ICAAC 2013
C2-1635

Activity of Ceftazidime-Avibactam Tested Against Contemporary Pathogens from Hospitalized Pneumonia Patients in the USA (2012)

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Abstract

Background: The investigational β-lactam-β-lactamase inhibitor combination, ceftazidime-avibactam (CAZ-AVI), is in Phase III development including studies in complicated intraabdominal and urinary tract infections. The results of *in vitro* testing of CAZ-AVI and comparators against a contemporary collection of pathogens from patients hospitalized with pneumonia in the USA are reported here.

Methods: Unique clinical isolates (one per patient) were collected from hospitalized patients with pneumonia in 163 USA medical centers. Isolates were processed at the medical centers and forwarded to a central laboratory (JMI Laboratories, North Liberty, IA, USA) for confirmatory identification and susceptibility (S) testing using CLSI methods.

Results: CAZ-AVI activity against staphylococci, enterococcci, and streptococci was similar to that of CAZ. CAZ-AVI was potent against the Enterobacteriaceae (ENT) with $MIC_{50/90}$ values at 0.12/0.25 µg/mL. For ENT, S was highest for meropenem (MER, 97.4%), while 17.1% were resistant (R) to levofloxacin (LEV). 17.5% of *E. coli* and 19.3% of *Klebsiella* spp. were ESBL-phenotype positive. LEV-R was 44.5% for all *E. coli* and 85.5% for the ESBL-phenotype. LEV-R in *Klebsiella* spp. was at 12.9 and 62.6% (ESBL-phenotype), respectively. One *E. coli* isolate from New York and 40 *K. pneumoniae* isolates from various states were refractory to MER (MER-non-S, MIC ≥2 µg/mL). The CAZ- AVI MIC_{90} values for ESBL-phenotype *E. coli* and *Klebsiella* spp. were 0.25 and 1 µg/mL, respectively. CAZ-AVI also demonstrated potent activity against *P. aeruginosa* with 95.8% of isolates inhibited at an MIC of ≤8 µg/mL compared to 79.5% for CAZ tested alone. Further, 79.6% of CAZ-non-S *P. aeruginosa* and 85.0% of MER-non-S were inhibited by CAZ-AVI at ≤8 µg/mL.

Conclusions: CAZ-AVI demonstrated potent activity against contemporary (2012) Gram-negative pathogens from USA patients hospitalized with pneumonia. The spectrum and potency shown by CAZ-AVI indicates that further study in pneumonia patients appears warranted.

Organism (no. tested)	CAZ-AVI[a]			Ceftazidime[a]			Meropenem[a]		
	MIC_{50}	MIC_{90}	% at ≤4[b]	MIC_{50}	MIC_{90}	%S	MIC_{50}	MIC_{90}	%S
Enterobacteriaceae (1,738)	0.12	0.25	99.4	0.25	32	85.5	≤0.06	≤0.06	97.4
E. coli (355)	0.12	0.25	100.0	0.25	16	88.2	≤0.06	≤0.06	99.7
ESBL-positive (62)	0.12	0.25	100.0	16	>32	32.3	≤0.06	≤0.06	98.4
Klebsiella spp. (596)	0.12	0.5	99.7	0.12	>32	84.1	≤0.06	≤0.06	93.3
ESBL-positive (115)	0.25	1	98.3	>32	>32	17.4	≤0.06	>8	65.2
Enterobacter cloacae (244)	0.12	0.5	100.0	0.25	>32	75.8	≤0.06	≤0.06	100.0
CAZ-non-S *E. cloacae* (59)	0.5	1	100.0	>32	>32	0.0	≤0.06	0.12	100.0
P. aeruginosa (881)	2	8	95.8	2	32	79.5	0.5	8	78.8
CAZ-non-S *P. aeruginosa* (181)	4	16	79.6	32	>32	0.0	4	>8	44.8
MER-non-S *P. aeruginosa* (187)	4	16	85.0	16	>32	46.5	8	>8	0.0

a. MIC in µg/mL b. % at ≤8 µg/mL for *P. aeruginosa*

Introduction

Emerging drug resistance in Gram-negative bacteria is limiting the use of current therapies and leading to increased morbidity and mortality in a variety of disease states. In patients hospitalized with bacterial pneumonia, infections may be caused by resistant Gram-negative bacteria including *Pseudomonas aeruginosa*, *Klebsiella* species, *Escherichia coli*, *Acinetobacter* species, and *Enterobacter* species. Other Gram-negative pathogens that occur less frequently include other Enterobacteriaceae (not mentioned above) and *Stenotrophomonas maltophilia*. *Staphylococcus aureus* and community-acquired pathogens, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, may also occur.

Ceftazidime-avibactam is an experimental combination antimicrobial containing the novel non-β-lactam β-lactamase inhibitor avibactam and the cephalosporin ceftazidime. Avibactam has been shown to have high affinity for β-lactamases including Class A, C and some Class D enzymes. When in combination with ceftazidime, avibactam protects ceftazidime from hydrolysis by the listed β-lactamases. Currently, ceftazidime-avibactam is undergoing evaluation in Phase III clinical trials for complicated urinary tract, intraabdominal, and nosocomial pneumonia infections.

