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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 2009-2017: CANWARD Surveillance Study

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Introduction

Antimicrobial resistance is a growing problem among Gram-negative isolates worldwide. Most concerning is the emergence and rapid global spread of pathogenic extended-spectrum beta-lactamase (ESBL)-producing and carbapenemase-producing *Enterobacteriaceae*. (1) Furthermore, the increasing prevalence of inhibitor-resistant AmpC-producing *Enterobacteriaceae* and recent MERINO trial results suggest that conventional beta-lactam-inhibitor combinations such as piperacillin-tazobactam may be loosing clinical efficacy (2). Beyond infections caused by *Enterobacteriaceae*, multi-drug-resistant *Acinetobacter* spp. and *Pseudomonas aeruginosa* can cause severe infections and treatment choices are increasingly limited by antimicrobial resistance. Further complicating management of beta-lactam-resistant organisms is that genes conferring resistance to cephalosporins and carbapenems frequently co-exist on plasmids with genes conferring resistance to sulfonamides, aminoglycosides, quinolones (e.g. AAC(6')-Ib-cr, *qnr*) and more recently colistin (3).

Avibactam is a broad-spectrum non-β-lactam β-lactamase inhibitor formulated in combination with ceftazidime and being studied in combination with aztreonam 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 (4).

Materials and Methods

Bacterial Isolates

Isolates were collected as part of the CANWARD 2009 through to CANWARD 2017 studies occurring between January 2009 and December 2017. 15 Canadian centers in 8 provinces contributed clinically relevant isolates. Only Gram-negative species with >100 isolates submitted were considered in this study. A total of 14,330 Gram-negative isolates were included.

Antimicrobial Susceptibility Testing

Susceptibility testing was done by broth microdilution in accordance with the CLSI M07-A10 document (5). Serial two-fold 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-S28 (6) document with exceptions noted in the results table (3). Third generation cephalosporin-resistant *Escherichia coli* and *Klebsiella* spp. isolates were phenotypically characterized for ESBL-production by using the CLSI disk diffusion method (6) 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 antibiotic-resistant isolates for ceftazidime-avibactam and comparators

Organism (n)	MIC_{50}/MIC_{90} (μg/mL)					
	Ceftazidime-avibactam	Ceftazidime	Ceftriaxone	Meropenem	Piperacillin-tazobactam	Ceftolozane-tazobactam
Escherichia coli (6347)	0.12/0.25	≤0.25/2	≤0.25/1	≤0.03/≤0.03	2/4	≤0.12/0.5
E. coli CRO-R (597)	0.25/0.5	16/>32	64/>64	≤0.03/0.06	4/16	0.25/1
E. coli ESBL (503)	0.25/0.5	16/>32	>64/>64	≤0.03/0.06	4/16	0.25/1
Pseudomonas aeruginosa (3227)	2/8	4/32	16/>64	0.5/8	4/64	0.5/2
P. aeruginosa (CAZ-R) (382)	8/>16	>32/>32	>64/>64	4/32	128/512	2/8
P. aeruginosa (TZP-R) (248)	8/>16	>32/>32	>64/>64	4/32	256/512	2/8
P. aeruginosa (MER-R) (399)	8/16	16/>32	>64/>64	16/32	32/256	1/4
Klebsiella pneumoniae (2097)	0.12/0.5	≤0.25/1	≤0.25/≤0.25	≤0.03/0.06	2/8	0.25/0.5
K. pneumoniae CRO-R (120)	0.5/2	>32/>32	>64/>64	≤0.03/0.25	16/>512	1/64
K. pneumoniae ESBL (110)	0.5/2	32/>32	>64/>64	≤0.03/0.12	16/>512	1/32
Enterobacter cloacae (902)	0.25/1	0.5/>32	≤0.25/>64	≤0.03/0.12	2/64	0.25/8
E. cloacae CRO-R (223)	0.5/2	>32/>32	>64/>64	0.06/0.25	32/128	4/16
E. cloacae ERT-R (36)	1/8	>32/>32	>64/>64	0.25/2	128/>512	16/>64
Serratia marcescens (529)	0.25/0.5	≤0.25/1	≤0.25/1	0.06/0.06	≤1/4	0.5/1
Klebsiella oxytoca (564)	0.12/0.5	≤0.25/0.5	≤0.25/1	≤0.03/≤0.03	2/32	≤0.12/0.5
Proteus mirabilis (485)	≤0.06/0.12	≤0.25/≤0.25	≤0.25/≤0.25	0.06/0.12	≤1/≤1	0.5/0.5
Klebsiella aerogenes (228)	0.25/0.5	0.5/>32	≤0.25/16	0.06/0.12	4/32	0.25/2
Acinetobacter baumannii (146)	8/>16	8/32	8/32	0.5/2	2/64	0.25/4
Stenotrophomonas maltophilia (545)	>16/>16	>32/>32	>64/>64	>32/>32	256/>512	32/>64

