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Ceftazidime-Avibactam Activity against Multidrug-Resistant *Pseudomonas aeruginosa* Isolated in U.S. Medical Centers in 2012 and 2013

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Pseudomonas aeruginosa **isolates ($n = 3,902$) from 75 U.S. medical centers were tested against ceftazidime-avibactam and comparator agents by the reference broth microdilution method. Overall, 96.9% of the strains were susceptible (MIC, ≤8 μg/ml) to ceftazidime-avibactam, while the rates of susceptibility for ceftazidime, meropenem, and piperacillin-tazobactam were 83.8, 81.9, and 78.5%, respectively. Multidrug-resistant and extensively drug-resistant phenotypes were observed in 14.9 and 8.7% of the strains, respectively, and 81.0 and 73.7% of the strains were susceptible to ceftazidime-avibactam, respectively.**

Pseudomonas aeruginosa causes a wide range of serious clinical infections, including hospital-acquired pneumonia, ventilator-associated pneumonia (VAP), bacteremia, skin and skin structure infections, and urinary tract infections (UTI). Data from the Healthcare Safety Network indicate that *P. aeruginosa* was responsible for 7.5% of all health care-associated infections from 2009 to 2010 (1). When stratified by type of infection, *P. aeruginosa* was responsible for 16.6% of VAP (second only to *Staphylococcus aureus*), 11.3% of catheter-related UTI, 5.5% of surgical site infections, and 3.8% of central line-associated bloodstream infections.

P. aeruginosa presents a serious therapeutic challenge because it exhibits intrinsically decreased susceptibility to a range of antimicrobials and possesses a great ability to develop resistance to multiple classes of agents (2, 3). *P. aeruginosa* carries an inducible AmpC cephalosporinase, which is similar to the chromosomally encoded AmpC found in *Enterobacteriaceae*, and when AmpC production is significantly increased, *P. aeruginosa* exhibits resistance to all β-lactams currently available for clinical use, with the exception of the carbapenems (3). Furthermore, upregulation of MexA-MexB-OprM and the loss of OprD are considered the most prevalent mechanisms of carbapenem resistance in *P. aeruginosa*, and these mechanisms are usually associated with AmpC hyperproduction (2, 4–6).

Avibactam is a member of a novel class of non-β-lactam β-lactamase inhibitors, the diazabicyclooctanes (DBOs) (7). Compared to the inhibitors currently available for clinical use, DBOs are more potent and have a broader spectrum and different mechanism of action. Avibactam effectively inactivates class A (including *Klebsiella pneumoniae* carbapenemase [KPC]), class C (AmpC), and some class D (OXA) β-lactamases, with low 50% inhibitory concentration (IC_{50}) values and low turnover numbers. Thus, avibactam extends the antibacterial activity of ceftazidime against most ceftazidime-resistant organisms that produce those cited enzymes, including *P. aeruginosa* (8–10). Ceftazidime-avibactam is approved by the U.S. Food and Drug Administration (FDA) for the treatment of complicated intra-abdominal and complicated urinary tract infections (11). In this study, we evaluated the activity of ceftazidime combined with avibactam when tested against a large collection of contemporary *P. aeruginosa* clinical isolates recovered in U.S. medical centers in 2012 and 2013.

A total of 3,902 *P. aeruginosa* isolates were collected from 75 U.S. hospitals from January 2012 to December 2013 as part of the International Network for Optimal Resistance Monitoring (INFORM) program. The participant medical centers were distributed among 31 states from all nine U.S. Census regions, with one to four medical centers per state (6 to 14 centers by Census regions), and the majority of the medical centers were large tertiary hospitals. These isolates were collected from patients hospitalized with pneumonia (46.6%), skin and soft tissue infections (26.9%), bloodstream infections (7.5%), urinary tract infections (7.9%), intra-abdominal infections (3.7%), and other infection types (7.5%), according to defined protocols (10). Only clinically significant isolates were included in the study (one per patient episode). Species identification was confirmed when necessary by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) using the Bruker Daltonics MALDI Biotyper (Billerica, MA, USA), according to the manufacturer's instructions.

