FRIDAY - 48

In Vitro Activity of Ceftazidime-Avibactam (CAZ-AVI) and Comparators against Gram-Negative Pathogens Isolated from Patients in Canadian Hospitals in 2009-2016: 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 (AVI; 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 (M100-S27, 2017), 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 DNA sequence analysis.

Results: The activity of CAZ-AVI and comparators is summarized in the tables.

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 (94.6%), while CAZ, MER and TZP-resistant P. aeruginosa were moderately susceptible (68.6-76.4%) to CAZ-AVI. Activity against *A. baumannii* was not improved compared to CAZ alone. Activity against *S. maltophilia* was poor and marginally better than CAZ alone.

BACKGROUND

Antimicrobial resistance is a growing problem among Gram-negative isolates worldwide. Multi-drug resistant (MDR) *P. aeruginosa*, ESBL-, KPC-, OXA- and AmpC-producing *Enterobacteriaceae*, and MDR *Acinetobacter* spp. can cause severe infections and treatment choices are increasingly limited by antimicrobial resistance. Genes conferring beta-lactamase-mediated resistance to these agents frequently co-occurs on plasmids with genes also conferring resistance to sulfonamides, aminoglycosides, quinolones (e.g. AAC(6')-Ib-cr, *qnr*) and more recently colistin. 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 2016 studies occurring between January 2009 and December 2016. 15 Canadian centers in 8 provinces contributed clinically relevant isolates. Only species with >100 isolates submitted were considered in this study. A total of 13,421 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-S27 document (3), except for ceftazidime-avibactam where the FDA susceptibility breakpoint (≤8/4 µg/mL) was used. 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 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 (5698)	0.12/0.25	≤0.25/1	≤0.25/0.5	≤0.03/≤0.03	2/4	≤0.25/0.25
E. coli CRO-R (516)	0.12/0.5	16/>32	64/>64	≤0.03/≤0.03	4/16	0.25/1
E. coli ESBL (431)	0.12/0.5	16/>32	>64/>64	≤0.03/≤0.03	4/16	0.25/1
Pseudomonas aeruginosa (2856)	2/8	4/32	16/>64	0.5/8	4/64	0.5/1
P. aeruginosa CAZ-R (324)	8/>16	>32/>32	>64/>64	4/32	128/512	2/8
P. aeruginosa TZP-R (207)	8/>16	>32/>32	>64/>64	8/32	256/512	2/8
P. aeruginosa MER-R (348)	8/16	16/>32	>64/>64	16/32	32/256	1/4
Klebsiella pneumoniae (1853)	0.12/0.5	≤0.25/1	≤0.25/≤0.25	≤0.03/≤0.03	2/8	0.25/0.5
K. pneumoniae CRO-R (96)	0.5/2	32/>32	>64/>64	≤0.03/0.5	16/512	1/>64
K. pneumoniae ESBL (90)	0.5/2	32/>32	>64/>64	≤0.03/0.12	16/>512	1/>64
Enterobacter cloacae (783)	0.25/1	0.5/>32	≤0.25/>64	≤0.03/0.12	2/64	0.25/8
E. cloacae CRO-R (190)	0.5/2	>32/>32	>64/>64	0.06/0.25	32/128	4/16
E. cloacae ERT-R (27)	1/8	>32/>32	>64/>64	0.25/4	64/256	8/16
Serratia marcescens (467)	0.25/0.5	≤0.25/1	≤0.25/1	0.06/0.06	≤1/4	0.5/1
Klebsiella oxytoca (491)	0.12/0.5	≤0.25/0.5	≤0.25/1	≤0.03/≤0.03	2/32	≤0.25/0.5
Proteus mirabilis (442)	≤0.06/0.12	≤0.25/≤0.25	≤0.25/≤0.25	0.06/0.12	≤1/≤1	0.5/0.5
Enterobacter aerogenes (201)	0.25/0.5	0.5/32	≤0.25/16	≤0.03/0.06	4/32	0.25/2
Acinetobacter baumannii (130)	8/>16	8/32	8/32	0.5/1	≤1/32	0.25/2
Stenotrophomonas maltophilia (500)	>32/>32	>16/>16	>64/>64	>32/>32	256/>512	32/>64

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 antibiotic-resistant isolates to ceftazidime-avibactam and comparators

Organism (n)	% Susceptible					
	Ceftazidime-Avibactam	Ceftazidime	Ceftriaxone	Meropenem	Piperacillin-tazobactam	Ceftolozane-tazobactam
Escherichia coli (5698)	100	93.4	90.7	100	97.7	99.6
E. coli CRO-R (516)	99.8	31.8	0	99.8	92.6	97.0
E. coli ESBL (431)	99.8	36.0	2.3	99.8	94.2	97.5
Pseudomonas aeruginosa (2856)	94.5	82.3	N/A	80.6	84.2	98.1
P. aeruginosa CAZ-R (324)	67.9	0	N/A	44.8	9.0	88.0
P. aeruginosa TZP-R (207)	66.7	1.5	N/A	39.6	0	88.4
P. aeruginosa MER-R (348)	75.3	40.3	N/A	0	44.8	92.2
Klebsiella pneumoniae (1853)	99.9	95.5	95.0	99.6	96.9	98.1
K. pneumoniae CRO-R (96)	97.9	15.6	0	91.7	61.5	71.6
K. pneumoniae ESBL (90)	99.9	23.3	7.8	94.4	62.2	76.5
Enterobacter cloacae (783)	99.7	77.3	73.4	99.1	85.8	85.4
E. cloacae CRO-R (190)	99.0	8.4	0	96.3	41.6	43.8
E. cloacae ERT-R (27)	92.6	7.4	0	74.1	25.9	33.3
Serratia marcescens (467)	100	99.6	94.7	99.6	96.5	99.7
Klebsiella oxytoca (491)	100	98.6	92.1	100	89.6	100
Proteus mirabilis (442)	100	99	97.7	100	99.8	99.6
Enterobacter aerogenes (201)	99.5	75.1	71.6	99.5	88.0	93.7
Acinetobacter baumannii (130)	61.5*	81.5	53.9	96.1	85.4	N/A
Stenotrophomonas maltophilia (500)	30.2*	23.6	N/A	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. *MIC ≤ 8µg/mL.

CONCLUSIONS

Avibactam reduced the 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* (76.3 - 99.5% for ceftazidime alone), 94.5% for *P. aeruginosa* (82.3% for ceftazidime alone) and ~70% for *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.*

Assuming ceftazidime-avibactam breakpoints used for *Enterobacteriaceae* and *Pseudomonas aeruginosa* apply to *Acinetobacter* and *Stenotrophomonas*, ceftazidime-avibactam does not provide any susceptibility benefit over ceftazidime alone in these organisms and may antagonize ceftazidime in *Acinetobacter.*

ACKNOWLEDGMENTS

We acknowledge the contributions of the directors and technologists of the contributing site microbiology laboratories.

The CANWARD study was supported in part by the University of Manitoba, National Microbiology Lab, Winnipeg, Canada and Cerexa/Forest.

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