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Antimicrobial Activity of Ceftazidime-Avibactam against Gram-Negative Bacteria Isolated from Patients Hospitalized with Pneumonia in U.S. Medical Centers, 2011 to 2015

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ABSTRACT Bacterial isolates were collected from patients hospitalized with pneumonia (PHP), including ventilator-associated pneumonia (VAP), from 76 U.S. medical centers in 2011 to 2015. The Gram-negative organisms (n = 11,185, including 1,097 from VAP) were tested for susceptibility to ceftazidime-avibactam and comparators by the broth microdilution method. β-Lactamase-encoding genes were screened using a microarray-based assay on selected isolates. *Pseudomonas aeruginosa* and *Klebsiella* spp. were the most common Gram-negative bacteria isolated from PHP and VAP. Ceftazidime-avibactam was very active against *P. aeruginosa* (n = 3,402; MIC_{50}/MIC_{90}, 2 and 4 μg/ml; 96.6% susceptible), including isolates nonsusceptible to meropenem (86.3% susceptible to ceftazidime-avibactam), piperacillin-tazobactam (85.6% susceptible), or ceftazidime (80.6% susceptible). Ceftazidime-avibactam was also highly active against *Enterobacteriaceae* (MIC_{50}/MIC_{90}, 0.12 and 0.5 μg/ml; 99.9% susceptible), including carbapenem-resistant *Enterobacteriaceae* (CRE) (n = 189; MIC_{50}/MIC_{90}, 0.5 and 2 μg/ml; 98.0% susceptible) and multidrug-resistant (MDR) (n = 674; MIC_{50}/MIC_{90}, 0.25 and 1 μg/ml; 98.8% susceptible) and extensively drug-resistant (XDR) (n = 156; MIC_{50}/MIC_{90}, 0.5 and 2 μg/ml; 98.1% susceptible) *Enterobacteriaceae* isolates, as well as *Klebsiella* species isolates showing an extended-spectrum β-lactamase (ESBL) screening-positive phenotype (n = 433; MIC_{50}/MIC_{90}, 0.25 and 1 μg/ml; 99.5% susceptible). Among *Enterobacter* spp. (24.8% ceftazidime nonsusceptible), 99.8% of the isolates, including 99.4% of ceftazidime-nonsusceptible isolates, were susceptible to ceftazidime-avibactam. The most common β-lactamases detected among *Klebsiella pneumoniae* and *E. coli* isolates were *K. pneumoniae* carbapenemase (KPC)-like and CTX-M-15, respectively. Only 8 of 6,209 *Enterobacteriaceae* isolates (0.1%) were ceftazidime-avibactam nonsusceptible, three NDM-1-producing strains with ceftazidime-avibactam MIC values of >32 μg/ml and five isolates with ceftazidime-avibactam MIC values of 16 μg/ml and negative results for all β-lactamases tested. Susceptibility rates among isolates from VAP were generally similar or slightly higher than those from all PHP.

KEYWORDS ceftazidime-avibactam, pneumonia, ventilator-associated pneumonia, *Pseudomonas aeruginosa*, NDM-1, *Klebsiella pneumoniae* carbapenemase

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Pneumonia is the second most common infection in hospitalized patients, and the initial antimicrobial management of patients with pneumonia is driven mainly by an understanding of the causative pathogens (1–3). Although *Staphylococcus aureus* is a significant cause of pneumonia in hospitalized patients, the importance of Gram-negative organisms, such as *Pseudomonas aeruginosa* and *Enterobacteriaceae* species,

mainly *Klebsiella pneumoniae*, *Enterobacter* spp., and *Escherichia coli*, has increased substantially in recent years (4–6).

Avibactam is a member of a novel class of non-β-lactam β-lactamase inhibitors, the diazabicyclooctanes (DBOs). Compared to currently available inhibitors for clinical use, DBOs are more potent and have a broader spectrum and a different mechanism of action. Avibactam effectively inactivates class A (including *K. pneumoniae* carbapenemase [KPC]), class C (AmpC), and some class D (OXA) β-lactamases with low 50% inhibitory concentration (IC_{50}) (the concentration resulting in 50% inhibition) values and low turnover numbers (7). Avibactam does not inhibit metallo-β-lactamases (MBLs) (8, 9).

Ceftazidime-avibactam has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of complicated intra-abdominal infections (in combination with metronidazole) and complicated urinary tract infections, including pyelonephritis, in patients with limited or no alternative treatment options (10). In Europe, ceftazidime-avibactam is also approved for these indications and for the treatment of hospital-acquired pneumonia, including ventilator-associated pneumonia (VAP) (11). In this study, we evaluated the activity of ceftazidime combined with avibactam when tested against a large collection of contemporary clinical isolates recovered from patients hospitalized with pneumonia (PHP) in U.S. medical centers in 2011 to 2015.

RESULTS

The frequencies of organisms isolated from PHP and VAP in 2015 are shown in Fig. 1. The five most common organisms in both groups (shown as percentages of the total for PHP and VAP) were as follows: *S. aureus* (29.8% and 27.1%), *P. aeruginosa* (20.9% and 22.7%), *Klebsiella* spp. (9.9% and 11.8%), *E. coli* (6.6% and 9.0%), and *Enterobacter* spp. (6.4% and 6.8%). Overall, Gram-negative organisms were isolated from 66.0% of patients, including 70.5% of those with VAP.

