

# In Vitro Activity of Ceftazidime-Avibactam (CAZ-AVI) and Comparators Against Gram-negative Pathogens Isolated from Patients in Canadian Hospitals in 2009-2014: CANWARD Surveillance Study

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and the CANADIAN ANTIMICROBIAL RESISTANCE ALLIANCE (CARA)

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## ABSTRACT

**Background:** Avibactam, a  $\beta$ -lactamase inhibitor of Ambler class A, C and some class D enzymes in combination with ceftazidime, is FDA approved for the treatment of complicated urinary tract and intra-abdominal infections in adults. We determined the in vitro activity of ceftazidime (CAZ) with avibactam (fixed 4  $\mu$ g/mL concentration) and comparators versus Gram-negative pathogens, including extended-spectrum  $\beta$ -lactamase producing (ESBL), AmpC-producing (AmpC) *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolates recovered from January 2009 to October 2014 from patients in medical and surgical wards, intensive care units, clinics, and emergency rooms at 15 Canadian hospitals.

**Methods:** Antimicrobial susceptibility testing was performed using broth microdilution panels following CLSI recommendations (M07-A10). Susceptibility was defined in accordance with CLSI, except for CAZ-AVI, where the FDA breakpoints were used. Cephalosporin-resistant *Escherichia coli* and *Klebsiella* spp. isolates were genetically characterized for ESBL-production using PCR and sequence analysis.

**Results:** The activity of CAZ-AVI and comparators is summarized in Table 1 and 2.

**Conclusions:** CAZ-AVI demonstrated potent in vitro activity against recent clinical isolates of *Enterobacteriaceae*, including those with resistance to oxyminocephalosporins by a variety of mechanisms. MIC<sub>90</sub> of CAZ-AVI against *P. aeruginosa* was comparable to meropenem and 4 fold lower than CAZ alone. CAZ-AVI was the most active agent against CAZ, MER and TZP-resistant *P. aeruginosa*. Activity against *A. baumannii* was not improved compared to CAZ alone. Activity against *S. maltophilia* was poor but somewhat better than CAZ alone. CAZ-AVI may be useful for the treatment of infections caused by  $\beta$ -lactam-resistant *Enterobacteriaceae* and *P. aeruginosa*.

## BACKGROUND

Antimicrobial resistance is a growing problem among Gram-negative isolates worldwide. Multi-drug resistant (MDR) *P. aeruginosa*, ESBL-, KPC- and AmpC-producing *Enterobacteriaceae*, and MDR *Acinetobacter* spp. can cause severe infections and treatment choices are limited. Avibactam is a broad-spectrum non- $\beta$ -lactam  $\beta$ -lactamase inhibitor being studied in combination with ceftazidime to restore the parent drug activity against a wide range of cephalosporin-resistant Gram-negative pathogens expressing Ambler class A and C, and some class D,  $\beta$ -lactamases (1).

## MATERIALS & METHODS

Isolates were collected as part of the CANWARD 2009 through to CANWARD 2014 studies occurring between January 2009 and October 2014. 15 Canadian centers in 8 provinces contributed clinically relevant isolates. Only species with >100 isolates submitted were considered in this study. A total of 9586 Gram-negative isolates were included. Susceptibility testing was done by broth microdilution in accordance with the CLSI M07-A10 document (2). Serial dilutions of ceftazidime with and without a fixed concentration of 4  $\mu$ g/mL avibactam, piperacillin-tazobactam, ceftriaxone, meropenem and tigecycline were included on the panel. Susceptibility was defined in accordance with CLSI, except for CAZ-AVI, where the FDA breakpoints were used. Cephalosporin-resistant *Escherichia coli* and *Klebsiella* spp. isolates were genetically characterized for ESBL-production using PCR and sequence analysis.

