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Ceftazidime/avibactam activity tested against Gram-negative bacteria isolated from bloodstream, pneumonia, intra-abdominal and urinary tract infections in US medical centres (2012)

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Objectives: The activity of ceftazidime/avibactam and comparator agents was monitored at 73 medical centres across all nine US census bureau regions during 2012.

Methods: Bacterial isolates were collected from patients hospitalized with pneumonia, urinary tract infections (UTI), intra-abdominal infections (IAI) and bloodstream infections (BSI). The study protocol predetermined the target numbers of strains for each of the requested bacterial species that sites were to collect. Isolates were determined to be clinically relevant at the medical centre and only one isolate per patient episode was collected.

Results: There were 1466 Gram-negative isolates from BSI, 3245 from pneumonia patients, 501 from IAI and 2356 from UTI. Ceftazidime/avibactam was active against Enterobacteriaceae from each infection type. The MIC_{90} values for ceftazidime/avibactam against Enterobacteriaceae isolates from BSI, pneumonia patients, IAI or UTI were 0.25 mg/L. The extended-spectrum cephalosporin resistance rates for *Escherichia coli* were 8.5% (UTI), 10.4% (IAI), 12.7% (BSI) and 17.5% (pneumonia patients). The extended-spectrum cephalosporin resistance rates for *Klebsiella* spp. were 13.0% (UTI), 13.9% (BSI), 16.3% (IAI) and 19.3% (pneumonia patients). A total of 96.5% of the *Pseudomonas aeruginosa* isolates from BSI, 95.8% from pneumonia patients, 96.3% from IAI and 98.7% from UTI exhibited a ceftazidime/avibactam MIC of ≤8 mg/L (CLSI susceptible breakpoint for ceftazidime when tested alone against *P. aeruginosa*). Most tested agents showed limited activity against *Acinetobacter baumannii*, except for colistin. A total of 31.2% of *A. baumannii* displayed ceftazidime/avibactam MIC values of ≤8 mg/L.

Conclusions: Ceftazidime/avibactam demonstrated potent broad-spectrum activity against Gram-negative pathogens collected in the USA during 2012 from BSI, pneumonia patients, IAI and UTI.

Keywords: *Pseudomonas aeruginosa*, Enterobacteriaceae, β-lactamase inhibitors

Introduction

Ceftazidime/avibactam is an investigational intravenous antimicrobial that consists of a combination of ceftazidime and the novel non-β-lactam β-lactamase inhibitor avibactam. Avibactam has little intrinsic antibacterial activity; however, it has a high degree of affinity for class A, class C and some class D β-lactamases.[1–5] In combination, avibactam prevents or reduces ceftazidime hydrolysis, thus allowing ceftazidime to remain active.[6–11] Ceftazidime/avibactam has been studied in patients with complicated urinary tract infections (UTI) and has been shown to have efficacy and safety similar to the comparator agent imipenem/cilastatin.[12] It has also been studied in patients with complicated intra-abdominal infections (IAI), where ceftazidime/avibactam plus metronidazole was found to be effective and well tolerated, similar to meropenem.[13]

Gram-negative bacterial resistance to currently used antimicrobial agents is a significant problem.[14–17] The Infectious Diseases Society of America (IDSA) has specifically identified certain organisms (ESKAPE pathogens) as increasing in occurrence and causing significant morbidity and mortality.[14,17] Included among these organisms are ESBL-producing *Escherichia coli* and *Klebsiella* spp., carbapenemase-producing *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp.[14,17]

In this report, we present the results of a surveillance study to evaluate the activity of ceftazidime/avibactam and comparator agents tested against contemporary Gram-negative bacterial

isolates in US medical centres from patients hospitalized with bloodstream infections (BSI), pneumonia, IAI and UTI in an effort to characterize the current activity of this novel combination. These data will provide baseline results to use as sentinel monitoring of resistance to this investigational combination agent.

Materials and methods

Bacteria tested

Organisms were collected from patients hospitalized with pneumonia, UTI, IAI and BSI at US medical centres during 2012. All isolates were determined to be clinically relevant at the medical centre and only one isolate per patient episode was collected. The study protocol predetermined the target numbers of strains for each of the requested bacterial species that sites were to collect. A total of 73 medical centres representing all nine US census bureau regions submitted isolates. Isolates were referred to a central coordinating laboratory (JMI Laboratories, North Liberty, IA, USA) for confirmatory identification and reference susceptibility testing.