Ceftazidime-avibactam was very active against *P. aeruginosa* ($n = 3{,}402$; MIC_{50}/MIC_{90}, 2 and 4 μg/ml; 96.6% susceptible), including isolates nonsusceptible to meropenem (MIC_{50}/MIC_{90}, 4 and 16 μg/ml; 86.3% susceptible to ceftazidime-avibactam), piperacillin-tazobactam (MIC_{50}/MIC_{90}, 4 and 16 μg/ml; 85.6% susceptible), or ceftazidime (MIC_{50}/MIC_{90}, 4 and 16 μg/ml; 80.6% susceptible) (Tables 1 and 2). Furthermore, ceftazidime-avibactam retained potent *in vitro* activity against *P. aeruginosa* isolates with multidrug-resistant (MDR) (MIC_{50}/MIC_{90}, 4 and 16 μg/ml; 82.7% susceptible) and extensively drug-resistant (XDR) (MIC_{50}/MIC_{90}, 8 and 32 μg/ml; 76.2% susceptible) phenotypes, as well as isolates nonsusceptible to meropenem, piperacillin-tazobactam, and ceftazidime (MIC_{50}/MIC_{90}, 8 and 32 μg/ml; 69.9% susceptible) (Table 1).

The most active agent tested against *P. aeruginosa* was colistin (MIC_{50}/MIC_{90}, 1 and 2 μg/ml; 99.6% susceptible [Clinical and Laboratory Standards Institute {CLSI}]), followed by ceftazidime-avibactam (MIC_{50}/MIC_{90}, 2 and 4 μg/ml; 96.6% susceptible) and amikacin (MIC_{50}/MIC_{90}, 4 and 16 μg/ml; 95.3% susceptible), and no major differences were observed between the susceptibility rates of *P. aeruginosa* isolates from VAP compared to those from PHP (Tables 2 and 3). The addition of avibactam increased ceftazidime coverage (percentage inhibited at $\leq$8 μg/ml) from 82.4% to 96.6% (Tables 2 and 3).

Ceftazidime-avibactam inhibited 99.9% of all *Enterobacteriaceae* at the susceptible breakpoint of $\leq$8 μg/ml (Tables 1 to 3) and was highly active against carbapenem-resistant *Enterobacteriaceae* (CRE) ($n = 189$; MIC_{50}/MIC_{90}, 0.5 and 2 μg/ml; 97.9% susceptible) and MDR ($n = 674$; MIC_{50}/MIC_{90}, 0.25 and 1 μg/ml; 98.8% susceptible) and XDR ($n = 156$; MIC_{50}/MIC_{90}, 0.5 and 2 μg/ml; 98.1% susceptible) isolates (Tables 1 and 2). Only 8 of 6,209 *Enterobacteriaceae* strains (0.1%) were ceftazidime-avibactam nonsusceptible: three NDM-1-producing strains (two *K. pneumoniae* and one *E. coli*) with ceftazidime-avibactam MIC values of $>$32 μg/ml (Table 4) and five isolates (two *Serratia marcescens*, one *Enterobacter aerogenes*, one *Enterobacter cloacae*, and one *Providencia stuartii*) with ceftazidime-avibactam MIC values of 16 μg/ml and negative results for all β-lactamases tested (data not shown).

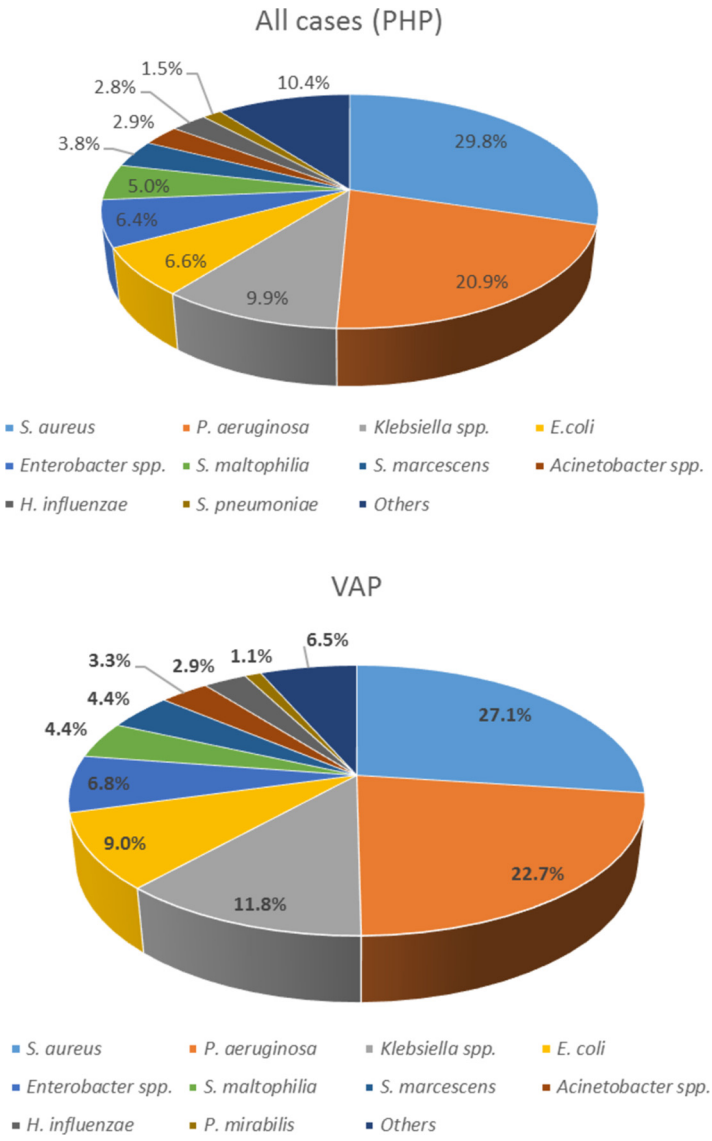

FIG 1 Frequency of occurrence of isolates from PHP in 2015.

