

# Activity of Ceftazidime-Avibactam Tested Against Contemporary (2012) Pathogens from Urinary Tract and Intraabdominal Infections from Patients in the USA

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## Abstract

**Background:** The investigational antimicrobial combination of ceftazidime (CAZ) and the non  $\beta$ -lactam  $\beta$ -lactamase inhibitor avibactam (AVI) is undergoing Phase III clinical development. In this report, we present the results of testing CAZ-AVI and comparators against a recent collection of pathogens from patients with urinary tract (UTI) or intraabdominal (IAI) infections.

**Methods:** UTI and IAI isolates (one per patient episode) were collected during 2012 at 73 USA medical centers. Isolates were processed at the medical centers and forwarded to a central laboratory for confirmatory identification and susceptibility (S) testing using CLSI methods.

**Results:** CAZ-AVI demonstrated potent activity against Enterobacteriaceae (ENT) isolated from both UTI and IAI (MIC<sub>50</sub>, 0.25  $\mu$ g/mL for both). The most active agent against ENT for both UTI and IAI was meropenem (MER; MIC<sub>50/90</sub>,  $\leq$ 0.06/0.06  $\mu$ g/mL, S = 98.8% and MIC<sub>50/90</sub>,  $\leq$ 0.06/0.06  $\mu$ g/mL, S = 97.8%, respectively). ENT levofloxacin-resistance (LEV-R) was at 16.1/16.6%, respectively for UTI/IAI. The ESBL-phenotype rate for *E. coli* (EC) for UTI/IAI was 8.5/10.4% and for *Klebsiella* spp. (KSP), 13.0/16.3%, respectively. The CAZ-AVI MIC<sub>90</sub> for ESBL-positive-phenotype EC and KSP from UTI was at 0.25 and 1  $\mu$ g/mL, respectively. From IAI, the MIC<sub>90</sub> values were at 0.5 and 2  $\mu$ g/mL, respectively. The LEV-R rates among ESBL-positive EC and KSP were 70.5/69.2% for UTI and 94.1/76.5% for IAI. CAZ-AVI inhibited 98.7 and 96.3% of *Pseudomonas aeruginosa* (PSA) from UTI and IAI at a MIC of  $\leq$ 8  $\mu$ g/mL. Amikacin-, colistin- and gentamicin-S ranged from 90.3-98.1% for UTI and 92.7-97.6% for IAI. A total of 93.8% of CAZ-non-S PSA isolates from UTI and 75.0% from IAI were inhibited at a CAZ-AVI MIC value of  $\leq$ 8  $\mu$ g/mL. Amikacin and colistin against CAZ-non-S PSA in UTI and amikacin, colistin and gentamicin in IAI were the only agents exhibiting S at >90.0%. Against MER-non-S PSA, 97.0 and 76.9% of UTI and IAI isolates, respectively were inhibited at a CAZ-AVI MIC value  $\leq$ 8  $\mu$ g/mL.

**Conclusions:** CAZ-AVI demonstrated potent activity against contemporary Gram-negative pathogens including multidrug-resistant isolates from patients with UTI and IAI in USA hospitals. These data may support CAZ-AVI as a new treatment option in these common hospital infections.

Organism (no. tested UTI/IAI)	Urinary tract		Intraabdominal	
	MIC in $\mu$ g/mL			
	Ceftazidime-avibactam/ceftazidime	MIC <sub>50</sub>	MIC <sub>90</sub>	Ceftazidime-avibactam/ceftazidime
Enterobacteriaceae (2,188/410)	0.06/0.12	0.25/2	0.12/0.25	0.25/32
<i>E. coli</i> (913/164)	0.06/0.12	0.12/0.5	0.06/0.12	0.12/1
ESBL-positive (78/17)	0.12/8	0.25/32	0.12/16	0.5/>32
<i>Klebsiella</i> spp. (501/104)	0.12/0.12	0.25/8	0.12/0.12	0.5/32
ESBL-positive (65/17)	0.5/>32	1/>32	0.5/>32	2/>32
<i>Enterobacter cloacae</i> (112/60)	0.12/0.25	0.5/>32	0.12/0.5	0.5/>32
CAZ-non-S <i>E. cloacae</i> (23/20)	0.5/>32	1/>32	0.5/>32	1/>32
<i>P. aeruginosa</i> (155/82)	2/2	4/16	2/2	4/32
CAZ-non-S <i>P. aeruginosa</i> (16/12)	2/32	8/>32	4/32	16/>32
MER-non-S <i>P. aeruginosa</i> (33/13)	4/4	8/>32	4/8	16/>32

