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Pseudomonas aeruginosa Antimicrobial Susceptibility Results from Four Years (2012 to 2015) of the International Network for Optimal Resistance Monitoring Program in the United States

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ABSTRACT *Pseudomonas aeruginosa* represents a major cause of health care-associated infections, and inappropriate initial antimicrobial therapy is associated with increased morbidity and mortality. The International Network for Optimal Resistance Monitoring (INFORM) program monitors the *in vitro* activity of ceftazidime-avibactam and many comparator agents. We evaluated the antimicrobial susceptibility of 7,452 *P. aeruginosa* isolates collected from 79 U.S. medical centers in 2012 to 2015. The isolates were collected and tested consecutively for susceptibility by broth microdilution method. Infection types included mainly pneumonia (50.5%), skin and skin structure (24.0%), urinary tract (7.8%), and bloodstream (7.7%) infections. The only compounds with >90% susceptibility rates were colistin ($MIC_{50/90}$, 1/2 mg/liter, respectively; 99.4% susceptible), ceftazidime-avibactam ($MIC_{50/90}$, 2/4 mg/liter, respectively; 97.0% susceptible), and amikacin ($MIC_{50/90}$, 2/8 mg/liter, respectively; 97.0/93.0% susceptible [CLSI/EUCAST, respectively]). The addition of avibactam to ceftazidime increased the percentage of susceptible *P. aeruginosa* isolates from 84.3% to 97.0%. Multidrug resistance (MDR) and extensive drug resistance (XDR) phenotypes were observed among 1,151 (15.4%) and 698 (9.4%) isolates, respectively, and ceftazidime-avibactam inhibited 82.1 and 75.8% of these isolates at ≤8 mg/liter, respectively. High rates of cross-resistance were observed with ceftazidime, meropenem, and piperacillin-tazobactam, whereas ceftazidime-avibactam retained activity against isolates nonsusceptible to ceftazidime (81.0% susceptible), meropenem (86.2% susceptible), and piperacillin-tazobactam (85.4% susceptible), as well as isolates nonsusceptible to these three β-lactams (71.2% susceptible). The only antimicrobial combinations that provided a better overall anti-*Pseudomonas* coverage than ceftazidime-avibactam (97.0% susceptibility rate) were those including amikacin (97.0 to 98.4% coverage). Susceptibility rates remained stable during the study period. The results of this investigation highlight the challenge of optimizing empirical antimicrobial therapy for *P. aeruginosa* infections.

KEYWORDS antimicrobial resistance, ceftazidime-avibactam, health care-associated infection

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Pseudomonas aeruginosa represents a major cause of health care-associated infections, including nosocomial pneumonia, bloodstream infections, urinary tract infections, and skin and skin structure infections. It is estimated that 51,000 health care-associated *P. aeruginosa* infections occur in the United States every year, and approximately 13% of these cases are cause by multidrug-resistant (MDR) isolates (1). Thus, *P. aeruginosa* presents a serious therapeutic challenge, and prompt initiation of effective antimicrobial therapy is essential to optimize clinical outcome. Unfortunately,

TABLE 1 Activity of ceftazidime-avibactam and comparator antimicrobial agents when tested against *Pseudomonas aeruginosa* isolates from U.S. medical centers (2012 to 2015)[d]