In this study, isolates were collected from patients hospitalized with pneumonia in the USA during 2012. Ceftazidime-avibactam and comparator agents were evaluated for their *in vitro* antimicrobial activity against the contemporary collection of bacterial isolates. The results of this study are presented herein.

Methods

Bacterial Strains. Unique clinical isolates (one per patient) were collected from patients hospitalized with pneumonia in 163 USA medical centers in the USA during 2012. Isolates were processed at the medical centers and forwarded to a central laboratory (JMI Laboratories, North Liberty, Iowa, USA) for confirmatory identification and susceptibility testing following Clinical and Laboratory Standards Institute (CLSI) methods.

Susceptibility Test Methods. Susceptibility testing was performed in validated dry-form broth microdilution trays (ThermoFisher Scientific, formerly TREK Diagnostics [Cleveland, Ohio, USA]) following CLSI methods (M07-A9; 2012). Interpretive criteria applied were those of CLSI (M100-S23; 2013). USA-FDA criteria were used for tigecycline as an alternative breakpoint source, as CLSI breakpoints were not available. Quality control (QC) strains were tested concurrently and all values were within established CLSI ranges (M100-S23). Six QC strains were tested: *S. aureus* ATCC 29213; *Enterococcus faecalis* ATCC 29212; *S. pneumoniae* ATCC 49619; *E. coli* ATCC 25922; *Klebsiella pneumoniae* ATCC 700603 and *H. influenzae* ATCC 49247. ESBL screen-positive phenotype for *E. coli*, *Klebsiella* spp., *K. pneumoniae*, *K. oxytoca* and *Proteus mirabilis* was defined as a MIC at ≥2 µg/mL for ceftriaxone or ceftazidime or aztreonam [CLSI, 2013]. *H. influenzae* β-lactamase detection was performed using Remel Nitrocefin Disk (Remel, Lenexa, Kansas, USA).

Results

Selected Gram-negative bacteria:

- Enterobacteriaceae. The MIC_{50} and MIC_{90} for ceftazidime-avibactam for 1,738 isolates were 0.12 and 0.25 µg/mL, respectively (Tables 1 and 2). A total of 99.0% and 99.4% of isolates were at ≤1 and ≤4 µg/mL, respectively, for ceftazidime-avibactam (Table 1). For ceftazidime, the MIC_{50} and MIC_{90} values were 0.25 and 32 µg/mL, respectively (Tables 1 and 2); 83.0% and 85.5% of isolates were at ≤1 and ≤4 µg/mL, respectively (Table 1). Only 80.1% of isolates were susceptible to levofloxacin and 63.9% were susceptible to tetracycline (Table 2). The highest degree of susceptibility observed was for meropenem (97.4%) and tigecycline (98.7%; Table 2).
- *E. coli*. The MIC_{50} and MIC_{90} of ceftazidime-avibactam for 355 isolates were 0.12 and 0.25 µg/mL, respectively (Table 1). All MIC values were ≤1 µg/mL for ceftazidime-avibactam. The MIC_{50} and MIC_{90} of ceftazidime were 0.25 and 16 µg/mL, respectively (Tables 1 and 2). A total of 17.5% of *E. coli* showed an ESBL-phenotype (Tables 1 and 2). There was one meropenem-non-susceptible isolate from New York with a KPC-phenotype; its ceftazidime-avibactam MIC was 0.25 µg/mL.
- *K. pneumoniae*. The MIC_{50} and MIC_{90} of ceftazidime-avibactam for 479 isolates were 0.12 and 0.5 µg/mL, respectively (Tables 1 and 2). A total of 98.7% and 99.6% of isolates were at ≤1 and ≤4 µg/mL, respectively, for ceftazidime-avibactam (Table 1). For ceftazidime, the MIC_{50} and MIC_{90} values were 0.12 and >32 µg/mL, respectively (Tables 1 and 2). 79.5% and 81.0% of isolates were at ≤1 and ≤4 µg/mL, respectively (Table 1). A high degree of susceptibility was observed for meropenem (91.6%) and tigecycline (99.6%; Table 2). 19.3% of *Klebsiella* spp. and 20.5% of *K. pneumoniae* exhibited an ESBL-phenotype (Tables 1 and 2). The MIC_{50} and MIC_{90} for ceftazidime-avibactam for ESBL-phenotype *K. pneumoniae* were 0.5 and 1 µg/mL, respectively (Tables 1 and 2). There were 40 meropenem-non-susceptible *K. pneumoniae* encountered in various states which were likely KPC-producing organisms.
- *Enterobacter* spp. There were 244 *E. cloacae* which exhibited a MIC_{50} and MIC_{90} for ceftazidime-avibactam of 0.12 and 0.5 µg/mL, respectively (Tables 1 and 2). The MIC_{50} and MIC_{90} of ceftazidime were 0.25 and >32 µg/mL, respectively (Tables 1 and 2). For *E. aerogenes* (n=121), the MIC_{50} and MIC_{90} of ceftazidime-avibactam were 0.12 and 0.25 µg/mL, respectively (Table 1).
- *Serratia marcescens*. The MIC_{50} and MIC_{90} for ceftazidime-avibactam and ceftazidime for 200 isolates were both at 0.12 and 0.5 µg/mL, respectively (Tables 1 and 2). A total of 98.5% and 99.0% of isolates MIC values for ceftazidime-avibactam were at ≤1 and ≤4 µg/mL, respectively (Table 1).
- *P. mirabilis*. The MIC_{50} and MIC_{90} for ceftazidime-avibactam for 96 isolates was at 0.03 and 0.06 µg/mL, respectively (Tables 1 and 2). The highest MIC value for ceftazidime-avibactam was only 0.25 µg/mL (Tables 1 and 2).
- *P. aeruginosa*. The MIC_{50} and MIC_{90} for ceftazidime-avibactam for 881 isolates was 2 and 8 µg/mL, respectively (Tables 1 and 2). For ceftazidime, the MIC_{50} and MIC_{90} values were 2 and 32 µg/mL, respectively (Tables 1 and 2). A total of 89.4% and 95.8% of MIC values for ceftazidime-avibactam were at ≤4 and ≤8 µg/mL, respectively (Table 1). 79.6% of ceftazidime-non-susceptible isolates exhibited a ceftazidime-avibactam MIC value at ≤8 µg/mL, and 85.0% of meropenem-non-susceptible isolates exhibited a ceftazidime-avibactam MIC value at ≤8 µg/mL (Table 1).
- *Acinetobacter* spp. The MIC_{50} and MIC_{90} for 139 isolates for ceftazidime-avibactam was elevated at 32 and >32 µg/mL, respectively (Table 1).

