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In Vitro Activity of Ceftazidime-Avibactam (CAZ-AVI) and Comparators against Gram-Negative Pathogens Isolated from Patients in Canadian Hospitals in 2009-2015: CANWARD Surveillance Study

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ABSTRACT

Background: Avibactam, a β-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 µg/mL concentration) and comparators versus Gram-negative pathogens, including extended-spectrum β-lactamase producing (ESBL) and cephalosporin-resistant, non-ESBL-producing *Enterobacteriaceae*, and *Pseudomonas aeruginosa* isolates recovered from January 2009 to December 2015 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. 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 Table 2.
Conclusions: CAZ-AVI demonstrated potent in vitro activity against recent clinical isolates of *Enterobacteriaceae*, including those with resistance to oximinocephalosporins by a variety of mechanisms. *P. aeruginosa* were highly susceptible to CAZ-AVI overall, while CAZ, MER and TZP-resistant *P. aeruginosa* were moderately susceptible to CAZ-AVI. Activity against *A. baumannii* was not improved compared to CAZ alone. *S. maltophilia susceptibility* was poor but somewhat better than CAZ alone when applying the ≤8µg/mL breakpoint. CAZ-AVI may be useful for the treatment of complicated urinary tract and intra-abdominal infections caused by β-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 increasingly limited by antimicrobial resistance. Avibactam is a broad-spectrum non-β-lactam β-lactamase inhibitor formulated 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, β-lactamases (1).

MATERIALS & METHODS

Isolates were collected as part of the CANWARD 2009 through to CANWARD 2015 studies occurring between January 2009 and December 2015. 15 Canadian centers in 8 provinces contributed clinically relevant isolates. Only species with >100 isolates submitted were considered in this study. A total of 11,952 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 µg/mL avibactam, piperacillin-tazobactam, ceftriaxone and meropenem were included on the panel. Susceptibility was defined in accordance with the CLSI M100-S26 document (3), except for ceftazidime-avibactam where the FDA susceptibility breakpoint (≤8/4 µg/mL). Cephalosporin-resistant *Escherichia coli* and *Klebsiella* spp. isolates were phenotypically characterized for ESBL-production by using the CLSI disk diffusion method and genotypically characterized by using PCR for CTX, SHV, OXA and TEM genes with sequence analysis to determine the genotype of ESBL implicated.

RESULTS

Table 1. MIC_{50} and MIC_{90} for all isolates and cephalosporin-resistant isolates for ceftazidime-avibactam and comparators

Organism (n)	MIC_{50}/MIC_{90} (µg/mL)				
	Ceftazidime-Avibactam	Ceftazidime	Ceftriaxone	Meropenem	Piperacillin-tazobactam
Escherichia coli (5094)	0.12/0.25	≤0.25/1	≤0.25/0.5	≤0.03/≤0.03	2/4
E. coli CRO-R (444)	0.12/0.5	16/>32	64/>64	≤0.03/0.06	4/16
E. coli ESBL (364)	0.12/0.5	16/>32	>64/>64	≤0.03/≤0.03	4/16
Pseudomonas aeruginosa (2531)	2/8	4/32	16/>64	0.5/8	4/64
P. aeruginosa (CAZ-R) (283)	8/>16	>32/>32	>64/>64	4/32	128/512
P. aeruginosa (TZP-R) (177)	8/>16	>32/>32	>64/>64	8/32	256/512
P. aeruginosa (MER-R) (314)	8/16	16/>32	>64/>64	16/>32	32/256
Klebsiella pneumoniae (1668)	0.12/0.5	≤0.25/1	≤0.25/≤0.25	≤0.03/≤0.03	2/8
K. pneumoniae CRO-R (78)	0.5/2	32/>32	64/>64	≤0.03/0.25	8/512
K. pneumoniae ESBL (71)	0.5/2	32/>32	64/>64	≤0.03/0.12	8/>512
Enterobacter cloacae (687)	0.25/1	0.5/>32	≤0.25/>64	≤0.03/0.12	2/64
E. cloacae CRO-R (167)	0.5/2	>32/>32	>64/>64	0.06/0.25	32/128
E. cloacae ERT-R (25)	0.5/4	>32/>32	>64/>64	0.5/4	64/256
Serratia marcescens (406)	0.25/0.5	≤0.25/1	≤0.25/1	0.06/0.06	≤1/4
Klebsiella oxytoca (424)	0.12/0.5	≤0.25/0.5	≤0.25/1	≤0.03/≤0.03	2/128
Proteus mirabilis (402)	≤0.06/0.12	≤0.25/≤0.25	≤0.25/≤0.25	0.06/0.12	≤1/≤1
Enterobacter aerogenes (186)	0.25/0.5	0.5/>32	≤0.25/16	≤0.03/0.12	4/32
Acinetobacter baumannii (115)	8/>16	8/32	8/32	0.5/1	≤1/64
Stenotrophomonas maltophilia (439)	>32/>32	>16/>16	>64/>64	>32/>32	256/>512