## RESULTS

**TABLE 1: MIC<sub>50</sub> and MIC<sub>90</sub> for all isolates and cephalosporin-resistant isolates for ceftazidime-avibactam and comparators.**

Organism (n)	MIC <sub>50</sub> /MIC <sub>90</sub> ( $\mu$ g/mL)				
	Ceftazidime-Avibactam	Ceftazidime	Ceftriaxone	Meropenem	Piperacillin-tazobactam
<i>Escherichia coli</i> (4533)	0.12/0.25	$\leq$ 0.25/1	$\leq$ 0.25/0.5	$\leq$ 0.03/ $\leq$ 0.03	2/4
<i>E. coli</i> CRO-R (372)	0.12/0.5	16/>32	64/>64	$\leq$ 0.03/ $\leq$ 0.03	4/16
<i>E. coli</i> ESBL (295)	0.12/0.5	16/>32	>64/>64	$\leq$ 0.03/ $\leq$ 0.03	4/16
<i>Pseudomonas aeruginosa</i> (2168)	2/8	4/32	16/>64	0.5/8	4/64
<i>P. aeruginosa</i> (CAZ-R) (251)	8/>16	>32/>32	>64/>64	4/32	128/512
<i>P. aeruginosa</i> (TZP-R) (155)	8/>16	>32/>32	>64/>64	8/32	256/512
<i>P. aeruginosa</i> (MER-R) (258)	8/16	16/>32	>64/>64	16/>32	32/256
<i>Klebsiella pneumoniae</i> (1472)	0.12/0.5	$\leq$ 0.25/1	$\leq$ 0.25/ $\leq$ 0.25	$\leq$ 0.03/ $\leq$ 0.03	2/8
<i>K. pneumoniae</i> CRO-R (68)	0.5/2	32/>32	64/>64	$\leq$ 0.03/0.25	8/512
<i>K. pneumoniae</i> ESBL (62)	0.5/2	32/>32	64/>64	$\leq$ 0.03/0.12	8/>512
<i>Enterobacter cloacae</i> (598)	0.25/1	0.5/>32	$\leq$ 0.25/>64	$\leq$ 0.03/0.12	2/64
<i>E. cloacae</i> CRO-R (144)	0.5/2	>32/>32	>64/>64	0.06/0.25	32/128
<i>E. cloacae</i> ERT-R (21)	0.5/4	>32/>32	>64/>64	0.5/2	64/256
<i>Serratia marcescens</i> (373)	0.25/0.5	$\leq$ 0.25/1	$\leq$ 0.25/1	0.06/0.06	$\leq$ 1/4
<i>Klebsiella oxytoca</i> (379)	0.12/0.5	$\leq$ 0.25/0.5	$\leq$ 0.25/1	$\leq$ 0.03/ $\leq$ 0.03	2/128
<i>Proteus mirabilis</i> (352)	$\leq$ 0.06/0.1	$\leq$ 0.25/ $\leq$ 0.25	$\leq$ 0.25/ $\leq$ 0.25	0.06/0.12	$\leq$ 1/ $\leq$ 1
<i>Enterobacter aerogenes</i> (168)	0.25/0.5	0.5/>32	$\leq$ 0.25/16	$\leq$ 0.03/0.12	4/32
<i>Acinetobacter baumannii</i> (104)	8/32	8/>16	8/64	0.5/1	$\leq$ 1/64
<i>Stenotrophomonas maltophilia</i> (370)	>32/>32	>16/>16	>64/>64	>32/>32	256/>512

**TABLE 2: Percent susceptible for all isolates and cephalosporin-resistant isolates to ceftazidime-avibactam and comparators.**