## Introduction

Avibactam is an investigational non- $\beta$ -lactam  $\beta$ -lactamase inhibitor that displays a broad-spectrum inhibition profile against both class A and class C  $\beta$ -lactamases, including extended spectrum  $\beta$ -lactamases and KPC serine-carbapenemases, as well as activity against some class D enzymes. Avibactam alone has very limited intrinsic antibacterial activity. When combined with ceftazidime, the combination has shown potent in vitro activity against Enterobacteriaceae and *Pseudomonas aeruginosa* including multidrug-resistant strains.

The efficacy of the combination has been shown in Phase II clinical trials for complicated urinary tract (cUTI) and complicated intraabdominal infections (cIAI). In a Phase II clinical trial in the treatment of cUTI, ceftazidime-avibactam was shown to have efficacy and safety similar to the comparator imipenem-cilastatin. In a Phase II trial for cIAI in hospitalized adults, ceftazidime-avibactam plus metronidazole was shown to be effective and well tolerated, similar to meropenem. The ceftazidime-avibactam combination is currently undergoing further clinical development in Phase 3 studies of cUTI, cIAI and nosocomial pneumonia.

The aim of this study was to evaluate the activity of ceftazidime-avibactam and comparator agents against a contemporary collection of isolates from patients with UTI and IAI in the USA (2012).

## Methods

**Bacterial isolates:** Isolates from patients with UTI or IAI (as protocol does not specify, these may be from either complicated or uncomplicated cases; one per patient episode) were processed at 73 USA medical centers during 2012 and forwarded to a central laboratory (JMI Laboratories, North Liberty, Iowa, USA) for confirmatory identification and susceptibility testing. Only clinically significant isolates were included in the study. A total of 2,879 isolates from UTI infections and 759 from IAI were collected. Of these, 2,188 were Enterobacteriaceae from UTI and 410 from IAI. For *P. aeruginosa*, the isolate totals were 155 from UTI and 82 from IAI.

**Antimicrobial susceptibility testing:** All isolates were susceptibility tested with dry-form panels using reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI). Interpretations of susceptibility for antimicrobials were those found in CLSI M100-S23 (2013) and quality control (QC) was performed using *Staphylococcus aureus* ATCC 29213; *Enterococcus faecalis* ATCC 29212; *Streptococcus pneumoniae* ATCC 49619; *Escherichia coli* ATCC 25922; and *P. aeruginosa* ATCC 27853. All QC results were within ranges as published in CLSI (M100-S23, 2013) documents.

## Results

The MIC<sub>50</sub> and MIC<sub>90</sub> for ceftazidime-avibactam against Enterobacteriaceae were  $\leq$ 0.06 and 0.25  $\mu$ g/mL for UTI isolates and 0.12/0.25  $\mu$ g/mL for IAI isolates (Table 1). For UTI isolates, the susceptibility for ceftazidime, piperacillin-tazobactam, meropenem, and tigecycline was 91.8, 94.5, 98.8, and 97.9%, respectively. For IAI isolates, susceptibility values were 86.1, 88.5, 97.8, and 97.8%, respectively (Table 2). Levofloxacin resistance for UTI and IAI isolates was 16.1 and 16.6%, respectively (Table 2)

In UTI, the ESBL-positive-phenotype rate for *E. coli* was 8.5% and for IAI isolates 10.4% (Table 1). For *Klebsiella* spp. the ESBL-positive-phenotype rates were more elevated, 13.0 and 16.3%, respectively (Table 1). The ceftazidime-avibactam MIC<sub>50</sub> and MIC<sub>90</sub> for ESBL-positive-phenotype *E. coli* from UTI was 0.12 and 0.25  $\mu$ g/mL (Tables 1 and 2). For ESBL-phenotype *E. coli* isolates from IAI, the MIC<sub>50</sub> and MIC<sub>90</sub> were similar 0.12 and 0.5  $\mu$ g/mL (Tables 1 and 2). Meropenem susceptibility rates were high among ESBL-positive-phenotype *E. coli* at 98.7/100.0% for UTI/IAI isolates (Table 2). Tigecycline susceptibility was also high at 100.0% in UTI/IAI (Table 2). Piperacillin-tazobactam and levofloxacin susceptibility were low at 80.8/26.9% in UTI and 70.6/5.9% in IAI (Table 2)

