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Antimicrobial Activity of Ceftazidime-avibactam and Comparator Agents Tested Against Gram-negative Organisms Isolated from Urinary Tract Infections (UTI): Results from the International Network for Optimal Resistance Monitoring (INFORM) Program

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Abstract

Background:
Ceftazidime-avibactam (CAZ-AVI) consists of CAZ combined with the novel non-β-lactam β-lactamase (BL) inhibitor AVI, a non-β-lactam BL inhibitor that inhibits Ambler classes A (eg, ESBL and KPC), C and some D enzymes.

Methods:
7272 unique patient organisms were collected from 71 USA medical centers from patients with UTI in 2012-2014. Susceptibility (S) testing was performed for CAZ-AVI (AVI at fixed 4 µg/mL) and comparators by reference broth microdilution methods. Enterobacteriaceae (ENT) with an ESBL phenotype were evaluated for the presence of genes encoding ESBLs, KPC, NDM and transferable AmpC enzymes using a microarray-based assay.

Results:
An ESBL phenotype was observed among 11.5, 13.9 and 4.7% of *E. coli* (EC), *Klebsiella* spp. (KSP) and *P. mirabilis* (PM), respectively. CAZ-AVI inhibited >99.9% of all ENT, including all EC and PM isolates, at the S breakpoint of ≤8 µg/mL. CAZ-AVI was also highly active against KSP, including ESBL-phenotype ($MIC_{50/90}$, 0.25/1 µg/mL; 99.5% S) and meropenem (MEM)-non-S *K. pneumoniae* (KPN; $MIC_{50/90}$, 0.5/2 µg/mL; 98.6% S). Among *E. cloacae* (ECL; 23.3% CAZ-non-S), 99.7% of isolates, including 98.8% of CAZ-non-S strains, were S to CAZ-AVI. Overall, only 3 of 6773 ENT (0.04%) were non-S to CAZ-AVI, one KPN with VIM-4, KPC-2 and CMY-2, and one ECL and one *Providencia* spp. with negative results for all BL tested. CAZ-AVI was also highly active against *P. aeruginosa* (PSA; $MIC_{50/90}$, 2/4 µg/mL; 97.7% S), including the majority of isolates non-S to MEM (90.5% S to CAZ-AVI) or CAZ (82.7% S). Further, CAZ-AVI inhibited 77.8% (21/27) of PSA isolates non-S to MEM, CAZ and piperacillin/tazobactam at ≤8 µg/mL. CAZ-AVI showed limited activity against *Acinetobacter* spp. (57 isolates [0.8% of total], $MIC_{50/90}$, 16/>32 µg/mL).

Conclusions:
CAZ-AVI demonstrated potent activity against a large collection of contemporary (2012-2014) Gram-negative bacilli isolated from patients with UTI in USA hospitals, and provided greater coverage than agents currently available in the USA.

Introduction

Urinary tract infections (UTI) are among the most frequent healthcare-associated infections and represent a major source of Gram-negative bacteremia. *Escherichia coli* is, by a large margin, the most common cause of community, as well as healthcare-associated UTI (HA-UTI). In recurrent UTI, especially in the presence of structural abnormalities of the urinary tract, the relative frequency of *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp. and *Pseudomonas aeruginosa* increases. Since instrumentation and repeat courses of antimicrobial therapy are common in these complicated patients, antimicrobial-resistant isolates might be expected.

Ceftazidime-avibactam is a combination agent consisting of the non-β-lactam β-lactamase inhibitor avibactam and the broad-spectrum cephalosporin, ceftazidime. Avibactam is a member of a novel class of β-lactamase inhibitors called the diazabicyclooctanes. Compared with current inhibitors available for clinical use, diazabicyclooctanes are more potent, have a broader spectrum of enzyme inhibition and a different mechanism of action. Avibactam protects β-lactams from hydrolysis by a variety of clinically-relevant enzymes.

Ceftazidime-avibactam has been approved by the United States (USA) Food and Drug Administration (FDA) for treatment of complicated intra-abdominal infections, in combination with metronidazole and complicated UTIs, including pyelonephritis, in patients with limited or no alternative treatment options. Ceftazidime-avibactam is also under clinical development for treatment of nosocomial pneumonia (http://clinicaltrials.gov; NCT01808092). In this investigation, the activity of ceftazidime combined with avibactam was evaluated against a large collection of contemporary Gram-negative organisms isolated from patients with UTI in USA hospitals.