Susceptibility testing methods

The susceptibility of all organisms to ceftazidime/avibactam and comparator agents was tested by reference broth microdilution at the coordinating laboratory using custom dry-form panels produced by Thermo Fisher (formerly TREK Diagnostics; Cleveland, OH, USA) following CLSI methods (M07-A9[18] and M45-A2[19]). *Haemophilus* spp. were tested in Haemophilus Test Medium (M07-A9[18]). *Moraxella catarrhalis* and *Haemophilus influenzae* were also tested in frozen-form reference panels produced at JMI Laboratories (M07-A9[18] and M45-A2[19]). Avibactam was tested at a fixed concentration of 4 mg/L. CLSI interpretive criteria were applied as per M100-S23.[20] US FDA breakpoint criteria for tigecycline were applied when available.[21]

Quality control strains were tested concurrently and included: *E. coli* ATCC 25922 and 35218; *H. influenzae* ATCC 49247 and 49766; and *P. aeruginosa* ATCC 27853. All quality control results were within published CLSI ranges.[20] *E. coli* and *Klebsiella* spp. isolates that exhibited ceftriaxone and/or ceftazidime and/or aztreonam MIC values ≥2 mg/L were defined as extended-spectrum cephalosporin resistant.[20]

Results

Ceftazidime/avibactam was highly active against Enterobacteriaceae from each of the infection types evaluated. A total of 99.8% of Enterobacteriaceae isolates from BSI, 99.4% from pneumonia patients and 100.0% from IAI and UTI exhibited a ceftazidime/avibactam MIC of ≤4 mg/L, which is the CLSI[20] susceptible breakpoint for ceftazidime when tested alone against Enterobacteriaceae (Table 1). The highest susceptibility rates for Enterobacteriaceae from BSI were to meropenem (99.0% susceptible) and tigecycline (98.6%; Table 2). A total of 99.8% of ceftazidime/avibactam MIC values were ≤4 mg/L. Susceptibility rates for Enterobacteriaceae from pneumonia patients to the various antimicrobials were generally similar to or slightly lower than for BSI (Table 2). For IAI isolates, meropenem, tigecycline and ceftazidime/avibactam remained highly active (Table 2). For UTI isolates, susceptibility rates of >90% were exhibited for meropenem, tigecycline, gentamicin, piperacillin/tazobactam and ceftazidime (Table 2).

For *E. coli*, ceftazidime/avibactam was highly active against isolates from BSI, IAI, pneumonia and UTI (Table 2). Susceptibility rates of >90% for isolates from each of the four infection types were exhibited for meropenem (99.7%–100.0% of isolates susceptible) and tigecycline (100.0%; Table 2). Ceftazidime/avibactam MIC values for all *E. coli* were ≤4 mg/L. By contrast, for all four infection types, levofloxacin non-susceptibility ranged from 23.1% to 44.8% and gentamicin non-susceptibility from 11.0% to 18.4% (Table 2). The *E. coli* extended-spectrum cephalosporin-resistant phenotype occurred in 8.5% (UTI), 10.4% (IAI), 12.7% (BSI) and 17.5% of isolates from pneumonia patients (Table 2). Susceptibility rates to all tested agents except tigecycline were lower for the isolates with an extended-spectrum cephalosporin-resistant phenotype compared with the non-extended-spectrum cephalosporin-resistant phenotype. For ceftazidime/avibactam, MIC_{90} values for the extended-spectrum cephalosporin-resistant phenotype *E. coli* remained low and ranged from 0.25 to 0.5 mg/L for isolates from each of the four infection types (Table 2) compared with 0.12 mg/L for non-extended-spectrum cephalosporin-resistant phenotype *E. coli* (data not shown). A total of >99.9% of *E. coli* isolates had ceftazidime/avibactam MIC values ≤1 mg/L (there was one BSI isolate with an MIC of 2 mg/L; data not shown). Rates of susceptibility to meropenem were high (>98%) for extended-spectrum cephalosporin-resistant phenotype *E. coli* from each of the infection types (Table 2).

For *Klebsiella* spp., ceftazidime/avibactam, meropenem and tigecycline were highly active against isolates from each of the four infection types tested (Table 2). Against *Klebsiella* spp. isolated from BSI, IAI and UTI, ceftazidime/avibactam MIC values were ≤4 mg/L (data not shown). There were two isolates from pneumonia patients, both meropenem-resistant *K. pneumoniae* with ceftazidime/avibactam MIC values >32 mg/L; the remainder of the *Klebsiella* spp. isolates from pneumonia patients (99.7%) had ceftazidime/avibactam MIC values ≤4 mg/L (data not shown). The *Klebsiella* spp. extended-spectrum cephalosporin-resistant phenotype occurred in 13.0% (UTI), 13.9% (BSI), 16.3% (IAI) and 19.3% of isolates from pneumonia patients (Table 2). Susceptibility rates to ceftazidime, ceftriaxone, meropenem, piperacillin/tazobactam, levofloxacin and gentamicin were much lower for the extended-spectrum cephalosporin-resistant phenotype isolates compared with the non-extended-spectrum cephalosporin-resistant phenotype isolates. For ceftazidime/avibactam, MIC_{90} values for the extended-spectrum cephalosporin-resistant phenotype *Klebsiella* spp. ranged from 1 to 2 mg/L for isolates from each of the four infection types (Table 2) compared with 0.25 mg/L for non-extended-spectrum cephalosporin-resistant phenotype isolates (data not shown). A total of 99.2% of extended-spectrum cephalosporin-resistant phenotype *Klebsiella* spp. isolates displayed ceftazidime/avibactam MIC values ≤2 mg/L, with only two isolates with a higher value, both >32 mg/L (data not shown).