Ceftazidime-avibactam MIC<sub>50</sub> and MIC<sub>90</sub> values for ESBL-positive-phenotype *Klebsiella* spp. from UTI were 0.5 and 1  $\mu$ g/mL (Tables 1 and 2). For ESBL-positive-phenotype *Klebsiella* spp. isolates from IAI, the MIC<sub>50</sub> and MIC<sub>90</sub> were 0.5 and 2  $\mu$ g/mL (Tables 1 and 2). Tigecycline susceptibility rates were high for ESBL-positive-phenotype *Klebsiella* spp. at 96.9/100.0% for UTI/IAI isolates (Table 2), but piperacillin-tazobactam, meropenem, and levofloxacin susceptibility were low at 30.8/64.6/24.6% in UTI and 11.8/58.8/23.5% in IAI (Table 2)

Ceftazidime-avibactam inhibited 98.7 and 96.3% of *P. aeruginosa* isolates from UTI and IAI at a MIC of  $\leq$ 8  $\mu$ g/mL (Table 1). The MIC<sub>50</sub> and MIC<sub>90</sub> for isolates from either UTI or IAI were 2 and 4  $\mu$ g/mL, respectively (Tables 1 and 2). Against meropenem-non-susceptible isolates of *P. aeruginosa*, 97.0 and 76.9% of UTI and IAI isolates, respectively were inhibited at a ceftazidime-avibactam MIC value  $\leq$ 8  $\mu$ g/mL (Table 1). A total of 93.8 and 75.0% of ceftazidime-non-susceptible isolates from UTI/IAI were inhibited at a ceftazidime-avibactam MIC value of  $\leq$ 8  $\mu$ g/mL (Table 1). For all *P. aeruginosa*, amikacin susceptibility for UTI/IAI isolates was at 98.1/97.6% and for colistin, the rates were the same (Table 2). Susceptibility for most other antimicrobials was decreased against the meropenem-non-susceptible and ceftazidime-non-susceptible *P. aeruginosa* isolates from either UTI or IAI. Amikacin and colistin were exceptions, their susceptibility remained >90.0% (Table 2).

Table 1. Summary of ceftazidime-avibactam activity tested against select organisms from urinary tract and intrabdominal infections from the USA (2012)

