

# Activity of Ceftazidime-Avibactam and Comparator Agents Tested Against Isolates from Europe-Mediterranean Region Surveillance (2011)

R.K. Flamm, H.S. Sader, R.N. Jones  
JMI Laboratories, North Liberty, Iowa, USA

Contact Information:  
Robert K. Flamm, PhD  
JMI Laboratories  
345 Beaver Creek Ctr, Ste A  
North Liberty, Iowa, 52317, USA  
Tel: 319-665-3370  
Fax: 319-665-3371  
Email: robert-flamm@jmilabs.com

## Abstract

**Background:** The *in vitro* activity of ceftazidime-avibactam (CAZ-AVI), a novel  $\beta$ -lactamase inhibitor cephalosporin combination, and comparator agents was evaluated against isolates collected in 2011 from the Europe-Mediterranean (EMR) region.

**Methods:** A total of 12,054 bacterial isolates were isolated from patients at 46 medical centers located in 20 countries; 17 countries in the European Union plus Russia, Turkey, and Israel. Clinical isolates were collected (one per patient episode), processed locally and forwarded to a central laboratory (JMI Laboratories, North Liberty, Iowa, USA) for confirmatory identification and susceptibility (S) testing by CLSI methods. CLSI and EUCAST interpretive criteria were applied. Avibactam was tested at a fixed concentration of 4  $\mu$ g/mL.

**Results:** The Gram-positive activity of CAZ-AVI was similar to CAZ alone. CAZ-AVI was highly potent against Enterobacteriaceae including ESBL-phenotype strains, *Klebsiella* spp. with decreased carbapenem susceptibility and CAZ-non-susceptible (CAZ-N-S) *Enterobacter* spp. A total of 98.7% of Enterobacteriaceae strains in the EMR were inhibited at a CAZ-AVI MIC of  $\leq 1$   $\mu$ g/mL (EUCAST S breakpoint for CAZ alone) and 99.4% at a CAZ-AVI MIC of  $\leq 4$   $\mu$ g/mL (CLSI S breakpoint for CAZ alone). CAZ-AVI activity against *P. aeruginosa* was enhanced compared to the activity of CAZ. Against *P. aeruginosa* in the EMR, CAZ-AVI MIC values for 86.2% of isolates were at  $\leq 8$   $\mu$ g/mL and 90.0% of MIC values were at  $\leq 16$   $\mu$ g/mL, 8 and 16  $\mu$ g/mL, respectively, are the CLSI S and intermediate breakpoints for CAZ alone. A total of 67.9/69.4% of CAZ-AVI MIC values were at  $\leq 8/\leq 16$   $\mu$ g/mL when tested against CAZ-N-S *P. aeruginosa* and 61.8/72.0% of MIC values were at  $\leq 8/\leq 16$   $\mu$ g/mL when tested against meropenem-non-susceptible *P. aeruginosa*.

**Conclusions:** CAZ-AVI exhibited potent activity against carbapenem and CAZ resistant Gram-negative organisms and may provide an option in serious difficult to treat infections where resistant Gram-negative bacteria may occur. Additional studies are warranted.

Organism (no. tested)	CAZ-AVI (MIC in $\mu$ g/mL)			CAZ (MIC in $\mu$ g/mL)			MER (MIC in $\mu$ g/mL)		
	MIC <sub>50</sub>	MIC <sub>90</sub>	% at $\leq 4^*$	MIC <sub>50</sub>	MIC <sub>90</sub>	% S	MIC <sub>50</sub>	MIC <sub>90</sub>	% S
<i>S. aureus</i> (3001)	8	>32	69.4	8	>32	68.6	0.12	>8	70.2
Enterobacteriaceae (4627)	0.06	0.25	99.4	0.25	32	79.1	$\leq 0.06$	$\leq 0.06$	97.3
<i>E. coli</i> (2113)	0.06	0.12	100.0	0.12	16	86.2	$\leq 0.06$	$\leq 0.06$	99.9
ESBL-positive (425)	0.12	0.25	100.0	16	>32	31.3	$\leq 0.06$	$\leq 0.06$	99.3
<i>Klebsiella</i> spp. (1018)	0.12	0.5	98.7	0.5	>32	59.1	$\leq 0.06$	1	90.6
ESBL-positive (473)	0.25	1	97.3	>32	>32	12.1	$\leq 0.06$	>8	79.7
<i>Enterobacter</i> spp. (530)	0.12	0.5	97.7	0.25	>32	70.4	$\leq 0.06$	$\leq 0.06$	97.0
CAZ-N-S <i>Enterobacter</i> spp. (157)	0.5	1	92.4	>32	>32	0.0	$\leq 0.06$	2	89.8
<i>P. aeruginosa</i> (1137)	2	16	86.2	4	>32	67.2	1	>8	65.4
CAZ-N-S <i>P. aeruginosa</i> (373)	8	>32	57.9	32	>32	0.0	8	>8	29.5