Selected Gram-positive bacteria:

- *S. aureus*. The MIC_{50} and MIC_{90} for 1,652 isolates for ceftazidime-avibactam and ceftazidime were 16 and >32 µg/mL, respectively (Tables 1 and 2). A total of 49.3% of isolates were methicillin-resistant (MRSA; Table 2).
- β-haemolytic streptococci. The MIC_{50} and MIC_{90} for 73 isolates for ceftazidime-avibactam and ceftazidime were 0.5 and 0.5 µg/mL, respectively (Table 1).
- *S. pneumoniae*. The MIC_{50} and MIC_{90} for 878 isolates for ceftazidime-avibactam and ceftazidime were 0.5 and 16 µg/mL, respectively (Tables 1 and 2). A total of 12.4% of isolates were non-susceptible to penicillin (penicillin MIC, ≥4 µg/mL; Tables 1 and 2).

Table 1. Summary of ceftazidime-avibactam (CAZ-AVI) and ceftazidime activity tested against select organisms and resistant subsets of isolates from patients with hospitalized pneumonia in the USA (2012)

Organism/resistant subset	Antimicrobial	No. of Isolates	No. of isolates (cumulative %) inhibited at MIC (µg/mL) of: ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}
Staphylococcus aureus	CAZ-AVI	1652	--	--	--	--	--	--	--	7 (0.4)	58 (3.9)	719 (47.5)	141 (56.0)	209 (68.6)	518 (100.0)	16	>32
	Ceftazidime	1652	--	--	--	--	--	--	--	3 (0.2)	46 (3.0)	719 (46.5)	156 (55.9)	208 (68.5)	520 (100.0)	16	>32
Streptococcus pneumoniae	CAZ-AVI	878	2 (0.2)	3 (0.6)	10 (1.7)	213 (26.0)	183 (46.8)	67 (54.4)	78 (63.3)	35 (67.3)	41 (72.0)	129 (86.7)	83 (96.1)	28 (99.3)	6 (100.0)	0.5	16
	Ceftazidime	878	2 (0.2)	0 (0.2)	10 (1.4)	167 (20.4)	228 (46.4)	65 (53.8)	81 (63.0)	35 (67.0)	40 (71.5)	125 (85.8)	89 (95.9)	30 (99.3)	6 (100.0)	0.5	16
β-haemolytic streptococci	CAZ-AVI	73	--	--	2 (2.7)	24 (35.6)	3 (39.7)	41 (95.9)	1 (97.3)	1 (98.6)	1 (100.0)	--	--	--	--	0.5	0.5
	Ceftazidime	73	--	--	3 (4.1)	23 (35.6)	1 (37.0)	43 (95.9)	1 (97.3)	1 (98.6)	1 (100.0)	--	--	--	--	0.5	0.5
Enterobacteriaceae	CAZ-AVI	1738	29 (1.7)	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)	0 (99.9)	2 (100.0)	0.12	0.25
	Ceftazidime	1738	1 (0.1)	47 (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)	56 (92.0)	139 (100.0)	0.25	32
Escherichia coli	CAZ-AVI	355	16 (4.5)	19 (9.9)	131 (46.8)	147 (88.2)	37 (98.6)	3 (99.4)	2 (100.0)	--	--	--	--	--	--	0.12	0.25
	Ceftazidime	355	1 (0.3)	0 (0.3)	25 (7.3)	113 (39.2)	102 (67.9)	47 (81.1)	10 (83.9)	9 (86.5)	6 (88.2)	5 (89.6)	7 (91.5)	17 (96.3)	13 (100.0)	0.25	16
ESBL-phenotype	CAZ-AVI	62	1 (1.6)	0 (1.6)	7 (12.9)	32 (64.5)	17 (91.9)	3 (96.8)	2 (100.0)	--	--	--	--	--	--	0.12	0.25
	Ceftazidime	62	--	--	--	--	--	1 (1.6)	4 (8.1)	9 (22.6)	6 (32.3)	5 (40.3)	7 (51.6)	17 (79.0)	13 (100.0)	16	>32