Ceftazidime/avibactam was highly potent against a variety of other species of Enterobacteriaceae from each of the four infection types (Table 2), including *Enterobacter* spp., *Citrobacter* spp., *Morganella morganii*, *Proteus mirabilis* and *Serratia marcescens* (Table 2). Meropenem and tigecycline were highly active against Enterobacteriaceae isolates from each of the four infection types, with the exception of tigecycline activity against *P. mirabilis* isolates from UTI (77.8% susceptible; Table 2).

Against *P. aeruginosa*, the $MIC_{50/90}$ for ceftazidime/avibactam tested against isolates from either BSI or pneumonia patients was 2/8 mg/L (Tables 1 and 3). A total of 96.5% of isolates from BSI, 95.8% from pneumonia patients, 96.3% from IAI and 98.7% from UTI showed a ceftazidime/avibactam MIC of ≤8 mg/L,

Table 1. Summary of ceftazidime/avibactam and ceftazidime (alone) activity tested against selected Gram-negative bacterial isolates from patients at US medical centres (2012)

Organism	Infection type (*n*)	Antimicrobial	No. of isolates (cumulative %) inhibited at MIC (mg/L) of:											MIC_{50} (mg/L)	MIC_{90} (mg/L)
			≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	≥32		
Enterobacteriaceae	BSI (1269)	ceftazidime/avibactam	121 (11.7)	464 (48.2)	450 (83.7)	137 (94.5)	53 (98.7)	12 (99.6)	3 (99.8)	0 (99.8)	1 (99.9)	1 (100.0)	—	0.12	0.25
		ceftazidime	26 (2.0)	201 (17.9)	428 (51.6)	295 (74.9)	111 (83.6)	31 (86.1)	15 (87.2)	9 (87.9)	22 (89.7)	36 (92.5)	34 (100.0)	0.12	16
	pneumonia (1738)	ceftazidime/avibactam	125 (8.9)	460 (35.3)	682 (74.6)	280 (90.7)	100 (96.4)	44 (99.0)	6 (99.3)	1 (99.4)	6 (99.7)	3 (99.9)	2 (100.0)	0.12	0.25
		ceftazidime	48 (2.8)	241 (16.6)	514 (46.2)	409 (69.7)	185 (80.4)	45 (83.0)	27 (84.5)	17 (85.5)	24 (86.9)	33 (88.8)	195 (100.0)	0.25	32
	IAI (410)	ceftazidime/avibactam	36 (11.5)	122 (41.2)	157 (79.5)	43 (90.0)	28 (96.8)	10 (99.3)	3 (100.0)	—	—	—	—	0.12	0.25
		ceftazidime	12 (2.9)	46 (14.1)	143 (49.0)	91 (71.2)	38 (80.5)	17 (84.6)	4 (85.6)	2 (86.1)	6 (87.6)	7 (89.3)	44 (100.0)	0.25	32
	UTI (2188)	ceftazidime/avibactam	309 (17.0)	771 (52.3)	731 (85.7)	208 (95.2)	75 (98.6)	22 (99.6)	3 (99.8)	4 (100.0)	1 (100.0)	—	—	0.06	0.25
		ceftazidime	79 (3.6)	405 (22.1)	774 (57.5)	492 (80.0)	154 (87.0)	53 (89.4)	34 (91.0)	18 (91.8)	23 (92.9)	29 (94.2)	127 (100.0)	0.12	2
P. aeruginosa	BSI (141)	ceftazidime/avibactam				1 (0.7)	4 (3.5)	56 (43.3)	46 (75.9)	18 (88.7)	11 (96.5)	1 (97.2)	4 (100.0)	2	8
		ceftazidime					2 (1.4)	13 (10.6)	70 (60.3)	25 (78.0)	7 (83.0)	2 (84.4)	22 (100.0)	2	>32
	pneumonia (881)	ceftazidime/avibactam		3 (0.3)	2 (0.6)	15 (2.3)	59 (9.0)	312 (44.4)	265 (74.5)	132 (89.4)	56 (95.8)	25 (98.6)	12 (100.0)	2	8
		ceftazidime		1 (0.1)	2 (0.3)	2 (0.6)	30 (4.0)	143 (20.2)	328 (57.4)	133 (72.5)	61 (79.5)	45 (84.6)	136 (100.0)	2	32
	IAI (82)	ceftazidime/avibactam						35 (42.7)	30 (79.3)	11 (92.7)	3 (96.3)	2 (98.8)	1 (100.0)	2	4
		ceftazidime						11 (13.4)	39 (61.0)	12 (75.6)	8 (85.4)	1 (86.6)	11 (100.0)	2	32
	UTI (155)	ceftazidime/avibactam					9 (5.8)	47 (36.1)	63 (76.8)	23 (91.6)	11 (98.7)	1 (99.4)	1 (100.0)	2	4
		ceftazidime					5 (3.2)	18 (14.8)	70 (60.0)	30 (79.4)	16 (89.7)	6 (93.5)	10 (100.0)	2	16

Table 2. Activity of ceftazidime/avibactam and comparator antimicrobial agents tested against Enterobacteriaceae from patients with BSI, pneumonia, IAI and UTI at US medical centres (2012)