CRO-R: ceftriaxone-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 select antibiotic-resistant isolates for ceftazidime-avibactam and comparators

Organism (n)	% susceptible (μg/mL)					
	Ceftazidime-avibactam	Ceftazidime	Ceftriaxone	Meropenem	Piperacillin-tazobactam	Ceftolozane-tazobactam
Escherichia coli (6347)	100	92.9	90.3	100	97.5	99.6
E. coli CRO-R (597)	99.8	29.5	0	99.8	91.6	96.7
E. coli ESBL (503)	99.8	32.8	2.0	99.8	93.2	97.4
Pseudomonas aeruginosa (3227)	94.1	81.4	N/A	80.8	83.7	97.9
P. aeruginosa (CAZ-R) (382)	66.8	0	N/A	46.3	10.2	86.1
P. aeruginosa (TZP-R) (248)	65.2	2.0	N/A	39.9	0	85.1
P. aeruginosa (MER-R) (399)	73.2	39.8	N/A	0	43.6	91.2
Klebsiella pneumoniae (2097)	99.9	94.9	94.0	99.6	96.6	97.9
K. pneumoniae CRO-R (120)	98.3	17.5	0	93.3	64.2	71,4
K. pneumoniae ESBL (110)	99.1	21.8	6.4	95.5	63.6	73.9
Enterobacter cloacae (902)	99.8	77.2	73.2	99.2	85.6	85.1
E. cloacae CRO-R (223)	99.1	9.9	0	96.9	41.7	43.5
E. cloacae ERT-R (36)	94.4	5.6	0	80.6	19.4	23.3
Serratia marcescens (529)	100	99.4	93.8	99.4	96.6	98.9
Klebsiella oxytoca (564)	100	98.8	91.5	100	89.4	99.7
Proteus mirabilis (485)	100	99.0	97.9	100	99.6	99.7
Klebsiella aerogenes (228)	99.6	75.0	71.9	98.7	86.8	92.2
Acinetobacter baumannii (146)	58.2‡	78.1	50.0	95.9	83.6	N/A
Stenotrophomonas maltophilia (545)	30.1‡	23.6	N/A	N/A	N/A	N/A

CRO-R: ceftriaxone-resistant; CAZ-R: ceftazidime-resistant; TZP-R: piperacillin-tazobactam -resistant, ERT-R: ertapenem-resistant, ESBL: extended-spectrum β-lactamase-producing.
‡ MIC ≤8 μg/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* including strains resistant to meropenem, piperacillin-tazobactam and ceftazidime.

Ceftazidime-avibactam susceptibility rates are >99% for all *Enterobacteriaceae* (75.9 - 98.9% for ceftazidime alone), 94.2% for *P. aeruginosa* (81.6% 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.*

If ceftazidime-avibactam breakpoints used for *Enterobacteriaceae* and *Pseudomonas aeruginosa* are applied to *Acinetobacter* and *Stenotrophomonas*, ceftazidime-avibactam does not provide any susceptibility benefit over ceftazidime alone in these organisms.

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