Organism (n)	% Susceptible				
	Ceftazidime-Avibactam <sup>1</sup>	Ceftazidime <sup>2</sup>	Ceftriaxone <sup>2</sup>	Meropenem <sup>2</sup>	Piperacillin-tazobactam <sup>2</sup>
<i>Escherichia coli</i> (4533)	100	93.8	91.6	100	97.8
<i>E. coli</i> CRO-R (372)	99.7	30.1	0	99.7	91.7
<i>E. coli</i> ESBL (295)	99.7	34.2	2.7	99.7	93.2
<i>Pseudomonas aeruginosa</i> (2168)	94.4	82.5	N/A	80.5	84.5
<i>P. aeruginosa</i> (CAZ-R) (251)	66.9	0	N/A	45.8	11.2
<i>P. aeruginosa</i> (TZP-R) (155)	67.7	1.9	N/A	41.3	0
<i>P. aeruginosa</i> (MER-R) (258)	74.4	39.9	N/A	0	43.8
<i>Klebsiella pneumoniae</i> (1472)	100	96.1	95	99.7	97.4
<i>K. pneumoniae</i> CRO-R (68)	100	4.4	0	94.1	64.7
<i>K. pneumoniae</i> ESBL (62)	100	4.8	6.5	96.8	64.5
<i>Enterobacter cloacae</i> (598)	99.7	77.8	73.7	99.2	86.0
<i>E. cloacae</i> CRO-R (144)	98.6	9.7	0	96.5	41.7
<i>E. cloacae</i> ERT-R (21)	90.5	4.8	0	76.2	28.6
<i>Serratia marcescens</i> (373)	100	99.5	94.1	99.5	95.7
<i>Klebsiella oxytoca</i> (379)	100	98.7	91.3	100	88.1
<i>Proteus mirabilis</i> (352)	100	99.4	98.3	100	100
<i>Enterobacter aerogenes</i> (168)	99.4	76.2	72.6	99.4	88.0
<i>Acinetobacter baumannii</i> (104)	N/A*	78.9	51.0	95.2	84.6
<i>Stenotrophomonas maltophilia</i> (370)	N/A**	23.8	N/A	N/A	N/A

CRO-R: Ceftriaxone-resistant; MER-R Meropenem-resistant; CAZ-R: Ceftazidime-resistant; TZP-R: piperacillin-tazobactam resistant; ERT-R: Ertapenem-resistant, ESBL: Extended spectrum  $\beta$ -lactamase-producing

<sup>1</sup>FDA breakpoints. <sup>2</sup>CLSI M100-S25 breakpoints. \*61.5% of isolates had MIC  $\leq$  8 $\mu$ g/mL. \*\*31.6% of isolates had MIC  $\leq$  8 $\mu$ g/mL.

## CONCLUSIONS

Avibactam reduced MIC<sub>50</sub> and MIC<sub>90</sub> of ceftazidime for all organisms tested except *A. baumannii* and *S. maltophilia*.

Avibactam restored the activity of ceftazidime for all *Enterobacteriaceae* with acquired resistance to ceftriaxone.

Avibactam resulted in a 2-fold reduction in MIC<sub>50</sub> and 4-fold reduction in MIC<sub>90</sub> compared with ceftazidime alone for *P. aeruginosa*.

Ceftazidime-avibactam susceptibility rates are >99% for all *Enterobacteriaceae* (77.8 - 99.2% for ceftazidime alone), 94.4% for *P. aeruginosa* (82.5% for ceftazidime alone) and 61.5% (using the ceftazidime breakpoint) for *A. baumannii* (78.9% for ceftazidime alone).

Ceftazidime-avibactam susceptibility rates are comparable with meropenem for *Enterobacteriaceae*, superior to meropenem for *P. aeruginosa*.

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## REFERENCES

- Lagacé-Wiens et al. Activity of NXL104 in Combination with  $\beta$ -Lactams against Genetically Characterized *Escherichia coli* and *Klebsiella pneumoniae* Isolates Producing Class A Extended-Spectrum  $\beta$ -Lactamases and Class C  $\beta$ -Lactamases. *Antimicrob. Agents Chemother.* 2011. 55:2434-2437.
- CLSI. *Methods for Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – Eighth Edition.* CLSI document M07-A10. Wayne, PA: Clinical and Laboratory Standards Institute; 2014.
- CLSI. *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fourth Informational Supplement.* CLSI document M100-S24. Wayne, PA: Clinical and Laboratory Standards Institute; 2014.