	BSI			Pneumonia			IAI			UTI		
	MIC (mg/L)			MIC (mg/L)			MIC (mg/L)			MIC (mg/L)		
Organism/antimicrobial agent	MIC_{50}	MIC_{90}	percentage susceptible[a]	MIC_{50}	MIC_{90}	percentage susceptible[a]	MIC_{50}	MIC_{90}	percentage susceptible[a]	MIC_{50}	MIC_{90}	percentage susceptible[a]
Enterobacteriaceae	*n*=1269			*n*=1738			*n*=410			*n*=2188		
ceftazidime/avibactam	0.12	0.25	—	0.12	0.25	—	0.12	0.25	—	0.06	0.25	—
ceftazidime	0.12	16	87.9	0.25	32	85.5	0.25	32	86.1	0.12	2	91.8
ceftriaxone	≤0.06	>8	85.2	0.12	>8	82.1	≤0.06	>8	82.9	≤0.06	4	88.8
piperacillin/tazobactam	2	16	91.9	2	64	87.1	2	32	88.5	2	8	94.5
meropenem	≤0.06	≤0.06	99.0	≤0.06	≤0.06	97.4	≤0.06	≤0.06	97.8	≤0.06	≤0.06	98.8
levofloxacin	≤0.12	>4	80.3	≤0.12	>4	80.1	≤0.12	>4	81.7	≤0.12	>4	81.7
gentamicin	≤1	8	89.7	≤1	8	89.8	≤1	8	89.5	≤1	4	90.1
tigecycline[b]	0.25	1	98.6	0.25	1	98.7	0.25	1	97.8	0.25	1	97.9
E. coli	*n*=568			*n*=355			*n*=164			*n*=913		
ceftazidime/avibactam	0.06	0.12	—	0.12	0.25	—	0.06	0.12	—	0.06	0.12	—
ceftazidime	0.12	4	90.3	0.25	16	88.2	0.12	1	92.1	0.12	0.5	94.6
ceftriaxone	≤0.06	>8	87.9	≤0.06	>8	84.8	≤0.06	8	89.6	≤0.06	0.25	92.2
piperacillin/tazobactam	2	8	94.5	2	32	89.2	2	8	94.5	2	8	97.5
meropenem	≤0.06	≤0.06	99.8	≤0.06	≤0.06	99.7	≤0.06	≤0.06	100.0	≤0.06	≤0.06	99.9
levofloxacin	≤0.12	>4	70.0	0.25	>4	55.2	≤0.12	>4	76.2	≤0.12	>4	76.9
gentamicin	≤1	>8	85.4	≤1	>8	81.6	≤1	>8	89.0	≤1	>8	88.8
tigecycline[b]	0.12	0.12	100.0	0.12	0.12	100.0	0.06	0.12	100.0	0.12	0.12	100.0
Extended-spectrum cephalosporin-resistant phenotype *E. coli*	*n*=72			*n*=62			*n*=17			*n*=78		
ceftazidime/avibactam	0.12	0.5	—	0.12	0.25	—	0.12	0.5	—	0.12	0.25	—
ceftazidime	16	>32	23.6	16	>32	32.3	16	>32	23.5	8	32	37.2
ceftriaxone	>8	>8	4.2	>8	>8	12.9	>8	>8	0.0	>8	>8	9.0
piperacillin/tazobactam	8	>64	75.0	8	>64	69.4	8	>64	70.6	8	64	80.8
meropenem	≤0.06	≤0.06	98.6	≤0.06	≤0.06	98.4	≤0.06	0.12	100.0	≤0.06	≤0.06	98.7
ciprofloxacin	>4	>4	22.2	>4	>4	14.5	>4	>4	5.9	>4	>4	26.9
levofloxacin	>4	>4	23.6	>4	>4	14.5	>4	>4	5.9	>4	>4	26.9
gentamicin	2	>8	57.7	2	>8	72.6	2	>8	52.9	2	>8	61.5
tigecycline[b]	0.12	0.25	100.0	0.12	0.25	100.0	0.12	0.25	100.0	0.12	0.25	100.0
Klebsiella spp.	*n*=353			*n*=596			*n*=104			*n*=501		
ceftazidime/avibactam	0.12	0.25	—	0.12	0.5	—	0.12	0.5	—	0.12	0.25	—
ceftazidime	0.12	16	88.1	0.12	>32	84.1	0.12	32	86.5	0.12	8	89.2
ceftriaxone	≤0.06	>8	87.0	≤0.06	>8	82.7	0.12	>8	84.6	≤0.06	>8	87.6
piperacillin/tazobactam	4	16	90.9	4	>64	84.0	4	>64	80.8	2	16	90.6
meropenem	≤0.06	≤0.06	96.6	≤0.06	≤0.06	93.3	≤0.06	≤0.06	93.3	≤0.06	≤0.06	95.4
levofloxacin	≤0.12	4	89.5	≤0.12	>4	86.1	≤0.12	>4	84.6	≤0.12	>4	88.8
gentamicin	≤1	≤1	93.5	≤1	4	91.3	≤1	8	89.4	≤1	≤1	93.2

