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Ceftazidime-Avibactam and Comparator Agents Tested Against Urinary Tract Isolates from a Global Surveillance Program (2011)

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Amended Abstract

Background: Ongoing Phase III clinical trials for ceftazidime-avibactam (CAZ-AVI) include complicated urinary tract infection (UTI) and intra-abdominal infections. In this study, we report results of *in vitro* testing of CAZ-AVI and comparator agents against a contemporary collection of UTI isolates from the USA, Europe and Mediterranean region (EMR), Latin America (LATAM), and the Asia-Pacific and South Africa (APAC) regions.

Methods: Clinical isolates (one per patient) were collected from hospitalized patients with a UTI during 2011. A total of 1,797 isolates were collected from 159 medical centers (no. of medical centers [no. of isolates]): 67 (821), USA; 46 (610), EMR; 16 (183), LATAM; and 30 (183), APAC. Isolates were processed at the medical centers and forwarded to a central laboratory (JMI Laboratories, North Liberty, Iowa, USA) for confirmatory identification and susceptibility (S) testing using CLSI methods. AVI was tested at a fixed concentration of 4 µg/mL.

Results: CAZ-AVI was highly active against Gram-negative (GN) bacteria including Enterobacteriaceae (ENT) and *P. aeruginosa* (PSA). In the USA, EMR, LATAM and APAC there were 560, 470, 130 and 137 ENT isolates, respectively. The MIC_{90} values for ENT in the USA, EMR and LATAM regions were 0.25-0.5 µg/mL; APAC MIC_{90} was 1 µg/mL. In the USA, all ENT MIC values were ≤2 µg/mL; 99.4% of values in the EMR were ≤4 µg/mL (CLSI S breakpoint for CAZ alone). In LATAM and APAC, 99.2 (129/130) and 94.9% (130/137) of ENT MIC values were ≤4 µg/mL. A total of 6.1% (8/131) of *E. coli* in the USA, 23.5% (43/183) in the EMR, 61.2% (30/49) in LATAM, and 75.0% (9/12) in APAC showed an ESBL-phenotype. The MIC_{90} values for all *E. coli* in the USA and EMR were 0.12 and 0.25 µg/mL, respectively, while for CAZ alone the MIC_{90} values were 0.5 and 32 µg/mL. A total of 1.6% (2/129) of *K. pneumoniae* isolates in the USA were meropenem-non-susceptible (MER-NS, MIC ≥2 µg/mL) and 10.3% (10/97) in the EMR. All isolates (17) of PSA in the USA and 80.9% (38/47) in the EMR were inhibited at a MIC of ≤8 µg/mL compared to 88.2% (15/17) and 61.7% (29/47) for CAZ alone. The 9 EMR PSA isolates with CAZ-AVI MIC values ≥32 µg/mL were from Romania (5), Portugal (3) and Poland (1).

Conclusions: CAZ-AVI demonstrated *in vitro* activity against GN bacteria from patients with UTI, including activity against multidrug-resistant organisms.

Introduction

Urinary tract infections are common in both the community and hospital settings. Increased morbidity and mortality may occur in complicated urinary tract infections (cUTIs), thus making the selection of appropriate initial therapy extremely important. Wide variation exists in the choice of antimicrobial agents and duration of treatment for cUTIs. These treatment differences occur due to concerns about bacterial resistance among uropathogens, drug availability and cost, expected efficacy and a desire to limit the effect of the antimicrobial on normal bacterial flora.

Ceftazidime-avibactam is a combination agent consisting of the non-β-lactam β-lactamase inhibitor avibactam and the cephalosporin ceftazidime. Ceftazidime-avibactam administered at 500 mg of ceftazidime and 125 mg of avibactam every 8 hours was shown to have efficacy and safety similar to imipenem-cilastatin (500 mg every 6 hours) in a Phase II study of cUTI (Vazquez et al 2012). A favorable microbiologic outcome of 70.4% in the microbiologically evaluable population was shown for ceftazidime-avibactam compared to 71.4% for imipenem-cilastatin. *Escherichia coli* was the predominant uropathogen recovered from amongst these patients.