\*Percentage of isolates at the CLSI susceptible breakpoint for ceftazidime alone for Enterobacteriaceae ( $\leq 4$   $\mu$ g/mL) and for *S. aureus* and *P. aeruginosa* where the percent of isolates at  $\leq 8$   $\mu$ g/mL is listed. MER, meropenem.

## Introduction

Gram-negative bacteria have the ability to accumulate multiple resistance determinants as evidenced by the presence of multiple  $\beta$ -lactamases in cephalosporin-resistant organisms. The genes encoding most  $\beta$ -lactamases reside on plasmids or transposons that can readily be acquired by other strains, and these structures usually carry additional genes encoding resistance to other antimicrobial classes. Of current concern is the emergence of several different  $\beta$ -lactamase groups, including members of KPC, NDM, VIM, IMP, and SPM which have been highlighted either for their epidemiologic impact or by the limitations that their dissemination can cause on contemporary antimicrobial therapy.

Avibactam is a novel non- $\beta$ -lactam  $\beta$ -lactamase inhibitor that displays a broad-spectrum inhibition profile against both class A and class C enzymes, including extended spectrum  $\beta$ -lactamases and KPC serine-carbapenemases, as well as activity against some class D enzymes. Avibactam has very limited intrinsic antibacterial activity. The combination ceftazidime-avibactam has demonstrated potent *in vitro* activity against Enterobacteriaceae strains producing class A and C  $\beta$ -lactamases, and its activity has also been confirmed in Phase II clinical trials for complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI). The ceftazidime-avibactam combination is in Phase III development for indications including cIAI and cUTI.

The aim of this study was to evaluate the activity of ceftazidime-avibactam and comparator agents against contemporary clinical isolates collected in Europe and Mediterranean region medical centers from January through December 2011.

## Materials and Methods

Clinical isolates (one per patient episode) were collected from patients at 46 medical centers located in 20 countries; 17 countries in the European Union plus Russia, Turkey, and Israel. Isolates were processed locally and forwarded to a central laboratory (JMI Laboratories, North Liberty, Iowa, USA) for confirmatory identification and susceptibility testing following the procedures of the Clinical and Laboratory Standards Institute (CLSI, M07-A9 [2012]).

Susceptibility testing was performed with validated broth microdilution panels (dry-form MIC panels produced by Thermo Fisher Scientific [Cleveland, Ohio, USA]). CLSI M100-S23 (2013) and EUCAST (2013) susceptibility interpretive criteria were applied. USA-FDA criteria were used as an alternative breakpoint source, where CLSI breakpoints were not available (example: tigecycline). Quality control (QC) organisms per M07-A9 and M100-S23 guidelines were tested concurrently with clinical isolates. Avibactam was tested at a fixed concentration of 4  $\mu$ g/mL in combination with ceftazidime.  $\beta$ -lactamase detection for *Haemophilus influenzae* was performed using Remel Nitrocefin Disks (Remel, Lenexa, Kansas, USA). ESBL-phenotype for *Escherichia coli*, *Klebsiella* spp., and *Proteus mirabilis* was defined as a MIC at  $\geq 2$   $\mu$ g/mL for ceftriaxone or ceftazidime or aztreonam (CLSI, 2013).