Klebsiella spp.	CAZ-AVI	596	6 (1.0)	22 (4.7)	199 (38.1)	234 (77.3)	67 (88.6)	42 (95.6)	20 (99.0)	3 (99.5)	1 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	2 (100.0)	0.12	0.5
	Ceftazidime	596	--	8 (1.3)	128 (22.8)	196 (55.7)	102 (72.8)	46 (80.5)	11 (82.4)	8 (83.7)	2 (84.1)	8 (85.4)	10 (87.1)	10 (88.8)	67 (100.0)	0.12	>32
ESBL-phenotype	CAZ-AVI	115	2 (1.7)	0 (1.7)	5 (6.1)	27 (29.6)	24 (50.4)	32 (78.3)	19 (94.8)	3 (97.4)	1 (98.3)	0 (98.3)	0 (98.3)	0 (98.3)	2 (100.0)	0.25	1
	Ceftazidime	115	--	--	1 (0.9)	4 (4.3)	3 (7.0)	1 (7.8)	1 (8.7)	8 (15.7)	2 (17.4)	8 (24.3)	10 (33.0)	10 (41.7)	67 (100.0)	>32	>32
Klebsiella pneumoniae	CAZ-AVI	479	6 (1.3)	14 (4.2)	154 (36.3)	188 (75.6)	55 (87.1)	39 (95.2)	17 (98.7)	3 (99.4)	1 (99.6)	0 (99.6)	0 (99.6)	0 (99.6)	2 (100.0)	0.12	0.5
	Ceftazidime	479	--	7 (1.5)	80 (18.2)	156 (50.7)	88 (69.1)	40 (77.5)	10 (79.5)	5 (80.6)	2 (81.0)	7 (82.5)	9 (84.3)	9 (86.2)	66 (100.0)	0.12	>32
ESBL-phenotype	CAZ-AVI	98	2 (2.0)	0 (2.0)	5 (7.1)	19 (26.5)	19 (45.9)	30 (76.5)	17 (93.9)	3 (96.9)	1 (98.0)	0 (98.0)	0 (98.0)	0 (98.0)	2 (100.0)	0.5	1
	Ceftazidime	98	--	--	--	--	--	--	--	5 (5.1)	2 (7.1)	7 (14.3)	9 (23.5)	9 (32.7)	66 (100.0)	>32	>32
meropenem-non-susceptible (MIC, ≥2 µg/mL)	CAZ-AVI	40	--	--	2 (5.0)	6 (20.0)	1 (22.5)	12 (52.5)	13 (85.0)	3 (92.5)	1 (95.0)	0 (95.0)	0 (95.0)	0 (95.0)	2 (100.0)	0.5	2
	Ceftazidime	40	--	--	--	--	--	--	--	--	--	--	1 (2.5)	2 (7.5)	37 (100.0)	>32	>32
Klebsiella oxytoca	CAZ-AVI	117	--	8 (6.8)	45 (45.3)	46 (84.6)	12 (94.9)	3 (97.4)	3 (100.0)	--	--	--	--	--	--	0.12	0.25
	Ceftazidime	117	--	1 (0.9)	48 (41.9)	40 (76.1)	14 (88.0)	6 (93.2)	1 (94.0)	3 (96.6)	0 (96.6)	1 (97.4)	1 (98.3)	1 (99.1)	1 (100.0)	0.12	0.5
ESBL-phenotype	CAZ-AVI	17	--	--	--	8 (47.1)	5 (76.5)	2 (88.2)	2 (100.0)	--	--	--	--	--	--	0.25	1
	Ceftazidime	17	--	--	1 (5.9)	4 (29.4)	3 (47.1)	1 (52.9)	1 (58.8)	3 (76.5)	0 (76.5)	1 (82.4)	1 (88.2)	1 (94.1)	1 (100.0)	0.5	32
Proteus mirabilis	CAZ-AVI	96	2 (2.1)	64 (68.8)	25 (94.8)	4 (99.0)	1 (100.0)	--	--	--	--	--	--	--	--	0.03	0.06
	Ceftazidime	96	--	32 (33.3)	51 (86.5)	7 (93.8)	3 (96.9)	1 (97.9)	0 (97.9)	0 (97.9)	1 (99.0)	1 (100.0)	--	--	--	0.06	0.12
ESBL-phenotype	CAZ-AVI	7	--	1 (14.3)	6 (100.0)	--	--	--	--	--	--	--	--	--	--	0.06	--
	Ceftazidime	7	--	--	--	4 (57.1)	1 (71.4)	0 (71.4)	0 (71.4)	0 (71.4)	1 (85.7)	1 (100.0)	--	--	--	0.12	--
Enterobacter cloacae	CAZ-AVI	244	3 (1.2)	2 (2.0)	16 (8.6)	105 (51.6)	74 (82.0)	33 (95.5)	10 (99.6)	1 (100.0)	--	--	--	--	--	0.12	0.5
	Ceftazidime	244	--	--	8 (3.3)	36 (18.0)	85 (52.9)	42 (70.1)	10 (74.2)	3 (75.4)	1 (75.8)	2 (76.6)	9 (80.3)	7 (83.2)	41 (100.0)	0.25	>32