Isolate group (*n*) and antimicrobial agent(s)	MIC_{50} (mg/liter)	MIC_{90} (mg/liter)	CLSI[a]			EUCAST[b]		
			% S	% I	% R	% S	% I	% R
All isolates (7,452)								
Ceftazidime-avibactam	2	4	97.0		3.0[c]	97.0		3.0
Ceftazidime	2	32	84.3	4.0	11.7	84.3		15.7
Cefepime	2	16	85.4	8.4	6.2	85.4		14.6
Piperacillin-tazobactam	4	>64	80.5	9.1	10.3	80.5		19.5
Meropenem	0.5	8	82.0	5.9	12.1	82.0	11.9	6.2
Ciprofloxacin	0.12	>4	77.5	5.3	17.2	71.8	5.7	22.5
Levofloxacin	0.5	>4	74.9	6.6	18.5	66.0	8.9	25.1
Gentamicin	≤1	8	88.3	3.7	8.1	88.3		11.7
Amikacin	2	8	97.0	1.2	1.8	93.0	4.0	3.0
Colistin	1	2	99.4	0.6	0.1	99.9		0.1
MDR isolates (1,151)								
Ceftazidime-avibactam	4	16	82.1		17.9[c]	82.1		17.9
Ceftazidime	32	>32	27.6	16.0	56.4	27.6		72.4
Cefepime	16	>16	26.5	39.5	34.0	26.5		73.5
Piperacillin-tazobactam	>64	>64	15.5	34.0	50.6	15.5		84.5
Meropenem	8	>8	21.4	18.1	60.6	21.4	44.4	34.2
Ciprofloxacin	>4	>4	21.3	12.3	66.5	12.4	8.9	78.7
Levofloxacin	>4	>4	14.8	14.6	70.6	8.4	6.3	85.2
Gentamicin	4	>8	51.1	10.3	38.7	51.1		48.9
Amikacin	8	32	87.1	5.0	8.0	74.5	12.6	12.9
Colistin	1	2	99.1	0.6	0.3	99.7		0.3
XDR isolates (698)								
Ceftazidime-avibactam	8	32	75.8		24.2[c]	75.8		24.2
Ceftazidime	32	>32	18.9	16.0	65.0	18.9		81.1
Cefepime	16	>16	14.3	42.0	43.7	14.3		85.7
Piperacillin-tazobactam	>64	>64	5.7	34.4	59.9	5.7		94.3
Meropenem	8	>8	7.6	17.6	74.8	7.6	46.3	46.1
Ciprofloxacin	>4	>4	10.2	12.2	77.7	3.3	6.9	89.8
Levofloxacin	>4	>4	4.2	14.2	81.7	2.1	2.0	95.8
Gentamicin	>8	>8	38.1	11.5	50.4	38.1		61.9
Amikacin	8	>32	83.2	6.2	10.6	68.1	15.2	16.8
Colistin	1	2	99.1	0.6	0.3	99.7		0.3

[a]Criteria as published by CLSI (18).
[b]Criteria as published by EUCAST (20).
[c]Breakpoints from FDA package insert (10).
[d]Abbreviations: MDR, multidrug resistant; XDR, extensively drug resistant (12); S, susceptible; I, intermediate; R, resistant.

selection of the most appropriate antimicrobial therapy is complicated by the great ability of *P. aeruginosa* to develop or acquire resistance to multiple classes of antimicrobials (2–4).

The International Network for Optimal Resistance Monitoring (INFORM) program monitors the *in vitro* activity of ceftazidime-avibactam and many comparator agents in U.S. medical centers (5). Ceftazidime-avibactam is the combination of a third-generation antipseudomonal cephalosporin with a well-established efficacy and safety profile, ceftazidime, with the novel non-β-lactam β-lactamase inhibitor avibactam (6–8). Avibactam inhibits a broad range of serine β-lactamases, including Ambler class A (ESBL and KPC), class C (AmpC), and some class D (such as OXA-48) enzymes, but not metallo-β-lactamases. In combination with ceftazidime, avibactam restores activity of ceftazidime against the vast majority of clinically relevant β-lactamase-producing *Enterobacteriaceae*, with the exception of those producing metallo-β-lactamases. Furthermore, ceftazidime-avibactam has demonstrated potent *in vitro* activity and extensive coverage of *P. aeruginosa*; the addition of avibactam is shown to increase the antipseudomonal spectrum of ceftazidime by approximately 10% (9).