## Results

- A total of 12,054 bacterial isolates were collected; results for Enterobacteriaceae, *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Staphylococcus aureus*, and *H. influenzae* are included in this report (Tables 1 and 2).
- Ceftazidime-avibactam and ceftazidime were modestly active against *S. aureus* (MIC<sub>50</sub>, 8  $\mu$ g/mL and MIC<sub>90</sub>, >32  $\mu$ g/mL for both compounds). MIC values for methicillin-resistant *S. aureus* for ceftazidime-avibactam and ceftazidime (MIC<sub>50</sub> and MIC<sub>90</sub>, >32  $\mu$ g/mL for both compounds) were higher than those for methicillin-susceptible *S. aureus* (MIC<sub>50</sub> and MIC<sub>90</sub>, 8  $\mu$ g/mL).
- Ceftazidime-avibactam and ceftazidime were highly potent against *H. influenzae* and their activity was not adversely affected by  $\beta$ -lactamase production. The highest ceftazidime-avibactam MIC value was only 0.12  $\mu$ g/mL.
- Overall, 98.7% of Enterobacteriaceae strains were inhibited at a ceftazidime-avibactam MIC of 1  $\mu$ g/mL or less, which is the susceptibility breakpoint established by the EUCAST for ceftazidime tested alone. A total of 99.4% of Enterobacteriaceae strains were inhibited at a ceftazidime-avibactam MIC of  $\leq 4$   $\mu$ g/mL which is the susceptibility breakpoint established by the CLSI for ceftazidime.
- Only 28 of 4,627 (0.6%) of Enterobacteriaceae strains exhibited a ceftazidime-avibactam MIC  $\geq 8$   $\mu$ g/mL (EUCAST resistant breakpoint), including 13 *Klebsiella* spp., 12 *Enterobacter* spp., two *Serratia marcescens* and one *Providencia* spp.
- A total of 2,113 *E. coli* were tested and an ESBL-phenotype was observed in 20.1% of isolates (Tables 1 and 2). The highest ceftazidime-avibactam MIC observed for *E. coli* was 2  $\mu$ g/mL (three isolates in total); two isolates from a unique medical center located in Ankara, Turkey and one isolate from a medical center in Frankfurt, Germany. 99.9% of all strains were inhibited at a MIC value of  $\leq 1$   $\mu$ g/mL (Tables 1 and 2).
- The ESBL-phenotype strains of *E. coli* were very susceptible to ceftazidime-avibactam (MIC<sub>50</sub>, 0.12  $\mu$ g/mL and MIC<sub>90</sub>, 0.25  $\mu$ g/mL; Table 1). Only three isolates of meropenem-non-susceptible *E. coli* were observed (two from Turkey and one from Israel) and these isolates had ceftazidime-avibactam MIC values of 0.25  $\mu$ g/mL.
- All non-ESBL-phenotype *E. coli* strains were inhibited at a ceftazidime-avibactam MIC of  $\leq 0.5$   $\mu$ g/mL (highest MIC, 0.5  $\mu$ g/mL).
- A total of 1,018 *Klebsiella* spp. isolates were tested (46.5% ESBL-phenotype), including 858 *Klebsiella pneumoniae* (51.0% ESBL-phenotype) and 160 *K. oxytoca* (21.9% ESBL-phenotype) (Tables 1 and 2). Ceftazidime-avibactam was active against non-ESBL *Klebsiella* spp. strains with 100.0% of strains inhibited at  $\leq 1$   $\mu$ g/mL. *Klebsiella* spp. strains with an ESBL-phenotype were also susceptible to ceftazidime-avibactam with a MIC<sub>50</sub> of 0.25  $\mu$ g/mL and a MIC<sub>90</sub> of 1  $\mu$ g/mL (Tables 1 and 2). Among meropenem-non-susceptible *K. pneumoniae* (93), 74.2% and 93.5% of isolates were inhibited at  $\leq 1$  and  $\leq 4$   $\mu$ g/mL, respectively (Table 1).
- The ceftazidime-avibactam MIC<sub>50</sub> for *Citrobacter* spp. was 0.25  $\mu$ g/mL (Tables 1 and 2). Ceftazidime-avibactam inhibited 99.5% of strains at  $\leq 1$   $\mu$ g/mL (Tables 1 and 2).
- A total of 530 *Enterobacter* spp. isolates were tested including 428 *E. cloacae* (99.0% ceftazidime-non-susceptible) and 102 *E. aerogenes* (32.4% ceftazidime-non-susceptible; Tables 1 and 2; data not shown). The ceftazidime-avibactam MIC<sub>50</sub> and MIC<sub>90</sub> for all *Enterobacter* spp. were 0.12 and 0.5  $\mu$ g/mL, respectively.

Table 1. Summary of ceftazidime-avibactam and ceftazidime activity tested against select organisms and resistant subsets from the European and Mediterranean Region (2011)