ceftazidime-non-susceptible (MIC, ≥8 µg/mL)	CAZ-AVI	59	--	--	--	4 (6.8)	18 (37.3)	26 (81.4)	10 (98.3)	1 (100.0)	--	--	--	--	--	0.5	1
	Ceftazidime	59	--	--	--	--	--	--	--	--	--	2 (3.4)	9 (18.6)	7 (30.5)	41 (100.0)	>32	>32
Enterobacter aerogenes	CAZ-AVI	121	1 (0.8)	1 (1.7)	35 (30.6)	57 (77.7)	22 (95.9)	4 (99.2)	1 (100.0)	--	--	--	--	--	--	0.12	0.25
	Ceftazidime	121	--	--	6 (5.0)	40 (38.0)	25 (58.7)	15 (71.1)	6 (76.0)	1 (76.9)	3 (79.3)	1 (80.2)	4 (83.5)	14 (95.0)	6 (100.0)	0.25	32
ceftazidime-non-susceptible (MIC, ≥8 µg/mL)	CAZ-AVI	25	1 (4.0)	0 (4.0)	0 (4.0)	8 (36.0)	14 (92.0)	1 (96.0)	1 (100.0)	--	--	--	--	--	--	0.25	0.25
	Ceftazidime	25	--	--	--	--	--	--	--	--	--	1 (4.0)	4 (20.0)	14 (76.0)	6 (100.0)	32	>32
Serratia marcescens	CAZ-AVI	200	--	2 (1.0)	18 (10.0)	103 (61.5)	54 (88.5)	16 (96.5)	4 (98.5)	1 (99.0)	0 (99.0)	1 (99.5)	1 (100.0)	--	--	0.12	0.5
	Ceftazidime	200	--	2 (1.0)	10 (6.0)	88 (50.0)	67 (83.5)	21 (94.0)	3 (95.5)	1 (96.0)	1 (96.5)	1 (97.0)	1 (97.5)	4 (99.5)	1 (100.0)	0.12	0.5
Pseudomonas aeruginosa	CAZ-AVI	881	--	--	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)	7 (99.4)	5 (100.0)	2	8
	Ceftazidime	881	--	--	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)	52 (90.5)	84 (100.0)	2	32
meropenem-non-susceptible (MIC, ≥4 µg/mL)	CAZ-AVI	187	--	--	--	--	--	4 (2.1)	18 (11.8)	49 (38.0)	49 (64.2)	39 (85.0)	18 (94.7)	6 (97.9)	4 (100.0)	4	16
	Ceftazidime	187	--	--	--	--	--	--	3 (1.6)	25 (15.0)	37 (34.8)	22 (46.5)	25 (59.9)	30 (75.9)	45 (100.0)	16	>32
ceftazidime-non-susceptible (MIC, ≥16 µg/mL)	CAZ-AVI	181	--	--	--	--	--	1 (0.6)	16 (9.4)	39 (30.9)	46 (56.4)	42 (79.6)	25 (93.4)	7 (97.2)	5 (100.0)	4	16
	Ceftazidime	181	--	--	--	--	--	--	--	--	--	--	45 (24.9)	52 (53.6)	84 (100.0)	32	>32
Acinetobacter baumannii	CAZ-AVI	139	--	--	--	--	1 (0.7)	0 (0.7)	2 (2.2)	1 (2.9)	12 (11.5)	22 (27.3)	29 (48.2)	21 (63.3)	51 (100.0)	32	>32
	Ceftazidime	139	--	--	--	--	--	--	2 (1.4)	11 (9.4)	18 (22.3)	11 (30.2)	8 (36.0)	5 (39.6)	84 (100.0)	>32	>32
Haemophilus influenzae	CAZ-AVI	368	251 (68.2)	99 (95.1)	13 (98.6)	5 (100.0)	--	--	--	--	--	--	--	--	--	≤0.015	0.03
	Ceftazidime	368	10 (2.7)	33 (11.7)	251 (79.9)	58 (95.7)	13 (99.2)	3 (100.0)	--	--	--	--	--	--	--	0.06	0.12
Haemophilus parainfluenzae	CAZ-AVI	53	49 (92.5)	4 (100.0)	--	--	--	--	--	--	--	--	--	--	--	≤0.015	≤0.015
	Ceftazidime	53	7 (13.2)	22 (54.7)	18 (88.7)	5 (98.1)	1 (100.0)	--	--	--	--	--	--	--	--	0.03	0.12
Moraxella catarrhalis	CAZ-AVI	119	23 (19.3)	20 (36.1)	49 (77.3)	19 (93.3)	8 (100.0)	--	--	--	--	--	--	--	--	0.06	0.12
	Ceftazidime	119	16 (13.4)	22 (31.9)	51 (74.8)	20 (91.6)	10 (100.0)	--	--	--	--	--	--	--	--	0.06	0.12