Ceftazidime-avibactam has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of complicated intra-abdominal infections (cIAI), in com-

TABLE 2 Antimicrobial activity of ceftazidime-avibactam tested against *P. aeruginosa* from U.S. medical centers (2012 to 2015)

Resistance group[b]	No. (cumulative %) of isolates at MIC (mg/liter):									MIC_{50} (mg/liter)	MIC_{90} (mg/liter)
	≤0.25	0.5	1	2	4	8	16	32	>32		
All isolates (n = 7,452)	128 (1.7)	390 (7.0)	2,843 (45.1)	2,409 (77.4)	1,043 (91.4)	415 (**97.0**)[a]	133 (98.8)	44 (99.4)	47 (100.0)	2	4
CAZ-NS (≥16 mg/liter; n = 1,168)	2 (0.2)	8 (0.9)	88 (8.4)	282 (32.5)	320 (59.9)	246 (**81.0**)[a]	131 (92.2)	44 (96.0)	47 (100.0)	4	16
MEM-NS (≥4 mg/liter; n = 1,341)	2 (0.1)	10 (0.9)	127 (10.4)	323 (34.5)	416 (65.5)	278 (**86.2**)[a]	104 (94.0)	37 (96.7)	44 (100.0)	4	16
PT-NS (≥32 mg/liter; n = 1,449)	2 (0.1)	15 (1.2)	113 (9.0)	326 (31.5)	442 (62.0)	340 (**85.4**)[a]	125 (94.1)	42 (97.0)	44 (100.0)	4	16
NS to CAZ, MEM, and PT (n = 607)		1 (0.2)	15 (2.6)	88 (17.1)	154 (42.5)	174 (**71.2**)[a]	98 (87.3)	36 (93.2)	41 (100.0)	8	32
Levofloxacin-NS (≥4 mg/liter; n = 1,868)	19 (1.0)	84 (5.5)	332 (23.3)	459 (47.9)	508 (75.1)	286 (**90.4**)[a]	101 (95.8)	36 (97.7)	43 (100.0)	4	8
Gentamicin-NS (≥8 mg/liter; n = 873)	16 (1.8)	42 (6.6)	155 (24.4)	242 (52.1)	190 (73.9)	120 (**87.6**)[a]	46 (92.9)	25 (95.8)	37 (100.0)	2	16
Amikacin-NS (≥32 mg/liter; n = 224)	6 (2.7)	13 (8.5)	38 (25.4)	52 (48.7)	46 (69.2)	23 (**79.5**)[a]	17 (87.1)	10 (91.5)	19 (100.0)	4	32
Colistin-NS (≥4 mg/liter; n = 45)	1 (2.2)	1 (4.4)	17 (42.2)	15 (75.6)	5 (86.7)	1 (**88.9**)[a]	3 (95.6)	0 (95.6)	2 (100.0)	2	16
MDR (n = 1,151)	4 (0.3)	8 (1.0)	74 (7.5)	241 (28.4)	333 (57.3)	285 (**82.1**)[a]	118 (92.4)	42 (96.0)	46 (100.0)	4	16
XDR (n = 698)	1 (0.1)	4 (0.7)	28 (4.7)	109 (20.3)	179 (46.0)	208 (**75.8**)[a]	88 (88.4)	36 (93.6)	45 (100.0)	8	32
PDR (n = 2)									2 (100.0)	>32	

[a]Values in bold indicate percent susceptible to ceftazidime-avibactam.

[b]Abbreviations: CAZ, ceftazidime; NS, nonsusceptible; MEM, meropenem; PT, piperacillin-tazobactam; MDR, multidrug resistant; XDR, extensively drug resistant; PDR, pan-drug resistant.

bination with metronidazole, as well as complicated urinary tract infections (cUTI), including pyelonephritis, in patients with limited or no alternative treatment options (10). Ceftazidime-avibactam is additionally approved for treatment of nosocomial pneumonia, including ventilator-associated pneumonia (VAP), in Europe (11). We evaluated the antimicrobial susceptibility of *P. aeruginosa* isolates collected from 79 U.S. medical centers in 2012 to 2015 through the INFORM program.