Organism/resistant subset	Antimicrobial	No. of isolates	No. of isolates (cumulative %) inhibited at MIC ( $\mu$ g/mL) of:										MIC <sub>50</sub>	MIC <sub>90</sub>		
			$\leq 0.03$	0.06	0.12	0.25	0.5	1	2	4	8	16			>32	
Enterobacteriaceae	Ceftazidime-avibactam	4,627	808 (17.5)	1521 (50.3)	1314 (78.7)	599 (91.7)	253 (97.1)	70 (98.7)	28 (99.3)	6 (99.4)	2 (99.4)	1 (99.5)	4 (99.5)	21 (100.0)	0.06	0.25
	Ceftazidime	4,627	77 (1.7)	582 (14.2)	1469 (46.0)	907 (65.6)	322 (72.6)	115 (77.4)	110 (77.4)	76 (79.1)	112 (81.5)	188 (85.5)	243 (90.8)	426 (100.0)	0.25	32
<i>E. coli</i>	Ceftazidime-avibactam	2,113	445 (21.1)	961 (66.5)	553 (72.7)	119 (98.3)	24 (99.5)	8 (99.9)	3 (100.0)	—	—	—	—	—	0.06	0.12
	Ceftazidime	2,113	2 (0.1)	157 (7.5)	914 (60.8)	483 (73.6)	124 (79.5)	45 (81.6)	55 (84.2)	41 (86.2)	46 (88.4)	97 (92.9)	85 (97.0)	64 (100.0)	0.12	16
ESBL-phenotype	Ceftazidime-avibactam	425	32 (7.5)	116 (34.8)	166 (73.9)	83 (93.4)	17 (97.4)	8 (99.3)	3 (100.0)	—	—	—	—	—	0.12	0.25
	Ceftazidime	425	—	—	—	10 (2.4)	27 (8.7)	55 (21.6)	41 (31.3)	46 (42.1)	97 (64.9)	85 (84.9)	64 (100.0)	16	>32	
<i>Klebsiella</i> spp.	Ceftazidime-avibactam	1,018	46 (4.5)	277 (31.7)	301 (61.3)	199 (80.8)	116 (92.2)	44 (96.6)	20 (98.5)	2 (98.7)	1 (98.8)	1 (98.9)	11 (100.0)	0.12	0.25	
	Ceftazidime	1,018	8 (0.8)	136 (14.1)	226 (36.3)	108 (47.0)	65 (63.3)	23 (55.6)	24 (58.0)	12 (59.1)	35 (62.6)	48 (67.3)	90 (76.1)	243 (100.0)	0.5	>32
ESBL-phenotype	Ceftazidime-avibactam	473	5 (1.1)	30 (7.4)	116 (31.9)	136 (67.0)	108 (63.5)	43 (92.6)	20 (96.8)	2 (97.3)	0 (97.3)	1 (97.7)	11 (100.0)	0.25	1	
	Ceftazidime	473	—	—	—	7 (1.5)	7 (1.5)	24 (9.5)	12 (12.1)	35 (19.5)	48 (29.6)	90 (46.8)	243 (100.0)	>32	>32	
<i>K. pneumoniae</i>	Ceftazidime-avibactam	858	37 (4.3)	213 (29.1)	255 (68.9)	176 (79.4)	105 (91.6)	44 (96.7)	20 (99.1)	2 (99.3)	0 (99.3)	0 (99.4)	5 (100.0)	0.12	0.25	
	Ceftazidime	858	4 (0.5)	81 (9.9)	176 (30.4)	90 (40.9)	57 (47.6)	16 (49.4)	18 (51.5)	11 (52.8)	34 (56.8)	48 (62.4)	90 (72.8)	233 (100.0)	2	>32
ESBL-phenotype	Ceftazidime-avibactam	458	5 (1.1)	29 (7.8)	112 (33.3)	123 (61.4)	98 (83.8)	43 (93.6)	20 (98.9)	2 (98.9)	0 (98.9)	0 (98.9)	5 (100.0)	0.25	1	
	Ceftazidime	458	—	—	—	3 (0.7)	1 (0.9)	18 (5.0)	11 (7.5)	34 (15.3)	48 (26.3)	90 (46.8)	233 (100.0)	>32	>32	
Meropenem-non-susceptible (MIC, $\geq 2$ $\mu$ g/mL)	Ceftazidime-avibactam	93	—	1 (1.1)	5 (6.5)	13 (20.4)	31 (63.8)	19 (74.2)	16 (91.4)	2 (93.5)	1 (94.6)	0 (94.6)	5 (100.0)	0.5	2	
	Ceftazidime	93	—	—	—	—	—	—	—	—	—	—	—	>32	>32	
<i>Citrobacter</i> spp.	Ceftazidime-avibactam	200	9 (4.5)	56 (32.5)	76 (70.5)	40 (90.5)	14 (67.5)	0 (99.5)	1 (100.0)	—	—	—	—	0.12	0.25	