In an effort to evaluate the activity of ceftazidime-avibactam against uropathogens on a global scale, the present study evaluated the activity of ceftazidime-avibactam and comparator agents against a contemporary collection of UTI isolates from the USA, Europe and Mediterranean region (EMR), Latin America (LATAM), and the Asia-Pacific and South Africa (APAC) regions.

Materials and Methods

Organism Collection:
A total of 1,797 isolates were identified as UTI pathogens (including pathogens from both complicated and uncomplicated infections) based on the infection site and/or specimen type recorded by the participant laboratory. Isolates were collected from patients at 159 medical centers (no. of medical centers [no. of isolates]): 67 (821), USA; 46 (610), EMR; 16 (183), LATAM; and 30 (183), APAC. Isolates were processed at the respective medical centers and forwarded to a coordinating laboratory (JMI Laboratories, North Liberty, Iowa, USA; Australian isolates, South Australia Pathology, Women's & Children's Hospital, Adelaide, Australia) for confirmatory identification and susceptibility testing using Clinical and Laboratory Standards Institute (CLSI) methods. Avibactam was tested at a fixed concentration of 4 µg/mL.

Susceptibility Testing:
Isolates were susceptibility tested against ceftazidime-avibactam and comparator agents by CLSI reference broth microdilution methods. CLSI interpretative criteria were applied per M100-S23, European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretations were based on EUCAST breakpoint tables version 3.0, January 2013. USA-FDA breakpoint criteria for tigecycline were also used. Isolates were tested in cation-adjusted Mueller-Hinton broth (CA-MHB). CA-MHB supplemented with 2.5-5% lysed horse blood was used for the fastidious streptococci. Extended spectrum β-lactamase (ESBL)-phenotype was defined as a MIC of ≥2 µg/mL for ceftazidime or ceftriaxone or aztreonam (CLSI, 2013). Concurrent quality control (QC) testing was performed including the following strains: *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Streptococcus pneumoniae* ATCC 49619 and *E. coli* ATCC 25922 and 35218; and all QC results were within published CLSI ranges.

Results

- Ceftazidime-avibactam was highly active against Enterobacteriaceae from UTI with MIC_{50} and MIC_{90} values for all isolates at 0.12 and 0.25 µg/mL (Table 1). The MIC_{90} value for ceftazidime alone tested against these organisms was 128-fold higher (32 µg/mL) than that for ceftazidime-avibactam.
- Enterobacteriaceae isolates from the APAC region had the highest ceftazidime-avibactam MIC_{90} at 1 µg/mL (>32 µg/mL for ceftazidime alone; Table 2). In the USA, all ceftazidime-avibactam MIC values for Enterobacteriaceae were ≤2 µg/mL; 99.4% and 99.2% of values in the EMR and LATAM were ≤4 µg/mL, respectively (CLSI susceptibility breakpoint for ceftazidime alone; data not shown).
- Ciprofloxacin resistance among all Enterobacteriaceae was at 23.5/26.1% (CLSI/EUCAST) and meropenem resistance at 1.9/1.0% (data not shown). Regional ciprofloxacin resistance varied from a low of 11.1/13.4% (CLSI/EUCAST) in the USA to a high of 40.0/45.4% in LATAM (Table 2). Meropenem resistance varied from a low of 0.8/0.0% in LATAM to a high of 3.7/2.9% in APAC (Table 2).
- The MIC_{50} and MIC_{90} for ceftazidime-avibactam tested against all *E. coli* from UTI were 0.06 and 0.12 µg/mL, respectively, compared to 0.25 and 32 µg/mL for ceftazidime alone (Table 1). Regional ceftazidime-avibactam MIC_{90} values were 0.12 µg/mL (USA), 0.25 µg/mL (EMR), 0.25 µg/mL (LATAM), and 0.25 µg/mL (APAC; Table 2).
- The overall ESBL-phenotype rate for *E. coli* was 24.0% (Table 1). When analyzed by region, 6.1% (8/131) of *E. coli* in the USA, 23.5% (43/183) in the EMR, 61.2% (30/49) in LATAM, and 75.0% (9/12) in APAC showed an ESBL-phenotype (data not shown).
- Ciprofloxacin resistance among all *E. coli* was at 37.9/37.9% (CLSI/EUCAST) and there was no meropenem resistance (data not shown). Regional ciprofloxacin resistance rates varied from a low of 22.1/22.1% in the USA (CLSI/EUCAST) to a high of 75.0/75.0% in APAC (Table 2).
- The MIC_{90} for ceftazidime-avibactam tested against all *Klebsiella pneumoniae* isolated from UTI was >64-fold lower than for ceftazidime alone (0.5 compared to >32 µg/mL; Table 1). Regional ceftazidime-avibactam MIC_{90} values were 0.25 µg/mL (USA), 1 µg/mL (EMR), and 0.25 µg/mL (LATAM; Table 2).
- The overall ESBL-phenotype rate for *K. pneumoniae* was 33.1% (Table 1). A total of 6.2% (8/129) of *K. pneumoniae* in the USA, 61.9% (60/97) in the EMR, 60.0% (15/25) in LATAM, and 33.3% (1/3) in APAC showed an ESBL-phenotype. Ciprofloxacin resistance among all *K. pneumoniae* was 26.4/29.1% (CLSI/EUCAST) and meropenem resistance was 4.3/3.2% (data not shown).
- Regional ciprofloxacin resistance (CLSI/EUCAST) for *K. pneumoniae* varied from a low of 5.4/5.4% in the USA to a high of 55.7/57.7% in the EMR (excluding APAC where only three isolates were recovered; Table 2). There were no meropenem-resistant *K. pneumoniae* in LATAM and APAC; however, in the USA the rate was 1.6/0.8% and in the EMR it was 9.3/7.2% (Table 2). All meropenem-non-susceptible *K. pneumoniae* strains in the USA and EMR exhibited a ceftzidime-avibactam MIC ≤4 µg/mL (Table 1).