tigecycline[b]	0.25	1	99.4	0.25	1	99.5	0.25	1	98.1	0.25	0.5	99.6
Extended-spectrum cephalosporin-resistant phenotype *Klebsiella* spp.	*n*=49			*n*=115			*n*=17			*n*=65		
ceftazidime/avibactam	0.25	1	—	0.25	1	—	0.5	2	—	0.5	1	—
ceftazidime	32	>32	14.3	>32	>32	17.4	>32	>32	17.6	>32	>32	16.9
ceftriaxone	>8	>8	6.1	>8	>8	10.4	>8	>8	5.9	>8	>8	4.6
piperacillin/tazobactam	64	>64	36.7	>64	>64	22.6	>64	>64	11.8	>64	>64	30.8
meropenem	≤0.06	>8	75.5	≤0.06	>8	65.2	≤0.06	>8	58.8	≤0.06	>8	64.6
levofloxacin	>4	>4	36.7	>4	>4	33.9	>4	>4	23.5	>4	>4	24.6
gentamicin	4	>8	55.1	4	>8	57.4	8	>8	47.1	4	>8	52.3
tigecycline[b]	0.5	2	98.0	0.5	1	99.1	0.5	1	100.0	0.5	1	96.9
Enterobacter spp.	*n*=150			*n*=365			*n*=69			*n*=183		
ceftazidime/avibactam	0.12	0.5	—	0.12	0.5	—	0.12	0.5	—	0.12	0.5	—
ceftazidime	0.25	>32	70.0	0.25	>32	77.0	0.5	>32	65.2	0.25	>32	79.2
ceftriaxone	0.5	>8	64.7	0.25	>8	72.9	0.5	>8	59.4	0.25	>8	75.1
piperacillin/tazobactam	4	64	78.7	4	64	82.4	4	>64	79.7	2	64	84.6
meropenem	≤0.06	≤0.06	100.0	≤0.06	≤0.06	99.7	≤0.06	0.12	98.6	≤0.06	≤0.06	99.5
levofloxacin	≤0.12	0.5	97.3	≤0.12	0.5	95.3	≤0.12	1	91.3	≤0.12	1	92.9
gentamicin	≤1	≤1	97.3	≤1	≤1	95.9	≤1	≤1	92.8	≤1	≤1	92.4
tigecycline[b]	0.25	1	97.3	0.25	0.5	99.7	0.25	2	95.7	0.25	1	99.5
Citrobacter spp.	*n*=25			*n*=59			*n*=23			*n*=110		
ceftazidime/avibactam	0.12	0.5	—	0.12	1	—	0.12	0.5	—	0.12	0.25	—
ceftazidime	0.25	>32	80.0	0.25	>32	83.1	0.5	>32	73.9	0.25	16	89.1
ceftriaxone	0.12	>8	80.0	0.12	>8	83.1	0.25	>8	73.9	0.12	4	89.1
piperacillin/tazobactam	4	64	75.0	2	>64	84.5	4	>64	82.6	2	16	92.7
meropenem	≤0.06	≤0.06	100.0	≤0.06	≤0.06	96.6	≤0.06	≤0.06	95.7	≤0.06	≤0.06	99.1
levofloxacin	≤0.12	0.5	92.0	≤0.12	4	89.8	≤0.12	4	87.0	≤0.12	1	94.5
gentamicin	≤1	≤1	100.0	≤1	≤1	93.2	≤1	>8	87.0	≤1	≤1	95.5
tigecycline[b]	0.12	0.5	96.0	0.12	0.5	100.0	0.25	1	95.7	0.12	0.25	100.0
M. morganii	*n*=23			*n*=23			*n*=8[c]			*n*=106		
ceftazidime/avibactam	0.03	0.12	—	0.06	0.12	—	—	—	—	0.06	0.25	—
ceftazidime	0.06	16	82.6	0.12	8	82.6	—	—	—	0.12	32	84.0
ceftriaxone	≤0.06	2	82.6	≤0.06	1	91.3	—	—	—	≤0.06	8	82.1
piperacillin/tazobactam	≤0.5	2	100.0	≤0.5	2	100.0	—	—	—	≤0.5	8	92.5
meropenem	≤0.06	0.12	100.0	≤0.06	0.12	100.0	—	—	—	≤0.06	0.12	100.0
levofloxacin	≤0.12	>4	69.6	1	>4	65.2	—	—	—	≤0.12	>4	69.8/
gentamicin	≤1	>8	87.0	≤1	>8	82.6	—	—	—	≤1	>8	79.2
tigecycline[b]	0.5	1	95.7	0.5	2	91.3	—	—	—	0.5	2	97.2
P. mirabilis	*n*=70			*n*=96			*n*=17			*n*=144		
ceftazidime/avibactam	0.03	0.06	—	0.03	0.06	—	0.03	0.06	—	0.03	0.06	—
ceftazidime	0.06	0.12	98.6	0.06	0.12	99.0	0.06	0.5	100.0	0.06	0.12	98.6
ceftriaxone	≤0.06	≤0.06	94.3	≤0.06	0.12	92.7	≤0.06	>8	88.2	≤0.06	≤0.06	97.9
piperacillin/tazobactam	≤0.5	1	100.0	≤0.5	1	100.0	≤0.5	1	100.0	≤0.5	1	99.3

