In-Vitro Antibacterial Activities of Cefiderocol (S-649266) Alone and With the Addition of Beta-Lactamase Inhibitors Against Multidrug-resistant *Acinetobacter baumannii*

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Poster number: 1297

Introduction

Background: *Acinetobacter baumannii*, a nonfermenting Gram-negative pathogen, is among the most challenging nosocomial pathogens to eradicate (1). Multidrug-resistant (MDR) (resistance to at least 3 different classes of antimicrobial agents) *A. baumannii* strains have been increasingly reported in the last decade, attributing to a rise in infections (2) .

Motivation: (Cefiderocol (CFDC) is a new parental siderophore cephalosporin that has displayed potent activity against Gram-negative bacteria, more specifically non-fermenting Gram-negative bacilli, including *A. baumannii* (3). Although uncommon, elevated minimum inhibitory concentrations (MICs) to CFDC have been reported, when tested against A. baumannii isolates, in-vitro. The addition of beta-lactamase inhibitors has been shown to be successful in decreasing elevated CFDC MICs (4).

Objective: The objective of this study was to evaluate the activity of several beta-lactamase inhibitors in combination with CFDC against *A. baumannii* strains with high CFDC MICs.

Significance: While beta-lactamase inhibitors have been shown to reduce the MICs of other cephalosporin antibiotics, the evaluation of sulbactam (SUL), tazobactam (TAZO), or clavulanic acid (CLAV) in addition to CFDC against A. baumannii isolates with elevated CFDC MICs, has yet to be reported. Potentially, in strains with elevated CFDC MIC's, the addition of the evaluated beta-lactamase inhibitors may show increases in CFDC susceptibility.

Methods

Bacterial strains: A total of 150 MDR (resistant to ≥ 1 antibiotic in ≥ 3 unique classes) A. baumannii, including 32 COL-resistant strains, selected from the Anti-infective Research Laboratory (ARL, Detroit, MI) strain library were included in the study for minimum inhibitory concentration (MIC) susceptibility testing. Six strains that exhibited elevated CFDC MICs,16-32 mg/L were included in the present study.

Media/ Antibiotics: CLAV, SUL, and TAZO were purchased through Sigma Chemical Company (St. Louis, MO), and AVI was purchased the Fisher Scientific. CFDC was provided by its manufacturer (Shionogi & Co. Ltd., Osaka, Japan). All in vitro testing for CFDC was completed with the use of iron-depleted cation-adjusted Mueller-Hinton broth (ID-CAMHB; iron concentration <0.1 mg/l) to ensure the induction of bacterial iron transporters per manufacturer standards (5).

Susceptibility Testing:. CFDC MICs were determined in duplicate by BMD using TREK panels supplied by International Health Management Associates, Inc. (IHMA, Inc.). For reference, the ATCC strain 25922 (*Escherichia coli*) and ATCC 27853 (*Pseudomonas aeruginosa*) were used in the MIC testing (MIC range; 0.06-0.5 mg/l). The MIC values of CFDC in combination with the beta-lactamase inhibitors were determined in duplicate by the broth microdilution (BMD) method in a 96-well plate, with an inoculum of approximately 10^6 CFU/ml per the CLSI guidelines. The beta-lactamase inhibitors were supplemented in the following ratios to CFDC: 8:1 for TAZO, 2:1 for SUL and 4:1 for CLAV and AVI.

Whole Genome Sequencing: Total genomic DNA was used as input material for library construction. DNA libraries were prepared using the Nextera XT™ library construction protocol and index kit (Illumina, San Diego, California, USA) and sequenced on a MiSeq Sequencer (Illumina) using a MiSeq Reagent Kit v3 (600 cycle).

