIC panels produced by Thermo Fisher Scientific (Cleveland, OH). Susceptibility interpretive criteria for comparator compounds included both CLSI (10) and EUCAST (European Committee on Antimicrobial Susceptibility Testing) (11) breakpoint criteria, when available. The recently approved U.S. Food and Drug Administration (FDA) breakpoint interpretative criteria were applied for ceftazidime-avibactam (12). Quality-control (QC) testing included the following reference bacterial strains: *Escherichia coli* ATCC 25922, *E. coli* ATCC 35218, *Klebsiella pneumoniae* ATCC 700603, and *P. aeruginosa* ATCC 27853. All QC results for ceftazidime-avibactam and comparator compounds were within published ranges (10). Ceftazidime-nonsusceptible and meropenem-nonsusceptible isolates displayed intermediate or resistant MIC values (≥16 or ≥4 μg/ml, respectively) according to published breakpoint criteria (10, 11).

Table 1 lists ceftazidime-avibactam and comparator compound susceptibility testing results against 1,743 *P. aeruginosa* isolates collected in 2014, including the number of isolates tested, the MIC_{50}, the MIC_{90}, and the percentages of susceptible, intermediate, and resistant isolates by U.S. census region, categorized according to CLSI, EUCAST, and/or FDA breakpoint interpretive criteria. Ceftazidime-avibactam activity ($MIC_{50/90}$, 2/8 μg/ml; 96.3% susceptible at ≤8 μg/ml) against all 1,743 *P. aeruginosa* isolates was enhanced over that with ceftazidime when tested alone ($MIC_{50/90}$, 2/32 μg/ml; 84.0% susceptible at ≤8 μg/ml; Fig. 1; Table 1) and was more active than the other β-lactam comparators, including cefepime, meropenem, and piperacillin-tazobactam (86.5%, 83.0%, and 83.0% susceptible, respectively).

The addition of avibactam to ceftazidime increased the percentages of susceptible *P. aeruginosa* isolates across each of the census regions from 7.4% (West North Central region) to 16.3% (east South Central region) over those of ceftazidime tested alone (Table 1). The greatest restorations of ceftazidime activity by avibactam against *P. aeruginosa* were observed in the New England and East South Central regions (16.0% and 16.3%, respec-

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TABLE 1 Activities of ceftazidime-avibactam and comparator antimicrobial agents against contemporary *Pseudomonas aeruginosa* isolates by census region