Continued

Table 2. *Continued*

Organism/antimicrobial agent	BSI			Pneumonia			IAI			UTI		
	MIC (mg/L)		percentage susceptible[a]	MIC (mg/L)		percentage susceptible[a]	MIC (mg/L)		percentage susceptible[a]	MIC (mg/L)		percentage susceptible[a]
	MIC_{50}	MIC_{90}		MIC_{50}	MIC_{90}		MIC_{50}	MIC_{90}		MIC_{50}	MIC_{90}	
meropenem	≤0.06	0.12	100.0	≤0.06	≤0.06	100.0	≤0.06	0.12	100.0	≤0.06	0.12	100.0
levofloxacin	≤0.12	>4	65.7	≤0.12	>4	65.3	≤0.12	>4	76.5	≤0.12	>4	76.4
gentamicin	≤1	>8	84.3	≤1	8	86.5	≤1	4	94.1	≤1	4	92.3
tigecycline[b]	2	4	87.1	2	4	83.3	2	4	88.2	2	4	77.8
Proteus vulgaris	*n*=5[c]			*n*=5[c]			*n*=4[c]			*n*=75		
ceftazidime/avibactam	—	—	—	—	—	—	—	—	—	0.06	0.06	—
ceftazidime	—	—	—	—	—	—	—	—	—	0.06	0.12	100.0
ceftriaxone	—	—	—	—	—	—	—	—	—	0.12	4	73.3
piperacillin/tazobactam	—	—	—	—	—	—	—	—	—	≤0.5	1	100.0
meropenem	—	—	—	—	—	—	—	—	—	≤0.06	≤0.06	100.0
levofloxacin	—	—	—	—	—	—	—	—	—	≤0.12	0.25	100.0
gentamicin	—	—	—	—	—	—	—	—	—	≤1	2	98.7
tigecycline[b]	—	—	—	—	—	—	—	—	—	1	1	98.7
S. marcescens	*n*=506			*n*=200			*n*=11			*n*=45		
ceftazidime/avibactam	0.12	0.5	—	0.12	0.5	—	0.12	0.5	—	0.25	0.5	—
ceftazidime	0.25	0.5	97.4	0.12	0.5	96.5	0.25	0.5	100.0	0.25	1	100.0
ceftriaxone	0.25	2	89.8	0.25	2	87.4	0.25	0.5	90.0	0.25	1	93.3
piperacillin/tazobactam	2	4	96.6	2	8	94.9	2	4	100.0	2	4	97.8
meropenem	≤0.06	≤0.06	99.2	≤0.06	≤0.06	100.0	≤0.06	≤0.06	100.0	≤0.06	0.12	100.0
levofloxacin	≤0.12	1	94.7	≤0.12	1	95.0	0.25	2	90.9	≤0.12	1	95.6
gentamicin	≤1	2	97.0	≤1	2	96.5	≤1	≤1	100.0	≤1	2	100.0
tigecycline[b]	0.5	1	99.0	0.5	1	100.0	0.5	1	100.0	0.5	1	97.8

[a]Criteria as published by the CLSI.[20]
[b]In the absence of CLSI breakpoints, US FDA breakpoints were applied when available.[21]
[c]Susceptibility data not presented when number of isolates <10.

Table 3. Activity of ceftazidime/avibactam and comparator antimicrobial agents tested against *P. aeruginosa*, *A. baumannii*, *H. influenzae* and *M. catarrhalis* from patients with BSI, pneumonia, IAI and UTI at US medical centres (2012)