An extended-spectrum β-lactamase (ESBL) screening-positive phenotype (defined as a MIC of >1 μg/ml for ceftazidime, ceftriaxone, and/or aztreonam) was observed among 19.2, 20.8, 13.0, and 12.2% of *E. coli*, *K. pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* strains, respectively, and ceftazidime-avibactam retained potent *in vitro* activity against these organisms (Table 1). Ceftazidime-avibactam inhibited 99.5% of *Klebsiella* spp. isolates with an ESBL screening-positive phenotype ($n = 433$; MIC_{50}/MIC_{90}, 0.25 and 1 μg/ml), whereas only 64.7% of the organisms were susceptible to meropenem (Table 2). In addition, 98.7% of meropenem-nonsusceptible *K. pneumoniae* isolates ($n = 150$; MIC_{50}/MIC_{90}, 0.5 and 2 μg/ml) were susceptible to ceftazidime-avibactam (Table 1).

Among *Enterobacter* spp. ($n = 1,304$; 24.8% ceftazidime nonsusceptible), 99.8% of isolates (MIC_{50}/MIC_{90}, 0.12 and 0.5 μg/ml), including 99.4% of ceftazidime-nonsusceptible strains (MIC_{50}/MIC_{90}, 0.25 and 1 μg/ml), were ceftazidime-avibactam susceptible (Table 1). Meropenem and gentamicin were active against 92.9% and 88.6% of ceftazidime-nonsusceptible *Enterobacter* species isolates (Table 2). *E. coli* was the third most common *Enterobacteriaceae* species isolated from PHP and VAP (Fig. 1) and exhibited high rates of susceptibility to ceftazidime-avibactam (99.9%), meropenem (99.6%), and

TABLE 1 Summary of ceftazidime-avibactam activities (MIC distributions) when tested against the main Gram-negative organisms isolated from patients hospitalized with pneumonia in U.S. medical centers (2011 to 2015)

Organism/subset (no. of isolates)[a]	No. of isolates (cumulative %) inhibited at ceftazidime-avibactam MIC (μg/ml) of[b]:											MIC (μg/ml)	
	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	50%	90%
P. aeruginosa (3,402)			96 (2.8)	221 (9.3)	1,152 (43.2)	1,108 (75.7)	503 (90.5)	206 (**96.6**)	68 (98.6)	19 (99.1)	29 (100.0)	2	4
MEM-NS (710)			2 (0.3)	7 (1.3)	69 (11.0)	177 (35.9)	221 (67.0)	137 (**86.3**)	53 (93.8)	17 (96.2)	27 (100.0)	4	16
P/T-NS (743)			2 (0.3)	12 (1.9)	63 (10.4)	176 (34.1)	229 (64.9)	154 (**85.6**)	61 (93.8)	18 (96.2)	28 (100.0)	4	16
CAZ-NS (599)			2 (0.3)	7 (1.5)	52 (10.2)	146 (34.6)	170 (62.9)	106 (**80.6**)	98 (92.0)	19 (95.2)	29 (100.0)	4	16
MEM-NS, P/T-NS, CAZ-NS (299)				1 (0.3)	10 (3.7)	43 (18.1)	87 (47.2)	68 (**69.9**)	48 (86.0)	16 (91.3)	26 (100.0)	8	32
MDR (613)			4 (0.7)	6 (1.6)	46 (9.1)	140 (32.0)	173 (60.2)	138 (**82.7**)	60 (92.5)	18 (95.4)	28 (100.0)	4	16
XDR (365)			1 (0.3)	3 (1.1)	18 (6.0)	61 (22.7)	97 (49.3)	98 (**76.2**)	44 (88.2)	16 (92.6)	27 (100.0)	8	32
Enterobacteriaceae (6,209)	2,264 (36.5)	2,218 (72.2)	1,091 (89.8)	428 (96.7)	144 (99.0)	40 (99.6)	12 (99.8)	4 (**99.9**)	5 (>99.9)	0 (>99.9)	3 (100.0)	0.12	0.5
CRE (189)	11 (5.8)	13 (12.7)	25 (25.9)	55 (55.0)	58 (85.7)	19 (95.8)	3 (97.4)	1 (**97.9**)	1 (98.4)	0 (98.4)	3 (100.0)	0.5	2
MDR (674)	126 (18.7)	115 (35.8)	125 (54.3)	156 (77.4)	103 (92.7)	30 (97.2)	7 (98.2)	4 (**98.8**)	5 (99.6)	0 (99.6)	3 (100.0)	0.25	1
XDR (156)	10 (6.4)	9 (12.3)	18 (23.7)	48 (54.5)	48 (85.3)	12 (96.2)	2 (96.2)	3 (**98.1**)	1 (98.7)	0 (98.1)	2 (100.0)	0.5	2
Klebsiella spp. (2,260)	916 (40.5)	818 (76.7)	292 (89.6)	146 (96.1)	61 (98.8)	21 (99.7)	3 (99.9)	1 (**99.9**)	0 (99.9)	0 (99.9)	2 (100.0)	0.12	0.5
ESBL (433)[c]	53 (12.2)	98 (34.9)	96 (57.0)	99 (79.9)	60 (93.8)	21 (98.6)	3 (99.3)	1 (**99.5**)	0 (99.5)	0 (99.5)	2 (100.0)	0.25	1
MEM-NS KPN (150)	10 (6.7)	11 (14.0)	19 (26.7)	44 (56.0)	45 (86.0)	17 (97.3)	2 (98.7)	0 (**98.7**)	0 (98.7)	0 (98.7)	2 (100.0)	0.5	2
Enterobacter spp. (1,304)	211 (16.2)	551 (58.4)	341 (84.6)	132 (94.7)	54 (98.8)	7 (99.4)	6 (99.8)	0 (**99.8**)	2 (100.0)			0.12	0.5
CAZ-NS (324)	12 (4.6)	40 (17.0)	100 (47.8)	105 (80.2)	49 (95.4)	7 (97.5)	6 (99.4)	0 (**99.4**)	2 (100.0)			0.25	1
E. coli (1,222)	621 (50.8)	423 (85.4)	139 (96.8)	27 (99.0)	9 (99.8)	2 (99.9)	0 (99.9)	0 (**99.9**)	0 (99.9)	0 (99.9)	1 (100.0)	0.12	0.25
ESBL (235)	50 (21.3)	86 (57.9)	71 (88.1)	16 (94.9)	9 (98.7)	2 (99.6)	0 (99.6)	0 (**99.6**)	0 (99.6)	0 (99.6)	1 (100.0)	0.12	0.5
S. marcescens (716)	39 (5.4)	303 (47.8)	263 (84.5)	96 (97.9)	9 (99.2)	4 (99.7)	0 (99.7)	0 (**99.7**)	2 (100.0)			0.25	0.5
P. mirabilis (319)	302 (94.7)	13 (98.7)	1 (99.1)	2 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	1 (**100.0**)				≤0.03	0.06
ESBL (39)	30 (76.9)	6 (92.3)	1 (94.9)	1 (97.4)	0 (97.4)	0 (97.4)	0 (97.4)	1 (**100.0**)				0.06	0.12
Citrobacter spp. (228)	96 (42.1)	74 (74.6)	38 (91.2)	12 (96.8)	8 (100.0)							0.12	0.25
Acinetobacter spp. (443)				1 (0.2)	2 (0.7)	11 (3.2)	64 (17.6)	77 (35.0)	78 (52.6)	72 (68.8)	138 (100.0)	16	>32