Region and antimicrobial agent (no. tested)	MIC_{50}	MIC_{90}	CLSI[a]			EUCAST[a]		
			%S	%I	%R	%S	%I	%R
All regions (1,743)								
Ceftazidime-avibactam	2	8	96.3		3.7[b]			
Ceftazidime	2	32	84.0	4.5	11.5	84.0		16.0
Cefepime	2	16	86.5	8.0	5.5	86.5		13.5
Piperacillin-tazobactam	4	64	83.0	8.7	8.3	83.0		17.0
Meropenem	0.5	8	83.0	6.1	10.9	83.0	11.6	5.3
Ciprofloxacin	0.12	>4	77.9	4.9	17.2	72.0	5.9	22.1
Levofloxacin	0.5	>4	75.2	6.4	18.5	65.3	9.8	24.8
Gentamicin	≤1	8	88.0	3.7	8.3	88.0		12.0
Amikacin	2	8	96.7	1.2	2.1	93.2	3.5	3.3
Colistin	2	2	99.0	1.0	0.0	100.0		0.0
Region 1, New England (119)								
Ceftazidime-avibactam	1	4	100.0		0.0[b]			
Ceftazidime	2	32	84.0	5.9	10.1	84.0		16.0
Cefepime	2	16	85.7	12.6	1.7	85.7		14.3
Piperacillin-tazobactam	4	64	86.6	8.4	5.0	86.6	-	13.4
Meropenem	0.25	4	85.7	5.0	9.2	85.7	12.6	1.7
Ciprofloxacin	0.12	>4	75.6	5.9	18.5	72.3	3.4	24.4
Levofloxacin	0.5	>4	73.9	6.7	19.3	68.1	5.9	26.1
Gentamicin	≤1	>8	87.4	0.8	11.8	87.4		12.6
Amikacin	2	8	97.5	0.8	1.7	93.3	4.2	2.5
Colistin	2	2	99.2	0.8	0.0	100.0		0.0
Region 2, Mid-Atlantic (199)								
Ceftazidime-avibactam	2	8	96.0		4.0[b]			
Ceftazidime	2	32	80.9	7.5	11.6	80.9		19.1
Cefepime	2	16	84.9	10.1	5.0	84.9		15.1
Piperacillin-tazobactam	8	>64	77.9	11.6	10.6	77.9		22.1
Meropenem	0.5	8	79.9	8.5	11.6	79.9	14.6	5.5
Ciprofloxacin	0.12	>4	83.9	2.5	13.6	75.9	8.0	16.1
Levofloxacin	0.5	>4	79.9	6.0	14.1	69.8	10.1	20.1
Gentamicin	≤1	4	91.0	4.5	4.5	91.0		9.0
Amikacin	2	8	99.0	0.0	1.0	96.0	3.0	1.0
Colistin	2	2	100.0	0.0	0.0	100.0		0.0
Region 3, East North Central (299)								
Ceftazidime-avibactam	2	4	97.3		2.7[b]			
Ceftazidime	2	16	88.6	3.0	8.4	88.6		11.4
Cefepime	2	16	90.0	6.7	3.3	90.0		10.0
Piperacillin-tazobactam	4	32	86.6	7.4	6.0	86.6		13.4
Meropenem	0.5	8	83.3	6.4	10.4	83.3	11.4	5.4
Ciprofloxacin	0.12	>4	78.6	5.7	15.7	74.2	4.3	21.4
Levofloxacin	0.5	>4	77.9	4.7	17.4	67.6	10.4	22.1
Gentamicin	≤1	8	88.3	5.4	6.4	88.3		11.7
Amikacin	2	8	97.7	0.3	2.0	93.6	4.0	2.3
Colistin	2	2	98.7	1.3	0.0	100.0		0.0
Region 4, West North Central (191)								
Ceftazidime-avibactam	1	4	99.0		1.0[b]			
Ceftazidime	2	8	91.6	3.7	4.7	91.6		8.4
Cefepime	2	8	93.7	4.7	1.6	93.7		6.3
Piperacillin-tazobactam	4	16	93.2	3.7	3.1	93.2		6.8
Meropenem	0.25	2	94.8	1.6	3.7	94.8	2.6	2.6
Ciprofloxacin	0.12	4	85.3	4.2	10.5	80.6	4.7	14.7
Levofloxacin	0.5	>4	83.2	5.2	11.5	73.3	9.9	16.8
Gentamicin	≤1	4	95.3	2.6	2.1	95.3		4.7
Amikacin	2	8	99.5	0.5	0.0	97.9	1.6	0.5
Colistin	2	2	99.0	1.0	0.0	100.0		0.0

(Continued on following page)

TABLE 1 (Continued)