All isolates were tested for susceptibility using the reference broth microdilution method, as described by the Clinical and Laboratory Standards Institute (CLSI) (12). Ceftazidime was combined with avibactam at a fixed concentration of 4 μg/ml, as described in the ceftazidime-avibactam package insert (11). The combination of ceftazidime plus a constant 4 μg/ml avibactam was chosen for susceptibility testing over the alternatives and standardized by CLSI and the European Committee for Antimicrobial

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TABLE 1 Summary of ceftazidime-avibactam activity tested against *P. aeruginosa* isolates from U.S. hospitals (2012 to 2013), including antimicrobial-resistant subsets

Organism (no. tested)[a]	No. of isolates (cumulative %) inhibited at ceftazidime-avibactam MIC (μg/ml) of:									MIC	
	≤0.25	0.5	1	2	4	8	16	32	>32	50%	90%
All isolates (3,902)	60 (1.5)	194 (6.5)	1,523 (45.5)	1,217 (76.7)	563 (91.2)	223 (96.9[b])	74 (98.8)	23 (99.4)	25 (100.0)	2	4
CAZ-NS (634)		1 (0.2)	41 (6.6)	149 (30.1)	181 (58.7)	141 (80.9[b])	73 (92.4)	23 (96.1)	25 (100.0)	4	16
MEM-NS (702)		8 (1.1)	63 (10.1)	172 (34.6)	218 (65.7)	146 (86.5[b])	54 (94.2)	18 (96.7)	23 (100.0)	4	16
P-T-NS (837)		4 (0.5)	62 (7.9)	189 (30.5)	267 (62.4)	196 (85.8[b])	72 (94.4)	22 (97.0)	25 (100.0)	4	16
MER-NS, CAZ-NS, and P-T-NS (330)		1 (0.3)	4 (1.5)	45 (15.2)	87 (45.1)	100 (71.8[b])	53 (87.9)	17 (93.0)	23 (100.0)	8	32
MDR (580)	1 (0.2)	3 (0.7)	31 (6.0)	113 (25.5)	174 (55.5)	148 (81.0[b])	64 (92.1)	21 (95.7)	25 (100.0)	4	16
XDR (338)		1 (0.3)	8 (2.7)	51 (17.8)	88 (43.8)	101 (73.7[b])	46 (87.3)	18 (92.6)	25 (100.0)	8	32

[a] CAZ, ceftazidime; MEM, meropenem; P-T, piperacillin-tazobactam; NS, nonsusceptible; MDR, multidrug resistant; XDR, extensively drug-resistant.
[b] Percent susceptible according to the U.S. FDA breakpoint criteria (11).

Susceptibility Testing (EUCAST), based on the pharmacokinetic characteristics of avibactam and the ability of this combination to separate isolates that have been predefined as susceptible or resistant based on the β-lactamases expressed and the known β-lactamase inhibition profile of avibactam (13, 14).

Categorical interpretations for all antimicrobials were those found in CLSI document M100-S24 (15) and EUCAST (16) breakpoint tables. U.S. FDA breakpoint criteria were applied for ceftazidime-avibactam (11). To better evaluate ceftazidime-avibactam activity against resistant subsets of *P. aeruginosa*, the strains were stratified by their susceptibility patterns to ceftazidime, meropenem, and piperacillin-tazobactam. Multidrug-resistant (MDR) and extensively drug-resistant (XDR) bacteria were classified per recently recommended guidelines (17), using the following antimicrobial class representative agents and CLSI interpretive criteria (15): ceftazidime, ≥16 μg/ml; meropenem, ≥4 μg/ml; piperacillin-tazobactam, ≥32 μg/ml; levofloxacin, ≥4 μg/ml; gentamicin, ≥8 μg/ml; and colistin, ≥4 μg/ml. Classifications were based on the following recommended resistance parameters: MDR, nonsusceptible to ≥1 agent in ≥3 antimicrobial classes; XDR, nonsusceptible to ≥1 agent in all but ≤2 antimicrobial classes (17). Quality control (QC) was performed using *Escherichia coli* strain ATCC 25922 and *P. aeruginosa* strain ATCC 27853. All QC results were within acceptable ranges, as published in recent CLSI documents (15).

Ceftazidime-avibactam ($MIC_{50/90}$, 2/4 μg/ml; 96.9% susceptible at ≤8 μg/ml [11]; Table 1) exhibited greater *in vitro* activity than ceftazidime tested alone ($MIC_{50/90}$, 2/32 μg/ml; 83.8% susceptible at ≤8 μg/ml; Table 2) when processed against the entire collection of *P. aeruginosa*. The overall susceptibility (by CLSI criteria, Table 2) rates for cefepime (83.6%) and meropenem (81.9%) were similar to that of ceftazidime (83.8%) and lower than that of ceftazidime-avibactam, at ≤8 μg/ml (96.9%). Piperacillin-tazobactam ($MIC_{50/90}$, 8/>64 μg/ml) inhibited 78.5% of the strains at the CLSI susceptible breakpoint of ≤16 μg/ml, and 74.9 and 88.9% of strains were susceptible (CLSI) to levofloxacin and gentamicin, respectively (Table 2). Among the comparator agents, amikacin ($MIC_{50/90}$, 2/8 μg/ml; 97.4% susceptible at ≤16 μg/ml, per the CLSI criteria) and colistin ($MIC_{50/90}$, 1/2 μg/ml; 99.3% susceptible at ≤2 μg/ml, per the CLSI criteria]) were the most active compounds (Table 2).