[a]MEM-NS, meropenem nonsusceptible (MIC, ≥4 μg/ml for *P. aeruginosa* and ≥2 μg/ml for *Enterobacteriaceae*); P/T-NS, piperacillin-tazobactam nonsusceptible (MIC, ≥16 μg/ml for *P. aeruginosa* and *Enterobacteriaceae*); CAZ-NS, ceftazidime nonsusceptible (MIC, ≥16 μg/ml for *P. aeruginosa* and ≥8 μg/ml for *Enterobacteriaceae*); ESBL, ESBL-screen-positive phenotype (17).

[b]Susceptibility rates are in boldface.

[c]Includes 371 *K. pneumoniae* and 62 *K. oxytoca* isolates.

TABLE 2 Susceptibility rates for ceftazidime-avibactam and comparator antimicrobial agents when tested against Gram-negative organisms isolated from patients hospitalized with pneumonia (all cases combined [PHP] and VAP; United States, 2011 to 2015)

Organism/resistant subset (no. tested [PHP/VAP])[a]	% susceptible[b]											
	CAZ-AVI		Ceftazidime		Meropenem		Piperacillin-tazobactam		Gentamicin		Levofloxacin	
	PHP	VAP	PHP	VAP	PHP	VAP	PHP	VAP	PHP	VAP	PHP	VAP
P. aeruginosa (3,402/415)	96.6	97.8	82.4	85.8	79.1	78.8	78.2	79.5	84.8	90.1	72.5	78.3
MEM-NS (710/88)	86.3	92.0	54.2	64.8	0.0	0.0	42.8	42.0	64.8	72.7	31.8	43.2
P/T-NS (743/85)	85.6	90.6	27.2	38.8	45.3	40.0	0.0	0.0	69.4	80.0	42.8	52.9
CAZ-NS (599/59)	80.6	84.7	0.0	0.0	45.7	47.5	9.7	11.9	67.6	81.4	42.9	62.7
MDR (613/64)	82.7	87.5	31.2	42.2	22.0	10.9	19.1	15.6	48.0	57.8	16.6	28.1
XDR (365/32)	76.2	87.5	21.1	40.6	9.9	6.2	6.6	3.1	38.4	50.0	6.0	6.2
Enterobacteriaceae (6,209/604)	99.9	99.7	85.0	86.6	96.8	97.7	87.6	88.6	91.1	94.0	83.4	87.1
CRE (189/13)	97.9	84.6	5.8	15.4	1.6	0.0	3.2	7.7	54.0	53.8	24.9	46.2
MDR (674/40)	98.8	95.0	26.1	20.0	71.0	67.5	37.1	32.5	44.0	40.0	24.9	37.5
XDR (156/9)	98.1	77.8	2.6	11.1	14.1	22.2	3.8	0.0	36.5	22.0	9.6	0.0
Klebsiella spp. (2,260/196)	99.9	99.0	85.2	88.8	93.2	95.4	86.3	90.3	91.4	93.4	88.0	92.9
ESBL (433/29)	99.5	93.1	22.9	24.1	64.7	69.0	33.6	34.5	58.2	58.6	42.0	62.1
MEM-NS KPN (150/8)	98.7	75.0	2.7	0.0	0.0	0.0	1.3	0.0	57.3	62.5	16.7	37.5
Enterobacter spp. (1,304/145)	99.8	100.0	75.2	73.1	98.2	97.9	79.8	75.2	96.9	98.6	96.2	97.2
CAZ-NS (324/39)	99.4	100.0	0.0	0.0	92.9	94.9	21.0	10.3	88.6	94.9	86.7	92.3
E. coli (1,222/126)	99.9	100.0	86.2	88.1	99.6	99.2	90.5	92.1	84.6	88.0	59.5	61.1
ESBL (235/21)	99.6	100.0	28.1	28.6	97.9	95.2	74.8	81.0	66.8	71.4	18.3	33.3
S. marcescens (716/85)	99.7	100.0	99.7	97.6	98.2	98.8	93.3	96.5	96.6	97.6	96.1	96.5
P. mirabilis (319/24)	100.0	100.0	95.9	100.0	99.7	100.0	99.7	100.0	84.6	91.7	66.1	87.5
ESBL (39/−)	100.0		66.7		97.4		100.0		48.7		33.3	
Citrobacter spp. (228/19)	100.0	100.0	85.1	84.2	98.7	100.0	90.3	94.7	95.2	100.0	94.3	94.7
Acinetobacter spp. (443/39)	35.0[c]	38.5[c]	37.5	51.3	41.5	56.4	32.3	43.6	45.6	64.1	36.1	51.3