Table 2. Activity of ceftazidime-avibactam and ceftazidime activity tested against select organisms from patients with hospitalized pneumonia in the USA (2012)

Organism group (no. tested)/antimicrobial agent	MIC (µg/mL) 50%	90%	CLSI[a] %S / % I / %R
S. aureus (1652)			
Ceftazidime-avibactam	16	>32	- / - / -
Ceftazidime	16	>32	49.3 / 0.0 / 50.7
Ceftriaxone	8	>8	49.3 / 0.0 / 50.7
Oxacillin	>2	>2	49.3 / 0.0 / 50.7
Erythromycin	>16	>16	33.6 / 4.4 / 62.0
Clindamycin	≤0.25	>2	72.6 / 0.5 / 26.9
Levofloxacin	0.5	>4	51.3 / 0.9 / 47.8
TMP/SMX[b]	≤0.5	≤0.5	98.2 / 0.0 / 1.8
Tigecycline[c]	0.06	0.12	100.0 / - / -
Linezolid	1	2	99.9 / 0.0 / 0.1
Vancomycin	1	1	100.0 / 0.0 / 0.0
Daptomycin	0.25	0.5	99.9 / - / -
S. pneumoniae (878)			
Ceftazidime-avibactam	0.5	16	- / - / -
Ceftazidime	0.5	16	- / - / -
Penicillin[d]	≤0.06	4	87.6 / 11.0 / 1.4
Penicillin[e]	≤0.06	4	50.6 / 28.2 / 21.2
Ceftriaxone	≤0.06	2	89.3 / 8.9 / 1.8
Meropenem	≤0.06	1	74.2 / 13.0 / 12.8
Erythromycin	1	>16	49.0 / 0.8 / 50.2
Clindamycin	≤0.25	>2	79.2 / 0.6 / 20.2
Levofloxacin	1	1	97.8 / 0.4 / 1.8
Linezolid	1	1	100.0 / - / -
Tetracycline	0.25	32	72.2 / 0.6 / 27.2
Tigecycline[c]	0.03	0.03	100.0 / - / -
TMP/SMX[b]	≤0.5	>4	63.1 / 12.1 / 24.8
Vancomycin	0.25	0.5	100.0 / - / -
Enterobacteriaceae (1,738)[f]			
Ceftazidime-avibactam	0.12	0.25	- / - / -
Ceftazidime	0.25	32	85.5 / 1.4 / 13.1
Ceftriaxone	0.12	>8	82.1 / 1.2 / 16.8
Piperacillin/tazobactam	2	64	87.1 / 4.7 / 8.3
Meropenem	≤0.06	≤0.06	97.4 / 0.1 / 2.4
Levofloxacin	≤0.12	>4	80.1 / 2.8 / 17.1
Tetracycline	2	>32	63.9 / 6.1 / 30.0
Tigecycline[c]	0.25	1	98.7 / 1.2 / 0.1
TMP/SMX[b]	≤0.5	>4	80.9 / 0.0 / 19.1
E. coli (355)			
Ceftazidime-avibactam	0.12	0.25	- / - / -
Ceftazidime	0.25	16	88.2 / 1.3 / 10.4
Ceftriaxone	≤0.06	>8	84.8 / 0.0 / 15.2
Piperacillin/tazobactam	2	32	89.2 / 4.6 / 6.2
Meropenem	≤0.06	≤0.06	99.7 / 0.0 / 0.3
Levofloxacin	0.25	>4	55.2 / 0.3 / 44.5
Tetracycline	2	>32	62.3 / 0.2 / 37.5
Tigecycline[c]	0.12	0.12	100.0 / 0.0 / 0.0
TMP/SMX[b]	≤0.5	>4	62.0 / 0.0 / 38.0
ESBL-positive (62)			
Ceftazidime-avibactam	0.12	0.25	- / - / -
Ceftazidime	16	>32	32.3 / 8.0 / 59.7
Ceftriaxone	>8	>8	12.9 / 0.0 / 87.1
Piperacillin/tazobactam	8	>64	69.4 / 12.8 / 17.7
Meropenem	≤0.06	≤0.06	98.4 / 0.0 / 1.6
Levofloxacin	>4	>4	
Tetracycline	>32	>32	37.1 / 0.0 / 62.9
Tigecycline[c]	0.12	0.25	100.0 / 0.0 / 0.0
TMP/SMX[b]	>4	>4	43.5 / 0.0 / 56.5
K. pneumoniae (479)			
Ceftazidime-avibactam	0.12	0.5	- / - / -
Ceftazidime	0.12	>32	81.0 / 1.5 / 17.5
Ceftaroline-avibactam	0.06	0.25	- / - / -
Ceftriaxone	≤0.06	>8	81.6 / 0.2 / 18.2
Piperacillin/tazobactam	4	>64	82.8 / 2.9 / 14.3
Meropenem	≤0.06	≤0.06	91.6 / 0.4 / 8.1
Levofloxacin	≤0.12	>4	83.1 / 1.2 / 15.7
Tetracycline	2	>32	78.2 / 4.9 / 16.9
Tigecycline[c]	0.25	1	99.6 / 0.4 / 0.0
TMP/SMX[b]	≤0.5	>4	80.6 / 0.0 / 19.4
ESBL-positive (98)			
Ceftazidime-avibactam	0.5	1	- / - / -
Ceftazidime	>32	>32	7.1 / 7.2 / 85.7
Ceftriaxone	>8	>8	10.2 / 1.0 / 88.8
Piperacillin/tazobactam	>64	>64	22.4 / 11.3 / 66.3
Meropenem	≤0.06	>8	59.2 / 1.0 / 39.8
Levofloxacin	>4	>4	24.5 / 4.1 / 71.4
Tetracycline	8	>32	44.9 / 14.3 / 40.8
Tigecycline[c]	0.5	1	100.0 / 0.0 / 0.0
TMP/SMX[b]	>4	>4	23.5 / 0.0 / 76.5