RESULTS

The *P. aeruginosa* isolates were collected from patients with pneumonia (50.5%), skin and skin structure infections (24.0%), urinary tract infections (7.8%), bloodstream infections (7.7%), and other infection types (10.0%). The only compounds with >90% susceptibility rates were colistin ($MIC_{50/90}$, 1/2 mg/liter, respectively; 99.4% susceptible at ≤2 mg/liter [CLSI]), ceftazidime-avibactam ($MIC_{50/90}$, 2/4 mg/liter, respectively; 97.0% susceptible at ≤8 mg/liter [FDA susceptible breakpoint]), and amikacin ($MIC_{50/90}$, 2/8 mg/liter, respectively; 97.0 and 93.0% susceptible at ≤16 mg/liter [CLSI] and ≤8 mg/liter[EUCAST], respectively) (Table 1). Of note, the addition of avibactam to ceftazidime increased the percentage of susceptible *P. aeruginosa* isolates from 84.3% to 97.0% (Table 1).

Gentamicin was the fourth most active agent ($MIC_{50/90}$, ≤1/8 mg/liter, respectively; 88.3% susceptible [CLSI and EUCAST]), followed by cefepime ($MIC_{50/90}$, 2/16 mg/liter, respectively; 85.4% susceptible [CLSI and EUCAST]), ceftazidime ($MIC_{50/90}$, 2/32 mg/liter, respectively; 84.3% susceptible [CLSI and EUCAST]), meropenem ($MIC_{50/90}$, 0.5/8 mg/liter, respectively; 82.0% susceptible [CLSI and EUCAST]), piperacillin-tazobactam ($MIC_{50/90}$, 4/>64 mg/liter, respectively; 80.5% susceptible [CLSI and EUCAST]), and levofloxacin ($MIC_{50/90}$, 0.5/>4 mg/liter, respectively; 74.9 and 66.0% susceptible at ≤2 mg/liter [CLSI] and ≤1 mg/liter [EUCAST], respectively) (Table 1).

MDR and extensively drug-resistant (XDR) phenotypes (12) were observed among 1,151 (15.4%) and 698 (9.4%) isolates, respectively (Table 1). Colistin retained *in vitro* activity against >99% of MDR and XDR isolates, whereas amikacin was active against 87.1 and 83.2% of isolates at the CLSI susceptible breakpoint (74.5 and 68.1% at the EUCAST susceptible breakpoint) and ceftazidime-avibactam inhibited 82.1 and 75.8% of isolates at the FDA susceptible breakpoint, respectively (Tables 1 and 2). All other compounds evaluated exhibited very limited activity against these organism subsets (Table 1).

TABLE 3 Cross-resistance comparison of ceftazidime-avibactam, ceftazidime, meropenem, piperacillin-tazobactam, gentamicin, amikacin, and levofloxacin against *P. aeruginosa* isolates tested in this study[a]