Table 1. Cumulative MIC distribution values for ceftazidime-avibactam when tested against selected UTI isolates from all regions (2011)

Organism/resistant subset	No. of isolates	No. of isolates (cumulative %) inhibited at MIC (µg/mL) of:											
		≤0.06	0.12	0.25	0.5	1	2	4	8	16	≥32	MIC_{50}	MIC_{90}
Enterobacteriaceae	1,297	640 (49.3)	364 (77.4)	178 (91.1)	64 (96.1)	23 (97.8)	14 (98.9)	3 (99.2)	0 (99.2)	0 (99.2)	11 (100.0)	0.12	0.25
Escherichia coli	375	244 (65.1)	96 (90.7)	30 (98.7)	4 (99.7)	0 (99.7)	0 (99.7)	1 (100.0)	–	–	–	0.06	0.12
ESBL-phenotype	90	34 (37.8)	31 (72.2)	20 (94.4)	4 (98.9)	0 (98.9)	0 (98.9)	1 (100.0)	–	–	–	0.12	0.25
Klebsiella pneumoniae	254	103 (40.6)	86 (74.4)	33 (87.4)	18 (94.5)	6 (96.9)	7 (99.6)	1 (100.0)	–	–	–	0.12	0.5
ESBL-phenotype	84	10 (11.9)	25 (41.7)	20 (65.5)	15 (83.3)	6 (90.5)	7 (98.8)	1 (100.0)	–	–	–	0.25	1
MER-non-susceptible (MIC, ≥2 µg/mL)	12	–	2 (16.7)	1 (25.0)	4 (58.3)	1 (66.7)	3 (91.7)	1 (100.0)	–	–	–	0.5	2
Klebsiella oxytoca	42	21 (50.0)	10 (73.8)	6 (88.1)	5 (100.0)	–	–	–	–	–	–	0.06	0.5
Morganella morganii	127	105 (82.7)	12 (92.1)	9 (99.2)	1 (100.0)	–	–	–	–	–	–	0.06	0.12
Citrobacter spp.	176	53 (30.1)	59 (63.6)	41 (86.9)	14 (94.9)	4 (97.2)	1 (97.7)	1 (98.3)	0 (98.3)	0 (98.3)	3 (100.0)	0.12	0.5
Enterobacter spp.	159	26 (16.4)	64 (56.6)	37 (79.9)	14 (88.7)	10 (95.0)	5 (98.1)	0 (98.1)	0 (98.1)	0 (98.1)	3 (100.0)	0.12	1
Serratia marcescens	67	2 (3.0)	30 (47.8)	20 (77.6)	8 (89.6)	3 (94.0)	1 (95.5)	0 (95.5)	0 (95.5)	0 (95.5)	3 (100.0)	0.25	1
Pseudomonas aeruginosa	80	–	–	1 (1.3)	1 (2.5)	25 (33.8)	24 (63.7)	10 (76.3)	6 (83.8)	2 (86.3)	11 (100.0)	2	32
MER-non-susceptible (MIC, ≥4 µg/mL)	26	–	–	–	–	1 (3.8)	4 (19.2)	3 (30.8)	6 (53.8)	1 (57.7)	11 (100.0)	8	>32
CAZ-non-susceptible (MIC, ≥16 µg/mL)	26	–	–	–	–	1 (3.8)	3 (15.4)	4 (30.8)	5 (50.0)	2 (57.7)	11 (100.0)	8	>32
Staphylococcus aureus	88	–	–	–	–	–	–	12 (13.6)	30 (47.7)	9 (58.0)	37 (100.0)	16	>32
β-haemolytic streptococci	177	–	11 (6.2)	18 (16.4)	147 (99.4)	1 (100.0)	–	–	–	–	–	0.5	0.5