Methods

Organism collection: A total of 7,272 unique patient organisms were collected from patients with UTI in 71 USA medical centers during 2012–2014 as part of the International Network for Optimal Resistance Monitoring (INFORM) program. Only one isolate per patient was included in the surveillance study. Species identification was performed at the participating medical center and was confirmed at the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) using matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) (Bruker Daltonics, Billerica, Massachusetts, USA), as necessary. An extended-spectrum-β-lactamase (ESBL)-screen-positive phenotype was defined as a MIC of ≥2 µg/mL for ceftazidime or ceftriaxone or aztreonam.

Susceptibility testing: Broth microdilution test methods conducted according to the Clinical and Laboratory Standards Institute (CLSI) were performed to determine the antimicrobial susceptibility of ceftazidime-avibactam (inhibitor at fixed concentration of 4 µg/mL) and comparator agents. Validated minimum inhibitory concentration (MIC) panels were manufactured by Thermo Fisher Scientific Inc. (Cleveland, Ohio, USA). Concurrent quality control (QC) testing was performed including the following strains: *E. coli* ATCC 25922 and 35218, *Klebsiella pneumoniae* ATCC 700603 and BAA1705, and *P. aeruginosa* ATCC 27853; and all QC results were within published ranges.

Screening for β-lactamases: Enterobacteriaceae isolates with ceftazidime-avibactam MIC at >8 µg/mL 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. This kit detects CTX-M Groups 1, 2, 8+25 and 9, TEM wild-type (WT) and ESBL, SHV WT and ESBL, ACC, ACT/MIR, CMYII, DHA, FOX, KPC and NDM-1.