	BSI			Pneumonia			IAI			UTI		
	MIC (mg/L)			MIC (mg/L)			MIC (mg/L)			MIC (mg/L)		
Organism/antimicrobial agent	MIC_{50}	MIC_{90}	percentage susceptible[a]	MIC_{50}	MIC_{90}	percentage susceptible[a]	MIC_{50}	MIC_{90}	percentage susceptible[a]	MIC_{50}	MIC_{90}	percentage susceptible[a]
P. aeruginosa	*n*=141			*n*=881			*n*=82			*n*=155		
ceftazidime/avibactam	2	8	—	2	8	—	2	4	—	2	4	—
ceftazidime	2	>32	83.0	2	32	79.5	2	32	85.4	2	16	89.7
cefepime	2	>16	83.7	4	>16	80.9	2	16	81.7	4	16	86.5
piperacillin/tazobactam	8	>64	73.6	8	>64	75.2	8	>64	79.3	8	32	81.9
meropenem	0.5	8	79.4	0.5	8	78.8	0.5	8	84.1	0.5	8	78.7
levofloxacin	0.5	>4	79.4	0.5	>4	73.0	0.5	>4	78.0	0.5	>4	65.8
gentamicin	≤1	4	90.8	2	8	84.9	≤1	4	92.7	2	4	90.3
amikacin	2	8	99.3	2	8	96.6	2	8	97.6	2	8	98.1
colistin	1	2	99.3	1	2	98.4	2	2	97.6	2	2	98.1
Ceftazidime-non-susceptible *P. aeruginosa* (MIC ≥ 16 mg/L)	*n*=24			*n*=181			*n*=12			*n*=16		
ceftazidime/avibactam	8	>32	—	4	16	—	4	16	—	2	8	—
ceftazidime	>32	>32	0.0	32	>32	0.0	32	>32	0.0	32	>32	0.0
cefepime	>16	>16	12.5	16	>16	21.0	16	>16	8.3	16	>16	31.3
piperacillin/tazobactam	>64	>64	0.0	>64	>64	5.5	>64	>64	0.0	32	>64	18.8
meropenem	4	>8	41.7	4	>8	44.8	2	8	50.0	2	>8	50.0
levofloxacin	>4	>4	33.3	4	>4	39.8	2	>4	50.0	>4	>4	12.5
gentamicin	2	>8	58.3	4	>8	63.0	2	4	91.7	4	>8	81.3
amikacin	4	16	100.0	4	16	90.6	2	8	100.0	4	8	100.0
colistin	1	2	100.0	1	2	98.9	2	2	91.7	2	2	100.0
Meropenem-non-susceptible *P. aeruginosa* (MIC ≥ 4 mg/L)	*n*=29			*n*=187			*n*=13			*n*=33		
ceftazidime/avibactam	4	>32	—	4	16	—	4	16	—	4	8	—
ceftazidime	8	>32	51.7	16	>32	46.5	8	>32	53.8	4	>32	75.8
cefepime	16	>16	48.3	16	>16	46.5	>16	>16	38.5	8	>16	60.6
piperacillin/tazobactam	64	>64	31.0	64	>64	34.2 6	64	>64	38.5	16	>64	60.6
meropenem	8	>8	0.0	8	>8	0.0	8	>8	0.0	8	>8	0.0
levofloxacin	>4	>4	37.9	>4	>4	34.8	>4	>4	30.8	>4	>4	21.2
gentamicin	2	>8	58.6	4	>8	59.9	4	>8	76.9	4	>8	69.7
amikacin	4	16	96.6	8	16	90.4	4	16	92.3	4	16	93.9
colistin	1	2	100.0	1	2	96.8	2	2	92.3	2	2	97.0
A. baumannii	*n*=27			*n*=139			*n*=9[b]			*n*=13		
ceftazidime/avibactam	16	>32	—	32	>32	—	—	—	—	8	32	—
ceftazidime	8	>32	63.0	>32	>32	30.2	—	—	—	8	>32	69.2
piperacillin/tazobactam	16	>64	63.0	>64	>64	31.2	—	—	—	16	>64	69.2

Continued

Table 3. *Continued*

Organism/antimicrobial agent	BSI			Pneumonia			IAI			UTI		
	MIC (mg/L)		percentage susceptible[a]	MIC (mg/L)		percentage susceptible[a]	MIC (mg/L)		percentage susceptible[a]	MIC (mg/L)		percentage susceptible[a]
	MIC_{50}	MIC_{90}		MIC_{50}	MIC_{90}		MIC_{50}	MIC_{90}		MIC_{50}	MIC_{90}	
ampicillin/sulbactam	2	>32	66.7	16	>32	41.0	—	—	—	4	16	76.9
meropenem	1	>8	63.0	>8	>8	37.4	—	—	—	0.25	>8	76.9
levofloxacin	0.25	>4	59.3	>4	>4	30.9	—	—	—	0.5	>4	69.2
gentamicin	2	>8	70.4	>8	>8	37.4	—	—	—	≤1	>8	76.9
amikacin	4	>32	77.8	16	>32	54.7	—	—	—	4	16	92.3
colistin	1	2	96.3	1	2	95.0	—	—	—	1	1	100.0
H. influenzae	*n*=25			*n*=368			*n*=0[b]			*n*=0[b]		
ceftazidime/avibactam	≤0.015	0.03	—	≤0.015	0.03	—	—	—	—	—	—	—
ceftazidime	0.06	0.12	100.0	0.06	0.12	100.0	—	—	—	—	—	—
ampicillin	≤0.25	1	92.0	≤0.25	>8	74.7	—	—	—	—	—	—
ceftriaxone	≤0.06	≤0.06	100.0	≤0.06	≤0.06	100.0	—	—	—	—	—	—
amoxicillin/clavulanate	≤1	2	100.0	≤1	2	100.0	—	—	—	—	—	—
tigecycline	0.25	0.5	84.0	0.25	0.5	78.5	—	—	—	—	—	—
SXT	≤0.5	>4	84.0	≤0.5	>4	74.2	—	—	—	—	—	—
azithromycin	1	2	100.0	1	2	98.6	—	—	—	—	—	—
M. catarrhalis	*n*=4[b]			*n*=119			*n*=0[b]			*n*=0[b]		
ceftazidime/avibactam	—	—	—	0.06	0.12	—	—	—	—	—	—	—
ceftazidime	—	—	—	0.06	0.12	100.0	—	—	—	—	—	—
ceftriaxone	—	—	—	0.25	0.5	100.0	—	—	—	—	—	—
amoxicillin/clavulanate	—	—	—	≤1	≤1	100.0	—	—	—	—	—	—
tetracycline	—	—	—	0.25	0.25	100.0	—	—	—	—	—	—
SXT	—	—	—	≤0.5	≤0.5	97.5	—	—	—	—	—	—
levofloxacin	—	—	—	≤0.12	≤0.12	100.0	—	—	—	—	—	—

SXT, trimethoprim/sulfamethoxazole.
[a]Criteria as published by the CLSI.[20]
[b]Susceptibility data not presented when number of isolates <10.

which is the CLSI susceptible breakpoint for ceftazidime when tested alone against *P. aeruginosa* (Table 1). Two agents that showed >90.0% activity against *P. aeruginosa* isolates from all infection types studied were colistin [susceptibility range, 97.6% (IAI) to 99.3% (BSI)] and amikacin [96.6% (pneumonia patients) to 99.3% (BSI); Table 3].