Region and antimicrobial agent (no. tested)	MIC_{50}	MIC_{90}	CLSI[a]			EUCAST[a]		
			%S	%I	%R	%S	%I	%R
Region 5, South Atlantic (266)								
Ceftazidime-avibactam	2	8	95.1		4.9[b]			
Ceftazidime	2	32	82.0	5.3	12.8	82.0		18.0
Cefepime	4	16	83.5	7.5	9.0	83.5		16.5
Piperacillin-tazobactam	4	64	83.1	7.5	9.4	83.1		16.9
Meropenem	0.5	8	82.3	5.6	12.0	82.3	12.8	4.9
Ciprofloxacin	0.25	4	77.8	8.3	13.9	71.8	6.0	22.2
Levofloxacin	0.5	>4	74.8	7.9	17.3	62.8	12.0	25.2
Gentamicin	2	>8	85.0	3.8	11.3	85.0		15.0
Amikacin	4	16	91.7	3.0	5.3	86.1	5.6	8.3
Colistin	2	2	98.1	1.9	0.0	100.0		0.0
Region 6, East South Central (153)								
Ceftazidime-avibactam	2	8	95.4		4.6[b]			
Ceftazidime	4	32	79.1	4.6	16.3	79.1		20.9
Cefepime	2	16	81.0	13.1	5.9	81.0		19.0
Piperacillin-tazobactam	4	>64	75.2	9.2	15.7	75.2		24.8
Meropenem	0.5	8	78.4	7.2	14.4	78.4	15.7	5.9
Ciprofloxacin	0.12	>4	77.8	3.9	18.3	69.9	7.8	22.2
Levofloxacin	0.5	>4	71.9	9.2	19.0	63.4	8.5	28.1
Gentamicin	≤1	>8	85.6	2.0	12.4	85.6		14.4
Amikacin	2	8	98.7	0.7	0.7	95.4	3.3	1.3
Colistin	2	2	98.7	1.3	0.0	100.0		0.0
Region 7, West South Central (150)								
Ceftazidime-avibactam	2	4	96.7		3.3[b]			
Ceftazidime	2	32	82.7	5.3	12.0	82.7		17.3
Cefepime	2	16	86.7	8.0	5.3	86.7		13.3
Piperacillin-tazobactam	4	64	81.3	10.7	8.0	81.3		18.7
Meropenem	0.5	8	80.7	6.7	12.7	80.7	12.7	6.7
Ciprofloxacin	0.25	>4	68.0	4.0	28.0	62.7	5.3	32.0
Levofloxacin	0.5	>4	66.7	4.0	29.3	56.7	10.0	33.3
Gentamicin	≤1	8	88.7	2.0	9.3	88.7		11.3
Amikacin	2	8	96.7	2.0	1.3	94.7	2.0	3.3
Colistin	2	2	98.0	2.0	0.0	100.0		0.0
Region 8, Mountain (166)								
Ceftazidime-avibactam	2	8	97.0		3.0[b]			
Ceftazidime	2	32	81.9	4.2	13.9	81.9		18.1
Cefepime	2	16	87.3	6.6	6.0	87.3		12.7
Piperacillin-tazobactam	4	64	79.5	13.3	7.2	79.5		20.5
Meropenem	0.5	8	77.7	9.6	12.7	77.7	15.7	6.6
Ciprofloxacin	0.25	>4	75.3	1.8	22.9	68.1	7.2	24.7
Levofloxacin	0.5	>4	70.5	6.0	23.5	62.7	7.8	29.5
Gentamicin	≤1	8	89.8	4.8	5.4	89.8		10.2
Amikacin	2	8	99.4	0.6	0.0	98.2	1.2	0.6
Colistin	2	2	100.0	0.0	0.0	100.0		0.0
Region 9, Pacific (200)								
Ceftazidime-avibactam	2	8	91.5		8.5[b]			
Ceftazidime	2	>32	82.0	2.5	15.5	82.0		18.0
Cefepime	2	16	84.0	6.0	10.0	84.0		16.0
Piperacillin-tazobactam	4	>64	81.0	8.5	10.5	81.0		19.0
Meropenem	0.25	8	83.5	4.5	12.0	83.5	8.5	8.0
Ciprofloxacin	0.25	>4	74.5	6.0	19.5	68.5	6.0	25.5
Levofloxacin	0.5	>4	72.5	8.0	19.5	62.0	10.5	27.5
Gentamicin	2	>8	81.5	5.0	13.5	81.5		18.5
Amikacin	2	16	93.0	2.5	4.5	88.0	5.0	7.0
Colistin	1	2	100.0	0.0	0.0	100.0		0.0

[a] Criteria as published by the CLSI (9, 10) and EUCAST (11). %S, %I, and %R, percentage of susceptible, intermediate, and resistant isolates, respectively.
[b] Breakpoints are from the FDA product package insert (12).