CAZ, ceftazidime; MER, meropenem

Table 2. Activity by geographic region for ceftazidime-avibactam and comparator agents when tested against selected UTI Gram-negative clinical isolates (2011)

	USA				EMR				LATAM				APAC			
Antimicrobial agent (N)	MIC_{50}[b]	MIC_{90}[b]	CLSI[a] %S / %R	EUCAST[a] %S / %R	MIC_{50}[b]	MIC_{90}[b]	CLSI[a] %S / %R	EUCAST[a] %S / %R	MIC_{50}[b]	MIC_{90}[b]	CLSI[a] %S / %R	EUCAST[a] %S / %R	MIC_{50}[b]	MIC_{90}[b]	CLSI[a] %S / %R	EUCAST[a] %S / %R
Enterobacteriaceae	N=560				N=470				N=130				N=137			
Ceftazidime-avibactam	0.06	0.25	– / –	– / –	0.06	0.5	– / –	– / –	0.12	0.25	– / –	– / –	0.12	1	– / –	– / –
Ceftazidime	0.12	2	91.1 / 8.4	89.5 / 8.9	0.25	>32	73.2 / 23.6	69.6 / 26.8	2	>32	55.4 / 38.5	46.9 / 44.6	0.5	>32	65.0 / 32.8	58.4 / 35.0
Cefepime	≤0.5	≤0.5	97.5 / 1.4	93.9 / 2.9	≤0.5	>16	80.9 / 18.3	74.7 / 21.3	≤0.5	>16	67.7 / 27.7	56.9 / 39.2	≤0.5	>16	79.6 / 16.8	73.7 / 23.4
Ciprofloxacin	≤0.03	>4	86.6 / 11.1	85.0 / 13.4	0.06	>4	65.5 / 32.3	63.2 / 34.5	0.25	>4	54.6 / 40.0	51.5 / 45.4	0.12	>4	68.6 / 28.5	67.2 / 31.4
Meropenem	≤0.06	≤0.06	98.8 / 0.9	99.1 / 0.2	≤0.06	0.12	97.0 / 2.8	97.2 / 1.7	≤0.06	≤0.06	99.2 / 0.8	99.2 / 0.0	0.06	0.25	94.9 / 3.7	96.4 / 2.9
Piperacillin-tazobactam	2	8	94.3 / 3.2	92.7 / 5.7	2	64	82.3 / 9.0	78.9 / 17.7	4	32	83.8 / 4.6	73.8 / 16.2	2	64	81.0 / 9.5	75.9 / 19.0
Escherichia coli	N=131				N=183				N=49				N=12			
Ceftazidime-avibactam	0.06	0.12	– / –	– / –	0.06	0.25	– / –	– / –	0.06	0.25	– / –	– / –	0.12	0.5	– / –	– / –
Ceftazidime	0.12	0.5	96.9 / 2.3	94.7 / 3.1	0.25	32	80.9 / 15.8	77.0 / 19.1	8	32	44.9 / 44.9	42.9 / 55.1	4	>32	50.0 / 41.7	25.0 / 50.0
Cefepime	≤0.5	≤0.5	97.7 / 1.5	93.9 / 3.1	≤0.5	>16	84.2 / 14.2	78.7 / 16.9	>16	>16	46.9 / 51.0	38.8 / 59.2	16	>16	41.7 / 41.7	25.0 / 75.0
Ciprofloxacin	≤0.03	>4	77.9 / 22.1	77.9 / 22.1	≤0.03	>4	60.7 / 39.3	59.6 / 39.3	>4	>4	34.7 / 65.3	34.7 / 65.3	>4	>4	25.0 / 75.0	25.0 / 75.0
Meropenem	≤0.06	≤0.06	100.0 / 0.0	100.0 / 0.0	≤0.06	≤0.06	100.0 / 0.0	100.0 / 0.0	≤0.06	≤0.06	100.0 / 0.0	100.0 / 0.0	≤0.06	≤0.06	100.0 / 0.0	100.0 / 0.0