Ceftazidime-avibactam inhibited 80.9% of the ceftazidime-nonsusceptible *P. aeruginosa* isolates (ceftazidime MIC, ≥16 μg/ml; 634 isolates tested) at ≤8 μg/ml (Table 1). Ceftazidime-avibactam also showed potent activity against meropenem-nonsusceptible *P. aeruginosa* (meropenem MIC, ≥4 μg/ml; 702 isolates tested), inhibiting 86.5% of the strains at ≤8 μg/ml (Table 1). The most active antimicrobials tested against meropenem-nonsusceptible *P. aeruginosa* were ceftazidime-avibactam ($MIC_{50/90}$, 4/16 μg/ml; 86.5% susceptible; Table 1), amikacin ($MIC_{50/90}$, 4/16 μg/ml; 91.7% susceptible, per the CLSI criteria) and colistin ($MIC_{50/90}$, 1/2 μg/ml; 98.9% susceptible, per the CLSI criteria; data not shown). Moreover, ceftazidime-avibactam inhibited 71.8 and 87.9% of the *P. aeruginosa* strains nonsusceptible to ceftazidime, meropenem, and piperacillin-tazobactam at MICs of ≤8 and ≤16 μg/ml, respectively (Table 1). Ceftazidime-avibactam was also active against MDR ($MIC_{50/90}$, 4/16 μg/ml; 81.0% susceptible) and XDR ($MIC_{50/90}$, 8/32 μg/ml; 73.7% susceptible) *P. aeruginosa* (Tables 1 and 2). Besides ceftazidime-avibactam, only colistin ($MIC_{50/90}$, 1/2 μg/ml for both subsets; 98.8 to 99.0% susceptible, per the CLSI criteria) and amikacin ($MIC_{50/90}$, 4 to 8/32 μg/ml; 83.7 to 87.9% susceptible, per the CLSI criteria) exhibited good activity against MDR and XDR isolates of *P. aeruginosa* (Table 2).

Ceftazidime is a well-established cephalosporin with an excellent safety profile and broad-spectrum activity against Gram-negative organisms, including *P. aeruginosa* (18). Avibactam is a novel non-β-lactam β-lactamase inhibitor that protects β-lactams from hydrolysis by serine β-lactamases (7, 19), including AmpC, which represents an important resistance mechanism among *P. aeruginosa* (3, 4, 20). The results of the present study indicate that avibactam restores ceftazidime wild-type activity against most ceftazidime-nonsusceptible *P. aeruginosa* strains, consistent with the results of a similar study of European isolates of *P. aeruginosa* (21). Ceftazidime-avibactam ($MIC_{50/90}$, 2/4 μg/ml; 96.9% susceptible at ≤8 μg/ml) showed greater anti-*P. aeruginosa* activity than ceftazidime ($MIC_{50/90}$, 2/32 μg/ml; 83.8% susceptible) and inhibited 80.9% of the ceftazidime-nonsusceptible strains at ≤8 μg/ml. Moreover, ceftazidime-avibactam was active against *P. aeruginosa* strains exhibiting nonsusceptibility to meropenem ($MIC_{50/90}$, 4/16 μg/ml; 86.5% susceptible) or piperacillin-tazobactam ($MIC_{50/90}$, 4/16 μg/ml; 85.8% susceptible), and against many strains nonsusceptible to ceftazidime, meropenem, and piperacillin-tazobactam ($MIC_{50/90}$, 8/32 μg/ml; 71.8% susceptible).

Mushtaq, Warner, and Livermore (9) evaluated the *in vitro* activities of ceftazidime-avibactam and various antipseudomonal β-lactams against 26 AmpC mutant *P. aeruginosa* strains, includ-

TABLE 2 Activity of ceftazidime-avibactam and comparator antimicrobial agents when tested against *P. aeruginosa* from U.S. hospitals (2012 to 2013)