[a]MEM-NS, meropenem nonsusceptible (MIC, ≥4 μg/ml for *P. aeruginosa* and ≥2 μg/ml for *Enterobacteriaceae*); P/T-NS, piperacillin-tazobactam nonsusceptible (MIC, ≥16 μg/ml); CAZ-NS, ceftazidime nonsusceptible (MIC, ≥16 μg/ml for *P. aeruginosa* and ≥8 μg/ml for *Enterobacteriaceae*); ESBL, ESBL-screen-positive phenotype.
[b]U.S. FDA (CAZ-AVI [ceftazidime-avibactam]) or CLSI breakpoint criteria.
[c]Percentage inhibited at ≤8/4 μg/ml.

piperacillin-tazobactam (90.5%) (Table 2). In general, susceptibility rates among *Enterobacteriaceae* isolates from VAP were similar to or slightly higher than those from all PHP (Table 2), and no substantial yearly variation in susceptibility rates was noted (data not shown).

Ceftazidime-avibactam activity against *K. pneumoniae* ($n = 371$) and *E. coli* ($n = 235$) strains showing an ESBL screening-positive phenotype and stratified by β-lactamase production is presented in Table 4. The most common β-lactamases detected among *K. pneumoniae* isolates with an ESBL screening-positive phenotype (CLSI criteria) was KPC-like. A KPC-like-encoding gene was detected in 125 isolates (33.7%), and approximately half of the isolates (57/123; 46.3%) produced an ESBL and/or a plasmidic AmpC enzyme in addition to the KPC. The highest ceftazidime-avibactam MIC value among KPC-producing *K. pneumoniae* strains was only 2 μg/ml (MIC_{50}/MIC_{90}, 0.5 and 2 μg/ml) (Table 4). The second and third most common β-lactamases produced by *K. pneumoniae* were CTX-M-15 ($n = 105$ [28.3%]; ceftazidime-avibactam MIC_{50}/MIC_{90}, 0.25 and 1 μg/ml) and SHV-ESBL ($n = 58$ [15.6%]; MIC_{50}/MIC_{90}, 0.12 and 2 μg/ml), and only two isolates (0.5% of strains showing an ESBL screening-positive phenotype) produced an MBL, both NDM-1 (12) (Table 4). Among *E. coli* strains, CTX-M-15-like (113 strains [48.1%] and CTX-M-14 (46 strains [19.6%]) were the most common ESBLs detected. Furthermore, CMY-2-like was detected in 23 strains (9.8%), and only one strain (0.8%) produced an MBL (NDM-1). The highest ceftazidime-avibactam MIC value among *E. coli* isolates producing CTX-M-15, CTX-M-14, and/or CMY-2-like was only 1 μg/ml (Table 4).

Only colistin (MIC_{50}/MIC_{90}, 1 and 2 μg/ml; 93.7% susceptible) exhibited good *in vitro*

TABLE 3 Activities of ceftazidime-avibactam and comparator antimicrobial agents when tested against Gram-negative organisms isolated from patients hospitalized with pneumonia (United States, 2011 to 2015)