Indication	No. of Isolates	$\leq$ 0.06	No. of isolates (Cumulative %) MIC in $\mu$ g/mL								MIC <sub>50</sub>	MIC <sub>90</sub>		
			0.12	0.25	0.5	1	2	4	8	16			$\geq$ 32	
Enterobacteriaceae	UTI	2188	1,144 (52.3)	731 (85.7)	208 (95.2)	75 (98.6)	22 (99.6)	3 (99.8)	4 (>99.9)	1 (100.0)	--	--	$\leq$ 0.06	0.25
	IAI	410	169 (41.2)	157 (79.5)	43 (90.0)	28 (96.8)	10 (99.3)	3 (100.0)	--	--	--	--	0.12	0.25
<i>Escherichia coli</i>	UTI	913	501 (54.9)	351 (93.3)	54 (99.2)	7 (100.0)	--	--	--	--	--	--	$\leq$ 0.06	0.12
	IAI	164	88 (53.7)	64 (92.7)	9 (98.2)	2 (99.4)	1 (100.0)	--	--	--	--	--	$\leq$ 0.06	0.12
ESBL-phenotype	UTI	78	17 (21.8)	41 (74.4)	17 (96.2)	3 (100.0)	--	--	--	--	--	--	0.12	0.25
	IAI	17	--	12 (70.6)	3 (88.2)	1 (94.1)	1 (100.0)	--	--	--	--	--	0.12	0.5
<i>Klebsiella</i> spp.	UTI	501	226 (45.1)	182 (81.4)	52 (91.8)	29 (97.6)	10 (99.6)	1 (99.8)	1 (100.0)	--	--	--	0.12	0.25
	IAI	104	32 (30.8)	48 (76.9)	12 (88.5)	8 (96.2)	1 (97.1)	3 (100.0)	--	--	--	--	0.12	0.5
ESBL-phenotype	UTI	65	6 (9.2)	13 (29.2)	12 (47.7)	22 (81.5)	10 (96.9)	1 (98.5)	1 (100.0)	--	--	--	0.5	1
	IAI	17	1 (5.9)	3 (23.5)	3 (41.2)	6 (76.5)	1 (82.4)	3 (100.0)	--	--	--	--	0.5	2
<i>Klebsiella pneumoniae</i>	UTI	445	197 (44.3)	166 (81.6)	44 (91.5)	26 (97.3)	10 (99.6)	1 (99.8)	1 (100.0)	--	--	--	0.12	0.25
	IAI	85	23 (27.1)	43 (77.6)	8 (87.1)	7 (95.3)	1 (96.5)	3 (100.0)	--	--	--	--	0.12	0.5
<i>Enterobacter cloacae</i>	UTI	112	8 (7.1)	53 (54.5)	32 (83.0)	11 (92.9)	6 (98.2)	0 (98.2)	2 (100.0)	--	--	--	0.12	0.5
	IAI	60	4 (6.7)	26 (50.0)	13 (71.7)	11 (90.0)	6 (100.0)	--	--	--	--	--	0.12	0.5
<i>Morganella morganii</i>	UTI	106	82 (77.4)	13 (89.6)	7 (96.2)	2 (98.1)	2 (100.0)	--	--	--	--	--	$\leq$ 0.06	0.25
	IAI	8	8 (100.0)	--	--	--	--	--	--	--	--	--	$\leq$ 0.06	$\leq$ 0.06
<i>Serratia marcescens</i>	UTI	45	3 (6.7)	19 (48.9)	15 (82.2)	7 (97.8)	1 (100.0)	--	--	--	--	--	0.25	0.5
	IAI	11	1 (9.1)	6 (63.6)	2 (81.8)	2 (100.0)	--	--	--	--	--	--	0.12	0.5
<i>Pseudomonas aeruginosa</i>	UTI	155	--	--	--	9 (5.8)	47 (36.1)	63 (76.8)	23 (91.6)	11 (98.7)	1 (99.4)	1 (100.0)	2	4
	IAI	82	--	--	--	--	35 (42.7)	30 (79.3)	3 (96.3)	2 (98.8)	1 (100.0)	2	4	
MER-Non-S (MIC, $\geq$ 4 $\mu$ g/mL)	UTI	33	--	--	--	--	2 (6.1)	9 (33.3)	14 (75.8)	7 (97.0)	0 (97.0)	1 (100.0)	4	8
	IAI	13	--	--	--	--	2 (15.4)	4 (46.2)	3 (69.2)	1 (76.9)	2 (92.3)	1 (100.0)	4	16
CAZ-Non-S (MIC, $\geq$ 16 $\mu$ g/mL)	UTI	16	--	--	--	--	2 (12.5)	7 (56.3)	2 (68.8)	4 (93.8)	0 (93.8)	1 (100.0)	2	8
	IAI	12	--	--	--	--	--	4 (33.3)	4 (66.7)	1 (75.0)	2 (91.7)	1 (100.0)	4	16

Table 2. In vitro activity of ceftazidime-avibactam and comparator agents tested against UTI and IAI isolates from USA (2012)