Meropenem-non-susceptible (40)			
Ceftazidime-avibactam	0.5	2	- / - / -
Ceftazidime	>32	>32	0.0 / 0.0 / 100.0
Ceftriaxone	>8	>8	0.0 / 0.0 / 100.0
Piperacillin/tazobactam	>64	>64	0.0 / 0.0 / 100.0
Meropenem	>8	>8	0.0 / 2.5 / 97.5
Levofloxacin	>4	>4	2.5 / 0.0 / 97.5
Tetracycline	4	>32	57.5 / 22.5 / 20.0
Tigecycline[b]	0.5	1	100.0 / 0.0 / 0.0
TMP/SMX[b]	>4	>4	17.5 / 0.0 / 82.5
P. mirabilis (96)			
Ceftazidime-avibactam	0.03	0.06	- / - / -
Ceftazidime	0.06	0.12	99.0 / 1.0 / 0.0
Ceftriaxone	≤0.06	0.12	92.7 / 2.1 / 5.2
Piperacillin/tazobactam	≤0.5	1	100.0 / 0.0 / 0.0
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	>4	65.3 / 13.6 / 21.1
Tetracycline	32	>32	0.0 / 0.0 / 100.0
Tigecycline[c]	2	4	83.3 / 15.7 / 1.0
TMP/SMX[b]	≤0.5	>4	66.7 / 0.0 / 33.3
Enterobacter cloacae (244)			
Ceftazidime-avibactam	0.12	0.5	- / - / -
Ceftazidime	0.25	>32	75.8 / 0.8 / 23.4
Ceftriaxone	0.25	>8	71.6 / 1.7 / 26.7
Piperacillin/tazobactam	2	64	82.4 / 8.6 / 9.0
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	0.5	93.9 / 2.3 / 3.7
Tetracycline	2	8	87.2 / 5.0 / 7.8
Tigecycline[c]	0.25	0.5	100.0 / 0.0 / 0.0
TMP/SMX[b]	≤0.5	2	90.2 / 0.0 / 9.8
Ceftazidime-non-susceptible(MIC, ≥8 µg/mL; 59)			
Ceftazidime-avibactam	0.5	1	- / - / -
Ceftazidime	>32	>32	0.0 / 3.4 / 96.6
Ceftriaxone	>8	>8	0.0 / 0.0 / 100.0
Piperacillin/tazobactam	64	>64	27.1 / 35.6 / 37.3
Meropenem	≤0.06	0.12	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	4	84.7 / 6.8 / 8.5
Tetracycline	2	>32	75.9 / 10.3 / 13.8
Tigecycline[c]	0.25	2	100.0 / 0.0 / 0.0
TMP/SMX[b]	≤0.5	>4	74.6 / 0.0 / 25.4
Serratia marcescens (200)			
Ceftazidime-avibactam	0.12	0.5	- / - / -
Ceftazidime	0.12	0.5	96.5 / 0.5 / 3.0
Ceftriaxone	0.25	2	87.4 / 3.0 / 9.6
Piperacillin/tazobactam	2	8	94.9 / 3.1 / 2.0
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	1	95.0 / 4.0 / 1.0
Tetracycline	16	>32	10.0 / 30.5 / 59.5
Tigecycline[c]	0.5	1	100.0 / 0.0 / 0.0
TMP/SMX[b]	≤0.5	1	99.0 / 0.0 / 1.0
Pseudomonas aeruginosa (881)			
Ceftazidime-avibactam	2	8	- / - / -
Ceftazidime	2	32	79.5 / 5.1 / 15.4
Cefepime	4	>16	80.9 / 8.6 / 10.5
Piperacillin/tazobactam	8	>64	75.2 / 9.7 / 15.1
Meropenem	0.5	8	78.8 / 6.7 / 14.5
Ciprofloxacin	0.25	>4	75.4 / 6.0 / 18.6
Levofloxacin	0.5	>4	73.0 / 7.9 / 19.1
Gentamicin	2	8	84.9 / 5.5 / 9.6
Amikacin	2	8	96.6 / 2.2 / 1.2
Colistin	1	2	98.4 / 1.3 / 0.2
Ceftazidime-non-susceptible (MIC, ≥16 µg/mL; 181)			
Ceftazidime-avibactam	4	16	- / - / -
Ceftazidime	32	>32	0.0 / 24.9 / 75.1
Cefepime	16	>16	21.0 / 32.0 / 47.0
Piperacillin/tazobactam	>64	>64	5.5 / 23.2 / 71.3
Meropenem	4	>8	44.8 / 9.3 / 45.9
Ciprofloxacin	2	>4	42.5 / 10.0 / 47.5
Levofloxacin	4	>4	39.8 / 12.1 / 48.1
Gentamicin	4	>8	63.0 / 8.8 / 28.2
Amikacin	4	16	90.6 / 5.0 / 4.4
Colistin	1	2	98.9 / 0.5 / 0.6
Meropenem-non-susceptible (MIC, ≥4 µg/mL;187)			
Ceftazidime-avibactam	4	16	- / - / -
Ceftazidime	16	>32	46.5 / 13.4 / 40.1
Cefepime	16	>16	46.5 / 21.9 / 31.6
Piperacillin/tazobactam	64	>64	34.2 / 26.2 / 39.6
Meropenem	8	>8	0.0 / 31.6 / 68.4
Ciprofloxacin	4	>4	38.5 / 7.0 / 54.5
Levofloxacin	>4	>4	34.8 / 8.5 / 56.7
Gentamicin	4	>8	59.9 / 11.2 / 28.9
Amikacin	8	16	90.4 / 6.3 / 3.2
Colistin	1	2	96.8 / 2.2 / 1.1