Organism/antimicrobial agent (no. of isolates)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	CLSI[a]			EUCAST[a]		
			% S	% I	% R	% S	% I	% R
P. aeruginosa (3,402)								
Ceftazidime-avibactam	2	4	96.6		3.4[b]	96.6		3.4
Ceftazidime	2	32	82.4	4.6	13.0	82.4		17.6
Cefepime	4	16	83.4	10.0	6.6	83.4		16.6
Piperacillin-tazobactam	4	>64	78.2	10.6	11.3	78.2		21.8
Meropenem	0.5	8	79.1	7.0	13.9	79.1	13.7	7.1
Imipenem	1	8	71.9	9.4	18.8	81.2	15.6	3.1
Ciprofloxacin	0.25	>4	75.6	6.5	18.0	68.3	7.3	24.4
Levofloxacin	0.5	>4	72.5	8.0	19.5	61.9	10.6	27.5
Gentamicin	2	>8	84.8	4.8	10.4	84.8		15.2
Amikacin	4	16	95.3	1.8	2.8	89.9	5.4	4.7
Colistin	1	2	99.6	0.3	0.1	99.9		0.1
Enterobacteriaceae (6,209)								
Ceftazidime-avibactam	0.12	0.5	99.9		0.1[b]	99.9		0.1
Ceftazidime	0.25	32	85.0	1.5	13.5	82.2	2.9	15.0
Ceftriaxone	0.12	>8	80.7	1.3	18.0	80.7	1.3	18.0
Cefepime	0.06	8	88.0	3.2	8.8[b]	85.9	3.7	10.4
Ampicillin-sulbactam	16	>32	45.0	17.2	37.8	45.0		55.0
Piperacillin-tazobactam	2	64	87.6	4.8	7.6	83.0	4.6	12.4
Meropenem	≤0.06	≤0.06	96.8	0.5	2.8	97.2	1.0	1.7
Imipenem	≤0.12	1	94.3	2.4	3.3	96.7	1.8	1.5
Aztreonam	≤0.12	>16	84.5	1.4	14.1	82.4	2.1	15.5
Ciprofloxacin	≤0.03	>4	81.8	1.6	16.7	77.3	2.7	20.0
Levofloxacin	≤0.12	>4	83.4	1.7	14.9	79.1	2.7	18.2
Gentamicin	≤1	4	91.1	1.6	7.2	89.7	1.4	8.9
Amikacin	1	4	98.3	1.3	0.4	97.1	1.2	1.7
Tigecycline	0.25	1	98.5	1.5	<0.1[b]	93.5	5.0	1.5
Colistin	≤0.5	>8				77.3		22.7
A. baumannii (443)								
Ceftazidime-avibactam	16	>32						
Ceftazidime	>32	>32	37.5	4.1	58.5			
Cefepime	>16	>16	36.7	11.3	52.0			
Ampicillin-sulbactam	16	>32	48.5	15.4	36.1			
Piperacillin-tazobactam	>64	>64	32.3	9.8	58.0			
Meropenem	>8	>8	41.5	1.8	56.7	41.5	7.4	51.0
Ciprofloxacin	>4	>4	34.3	0.7	65.0	34.3		65.7
Levofloxacin	>4	>4	36.1	2.3	61.6	35.2	0.9	63.9
Gentamicin	>8	>8	45.6	4.1	50.3	45.6		54.4
Amikacin	8	>32	63.4	3.4	33.2	59.5	3.9	36.6
Colistin	1	2	93.7		6.3	93.7		6.3

[a]Criteria as published by CLSI (17) and EUCAST (14). R, resistant; I, intermediate; S, susceptible.
[b]Breakpoint from FDA package inserts (10, 20).

activity against *Acinetobacter baumannii* isolates (Table 3). Amikacin, the second most active compound, was active against only 63.4% of strains at the CLSI susceptible breakpoint, and all the other compounds had susceptibility rates of less than 50.0% (Table 3).

DISCUSSION

Prompt initiation of appropriate antimicrobial therapy is critical for the management of PHP, especially those with VAP, and empirical antimicrobial regimens should be guided primarily by an understanding of the causative pathogens and their antimicrobial resistance profiles (2). The frequency of occurrence of organisms observed in the present study for PHP is very similar to that reported for health care-associated pneumonia (HAP) and VAP by other investigators (2, 3, 6, 13). Although we were not able to separate community-acquired bacterial pneumonia (CABP) that required hospitalization from HAP, the fact that the main organisms responsible for

TABLE 4 Ceftazidime-avibactam activity stratified by organism β-lactamase production

Organism/β-lactamase (no. of isolates)	No. of isolates (cumulative %) inhibited at ceftazidime-avibactam MIC (μg/ml) of:										MIC (μg/ml)	
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8[a]	50%	90%
K. pneumoniae (371)	23 (6.2)	25 (12.9)	76 (33.4)	80 (55.0)	84 (77.6)	58 (93.3)	21 (98.9)	2 (99.5)	0 (99.5)	2 (100.0)	0.25	1
KPC-like (125)	5 (4.0)	5 (8.0)	9 (15.2)	19 (30.4)	34 (57.6)	40 (89.6)	13 (100.0)				0.5	2
CTX-M-15 (105)	7 (6.7)	9 (15.2)	29 (42.9)	29 (70.5)	18 (87.6)	12 (99.0)	1 (100.0)				0.25	1
SHV ESBL (59)	9 (15.3)	4 (22.0)	18 (52.5)	11 (71.2)	14 (94.9)	0 (94.9)	3 (100.0)				0.12	2
Metallo-β-lactamases (2)[b]										2 (100.0)	1	
Others (17)[c]		4 (23.5)	3 (41.2)	5 (70.6)	3 (88.2)	1 (94.1)	0 (94.1)	1 (100.0)			0.25	1
Negative (57)[d]	2 (3.5)	3 (8.8)	15 (35.1)	14 (59.7)	13 (82.4)	5 (91.2)	4 (98.2)	1 (100.0)			0.25	1
E. coli (235)	18 (7.7)	32 (21.3)	86 (57.9)	71 (88.1)	16 (94.9)	9 (98.7)	2 (99.6)	0 (99.6)	0 (99.6)	1 (100.0)	0.12	0.5
CTX-M-15 (113)	7 (6.2)	14 (18.6)	49 (61.9)	28 (86.7)	10 (95.6)	5 (100.0)					0.12	0.5
CTX-M-14 (46)	4 (8.7)	9 (28.3)	21 (73.9)	10 (95.7)	1 (97.8)	1 (100.0)					0.12	0.25
CMY-2 (23)	3 (13.0)	3 (26.1)	4 (43.5)	12 (95.7)	0 (95.7)	1 (100.0)					0.25	0.25
TEM-ESBL (9)	1 (11.1)	1 (22.2)	0 (22.2)	6 (88.9)	1 (100.0)						0.25	
SHV-ESBL (6)		2 (33.3)	0 (33.3)	3 (83.3)	1 (100.0)						0.25	
KPC-like (3)			1 (33.3)	2 (100.0)							0.25	
NDM-1 (1)										1 (100.0)		
Others (9)[e]			2 (22.2)	4 (66.7)	2 (88.9)	0 (88.9)	1 (100.0)				0.25	1
Negative (25)[d]	3 (12.0)	3 (24.0)	9 (60.0)	6 (84.0)	1 (8.0)	2 (96.0)	1 (100.0)				0.12	0.25