Resistance group	No. of isolates (%) susceptible to drug(s):										
	CAZ-AVI	CAZ	MEM	PT	GEN	AMK	LEV	CAZ + MEM	CAZ + PT	CAZ + GEN	CAZ + AMK
All (n = 7,452)	7,228 (97.0)	6,284 (84.3)	6,096 (82.0)	5,996 (80.5)	6,578 (88.3)	7,228 (97.0)	5,583 (74.9)	6,800 (91.3)	6,379 (85.6)	7,090 (95.1)	7,334 (98.4)
CAZ-NS (≥16 mg/liter; n = 1,168)	946 (81.0)	0 (0.0)	516 (44.3)	95 (8.1)	806 (69.1)	1,050 (89.9)	474 (40.6)	516 (44.2)	95 (8.1)	806 (69.0)	1,050 (89.9)
MEM-NS (≥4 mg/liter; n = 1,341)	1,156 (86.2)	691 (51.5)	0 (0.0)	550 (41.0)	870 (64.9)	1,217 (90.8)	411 (30.6)	691 (51.5)	734 (54.7)	1,048 (78.2)	1,251 (93.3)
PT-NS (≥32 mg/liter; n = 1,449)	1,238 (85.4)	376 (25.9)	655 (45.3)	0 (0.0)	1,020 (70.4)	1,328 (91.6)	588 (40.6)	840 (58.0)	376 (25.9)	1,122 (77.4)	1,349 (93.1)
NS to CAZ, MER, and PT (n = 607)	432 (71.2)	0 (0.0)	0 (0.0)	0 (0.0)	336 (55.4)	522 (86.0)	121 (19.9)	0 (0.0)	0 (0.0)	336 (55.4)	522 (86.0)
LEV-NS (≥4 mg/liter; n = 1,868)	1,688 (90.4)	1,174 (62.8)	937 (50.2)	1,006 (53.9)	1,257 (67.3)	1,726 (92.4)	0 (0.0)	1,351 (72.3)	1,220 (65.3)	1,555 (83.2)	1,775 (95.0)
GEN-NS (≥8 mg/liter; n = 873)	765 (87.6)	512 (58.6)	402 (46.0)	445 (51.0)	0 (0.0)	651 (74.6)	262 (30.0)	580 (66.4)	547 (62.7)	512 (58.6)	756 (86.6)
AMK-NS (≥32 mg/liter; n = 224)	178 (79.5)	106 (47.3)	100 (44.6)	103 (46.0)	2 (0.9)	0 (0.0)	82 (36.6)	134 (59.8)	124 (55.4)	107 (47.8)	106 (47.3)
COL-NS (≥4 mg/liter; n = 45)	40 (88.9)	39 (86.7)	35 (77.8)	36 (80.0)	40 (88.9)	43 (95.6)	35 (77.8)	40 (88.9)	39 (86.7)	43 (95.6)	43 (95.6)
CAZ-AVI-NS (n = 224)	0 (0.0)	2 (0.9)	39 (17.4)	13 (5.8)	116 (51.8)	178 (79.5)	44 (19.6)	39 (17.4)	15 (6.7)	116 (51.8)	178 (79.5)
MDR (n = 1,151)	945 (82.1)	318 (27.6)	246 (21.4)	178 (15.5)	588 (51.1)	1,002 (87.1)	170 (14.8)	510 (44.3)	362 (31.5)	794 (69.0)	1,037 (90.1)
XDR (n = 698)	529 (75.8)	132 (18.9)	53 (7.6)	40 (5.7)	266 (38.1)	581 (83.2)	29 (4.2)	170 (24.4)	151 (21.6)	370 (53.0)	602 (86.2)

[a]Abbreviations: CAZ, ceftazidime; NS, nonsusceptible; MEM, meropenem; PT, piperacillin-tazobactam; LEV, levofloxacin; GEN, gentamicin; AMK, amikacin; COL, colistin; CAZ-AVI, ceftazidime-avibactam; MDR, multidrug resistant; XDR, extensively drug resistant.

High rates of cross-resistance were observed with ceftazidime, meropenem, and piperacillin-tazobactam. Among piperacillin-tazobactam-nonsusceptible (NS) isolates, only 45.3 and 25.9% were susceptible to meropenem and ceftazidime, respectively (Table 3). Among meropenem-nonsusceptible isolates, only 41.0 and 51.5% were susceptible to piperacillin-tazobactam and ceftazidime, respectively, and among ceftazidime-nonsusceptible isolates, susceptibility rates for meropenem and piperacillin-tazobactam were 44.3 and 8.1%, respectively (Table 3). In contrast, ceftazidime-avibactam exhibited good activity against isolates nonsusceptible to ceftazidime (81.0% susceptible), meropenem (86.2% susceptible), or piperacillin-tazobactam (85.4% susceptible), as well as isolates nonsusceptible to all three drugs (71.2% susceptible) (Tables 2 and 3). Ceftazidime-avibactam was also active against isolates nonsusceptible to levofloxacin (90.4% susceptible), gentamicin (87.6% susceptible), amikacin (79.5% susceptible), or colistin (88.9% susceptible) (Tables 2 and 3).