Results

- Ceftazidime-avibactam inhibited >99.9% of all Enterobacteriaceae isolates, including all *E. coli* ($MIC_{50/90}$, 0.06/0.12 µg/mL) and *P. mirabilis* ($MIC_{50/90}$, 0.03/0.06 µg/mL) isolates, at the susceptible breakpoint of ≤8 µg/mL (Table 1 and Figure 1).
- Overall, only three of 6,773 tested Enterobacteriaceae isolates (0.04%) were non-susceptible to ceftazidime-avibactam (MIC, ≥16 µg/mL), one *K. pneumoniae* from New York, NY, with VIM-4, KPC-2 and CMY-2 (ceftazidime-avibactam MIC of >32 µg/mL), one *Enterobacter cloacae* (also from New York, NY, but a different medical center; MIC, 32 µg/mL) and one *Providencia stuartii* (from Winston Salem, NC; MIC, 16 µg/mL) with negative results for all β-lactamases tested (Table 1 and Figure 1).
- An ESBL phenotype was observed among 11.5% of *E. coli*, 13.9% of *Klebsiella* spp. and 4.7% of *P. mirabilis*, respectively.
- A total of 2,876 *E. coli* isolates were included in this investigation, and the most active compounds tested against these organisms were ceftazidime-avibactam ($MIC_{50/90}$, 0.06/0.12 µg/mL; 100.0% susceptible), tigecycline ($MIC_{50/90}$, 0.06/0.12 µg/mL; 100.0% susceptible), meropenem ($MIC_{50/90}$, ≤0.06/≤0.06 µg/mL; 97.7% susceptible) and ceftazidime ($MIC_{50/90}$, 0.12/2 µg/mL; 91.9% susceptible; Table 2).
- Ceftazidime-avibactam was highly active against *Klebsiella* spp. ($MIC_{50/90}$, 0.12/0.25 µg/mL; 99.9% susceptible), including ESBL-phenotype ($MIC_{50/90}$, 0.25/1 µg/mL; 99.5% susceptible) and meropenem-non-susceptible *K. pneumoniae* ($MIC_{50/90}$, 0.5/2 µg/mL; 98.6% susceptible; Table 1).
- Only ceftazidime-avibactam ($MIC_{50/90}$, 0.5/2 µg/mL; 98.6% susceptible) and tigecycline ($MIC_{50/90}$, 0.5/1 µg/mL; 97.3 and 94.6% susceptible at ≤2 µg/mL [CLSI] and ≤1 µg/mL [EUCAST], respectively) showed reasonable activity against meropenem-non-susceptible *K. pneumoniae* (Table 1). Colistin inhibited only 68.0% of strains at the EUCAST susceptible breakpoint of ≤2 µg/mL (Table 2).
- All *P. mirabilis* strains were susceptible to ceftazidime-avibactam ($MIC_{50/90}$, 0.03/0.06 µg/mL), meropenem ($MIC_{50/90}$, ≤0.06/0.12 µg/mL) and aztreonam ($MIC_{50/90}$, ≤0.12/≤0.12 µg/mL), and ≥99.6% were susceptible to ceftazidime ($MIC_{50/90}$, 0.06/0.12 µg/mL) and piperacillin/tazobactam ($MIC_{50/90}$, ≤0.5/1 µg/mL; Table 2).
- Among *E. cloacae* (ceftazidime-avibactam $MIC_{50/90}$, 0.25/0.5 µg/mL; 23.3% ceftazidime-non-susceptible), 99.7% of isolates, including 98.8% of ceftazidime-non-susceptible strains ($MIC_{50/90}$, 0.5/1 µg/mL), were susceptible to ceftazidime-avibactam (Table 1).
- Ceftazidime-avibactam was also very active against *P. aeruginosa* ($MIC_{50/90}$, 2/4 µg/mL; 97.7% susceptible), including the vast majority of isolates non-susceptible to meropenem (90.5% susceptible to ceftazidime-avibactam) or ceftazidime (82.7% susceptible). Furthermore, ceftazidime-avibactam inhibited 77.8% (21/27) of isolates non-susceptible to meropenem, ceftazidime and piperacillin/tazobactam at ≤8 µg/mL (Table 1).
- Among *P. aeruginosa*, susceptibility to ceftazidime-avibactam ($MIC_{50/90}$, 2/4 µg/mL) was 9.5% greater (97.7 vs. 88.2%) than that of ceftazidime ($MIC_{50/90}$, 2/16 µg/mL). Cefepime ($MIC_{50/90}$, 2/16 µg/mL), meropenem ($MIC_{50/90}$, 0.5/8 µg/mL) and piperacillin/tazobactam ($MIC_{50/90}$, 8/32 µg/mL) were active against 87.1, 80.9 and 83.0% of *P. aeruginosa* strains, respectively (Table 1 and Figure 2).
- *Acinetobacter* spp. (57 isolates) comprised only 0.8% of the collection and exhibited limited susceptibility to ceftazidime-avibactam ($MIC_{50/90}$, 16/>32 µg/mL) as well as all other β-lactam compounds tested (Table 2).

Figure 1. Summary of ceftazidime-avibactam activity when tested against 6,773 Enterobacteriaceae isolates from patients with urinary tract infections (USA, 2012-2014).

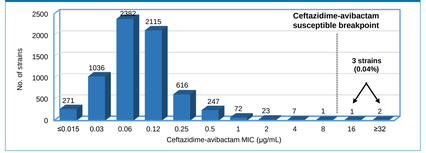
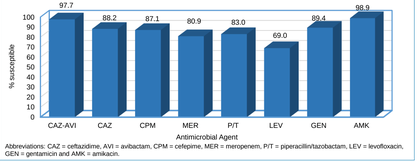


Figure 2. Antimicrobial susceptibility rates of *P. aeruginosa* strains from patients with UTI in USA hospitals (2012-2014).



Abbreviations: CAZ = ceftazidime, AVI = avibactam, CPM = cefepime, MER = meropenem, P/T = piperacillin/tazobactam, LEV = levofloxacin, GEN = gentamicin and AMK = amikacin.

Table 1. Summary of ceftazidime-avibactam activity tested against Gram-negative organisms isolated from patients with urinary tract infections from United States hospitals (2012-2014).