[a]All three isolates are NDM-1 producers with ceftazidime-avibactam MIC values of >32 μg/ml.
[b]Includes two isolates with NDM-1 (12).
[c]Includes isolates with CTX-M-14 (6); CTX-M-14 and SHV-ESBL (4); CTX-M-15 and SHV-ESBL (4); CTX-M-15, SHV-ESBL, and OXA-1/30 (1); SHV-ESBL and DHA-like (1); and SVH-ESBL, TEM-ESBL, and CMY-2 (1).
[d]Negative results by Check-Points for the following genes: CTX-M groups 1, 2, 8 plus 25, and 9; TEM ESBL; SHV ESBL; ACC; ACT/MIR; CMYII; DHA; FOX; KPC; and NDM-1.
[e]Includes isolates with CTX-M-15 and CMY-2 (3); CTX-M-15 and CTX-M-14 (2); CTX-M-15, CMY-2, and OXA-1/30 (1); CTX-M-14 and TEM-ESBL (1); SHV-ESBL and CMY-2 (1); and FOX-like (1).

CABP, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, represented a small percentage of isolates from PHP indicates that the vast majority of cases included in the study were HAP.

Interestingly, the frequency of occurrence of organisms isolated from VAP did not differ significantly from that observed with PHP. The top nine organisms were the same in both groups, with only small differences in the frequencies. It is important to note that the Gram-negative organisms were isolated from 66.0% of PHP and 70.5% of VAP cases in 2015, and *P. aeruginosa* and *Enterobacteriaceae* species comprised the vast majority of Gram-negative organisms.

In the present study, the antimicrobial susceptibilities of 11,185 Gram-negative isolates consecutively collected from hospitalized patients with pneumonia in U.S. medical centers were evaluated, and the results indicated that very few agents remain active against the most frequently isolated organisms. The carbapenems (meropenem and imipenem) and piperacillin-tazobactam showed only moderate coverage against *P. aeruginosa* and very limited activity against *Klebsiella* spp. with an ESBL screening-positive phenotype. Meropenem was active against only 79.1% of *P. aeruginosa* isolates and 64.7% of ESBL screening-positive phenotype *Klebsiella* spp.

Among other antimicrobial classes (non-β-lactams), the aminoglycosides were the most active compounds overall. Amikacin remained active against *P. aeruginosa* (95.3% and 89.9% susceptible by CLSI/EUCAST criteria) and *Enterobacteriaceae* (98.3% and 97.1% susceptible by CLSI/EUCAST criteria), whereas susceptibility rates for gentamicin were slightly lower (84.8% for *P. aeruginosa* and 91.1% for *Enterobacteriaceae* [CLSI]). Colistin exhibited good activity against *P. aeruginosa* and *A. baumannii* but was active against only 77.3% of *Enterobacteriaceae* isolates at the EUCAST susceptible breakpoint of ≤2 μg/ml (14). In contrast, tigecycline showed good *in vitro* activity against *Enterobacteriaceae* but very limited activity against *P. aeruginosa* (data not shown). Lastly, the fluoroquinolones levofloxacin and ciprofloxacin exhibited only moderate activity against *P. aeruginosa* and *Enterobacteriaceae*. Thus, no other agent tested provided better overall coverage than ceftazidime-avibactam.

The molecular characterization of *Enterobacteriaceae* isolates showing an ESBL

screening-positive phenotype (i.e., MIC, >1 μg/ml for ceftriaxone, ceftazidime, or aztreonam) revealed interesting results. Among *K. pneumoniae*, one-third of the isolates (125/371) produced a KPC-like β-lactamase, which confers resistance to all β-lactams and β-lactamase inhibitor combinations currently available for clinical use in the United States, except ceftazidime-avibactam. Furthermore, an MBL-encoding gene was detected in only two *K. pneumoniae* isolates (0.5%) (12). Among *E. coli* isolates, two-thirds of the isolates produced CTX-M-15-like or CTX-M-14-like (159/235), and only one MBL-producing strain was detected. In summary, ceftazidime-avibactam was highly active against all β-lactamase-producing *Enterobacteriaceae* except three MBL-producing strains (all NDM-1 producers), which still remain very uncommon in U.S. medical centers.