We also compared the spectrum of ceftazidime-avibactam with the spectrum of two comparator agents combined, i.e., the percentage of isolates susceptible to either one of two comparator agents combined (Table 3). Colistin alone was active against 99.4% of isolates, and any combination including colistin was active against ≥99.9% of isolates; these results were not included in Table 3. The only antimicrobial combinations that provided a better overall anti-*Pseudomonas* coverage, excluding those including colistin, than ceftazidime-avibactam (97.0% susceptibility rate) were those including amikacin (97.0 to 98.4% coverage) (Table 3). Combinations that did not include amikacin or colistin provided an overall coverage of 85.6% (ceftazidime plus piperacillin-tazobactam) to 95.1% (ceftazidime plus gentamicin). Furthermore, ceftazidime-avibactam plus amikacin provided 99.4% coverage (Table 3).

Ceftazidime-avibactam coverage was also greater than those provided by antimicrobial combination regimens that did not include amikacin against all resistance subsets (Table 3). When tested against MDR and XDR subsets, the best coverage was provided by ceftazidime-avibactam plus amikacin (96.0 and 93.7%, respectively), followed by the other amikacin combination regimens (87.2 to 90.1% and 83.2 to 86.2%, respectively), amikacin alone (87.1 and 83.2%, respectively), and ceftazidime-avibactam alone (82.1 and 75.8%, respectively) (Table 3). Among antimicrobial combination regimens not including amikacin, ceftazidime plus gentamicin was the most active, inhibiting 69.0 and 53.0% of MDR and XDR isolates, respectively (Table 3).

Susceptibility rates to all antimicrobial agents tested remained stable during the

TABLE 3 (Continued)

No. of isolates (%) susceptible to drug(s):											
CAZ + LEV	MEM + PT	MEM + GEN	MEM + AMK	MEM + LEV	PT + GEN	PT + AMK	PT + LEV	GEN + AMK	GEN + LEV	AMK + LEV	CAZ-AVI + AMK
6,758 (90.7)	6,658 (89.3)	6,981 (93.7)	7,328 (98.3)	6,521 (87.5)	7,023 (94.2)	7,331 (98.4)	6,590 (88.4)	7,230 (97.0)	6,841 (91.8)	7,310 (98.1)	7,405 (99.4)
474 (40.6)	559 (47.9)	875 (74.9)	1,078 (92.3)	651 (55.7)	841 (72.0)	1,068 (91.4)	520 (44.5)	1,051 (90.0)	855 (73.2)	1,075 (92.0)	1,123 (96.2)
824 (61.4)	550 (41.0)	870 (64.9)	1,217 (90.8)	411 (30.6)	1,001 (74.6)	1,241 (92.5)	724 (54.0)	1,218 (90.8)	924 (68.9)	1,239 (92.4)	1,298 (96.8)
801 (55.3)	655 (45.2)	1,109 (76.5)	1,349 (93.1)	832 (57.4)	1,020 (70.4)	1,328 (91.6)	588 (40.6)	1,328 (91.6)	1,072 (74.0)	1,347 (93.0)	1,407 (97.1)
121 (19.9)	0 (0.0)	336 (55.4)	522 (86.0)	121 (19.9)	336 (55.4)	522 (86.0)	121 (19.9)	522 (86.0)	358 (59.0)	531 (87.5)	567 (93.4)
1,174 (62.8)	1,251 (67.0)	1,451 (77.7)	1,766 (94.5)	937 (50.2)	1,491 (79.8)	1,766 (94.5)	1,006 (53.9)	1,727 (92.5)	1,257 (67.3)	1,726 (92.4)	1,827 (97.8)
560 (64.1)	533 (61.1)	402 (46.0)	750 (85.9)	456 (52.2)	445 (51.0)	752 (86.1)	496 (56.8)	651 (74.6)	262 (30.0)	732 (83.8)	828 (94.8)
131 (58.5)	124 (55.4)	101 (45.1)	100 (44.6)	122 (54.5)	103 (46.0)	103 (46.0)	122 (54.5)	2 (0.9)	83 (37.1)	82 (36.6)	178 (79.5)
41 (91.1)	39 (86.7)	42 (93.3)	43 (95.6)	39 (86.7)	43 (95.6)	43 (95.6)	41 (91.1)	43 (95.6)	41 (91.1)	43 (95.6)	43 (95.6)
46 (20.5)	49 (21.9)	122 (54.5)	181 (80.8)	63 (28.1)	125 (55.8)	183 (81.7)	54 (24.1)	179 (79.9)	125 (55.8)	183 (81.7)	178 (79.5)
465 (40.4)	397 (34.5)	697 (60.6)	1,035 (89.9)	392 (34.1)	728 (63.2)	1,032 (89.7)	336 (29.2)	1,004 (87.2)	645 (56.0)	1,026 (89.1)	1,105 (96.0)
155 (22.2)	93 (13.3)	319 (45.7)	590 (84.5)	82 (11.7)	306 (43.8)	589 (84.4)	68 (9.7)	581 (83.2)	294 (42.1)	591 (84.7)	654 (93.7)