	Ceftazidime	200	10 (5.0)	56 (33.0)	49 (67.5)	27 (71.0)	7 (74.5)	2 (75.5)	3 (77.0)	3 (78.5)	2 (79.5)	14 (86.5)	27 (100.0)	0.25	>32	
<i>Enterobacter</i> spp.	Ceftazidime-avibactam	530	12 (2.3)	44 (10.6)	232 (54.3)	148 (82.3)	69 (95.3)	10 (97.2)	1 (97.4)	2 (97.7)	2 (98.1)	1 (98.5)	8 (100.0)	0.12	0.5	
	Ceftazidime	530	—	—	—	—	—	—	—	—	—	—	—	>32	>32	
Ceftazidime-non-susceptible (MIC, $\geq 8$ $\mu$ g/mL)	Ceftazidime-avibactam	157	3 (1.9)	4 (4.5)	18 (15.9)	50 (47.8)	58 (84.7)	9 (90.4)	1 (91.1)	2 (92.4)	2 (93.6)	6 (94.9)	8 (100.0)	0.5	1	
	Ceftazidime	157	—	—	—	—	—	—	—	—	—	—	—	>32	>32	
<i>S. marcescens</i>	Ceftazidime-avibactam	273	2 (0.7)	33 (12.8)	122 (67.5)	83 (87.9)	26 (97.4)	3 (99.3)	0 (99.3)	0 (99.3)	0 (99.3)	1 (100.0)	0.12	0.5		
	Ceftazidime	273	2 (0.7)	15 (6.2)	126 (52.4)	78 (61.0)	27 (80.8)	8 (93.8)	1 (94.1)	3 (95.2)	1 (95.6)	4 (97.1)	5 (98.9)	3 (100.0)	0.12	0.5
<i>P. mirabilis</i>	Ceftazidime-avibactam	270	175 (64.8)	83 (95.6)	9 (98.9)	1 (99.3)	0 (99.3)	0 (99.3)	1 (100.0)	—	—	—	—	>32	>32	
	Ceftazidime	270	53 (19.6)	172 (83.3)	11 (87.4)	4 (88.9)	2 (89.6)	2 (90.4)	6 (92.6)	3 (93.7)	5 (95.6)	6 (97.8)	3 (100.0)	0.06	1	
ESBL-phenotype	Ceftazidime-avibactam	33	9 (27.3)	18 (81.8)	3 (90.9)	1 (63.9)	0 (93.9)	1 (63.9)	1 (100.0)	—	—	—	—	>32	>32	
	Ceftazidime	33	—	—	—	1 (12.1)	2 (18.2)	1 (12.1)	6 (99.4)	3 (48.5)	5 (63.6)	6 (81.8)	3 (90.9)	3 (100.0)	8	32
<i>P. aeruginosa</i>	Ceftazidime-avibactam	1,137	—	—	—	10 (0.9)	53 (5.5)	378 (38.8)	311 (66.1)	158 (80.0)	70 (86.2)	43 (90.0)	69 (96.0)	45 (100.0)	2	16
	Ceftazidime	1,137	—	—	—	2 (0.2)	15 (1.5)	138 (13.6)	365 (45.7)	154 (59.3)	90 (67.2)	79 (74.1)	126 (85.2)	168 (100.0)	4	>32
Meropenem-non-susceptible (MIC, $\geq 4$ $\mu$ g/mL)	Ceftazidime-avibactam	393	—	—	—	—	—	—	—	—	—	—	—	0.12	0.25	
	Ceftazidime	393	—	—	—	—	—	—	—	—	—	—	—	>32	>32	
Ceftazidime-non-susceptible (MIC, $\geq 16$ $\mu$ g/mL)	Ceftazidime-avibactam	373	—	—	—	1 (0.3)	2 (0.8)	20 (6.2)	69 (24.7)	67 (42.6)	57 (57.9)	43 (69.7)	45 (100.0)	8	>32	
	Ceftazidime	373	—	—	—	—	—	—	—	—	—	—	—	>32	>32	
<i>Acinetobacter</i> spp.	Ceftazidime-avibactam	457	—	—	—	1 (0.2)	2 (0.7)	5 (1.8)	10 (3.9)	42 (13.1)	75 (29.5)	114 (100.0)	16	>32		
	Ceftazidime	457	—	—												

---

**Activity of Ceftazidime-Avibactam and Comparator Agents Tested Against Isolates  
from Europe-Mediterranean Region Surveillance (2011)**

---

R.K. Flamm, H.S. Sader, R.N. Jones

*JMI Laboratories, North Liberty, Iowa, USA*

*Presented at the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy  
September 10–13, 2013, Denver, CO, USA*