The selection of appropriate antimicrobials should consider local microbial epidemiology, patient risk factors for MDR organisms, and patient-specific characteristics that may influence treatment options. Although resistance rates and microbial epidemiology may vary substantially from hospital to hospital, results from a large, well-monitored surveillance network, such as those presented here, can provide useful information by detecting signs of emerging pathogen populations/resistance patterns, as well as trends of antimicrobial resistance mechanisms. Limitations of the study include the lack of differentiation between CABP that needs hospitalization and HAP; thus, it is possible that some of the comparators may have shown better activity against the subset of isolates from patients hospitalized with CABP than against the organism collection evaluated in this investigation. Another limitation of the study is the fact that the criteria used to categorize a bacterial isolate as "clinically significant" were not defined in the study protocol and were based on local algorithms, which may vary among participating medical centers. However, it is very unlikely that these limitations introduced significant bias into the study. It is also important to note that avibactam does not inhibit metallo-β-lactamases, and ceftazidime-avibactam may be less active against MDR and XDR *Enterobacteriaceae* in geographic regions where these β-lactamases are more prevalent. Despite the limitations of the study, the results presented here indicate that ceftazidime-avibactam is very active against the vast majority of *P. aeruginosa* and *Enterobacteriaceae* isolates from patients with pneumonia hospitalized in U.S. medical centers, including isolates showing MDR and XDR phenotypes. These *in vitro* results support further development of ceftazidime-avibactam for treatment of HAP and VAP in the United States.

MATERIALS AND METHODS

Bacterial isolates. Isolates were collected from 76 medical centers distributed among 37 states from all nine U.S. census regions in 2011 to 2015 as part of the International Network for Optimal Resistance Monitoring (INFORM) program (15). Each participating center was requested to collect consecutive bacterial isolates from lower respiratory tract sites determined to be significant by local criteria as the reported probable cause of pneumonia. Only isolates from invasive sampling (transtracheal aspiration, bronchoalveolar lavage, protected brush samples, qualified sputum samples, etc.) were accepted. Although all bacterial species were collected, the INFORM program evaluates the antimicrobial susceptibility of only *Enterobacteriaceae*, *P. aeruginosa*, and *A. baumannii*. Therefore, the frequency of occurrence of organisms described in Results above was based on all the organisms collected from PHP in the same participating medical centers in 2015 (n = 5,417, including 543 from VAP). Species identification was confirmed by standard biochemical tests and using the MALDI Biotyper (Bruker Daltonics, Billerica, MA, USA) according to the manufacturer's instructions where necessary.

Susceptibility testing. Broth microdilution test methods were conducted according to the CLSI guidelines to determine the antimicrobial susceptibility of ceftazidime-avibactam (inhibitor at a fixed concentration of 4 μg/ml) and comparator agents (16). Concurrent quality control (QC) testing was performed to ensure proper test conditions and procedures. The QC strains included *E. coli* ATCC 25922 and 35218, *K. pneumoniae* ATCC 700603, and *P. aeruginosa* ATCC 27853. All QC results were within published ranges. CLSI and EUCAST susceptibility interpretive criteria (M100-S26) (14, 17) were used to determine susceptibility and resistance rates for comparator agents. Furthermore, U.S. FDA and EUCAST breakpoint criteria were applied for ceftazidime-avibactam when testing *Enterobacteriaceae* and *P. aeruginosa*, i.e., susceptible at ≤8 μg/ml and resistant at ≥16 μg/ml (10, 14).

Resistant subsets. *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *P. mirabilis* isolates were grouped as "ESBL screening-positive phenotype" based on the CLSI screening criteria for ESBL production, i.e., a MIC of >1 μg/ml for ceftazidime, ceftriaxone, and/or aztreonam (17), for the purpose of analysis of susceptibility testing results. Although other β-lactamases, such as AmpC and KPC, may also produce an ESBL screening-positive phenotype, these strains were grouped together because they usually demonstrate resistance to various broad-spectrum β-lactam compounds. CRE was defined as resistant (MIC, ≥4 μg/ml [CLSI]) to imipenem (imipenem was not applied to *P. mirabilis* and indole-positive Proteeae), meropenem,

or doripenem. Further, isolates were categorized as MDR, XDR, or pan-drug-resistant (PDR) according to criteria published by Magiorakos et al. (18), i.e., MDR is defined as nonsusceptible to ≥1 agent in ≥3 antimicrobial classes, XDR as nonsusceptible to ≥1 agent in all but ≤2 antimicrobial classes, and PDR as nonsusceptible (CLSI criteria) to all antimicrobial classes tested. The antimicrobial classes and representative drugs used in the analysis were broad-spectrum cephalosporins (ceftriaxone, ceftazidime, and cefepime), carbapenems (imipenem, meropenem, and doripenem), broad-spectrum penicillin combined with a β-lactamase inhibitor (piperacillin-tazobactam), fluoroquinolones (ciprofloxacin and levofloxacin), aminoglycosides (gentamicin, tobramycin, and amikacin), glycylcyclines (tigecycline), and the polymyxins (colistin) (EUCAST criteria) for *Enterobacteriaceae*, and 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), and the polymyxins (colistin) for *P. aeruginosa*.

Screening for β-lactamases. *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *P. mirabilis* isolates displaying the CLSI ESBL phenotypic criteria described above 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. The kit has the capability to detect CTX-M groups 1, 2, 8 plus 25, and 9; TEM wild type (WT) and ESBL; SHV WT and ESBL; ACC; ACT/MIR; CMYII; DHA; FOX; KPC; and NDM-1 (19).

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