Ceftazidime/avibactam was active against many ceftazidime-non-susceptible and meropenem-non-susceptible *P. aeruginosa* (Table 3). Among the ceftazidime-non-susceptible *P. aeruginosa*, 75.0% (IAI), 79.2% (BSI), 79.6% (pneumonia patients) and 93.8% (UTI) demonstrated ceftazidime/avibactam MIC values of ≤8 mg/L (data not shown). For meropenem-non-susceptible *P. aeruginosa* the percentages of isolates with ceftazidime/avibactam MIC values of ≤8 mg/L were 76.9% (IAI), 85.0% (pneumonia patients), 86.2% (BSI) and 97.0% (UTI) (data not shown). Colistin and amikacin were the only two tested agents to which susceptibility was >90.0% for meropenem-non-susceptible isolates from each infection type (colistin range, 92.3%–100.0%; amikacin, 90.4%–96.6%; Table 3).

Ceftazidime/avibactam and a number of other agents were highly active against *H. influenzae* (23.4% β-lactamase positive) regardless of β-lactamase status and against *M. catarrhalis* (Table 3). Most agents tested exhibited generally poor activity against *A. baumannii*, except for colistin (Table 3). Only 31.2% of *A. baumannii* had ceftazidime/avibactam MIC values of ≤8 mg/L (data not shown).

Discussion

Bacterial resistance in Gram-negative infections may lead to increased morbidity and longer length of hospital stay.[22–25] The choice of appropriate initial therapy therefore plays an important role in preventing adverse outcomes.[23,24,26] The emergence of resistance in Gram-negative bacteria that may occur in a variety of infections, including BSI, pneumonia patients, IAI and UTI, complicates the choice of appropriate therapy.[12,27–32] Unfortunately, there are a limited number of agents with activity against multidrug-resistant Gram-negative bacteria. Due to a number of confounding factors, there have been relatively few new antimicrobial agents introduced recently and even fewer with activity against Gram-negative bacteria.[14,17,33]

The IDSA has listed seven experimental intravenous antimicrobials in Phase II or III clinical development with activity against resistant Gram-negative bacteria.[17] Unfortunately, none of these is active against metallo-β-lactamase-producing bacteria or *Acinetobacter* spp., owing to either a lack of activity against the β-lactamase or the presence of additional resistance mechanisms independent of β-lactamase. Ceftazidime/avibactam is one of the two experimental agents identified by the IDSA as having activity against extended-spectrum cephalosporin-resistant and serine carbapenemase-producing Enterobacteriaceae, as well as against wild-type *P. aeruginosa*.[17] Phase III studies in complicated UTI, complicated IAI and nosocomial pneumonia are ongoing with this agent.

In this large surveillance study conducted in the USA in 2012, ceftazidime/avibactam was demonstrated to be highly active against a collection of contemporary Gram-negative bacteria from BSI, pneumonia patients, IAI and UTI. Included in the spectrum of activity for ceftazidime/avibactam were extended-spectrum cephalosporin-resistant phenotype Enterobacteriaceae. A total of 99.8% of all Enterobacteriaceae exhibited an MIC of ≤4 mg/L for ceftazidime/avibactam. Also included in the spectrum of activity for ceftazidime/avibactam were *P. aeruginosa*, with 96.3% of isolates having an MIC of ≤8 mg/L. Ceftazidime/avibactam also showed activity against many ceftazidime-non-susceptible and meropenem-non-susceptible isolates. Among the ceftazidime-non-susceptible *P. aeruginosa*, 75.0% (IAI), 79.2% (BSI), 79.6% (pneumonia patients) and 93.8% (UTI) exhibited ceftazidime/avibactam MIC values ≤8 mg/L. For meropenem-non-susceptible *P. aeruginosa*, the percentages of isolates with ceftazidime/avibactam MIC values of ≤8 mg/L were 76.9% (IAI), 85.0% (pneumonia patients), 86.2% (BSI) and 97.0% (UTI). Colistin and amikacin were the only licensed agents to which high (>90.0%) susceptibility rates were shown by ceftazidime-non-susceptible and meropenem-non-susceptible *P. aeruginosa* isolates. The activity of ceftazidime/avibactam and many other agents in this study against *A. baumannii* was poor.

The results of this *in vitro* surveillance programme conducted in the USA during 2012 suggest that ceftazidime/avibactam has the potential to be a useful addition to the antimicrobial choices available to address the problem of multidrug-resistant Gram-negative bacteria. However, we look forward to the results of further clinical investigations.

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