Piperacillin-tazobactam	2	4	96.9 / 1.5	94.7 / 3.1	2	16	92.3 / 2.2	87.9 / 7.7	4	16	91.8 / 2.0	81.6 / 8.2	4	16	91.7 / 8.3	75.0 / 8.3
Klebsiella pneumoniae	N=129				N=97				N=25				N=3[c]			
Ceftazidime-avibactam	0.06	0.25	– / –	– / –	0.12	1	– / –	– / –	0.12	0.25	– / –	– / –	–	–	–	–
Ceftazidime	0.12	0.5	93.8 / 5.4	93.8 / 6.2	32	>32	42.3 / 53.6	40.2 / 57.7	4	>32	64.0 / 32.0	40.0 / 36.0	–	–	–	–
Cefepime	≤0.5	≤0.5	95.3 / 3.1	93.8 / 4.7	8	>16	50.5 / 48.5	41.2 / 53.6	8	>16	60.0 / 32.0	48.0 / 52.0	–	–	–	–
Ciprofloxacin	≤0.03	0.5	94.6 / 5.4	92.2 / 5.4	>4	>4	42.3 / 55.7	41.2 / 57.7	1	>4	56.0 / 24.0	48.0 / 44.0	–	–	–	–
Meropenem	≤0.06	≤0.06	98.5 / 1.6	98.5 / 0.8	≤0.06	2	89.7 / 9.3	90.7 / 7.2	≤0.06	≤0.06	100.0 / 0.0	100.0 / 0.0	–	–	–	–
Piperacillin-tazobactam	2	8	96.9 / 3.1	95.3 / 3.1	8	>64	56.7 / 23.7	50.5 / 43.3	8	>64	76.0 / 12.0	64.0 / 24.0	–	–	–	–
Enterobacter spp.	N=67				N=44				N=17				N=31			
Ceftazidime-avibactam	0.12	0.25	– / –	– / –	0.12	0.5	– / –	– / –	0.25	1	– / –	– / –	0.25	2	– / –	– / –
Ceftazidime	0.25	4	91.0 / 9.0	88.1 / 9.0	0.5	>32	63.6 / 34.1	61.4 / 36.4	32	>32	17.6 / 76.5	11.8 / 82.4	16	>32	41.9 / 58.1	35.5 / 58.1
Cefepime	≤0.5	≤0.5	95.5 / 3.0	91.0 / 4.5	≤0.5	8	93.2 / 6.8	79.5 / 13.6	1	>16	82.4 / 11.8	58.8 / 23.5	≤0.5	>16	71.0 / 25.8	67.7 / 29.0
Ciprofloxacin	≤0.03	0.25	92.5 / 6.0	92.5 / 7.5	≤0.03	>4	77.3 / 18.2	72.7 / 22.7	0.25	>4	64.7 / 35.3	58.8 / 35.3	0.12	>4	58.1 / 38.7	54.8 / 41.9
Meropenem	≤0.06	≤0.06	95.5 / 3.0	97.0 / 0.0	≤0.06	0.12	97.7 / 2.3	97.7 / 2.3	≤0.06	0.12	100.0 / 0.0	100.0 / 0.0	≤0.06	1	90.3 / 6.5	93.5 / 6.5
Piperacillin-tazobactam	4	8	94.0 / 4.5	92.5 / 6.0	4	>64	72.7 / 15.9	72.7 / 27.3	16	64	52.9 / 5.9	29.4 / 47.1	8	>64	58.1 / 29.0	51.6 / 41.9
Citrobacter spp.	N=93				N=37				N=11				N=35			
Ceftazidime-avibactam	0.12	0.25	– / –	– / –	0.12	0.5	– / –	– / –	0.12	0.5	– / –	– / –	0.12	0.5	– / –	– / –
Ceftazidime	0.25	>32	79.6 / 20.4	79.6 / 20.4	0.25	32	78.4 / 18.9	75.7 / 21.6	0.5	>32	63.6 / 27.3	54.5 / 36.4	0.5	>32	65.7 / 34.3	62.9 / 34.3
Cefepime	≤0.5	1	97.8 / 0.0	92.5 / 3.2	≤0.5	8	91.9 / 8.1	89.2 / 10.8	≤0.5	1	90.9 / 9.1	90.9 / 9.1	≤0.5	>16	82.9 / 14.3	77.1 / 20.0