period of the study. Susceptibility to ceftazidime-avibactam increased slightly from 96.9% in 2012 to 98.0% in 2015, whereas susceptibility rates for meropenem and amikacin exhibited a minor decrease from 82.0 and 97.5% in 2012 to 80.9 and 96.4% in 2015, respectively. Furthermore, the frequency of MDR and XDR phenotypes varied from 15.7 and 10.1% in 2012 to 14.4 and 8.4% in 2015, respectively (Table 4).

DISCUSSION

Inappropriate initial antimicrobial therapy and/or delay of appropriate antimicrobial therapy for serious *P. aeruginosa* infections is associated with increased mortality and longer hospital stays, emphasizing the importance of early introduction of effective empirical antimicrobial therapy (2–4). However, empirical treatment decisions are difficult due to high rates of resistance exhibited by this organism. In the present study, we evaluated a large ($n = 7,452$) contemporary collection of *P. aeruginosa* isolates from 79 U.S. medical centers and detected low rates of susceptibility to first-line agents used to treat *P. aeruginosa* infections, such as piperacillin-tazobactam (80.5%), meropenem (82.0%), and ceftazidime (84.3%). Furthermore, 15.4 and 9.4% of isolates exhibited an MDR and XDR phenotype, respectively. Our results are similar to those reported by the National Healthcare Safety Network (NHSN), a nationwide program coordinated by the

TABLE 4 Yearly susceptibility rates for *P. aeruginosa* isolates from U.S. medical centers (2012 to 2015)

Antimicrobial agent or phenotype	% susceptible[a]/frequency by yr (no. of isolates)			
	2012 (1,966)	2013 (1,935)	2014 (1,742)	2015 (1,809)
Ceftazidime-avibactam	96.9	96.8	96.3	98.0
Ceftazidime	83.2	84.3	84.0	85.8
Cefepime	83.8	83.5	86.6	87.9
Piperacillin-tazobactam	78.3	78.7	83.0	82.5
Meropenem	82.0	81.9	83.1	80.9
Ciprofloxacin	77.5	76.6	77.8	78.1
Levofloxacin	75.3	74.5	75.1	74.7
Gentamicin	88.8	89.0	88.0	87.2
Amikacin	97.5	97.3	96.8	96.4
Colistin	98.7	99.9	99.1	99.9
MDR phenotype	15.7	16.1	15.9	14.4
XDR phenotype	10.1	9.1	9.8	8.4

[a]According to FDA (10) and EUCAST (20) criteria for ceftazidime-avibactam and CLSI (18) criteria for comparators.