	No. of isolates (cumulative %) inhibited at ceftazidime-avibactam MIC (µg/mL):											
Organism (no.tested)	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	≥32	MIC_{50}	MIC_{90}
Enterobacteriaceae (6,773)	1307 (19.3)	2382 (54.5)	2115 (85.7)	616 (94.8)	247 (98.4)	72 (99.5)	23 (99.8)	7 (99.9)	1 (>99.9)	1 (>99.9)	2 (100.0)	0.06	0.25
E. coli (2,876)	508 (17.7)	1169 (58.3)	995 (92.9)	172 (98.9)	27 (99.8)	1 (99.9)	2 (99.9)	2 (100.0)				0.06	0.12
ESBL-phenotype (330)	24 (7.3)	53 (23.3)	159 (71.5)	74 (93.9)	15 (98.5)	1 (98.8)	2 (99.4)	2 (100.0)				0.12	0.25
Klebsiella spp. (1,484)	116 (7.8)	561 (45.6)	544 (82.3)	145 (92.0)	77 (97.2)	29 (99.2)	10 (99.9)	1 (99.9)	0 (99.9)	0 (99.9)	1 (100.0)	0.12	0.25
ESBL-phenotype (207)	12 (5.8)	12 (11.6)	45 (33.3)	38 (51.7)	61 (81.2)	27 (94.2)	10 (99.0)	1 (99.5)	0 (99.5)	0 (99.5)	1 (100.0)	0.25	1
MEM-non-S KPN (74)	6 (8.1)	1 (9.5)	4 (14.9)	8 (25.7)	30 (66.2)	14 (85.1)	9 (97.3)	1 (98.6)	0 (98.6)	0 (98.6)	1 (100.0)	0.5	2
P. mirabilis (493)	320 (64.9)	160 (97.4)	9 (99.2)	3 (99.8)	0 (99.8)	1 (100.0)						0.03	0.06
Providencia spp. (373)	92 (24.7)	90 (48.8)	97 (74.8)	53 (89.0)	26 (96.0)	5 (97.3)	6 (98.9)	2 (99.5)	1 (99.7)	1 (100.0)		0.12	0.5
E. cloacae (356)	6 (1.7)	24 (8.4)	147 (49.7)	102 (78.4)	48 (91.9)	23 (98.3)	3 (99.2)	2 (99.7)	0 (99.7)	0 (99.7)	1 (100.0)	0.25	0.5
CAZ-non-S (83)		1 (1.2)	5 (7.2)	25 (37.3)	28 (71.1)	19 (94.0)	2 (96.4)	2 (98.8)	0 (98.8)	0 (98.8)	1 (100.0)	0.5	1
M. morganii (305)	132 (43.3)	113 (80.3)	32 (90.8)	16 (96.1)	7 (98.4)	5 (100.0)						0.06	0.12
P. vulgaris (219)	104 (47.5)	97 (91.8)	12 (97.3)	2 (98.2)	4 (100.0)							0.06	0.06
C. freundii (204)	6 (2.9)	28 (16.7)	111 (71.1)	38 (89.7)	17 (98.0)	3 (99.5)	1 (100.0)					0.12	0.5
E. aerogenes (189)	8 (4.2)	58 (34.9)	72 (73.0)	30 (88.9)	19 (98.9)	2 (100.0)						0.12	0.5
C. koseri (150)	15 (10.0)	78 (62.0)	39 (88.0)	15 (98.0)	2 (99.3)	1 (100.0)						0.06	0.25
S. marcescens (124)		4 (3.2)	57 (49.2)	40 (81.5)	20 (97.6)	2 (99.2)	1 (100.0)					0.25	0.5
P. aeruginosa (442)			2 (0.5)	20 (5.0)	165 (42.3)	148 (75.8)	65 (90.5)	32 (97.7)	6 (99.1)	4 (100.0)	2	4	
CAZ-non-S (52)					3 (5.8)	12 (28.8)	11 (50.0)	17 (82.7)	5 (92.3)	4 (100.0)	4	16	
MER-non-S (84)					5 (6.0)	18 (27.4)	31 (64.3)	22 (90.5)	4 (95.2)	4 (100.0)	4	8	
CAZ-MER-P/T-non-S (27)					1 (3.7)	0 (3.7)	6 (25.9)	14 (77.8)	3 (88.9)	3 (100.0)	8	32	
Acinetobacter spp. (57)					3 (5.3)	3 (10.5)	14 (35.1)	8 (49.1)	19 (64.9)	20 (100.0)	16	>32	

Table 2. Activity of ceftazidime-avibactam and comparator antimicrobial agents tested against Gram-negative organisms isolated from patients with urinary tract infections from United States hospitals (2012-2014).