Antimicrobial agent[a]	MIC (μg/ml)			%S/%I/%R according to indicated criteria[b]	
	50%	90%	Range	CLSI	EUCAST
All isolates (n = 3,902)					
Ceftazidime-avibactam	2	4	0.03 to >32	96.9/0.0/3.1[c]	96.9/0.0/3.1[d]
Ceftazidime	2	32	0.06 to >32	83.8/3.6/12.6	83.8/0.0/16.2
Cefepime	2	16	≤0.5 to >16	83.6/8.4/8.0	83.6/0.0/16.4
Piperacillin-tazobactam	8	>64	≤0.5 to >64	78.5/9.1/12.4	78.5/0.0/21.5
Meropenem	0.5	8	≤0.06 to >8	81.9/5.8/12.3	81.9/11.9/6.2
Ciprofloxacin	0.12	>4	≤0.03 to >4	77.0/5.1/17.9	71.8/5.2/23.0
Levofloxacin	0.5	>4	≤0.12 to >4	74.9/6.4/18.7	66.5/8.4/25.1
Gentamicin	≤1	8	≤1 to >8	88.9/3.2/7.9	88.9/0.0/11.1
Amikacin	2	8	≤0.25 to >32	97.4/1.1/1.5	94.0/3.4/2.6
Colistin	1	2	0.12 to >8	99.3/0.6/0.1	99.9/0.0/0.1
MDR strains (n = 580)					
Ceftazidime-avibactam	4	16	0.25 to >32	81.0/0.0/19.0[c]	81.0/0.0/19.0[d]
Ceftazidime	32	>32	1 to >32	22.4/16.0/61.6	22.4/0.0/77.6
Cefepime	16	>16	1 to >16	22.9/34.9/42.2	22.9/0.0/77.1
Piperacillin-tazobactam	>64	>64	1 to >64	8.6/30.5/60.9	8.6/0.0/91.4
Meropenem	8	>8	≤0.06 to >8	21.6/16.3/62.1	21.6/43.9/34.5
Ciprofloxacin	>4	>4	≤0.03 to >4	20.9/10.1/69.0	13.6/7.3/79.1
Levofloxacin	>4	>4	≤0.12 to >4	15.0/13.3/71.7	9.8/5.2/85.0
Gentamicin	4	>8	≤1 to >8	51.4/9.5/39.1	51.4/0.0/48.6
Amikacin	4	32	≤0.25 to >32	87.9/5.0/7.1	76.6/11.3/12.1
Colistin	1	2	0.25 to >8	99.0/0.7/0.3	99.7/0.0/0.3
XDR strains (n = 338)					
Ceftazidime-avibactam	8	32	0.5 to >32	73.7/0.0/26.3[c]	73.7/0.0/26.3[d]
Ceftazidime	32	>32	1 to >32	10.1/17.1/72.8	10.1/0.0/89.9
Cefepime	>16	>16	4 to >16	11.8/32.3/55.9	11.8/0.0/88.2
Piperacillin-tazobactam	>64	>64	8 to >64	2.7/23.6/73.7	2.7/0.0/97.3
Meropenem	8	>8	0.12 to >8	7.1/14.8/78.1	7.1/47.3/45.6
Ciprofloxacin	>4	>4	0.12 to >4	7.7/9.5/82.8	2.7/5.0/92.3
Levofloxacin	>4	>4	0.25 to >4	3.6/11.2/85.2	2.1/1.4/96.5
Gentamicin	>8	>8	≤1 to >8	37.0/10.0/53.0	37.0/0.0/63.0
Amikacin	8	32	≤0.25 to >32	83.7/6.5/9.8	69.8/13.9/16.3
Colistin	1	2	0.25 to >8	98.8/0.9/0.3	99.7/0.0/0.3

[a] MDR, multidrug resistant; XDR, extensively drug resistant (17).
[b] S, susceptible; I, intermediate; R, resistant, according to criteria as published by the CLSI (15) and EUCAST (16).
[c] U.S. FDA breakpoint criteria were applied (11).
[d] EUCAST susceptibility criteria for ceftazidime alone were applied for comparison purposes only (16).

ing strains with derepressed AmpC associated with a lack of OprD; 22 of 26 strains had ceftazidime MICs of ≥64 μg/ml. The results showed that avibactam negated most AmpC-mediated resistance in *P. aeruginosa*, reducing ceftazidime MICs to the wild-type susceptible range, according to the current CLSI, U.S. Food and Drug Administration, and EUCAST susceptible breakpoint of ≤8 μg/ml (9). Ceftazidime-avibactam activity against *P. aeruginosa* resistant to ceftazidime, piperacillin-tazobactam, or meropenem (as well as MDR strains) has also been reported by Walkty et al. (22). These investigators evaluated 470 clinical isolates from 15 tertiary care medical centers in Canada and showed that the addition of avibactam to ceftazidime lowered the ceftazidime MIC by 2- to 4-fold, and 66.1% of the ceftazidime-resistant strains exhibited ceftazidime-avibactam MICs of ≤8 μg/ml (22).

In summary, the results of this study corroborate and expand those results of other investigations by testing a large collection (3,902) of contemporary clinical strains. 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 *P. aeruginosa* infections.

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