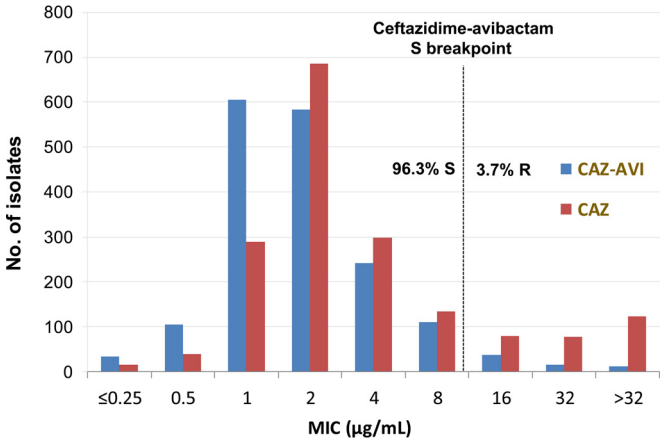

FIG 1 Ceftazidime-avibactam and ceftazidime MIC distributions for *Pseudomonas aeruginosa* (n = 1,743; United States, 2014). CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime.

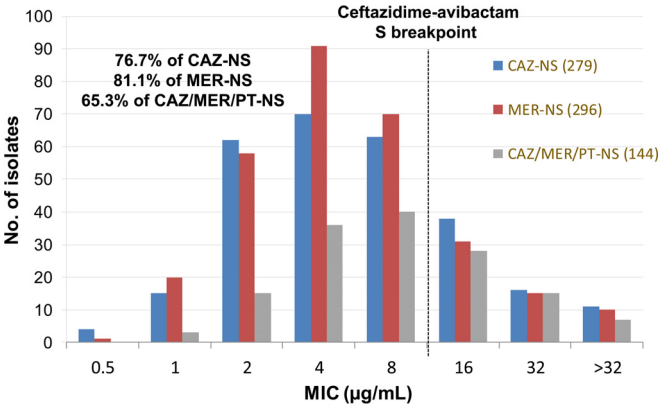

FIG 2 Ceftazidime-avibactam MIC distributions for resistant subsets of *Pseudomonas aeruginosa* isolates (Unites States, 2014). CAZ-NS, ceftazidime nonsusceptible; MER-NS, meropenem nonsusceptible; CAZ/MER/PT-NS, ceftazidime/meropenem/piperacillin-tazobactam nonsusceptible.

tively, susceptibility increases over ceftazidime tested alone). Additionally, ceftazidime-avibactam consistently demonstrated the highest percentages of susceptible isolates in each of the nine census regions (91.5% to 100.0% susceptible; Table 1) when compared with those of cefepime, meropenem, and piperacillin-tazobactam (81.0% to 93.7%, 77.7% to 94.8%, and 75.2% to 93.2% susceptible, respectively). Only colistin (98.0% to 100% susceptible) demonstrated higher susceptibility percentages (CLSI and EUCAST interpretive criteria).

Susceptibilities were lowest for ceftazidime, cefepime, and piperacillin-tazobactam against *P. aeruginosa* (79.1%, 81.0%, and 75.2% susceptible, respectively) in the East South Central region (95.4% susceptible to ceftazidime-avibactam) and for meropenem (77.7%) in the Mountain region (97.0% susceptible to ceftazidime-avibactam). Susceptibilities to ceftazidime-avibactam were lowest for *P. aeruginosa* in the Pacific region (91.5% susceptible); however, ceftazidime-avibactam remained more active than the ceftazidime, cefepime, meropenem, and piperacillin-tazobactam, fluoroquinolone (ciprofloxacin and levofloxacin), and aminoglycoside (gentamicin) comparators, with the exceptions of amikacin and colistin (93.0% and 100.0% susceptible, respectively; Table 1). Susceptibilities of *P. aeruginosa* to ceftazidime-avibactam were highest in the New England and West North Central regions (100.0% and 99.0% susceptible, respectively). Similarly, susceptibilities to ceftazidime, cefepime, meropenem, and piperacillin-tazobactam were also highest (91.6% to 94.8% susceptible) in the West North Central region.