Organism (no. tested)/	MIC (µg/mL):		CLSI[a]			EUCAST[a]	
Antimicrobial Agent	MIC_{50}	MIC_{90}	%S	%I	%R	%S	%I	%R
Enterobacteriaceae (6,773)								
Ceftazidime-avibactam[b]	0.06	0.25	>99.9	-	<0.1	-	-	-
Ceftazidime	0.12	4	90.3	1.4	8.3	88.0	2.3	9.7
Ceftriaxone	≤0.06	8	87.2	1.1	11.8	87.2	1.1	11.8
Ampicillin-sulbactam	8	>32	59.0	17.2	23.8	59.0	-	41.0
Piperacillin-tazobactam	2	8	94.2	2.4	3.3	91.9	2.3	5.8
Meropenem	≤0.06	≤0.06	98.6	0.1	1.3	98.7	0.4	0.9
Aztreonam	≤0.12	4	90.4	0.9	8.7	88.8	1.5	9.6
Levofloxacin	≤0.12	>4	80.8	2.1	17.0	79.4	1.5	19.2
Gentamicin	≤1	8	89.9	1.4	8.7	87.8	2.1	10.1
Tigecycline[b]	0.12	1	98.5	1.5	<0.1	93.5	4.9	1.5
Colistin	0.5	>8	-	-	-	75.4	-	24.6
Escherichia coli (2,876)								
Ceftazidime-avibactam[b]	0.06	0.12	100.0	-	0.0	-	-	-
Ceftazidime	0.12	2	91.9	1.7	6.4	89.6	2.4	8.1
Ceftriaxone	≤0.06	>8	89.3	0.1	10.6	89.3	0.1	10.6
Ampicillin-sulbactam	8	32	56.4	19.6	24.0	56.4	-	43.6
Piperacillin-tazobactam	2	8	96.9	1.9	1.2	94.9	2.0	3.1
Meropenem	≤0.06	≤0.06	99.7	0.1	0.2	99.8	0.2	0.0
Aztreonam	≤0.12	4	90.7	1.2	8.1	88.9	1.7	9.3
Levofloxacin	≤0.12	>4	74.5	0.7	24.8	74.3	0.2	25.5
Gentamicin	≤1	>8	88.2	0.3	11.4	87.5	0.7	11.8
Tigecycline[b]	0.06	0.12	100.0	0.0	0.0	100.0	0.0	0.0
Colistin	0.5	0.5	-	-	-	99.4	-	0.6
Klebsiella spp. (1,484)[c]								
Ceftazidime-avibactam[b]	0.12	0.25	99.9	-	0.1	-	-	-
Ceftazidime	0.12	16	88.5	0.9	10.6	87.1	1.3	11.5
Ceftriaxone	≤0.06	>8	87.0	0.3	12.7	87.0	0.3	12.7
Ampicillin-sulbactam	8	>32	75.9	7.5	16.6	75.9	-	24.1
Piperacillin-tazobactam	2	32	89.6	1.8	8.6	85.7	3.9	10.4
Meropenem	≤0.06	≤0.06	94.9	0.1	5.0	95.0	1.3	3.7
Aztreonam	≤0.12	>16	87.8	0.3	11.9	87.3	0.5	12.2
Levofloxacin	≤0.12	4	88.6	1.6	9.7	87.8	0.9	11.4
Gentamicin	≤1	2	91.9	1.2	6.9	90.8	1.1	8.1
Tigecycline[b]	0.25	0.5	99.7	0.3	0.1	97.4	2.3	0.3
Colistin	0.5	0.5	-	-	-	97.4	-	2.6
meropenem-non-susceptible *K. pneumoniae* (74)								
Ceftazidime-avibactam[b]	0.5	2	98.6	-	1.4	-	-	-
Ceftazidime	>32	>32	0.0	1.4	98.6	0.0	0.0	100.0
Ceftriaxone	>8	>8	0.0	0.0	100.0	0.0	0.0	100.0
Ampicillin-sulbactam	>32	>32	0.0	0.0	100.0	0.0	-	100.0
Piperacillin-tazobactam	>64	>64	0.0	1.4	98.6	0.0	0.0	100.0
Meropenem	>8	>8	0.0	2.7	97.3	2.7	24.3	73.0
Aztreonam	>16	>16	0.0	0.0	100.0	0.0	0.0	100.0