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

Table 2. Percent susceptible for all isolates and cephalosporin-resistant isolates to ceftazidime-avibactam and comparators

Organism (n)	% Susceptible[1]				
	Ceftazidime-Avibactam	Ceftazidime	Ceftriaxone	Meropenem	Piperacillin-tazobactam
Escherichia coli (5094)	100	93.6	91.1	100	97.8
E. coli CRO-R (444)	99.8	31.8	0	99.8	91.9
E. coli ESBL (364)	99.7	35.7	2.8	99.7	93.4
Pseudomonas aeruginosa (2531)	94.6	82.4	N/A	80.0	84.6
P. aeruginosa (CAZ-R) (283)	68.6	0	N/A	44.2	9.5
P. aeruginosa (TZP-R) (177)	68.9	1.7	N/A	39.6	0
P. aeruginosa (MER-R) (314)	76.4	40.8	N/A	0	46.2
Klebsiella pneumoniae (1668)	99.9	95.9	95.0	99.6	97.4
K. pneumoniae CRO-R (78)	98.7	16.7	0	92.3	64.1
K. pneumoniae ESBL (71)	100	23.9	7.0	95.8	64.8
Enterobacter cloacae (687)	99.7	77.4	73.1	99.0	85.9
E. cloacae CRO-R (167)	98.8	9.6	0	95.8	41.9
E. cloacae ERT-R (25)	92.0	8.0	0	72.0	28.0
Serratia marcescens (406)	100	99.5	94.6	99.5	96.1
Klebsiella oxytoca (424)	100	98.6	91.5	100	88.2
Proteus mirabilis (402)	100	99	97.8	100	100
Enterobacter aerogenes (186)	99.5	76.3	73.1	99.5	88.1
Acinetobacter baumannii (115)	62.6*	80.9	53.0	95.6	86.1
Stenotrophomonas maltophilia (439)	32.6*	25.1	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 β-lactamase-producing
[1]CLSI M100-S26 breakpoints. *MIC ≤ 8µg/mL.

CONCLUSIONS

Avibactam reduced MIC_{50} and MIC_{90} 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 whether by ESBL production or other mechanisms. Avibactam resulted in a 2-fold reduction in MIC_{50} and 4-fold reduction in MIC_{90} compared with ceftazidime alone for *P. aeruginosa*.

Ceftazidime-avibactam susceptibility rates are >99% for all *Enterobacteriaceae* (76.3 - 99.5% for ceftazidime alone), 94.6% for *P. aeruginosa* (82.4% for ceftazidime alone) and ~70% of *Pseudomonas* isolates with resistance to ceftazidime, meropenem or piperacillin-tazobactam. Overall, ceftazidime-avibactam susceptibility rates are comparable with meropenem for *Enterobacteriaceae* and superior to meropenem for *P. aeruginosa.*

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