Organism/antimicrobial agent (no. tested)	UTI Isolates			IAI Isolates			UTI Isolates			IAI Isolates			
	MIC ( $\mu$ g/mL)			MIC ( $\mu$ g/mL)			MIC ( $\mu$ g/mL)			MIC ( $\mu$ g/mL)			
	MIC <sub>50</sub>	MIC <sub>90</sub>	CLSI <sup>a</sup>	MIC <sub>50</sub>	MIC <sub>90</sub>	CLSI <sup>a</sup>	MIC <sub>50</sub>	MIC <sub>90</sub>	CLSI <sup>a</sup>	MIC <sub>50</sub>	MIC <sub>90</sub>	CLSI <sup>a</sup>	
Enterobacteriaceae (2,188)													
Ceftazidime-avibactam	0.06	0.25	3 <sup>b</sup> / - / -	0.12	0.25	- / - / -	Ceftazidime-avibactam	0.06	0.25	- / - / -	0.03	-	- / - / -
Ceftazidime	0.12	2	91.8 / 1.2 / 7.1	0.25	32	86.1 / 1.5 / 12.4	Ceftazidime	0.12	32	84.0 / 1.8 / 14.2	0.06	-	100.0 / 0.0 / 0.0
Piperacillin-tazobactam	2	8	94.5 / 2.4 / 3.1	2	32	88.5 / 3.2 / 8.3	Piperacillin-tazobactam	$\leq$ 0.5	8	92.5 / 2.8 / 4.7	$\leq$ 0.5	-	100.0 / 0.0 / 0.0
Meropenem	$\leq$ 0.06	$\leq$ 0.06	98.8 / <0.1 / 1.2	$\leq$ 0.06	$\leq$ 0.06	97.8 / 0.0 / 2.2	Meropenem	$\leq$ 0.06	0.12	100.0 / 0.0 / 0.0	$\leq$ 0.06	-	100.0 / 0.0 / 0.0
Levofloxacin	$\leq$ 0.12	>4	81.7 / 2.2 / 16.1	$\leq$ 0.12	>4	81.7 / 1.7 / 16.6	Levofloxacin	$\leq$ 0.12	>4	69.8 / 6.6 / 23.6	$\leq$ 0.12	-	87.5 / 0.0 / 12.5
Tigecycline <sup>c</sup>	0.25	1	97.9 / 2.1 / 0.0	0.25	1	97.8 / 2.2 / 0.0	Tigecycline <sup>c</sup>	0.5	2	97.2 / 2.8 / 0.0	0.5	-	100.0 / 0.0 / 0.0
TMP-SMX <sup>d</sup>	$\leq$ 0.5	>4	77.8 / 0.0 / 22.2	$\leq$ 0.5	>4	80.0 / 0.0 / 20.0	TMP-SMX <sup>d</sup>	$\leq$ 0.5	>4	64.2 / 0.0 / 35.8	$\leq$ 0.5	-	62.5 / 0.0 / 37.5
<i>Escherichia coli</i> (913)							<i>Morganella morganii</i> (106)						
Ceftazidime-avibactam	0.06	0.12	- / - / -	0.06	0.12	- / - / -	Ceftazidime-avibactam	0.25	0.5	- / - / -	0.12	0.5	- / - / -
Ceftazidime	0.12	0.5	94.6 / 1.2 / 4.3	0.12	1	92.1 / 1.9 / 6.1	Ceftazidime	0.25	1	100.0 / 0.0 / 0.0	0.25	0.5	100.0 / 0.0 / 0.0
Piperacillin-tazobactam	2	8	97.5 / 1.4 / 1.1	2	8	94.5 / 0.6 / 4.9	Piperacillin-tazobactam	2	4	97.8 / 2.2 / 0.0	2	4	100.0 / 0.0 / 0.0
Meropenem	$\leq$ 0.06	$\leq$ 0.06	99.9 / 0.1 / 0.0	$\leq$ 0.06	$\leq$ 0.06	100.0 / 0.0 / 0.0	Meropenem	$\leq$ 0.06	0.12	100.0 / 0.0 / 0.0	$\leq$ 0.06	$\leq$ 0.06	100.0 / 0.0 / 0.0
Levofloxacin	$\leq$ 0.12	>4	76.9 / 0.8 / 22.2	$\leq$ 0.12	>4	76.2 / 0.6 / 23.2	Levofloxacin	$\leq$ 0.12	1	95.6 / 2.2 / 2.2	0.25	2	90.9 / 0.0 / 9.1
Tigecycline <sup>c</sup>	0.12	0.12	100.0 / 0.0 / 0.0	0.06	0.12	100.0 / 0.0 / 0.0	Tigecycline <sup>c</sup>	0.5	1	97.8 / 2.2 / 0.0	0.5	1	100.0 / 0.0 / 0.0
TMP-SMX <sup>d</sup>	$\leq$ 0.5	>4	71.5 / 0.0 / 28.5	$\leq$ 0.5	>4	75.6 / 0.0 / 24.4	TMP-SMX <sup>d</sup>	$\leq$ 0.5	$\leq$ 0.5	97.8 / 0.0 / 2.2	$\leq$ 0.5	1	90.9 / 0.0 / 9.1
<i>Serratia marcescens</i> (45)							<i>Pseudomonas aeruginosa</i> (155)						
Ceftazidime-avibactam	0.25	0.5	- / - / -	0.12	0.5	- / - / -	Ceftazidime-avibactam	2	4	- / - / -	2	4	- / - / -
Ceftazidime	0.												