In vitro ceftazidime-avibactam activities were evaluated against resistant subgroups of *P. aeruginosa* (Fig. 2; Table 2), including ceftazidime-nonsusceptible (n = 279) and meropenem-nonsusceptible (n = 296) isolates. Ceftazidime-avibactam activity against ceftazidime-nonsusceptible *P. aeruginosa* (76.7% susceptible to ceftazidime-avibactam) was significantly greater than those for cefepime, meropenem, and piperacillin-tazobactam (31.9%, 40.1%, and 15.4% susceptible, respectively); moreover, ceftazidime-avibactam retained this improved *in vitro* potency against meropenem-nonsusceptible *P. aeruginosa* (81.1% ceftazidime-avibactam susceptible) isolates (40.5% to 46.3% susceptible to ceftazidime, cefepime, and piperacillin-tazobactam). It is interesting that, of the 144 *P. aeruginosa* isolates (8.3%) that were not susceptible to ceftazidime, meropenem, and piperacillin-tazobactam, 94 (65.3%) were susceptible to ceftazidime-avibactam (Fig. 2) at the FDA-approved breakpoint (12). In other studies, ceftazidime-avibactam resistance in *P. aeruginosa* isolates was primarily the result of decreased membrane permeability and upregulated efflux mechanisms and less frequently the result of a loss of outer membrane porins or the production of class B or D β-lactamases (13, 14).

The high level of *in vitro* activity observed for ceftazidime-avibactam against *P. aeruginosa* was corroborated by an additional study that showed similar activity (67.4% susceptible to ceftazidime-avibactam) against 396 *P. aeruginosa* isolates, obtained between 2011 and 2014, with nonsusceptibility to ceftazidime, cefepime, meropenem, and piperacillin-tazobactam (15).

In each of the census regions, ceftazidime-avibactam consistently demonstrated higher susceptibility rates than comparators commonly used as first-line agents for the treatment of *P. aeruginosa* infections. The potent *in vitro* activity observed in this surveillance study for ceftazidime-avibactam against *P. aeruginosa* isolates, including significant activity against isolates that are not susceptible to ceftazidime, meropenem, and piperacillin-tazobactam, highlight the potential clinical utility of this antibacterial combination against serious difficult-to-treat *P. aeruginosa* infection. These *in vitro* surveillance results also reinforce and support existing clinical data regarding ceftazidime-avibactam activity against *P. aeruginosa*.

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TABLE 2 Activities of ceftazidime-avibactam and comparator antimicrobial agents against two resistant subgroups of *Pseudomonas aeruginosa*

Region and antimicrobial agent (no. tested)	MIC_{50}	MIC_{90}	CLSI[a]			EUCAST[a]		
			%S	%I	%R	%S	%I	%R
Ceftazidime nonsusceptible (279)								
Ceftazidime-avibactam	4	16	76.7		23.3[b]			
Cefepime	16	>16	31.9	36.2	31.9	31.9		68.1
Piperacillin-tazobactam	64	>64	15.4	36.6	48.0	15.4		84.6
Meropenem	4	32	40.1	16.1	43.7	40.1		26.5
Meropenem nonsusceptible (296)								
Ceftazidime-avibactam	4	16	81.1		18.9[b]			
Ceftazidime	16	>32	43.6	13.5	42.9	43.6		56.4
Cefepime	16	>16	46.3	29.4	24.3	46.3		53.7
Piperacillin-tazobactam	32	>64	40.5	27.4	32.1	40.5		59.5

[a] Criteria as published by CLSI (9, 10) and EUCAST (11). %S, %I, and %R, percentage of susceptible, intermediate, and resistant isolates, respectively.
[b] Breakpoints are from the FDA product package insert (12).

pharm, Dipexium, Dong Wha, Durata, Enteris, Exela, Forest Research Institute, Furiex, Genentech, GSK, Helperby, ICPD, Janssen, Lannett, Longitude, Medpace, Meiji Seika Kasha, Melinta, Merck, Motif, Nabriva, Novartis, Paratek, Pfizer, Pocared, PTC Therapeutics, Rempex, Roche, Salvat, Scynexis, Seachaid, Shionogi, Tetraphase, The Medicines Company, Theravance, Thermo Fisher, VenatoRX, Vertex, Wockhardt, Zavante, and some other corporations. Some JMI employees are advisors/consultants for Allergan, Astellas, Cubist, Pfizer, Cempra, and Theravance. Regarding speakers' bureaus and stock options, the authors have nothing to declare.

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