Results

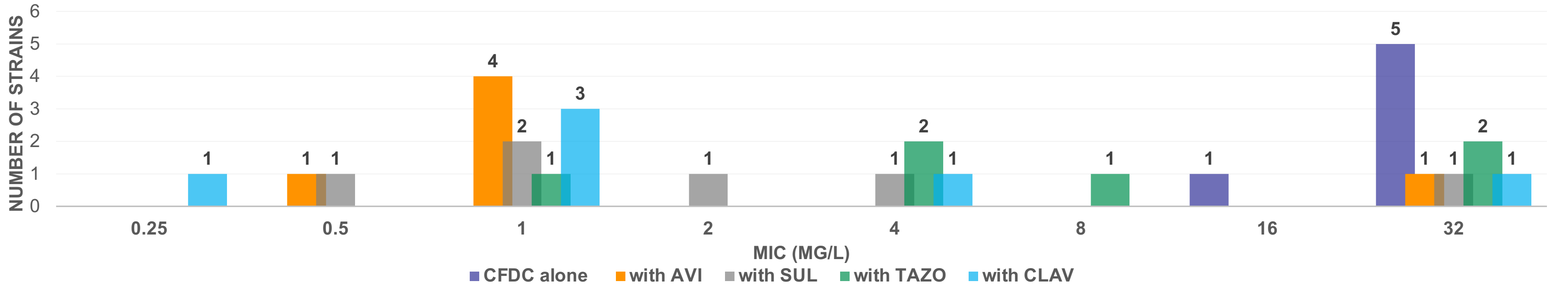
Table 1. *A. baumannii* Strains with CFDC MICs of 16-32 mg/L

Project Strain #	Isolate #	Species	CFDC MIC (mg/l)	CFDC +AVI MIC (mg/l)	CFDC+SUL MIC (mg/l)	CFDC+TAZO MIC (mg/l)	CFDC+CLAV MIC (mg/l)
1	11248	*A. baumannii*	32	0.5	2	8	1
2	10141	*A. baumannii*	32	1	32	32	32
3	9755	*A. baumannii*	32	1	0.5	4	1
4	11357	*A. baumannii*	16	1	1	1	1
5	11189	*A. baumannii*	32	1	1	4	0.25
6	10053	A. baumannii	32	8	4	32	4

Table 2.Beta-lactam Resistance Mechanisms among the *A. baumannii* strains with elevated CFDC MICs

Strain #	MLST	CFDC MIC (mg/L)	Efflux Pump Mutations	Acquired Beta-lactamases
11248	2	32	AdeB (T674S)	ADC-33, OXA-82, OXA-23
10141	823	32	AdeB (Q177R)	ADC-73, OXA-66, OXA-23, TEM-1
11189	2	32	AdeB (E90K)	ADC-73, OXA-66, OXA-23, TEM-1
10053	2	32	AdeB (T674S)	ADC-172, OXA-82, OXA-23
9755	3	32		ADC-79, OXA-71, OXA-23
11357	3	16		ADC-6-like, OXA-71, OXA-23

CFDC MICs in the Presence of the Beta-lactamase Inhibitors



Conclusions

- A decline in elevated CFDC MIC values was observed in each of the six *A. baumannii* strains, with the addition of each beta-lactamase inhibitor
- AVI showed the most potent activity when added to CFDC, with an average 28-fold reduction in MIC values observed
- SUL and CLAV produced similar fold reductions in the MIC values with an average 20-fold reduction observed with the addition of either agent to FDC, while TAZO presented with the lowest fold reduction
- Further research is warranted to determine the impact of beta-lactamase inhibitors on CFDC activity

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Disclosures

MJR has received funding support, consulted or participated in speaking bureaus for Allergan, Achaogen, Bayer, Melinta, Merck, Nabriva, Shionogi, Spero and Tetraphase, and NIAID. KSK.is supported by the National Institute of Allergy and Infectious Diseases (DMID Protocol Number: 10-0065 and R01-AI119446-01) and has served as a consultant for Xellia, and Merck. All other authors have no financial disclosures to make..