a. Criteria as published by the CLSI [2013].
b. Trimethoprim/sulfamethoxazole.
c. US-FDA breakpoints were applied when available [Tygacil Product Insert, 2012].
d. Criteria as published by the CLSI [2013] for 'Penicillin parenteral non-meningitis' (S≤2, I=4, R≥8 µg/mL).
e. Criteria as published by the CLSI [2013] for 'Penicillin oral penicillin V' (S≤0.06, I=0.12-1, R≥2 µg/mL).
f. Includes: *Citrobacter freundii* (20 strains), *C. koseri* (39 strains), *E. aerogenes* (121 strains), *E. cloacae* (244 strains), *E. coli* (355 strains), *K. oxytoca* (117 strains), *K. pneumoniae* (479 strains), *M. morganii* (23 strains), *P. mirabilis* (96 strains), *P. vulgaris* (5 strains), *P. rettgeri* (8 strains), *P. stuartii* (31 strains), and *S. marcescens* (200 strains).

Conclusions

- Ceftazidime-avibactam demonstrated potent activity against contemporary (2012) Gram-negative pathogens isolated from USA patients hospitalized with pneumonia, and showed similar activity to that of ceftazidime against Gram-positive bacteria.
- Ceftazidime-avibactam demonstrated activity against ESBL- and KPC-phenotypes of Enterobacteriaceae.
- Ceftazidime-avibactam also exhibited activity against ceftazidime-non-susceptible (79.6% at ≤8 µg/mL) and meropenem-non-susceptible (85.0% at ≤8 µg/mL) *P. aeruginosa*.
- The Gram-negative activity profile of ceftazidime-avibactam indicates that further study is warranted to evaluate its potential usefulness in infections where MDR-Gram-negatives may be suspected.

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Acknowledgments

This study was supported by Forest Laboratories, Inc. Forest Laboratories, Inc., was involved in the study design and in the decision to present these results. Forest Laboratories, Inc., had no involvement in the analysis, collection, and interpretation of data. Scientific Therapeutics Information, Inc., provided editorial coordination, which was funded by Forest Research Institute, Inc.