Ciprofloxacin	≤0.03	0.25	93.5 / 3.2	92.5 / 6.5	≤0.03	>4	86.5 / 10.8	86.5 / 13.5	≤0.03	0.25	90.9 / 9.1	90.9 / 9.1	0.06	4	80.0 / 17.1	80.0 / 20.0
Meropenem	≤0.06	≤0.06	97.8 / 1.1	98.9 / 0.0	≤0.06	≤0.06	100.0 / 0.0	100.0 / 0.0	≤0.06	≤0.06	90.9 / 9.1	90.9 / 0.0	≤0.06	≤0.06	94.3 / 2.9	97.1 / 0.0
Piperacillin-tazobactam	2	64	82.8 / 6.5	79.6 / 17.2	2	64			2	32	81.8 / 9.1	72.7 / 18.2	4	64	77.1 / 2.9	74.3 / 22.9
Morganella morganii	N=51				N=36				N=11				N=29			
Ceftazidime-avibactam	0.06	0.25	– / –	– / –	≤0.03	0.12	– / –	– / –	≤0.03	0.12	– / –	– / –	0.06	0.06	– / –	– / –
Ceftazidime	0.12	32	78.4 / 19.6	72.5 / 21.6	0.25	8	88.9 / 5.6	80.6 / 11.1	0.25	2	90.9 / 9.1	72.7 / 9.1	0.12	16	82.8 / 13.8	72.4 / 17.2
Cefepime	≤0.5	≤0.5	100.0 / 0.0	96.1 / 0.0	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0	≤0.5	16	81.8 / 0.0	81.8 / 8.2	≤0.5	1	100.0 / 0.0	93.1 / 0.0
Ciprofloxacin	≤0.03	>4	68.6 / 23.5	62.7 / 31.4	≤0.03	1	91.7 / 5.6	80.6 / 8.3	>4	>4	27.3 / 63.6	27.3 / 72.7	0.06	>4	69.0 / 24.1	65.5 / 31.0
Meropenem	≤0.06	0.12	100.0 / 0.0	100.0 / 0.0	≤0.06	0.12	100.0 / 0.0	100.0 / 0.0	≤0.06	0.12	100.0 / 0.0	100.0 / 0.0	0.12	0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin-tazobactam	≤0.5	2	98.0 / 2.0	98.0 / 2.0	≤0.5	2	100.0 / 0.0	100.0 / 0.0	≤0.5	2	100.0 / 0.0	100.0 / 0.0	≤0.5	4	100.0 / 0.0	93.1 / 0.0
Pseudomonas aeruginosa	N=17				N=47				N=13				N=3[c]			
Ceftazidime-avibactam	2	4	– / –	– / –	2	32	– / –	– / –	2	16	– / –	– / –	–	–	–	–
Ceftazidime	2	32	88.2 / 11.8	88.2 / 11.8	4	32	61.7 / 31.9	61.7 / 38.3	8	32	61.5 / 23.1	61.5 / 38.5	–	–	–	–
Cefepime	4	16	88.2 / 5.9	88.2 / 11.8	8	>16	66.0 / 21.3	66.0 / 34.0	8	>16	61.5 / 23.1	61.5 / 38.5	–	–	–	–
Ciprofloxacin	0.5	>4	64.7 / 35.3	52.9 / 35.3	0.5	>4	51.1 / 44.7	51.1 / 48.9	0.5	>4	61.5 / 38.5	53.8 / 38.5	–	–	–	–
Meropenem	0.25	8	88.2 / 11.8	88.2 / 5.9	0.5	>8	61.7 / 29.8	61.7 / 23.4	2	>8	61.5 / 30.8	61.5 / 30.8	–	–	–	–
Piperacillin-tazobactam	8	>64	76.5 / 11.8	76.5 / 23.5	16	>64	57.4 / 25.5	57.4 / 42.6	16	>64	53.8 / 15.4	53.8 / 46.2	–	–	–	–