Levofloxacin	>4	>4	2.7	4.1	93.2	2.7	0.0	97.3
Gentamicin	4	>8	51.4	6.8	41.9	37.8	13.5	48.6
Tigecycline[b]	0.5	1	97.3	2.7	0.0	94.6	2.7	2.7
Colistin	0.5	>8	-	-	-	68.0	-	32.0
Proteus mirabilis (493)								
Ceftazidime-avibactam[b]	0.03	0.06	100.0	-	0.0	-	-	-
Ceftazidime	0.06	0.12	99.6	0.4	0.0	98.0	1.6	0.4
Ceftriaxone	≤0.06	≤0.06	96.1	0.8	3.0	96.1	0.8	3.0
Ampicillin-sulbactam	1	8	91.1	5.9	3.0	91.1	-	8.9
Piperacillin-tazobactam	≤0.5	1	99.8	0.2	0.0	99.8	0.0	0.2
Meropenem	≤0.06	0.12	100.0	0.0	0.0	100.0	0.0	0.0
Aztreonam	≤0.12	≤0.12	100.0	0.0	0.0	99.8	0.2	0.0
Levofloxacin	≤0.12	>4	76.9	4.7	18.5	72.2	4.7	23.1
Gentamicin	≤1	4	91.0	2.9	6.1	87.7	3.3	9.0
Tigecycline[b]	1	4	86.4	13.2	0.4	50.7	35.7	13.6
Colistin	>8	>8	-	-	-	0.0	-	100.0
Enterobacter cloacae (356)								
Ceftazidime-avibactam[b]	0.25	0.5	99.7	-	0.3	-	-	-
Ceftazidime	0.5	>32	76.7	0.6	22.8	72.5	4.2	23.3
Ceftriaxone	0.25	>8	69.3	3.4	27.3	69.3	3.4	27.3
Ampicillin-sulbactam	32	>32	30.5	18.9	50.6	30.5	-	69.5
Piperacillin-tazobactam	2	64	83.1	9.0	7.9	80.2	2.8	16.9
Meropenem	≤0.06	≤0.06	98.6	0.0	1.4	98.6	1.1	0.3
Aztreonam	≤0.12	>16	75.8	1.7	22.5	73.5	2.3	24.2
Levofloxacin	≤0.12	>4	91.3	1.4	7.3	90.2	1.1	8.7
Gentamicin	≤1	≤1	92.1	0.8	7.0	91.9	0.3	7.9
Tigecycline	0.25	1	98.3	1.7	0.0	95.8	2.5	1.7
Colistin	0.5	>8	-	-	-	84.6	-	15.4
Pseudomonas aeruginosa (442)								
Ceftazidime-avibactam[b]	2	4	97.7	-	2.3	-	-	-
Ceftazidime	2	16	88.2	3.6	8.1	88.2	-	11.8
Cefepime	2	16	87.1	8.6	4.3	87.1	-	12.9
Piperacillin-tazobactam	8	32	83.0	10.6	6.3	83.0	-	17.0
Meropenem	0.5	8	80.9	5.5	13.6	80.9	13.2	5.9
Levofloxacin	0.5	>4	69.0	4.1	26.9	63.1	5.9	31.0
Gentamicin	≤1	8	89.4	2.3	8.4	89.4	-	10.6
Amikacin	2	8	98.9	0.7	0.5	96.2	2.7	1.1
Colistin	1	2	100.0	0.0	0.0	100.0	-	0.0
Acinetobacter baumannii (57)								
Ceftazidime-avibactam	16	>32	-	-	-	-	-	-
Ceftazidime	8	>32	52.6	7.0	40.4	-	-	-
Cefepime	16	>16	47.4	10.5	42.1	-	-	-
Ampicillin-sulbactam	8	>32	56.1	12.3	31.6	-	-	-
Piperacillin-tazobactam	32	>64	47.4	10.5	42.1	-	-	-
Meropenem	1	>8	59.6	0.0	40.4	59.6	3.5	36.8
Levofloxacin	0.5	>4	54.4	3.5	42.1	54.4	0.0	45.6
Gentamicin	2	>8	56.1	8.8	35.1	56.1	-	43.9
Amikacin	4	>32	73.7	3.6	23.2	67.9	5.4	26.8
Colistin	1	2	95.2	-	4.8	95.2	-	4.8