Centers for Disease Control and Prevention (CDC), which reported 19.3% resistance to carbapenems (meropenem, imipenem, or doripenem) and 14.2% of isolates with an MDR phenotype among *P. aeruginosa* isolates causing hospital-acquired infections in U.S. medical centers from 2011 to 2014 (13). Data from the NHSN also indicate that *P. aeruginosa* resistance rates for key antimicrobial agents have been stable or decreased slightly in the last few years (13).

Among the antimicrobial agents evaluated in this investigation, only three compounds provided >90% antipseudomonal coverage: amikacin (97.0%) and colistin (99.4%), both associated with important side effects and toxicity, and ceftazidime-avibactam (97.0% susceptibility). The value of combination antimicrobial therapy (β-lactam plus an aminoglycoside or one of these two agents plus a fluoroquinolone) compared to monotherapy remains controversial. However, empirical therapy with combination regimens is commonly used, especially in medical centers with high resistance rates, and the main objective of combination empirical therapy is to broaden antimicrobial coverage (14–17). Our results indicated that the coverage provided by the combinations including piperacillin-tazobactam, meropenem, or ceftazidime plus either gentamicin or levofloxacin varied from 87.5% (meropenem plus levofloxacin) to 95.1% (ceftazidime plus gentamicin), which is still lower than that of either ceftazidime-avibactam or amikacin monotherapy. Furthermore, only colistin (99.7% susceptible) (Table 1) and amikacin combined with ceftazidime (90.1%) or ceftazidime-avibactam (96.0%) provided >90% coverage against MDR organisms (Table 3).

Conclusion. The results of this investigation substantiate and expand those results of other reports and emphasize the challenge of optimizing empirical antimicrobial therapy for systemic *P. aeruginosa* infections (4). The availability of ceftazidime-avibactam with its demonstrated *in vitro* activity against antimicrobial-susceptible and -resistant *P. aeruginosa* offers a very promising alternative option for these difficult-to-treat infections.

MATERIALS AND METHODS

Bacterial isolates. A total of 7,452 *P. aeruginosa* isolates (one per infection episode) were consecutively collected from 79 medical centers distributed among 37 states from all nine U.S. census regions between January 2012 and December 2015 as part of the INFORM program. Only bacterial isolates determined to be significant by local criteria as the reported probable cause of an infection were included in this investigation. 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) according to the manufacturer's instructions.

Isolates were categorized as multidrug resistant (MDR), extensively drug resistant (XDR), and pandrug resistant (PDR) based on the criteria published by Magiorakos et al. (12), i.e., MDR indicates nonsusceptible (NS; per CLSI unless noted otherwise [18]) to ≥1 agent in ≥3 antimicrobial classes, XDR indicates NS to ≥1 agent in all but ≤2 antimicrobial classes, and PDR indicates NS to all antimicrobial classes tested. The antimicrobial classes and drug representatives used in the analysis were antipseudomonal cephalosporins (ceftazidime and cefepime), carbapenems (imipenem, meropenem, and doripenem), broad-spectrum penicillins combined with a β-lactamase inhibitor (piperacillin-tazobactam), fluoroquinolones (ciprofloxacin and levofloxacin), aminoglycosides (gentamicin, tobramycin, and amikacin), glycylcyclines (tigecycline), and the polymyxins (colistin [per EUCAST criteria]).

Antimicrobial susceptibility testing. All isolates were tested for susceptibility using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) (19). Ceftazidime was combined with a fixed concentration of 4 μg/ml of avibactam. Ceftazidime-avibactam breakpoints approved by the FDA and EUCAST (≤8/4 mg/liter for susceptible and ≥16/4 mg/liter for resistant) when testing *P. aeruginosa* were applied (10, 20). Susceptibility interpretations for comparator agents were those found in CLSI document M100-S26 (18) and/or EUCAST breakpoints (20). Quality control (QC) was performed using *Escherichia coli* ATCC 25922 and 35218, *Klebsiella pneumoniae* ATCC 700603 and BAA-1705, and *P. aeruginosa* ATCC 27853.

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