[a]Criteria as published by the CLSI (2013) and EUCAST (2013). As there are currently no established susceptibility criteria for ceftazidime-avibactam, no susceptibility interpretation was provided.
[b]Units in µg/mL.
[c]Susceptibility values were not presented when the number of isolates was <10.

- Against all *Pseudomonas aeruginosa* strains, ceftazidime-avibactam exhibited a MIC_{50} that was two-fold lower than ceftazidime alone (2 vs 4 µg/mL; Table 1). The MIC_{90} value for both ceftazidime-avibactam and ceftazidime alone was 32 µg/mL (Table 1). A total of 83.8% (ceftazidime-avibactam) and 67.5% (ceftazidime alone) of isolates exhibited MIC values at ≤8 µg/mL (Table 1). Ceftazidime-avibactam was more active against meropenem-non-susceptible and ceftazidime-non-susceptible strains than ceftazidime alone (Table 1). The MIC_{50} and MIC_{90} values for ceftazidime-avibactam against meropenem-non-susceptible *P. aeruginosa* were 8 and >32 µg/mL, while for ceftazidime alone the values were 32 and >32 µg/mL, respectively (Table 1). A total of 53.8% of meropenem-non-susceptible and 50.0% of ceftazidime-non-susceptible isolates exhibited a MIC value of ≤8 µg/mL, respectively, for ceftazidime-avibactam (Table 1).
- All *P. aeruginosa* isolates in the USA and 80.9% (38/47) in the EMR were inhibited at a ceftazidime-avibactam MIC of ≤8 µg/mL compared to 88.2% (15/17) and 61.7% (29/47), respectively, for ceftazidime alone (data not shown).
- In the EMR, all nine *P. aeruginosa* isolates with ceftazidime-avibactam MIC values ≥32 µg/mL were from Romania (5), Portugal (3) and Poland (1), indicating national differences for these resistant isolates.

Conclusions

- Ceftazidime-avibactam was highly active against Gram-negative bacteria isolated from UTI from a global surveillance program conducted during 2011.
- Against the Enterobacteriaceae, ceftazidime-avibactam demonstrated activity against a variety of resistant and multidrug-resistant bacteria, including ESBL- and KPC-phenotype strains. A total of 99.2% of all Enterobacteriaceae exhibited a ceftazidime-avibactam MIC of ≤4 µg/mL (the CLSI susceptible breakpoint for ceftazidime alone), a marked improvement over ceftazidime alone (78.3%).
- Ceftazidime-avibactam was more active than ceftazidime alone against *P. aeruginosa* strains, including those that were non-susceptible to meropenem or ceftazidime.
- The potent activity shown by ceftazidime-avibactam against Gram-negative bacteria from UTI that occurred in the USA, EMR, LATAM and Asia-Pacific regions demonstrates that clinical study in patients with UTI, including those with multi-drug-resistant strains, is merited.

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Ceftazidime-Avibactam and Comparator Agents Tested Against Urinary Tract Isolates from a Global Surveillance Program (2011)

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