a. Criteria as published by CLSI [2015] and EUCAST [2015].
b. Breakpoints from FDA Package Insert.
c. Organisms include: *Klebsiella oxytoca* (175), *K. pneumoniae* (1,309).

Conclusions

- Ceftazidime-avibactam demonstrated potent activity against a large collection of contemporary (2012-2014) Gram-negative bacilli isolated from patients with UTI in USA hospitals.
- Overall, >99.9% of Enterobacteriaceae and 97.7% of *P. aeruginosa* isolates were susceptible to ceftazidime-avibactam at USA-FDA breakpoints.
- Ceftazidime-avibactam represents an important addition to the armamentarium of antimicrobial agents used for the treatment of healthcare associated UTI, especially those infections caused by MDR Gram-negative organisms.

References

1. AVYCAZ Prescribing Information (2015). Available at http://www.avycaz.com. Accessed March 23, 2015.
2. Briongos-Figuero LS, Gomez-Traveso T, Bachiller-Luque P, Dominguez-Gil Gonzalez M, Gomez-Nieto A, Palacios-Martin T, et al. (2012). Epidemiology, risk factors and comorbidity for urinary tract infections caused by extended-spectrum beta-lactamase (ESBL)-producing enterobacteria. *Int J Clin Pract* 66: 891-6.
3. Castanheira M, Farrell SE, Krause KM, Jones RN, Sader HS (2014). Contemporary diversity of β-lactamases among Enterobacteriaceae in the nine United States census regions and ceftazidime-avibactam activity tested against isolates producing the most prevalent β-lactamase groups. *Antimicrob Agents Chemother* 58: 833-838.
4. Castanheira M, Mills JC, Farrell DJ, Jones RN (2014). Mutation-driven β-lactam resistance mechanisms among contemporary ceftazidime non-susceptible *Pseudomonas aeruginosa* isolates from USA hospitals. *Antimicrob Agents Chemother* 58: 6844-6850.
5. Clinical and Laboratory Standards Institute (2015). *M07-A10. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard-tenth edition*. Wayne, PA: CLSI.
6. Clinical and Laboratory Standards Institute (2015). *M100-S25. Performance standards for antimicrobial susceptibility testing: 25th informational supplement*. Wayne, PA: CLSI.
7. Coleman K (2011). Diazabicyclooctanes: a potent new class of non-β-lactam β-lactamase inhibitors. *Curr Opin Microbiol* 14: 550-555.
8. EUCAST (2015). Breakpoint tables for interpretation of MICs and zone diameters. Version 5.0, January 2015. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 2015.
9. Sader HS, Castanheira M, Flamm RK, Farrell DJ, Jones RN (2014). Antimicrobial activity of ceftazidime-avibactam against Gram-negative organisms collected from U.S. medical centers in 2012. *Antimicrob Agents Chemother* 58: 1684-1692.
10. Sader HS, Castanheira M, Flamm RK, Mendes RE, Farrell DJ, Jones RN (2015). Ceftazidime/avibactam tested against Gram-negative bacteria from intensive care unit (ICU) and non-ICU patients, including those with ventilator-associated pneumonia. *Int J Antimicrob Agents* 46: 53-59.
11. Wagenlehner FM, Cek M, Naber KG, Kiyota H, Bjerklund-Johansen TE (2012). Epidemiology, treatment and prevention of healthcare-associated urinary tract infections. *World J Urol* 30: 59-67.

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