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MECHANISMS OF RESISTANCE

In Vitro Antibacterial Activity of Cefiderocol against Multidrug-Resistant *Acinetobacter baumannii*

Jacinda C. Abdul-Mutakabbir,[a]* Logan Nguyen,[a] Philip T. Maassen,[a] Kyle C. Stamper,[a] Razieh Kebriaei,[a] Keith S. Kaye,[b] Mariana Castanheira,[c] Michael J. Rybak[a,d,e]

[a]Anti-Infective Research Laboratory, Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan, USA
[b]Division of Infectious Diseases, University of Michigan Medical School, Ann Arbor, Michigan, USA
[c]JMI Laboratories, North Liberty, Iowa, USA
[d]Division of Infectious Diseases, Department of Medicine, School of Medicine, Wayne State University, Detroit, Michigan, USA
[e]Department of Pharmacy Services, Detroit Receiving Hospital, Detroit Medical Center, Detroit, Michigan, USA

ABSTRACT Cefiderocol (CFDC), a novel siderophore cephalosporin, demonstrates strong activity against multidrug-resistant (MDR) *Acinetobacter baumannii*. Limited studies have evaluated CFDC alone and in combination with other Gram-negative antibiotics against MDR *A. baumannii* isolates. Susceptibility testing revealed lower CFDC MIC values (87% of MICs ≤ 4mg/liter) than the comparator Gram-negative agents. Six isolates, with elevated CFDC MICs (16 to 32 mg/liter) were selected for further experiments. Time-kill analyses presented with synergistic activity and beta-lactamase inhibitors increased CFDC susceptibility in each of the isolates.

KEYWORDS *A. baumannii*, Gram-negative, cefiderocol, multidrug-resistant infection

Multidrug-resistant (MDR) *Acinetobacter baumannii* remains one of the most challenging public health threats due to its ability to escape the activity of the majority of our antibiotic armamentarium (1–3). Carbapenems, as well as colistin (COL) and tigecycline (TGC), have been routinely utilized as appropriate therapy in the treatment of MDR *A. baumannii* in the clinical setting; however, the continued increase in *A. baumannii* resistance has led to the decreased efficacy of these agents (4–9), further attesting to the critical need for antibiotics with novel mechanisms of action for evading Gram-negative resistance (10).

Cefiderocol (CFDC) is a novel siderophore-cephalosporin conjugated with an iron-chelating catechol moiety at the 3-position side chain (11). The catechol moiety sequesters free iron to facilitate CFDC's entry across the outer cell membrane of Gram-negative bacteria in a "Trojan horse"-like approach, via the bacteria's iron-transport system (11, 12). CFDC has demonstrated strong *in vitro* activity against MDR *A. baumannii* isolates, including those that were identified as carbapenem resistant (13, 14). Although these studies lay groundwork to support the potential role for CFDC in mitigating MDR *A. baumannii* infections, important gaps in knowledge remain.

The objective of this study was to evaluate the antibacterial activity of CFDC against a diverse collection of 150 MDR *A. baumannii* isolates (including carbapenem-resistant and COL-resistant phenotypes) compared to and in combination with other commercially available Gram-negative antibiotics via broth microdilution (BMD) MIC testing and 24-h time-kill analyses (TKA).

The MIC values of meropenem (MEM), COL, TGC, minocycline (MIN), amikacin (AMK), ceftazidime (CAZ), and ampicillin-sulbactam (SAM) (all purchased through Sigma Chemical Company, St. Louis) were determined in duplicate by the broth microdilution (BMD) method in a 96-well plate, in standard Mueller-Hinton broth (MHB) (Difco, Detroit, MI) supplemented with 25 mg/liter calcium and 12.5 mg/liter magnesium, with an inoculum of

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Address correspondence to Michael J. Rybak, m.rybak@wayne.edu.

* Present address: Jacinda C. Abdul-Mutakabbir, Loma Linda University School of Pharmacy, Loma Linda, California, USA.

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TABLE 1 MIC range, MIC_{50}, and MIC_{90} against 118 carbapenem-resistant, COL-nonresistant isolates (mg/liter)

Antimicrobial agent[a]	MIC range 118 COL-non-R isolates	MIC range 32 COL-resistant isolates	MIC_{50} 118 COL-non-R isolates	MIC_{50} 32 COL-resistant isolates	MIC_{90} 118 COL-non-R isolates	MIC_{90} 32 COL-resistant isolates
CFDC	0.125–32	0.06–32	1	1	1	4
MEM	8–128	8–128	16	32	32	64
COL	0.25–2	4–256	0.5	16	1	32
TGC	2–32	4–32	4	8	8	8
AMK	8–>256	8–>256	256	256	>256	>256
CAZ	32–>256	32–>256	256	256	>256	>256
MIN	0.063–32	0.125–32	1	4	4	16
SAM	4/2–128/64	16/8–128/64	32/16	64/32	64/32	64/32

[a]CFDC, cefiderocol; MEM, meropenem; COL, colistin; TGC, tigecycline; AMK, amikacin; CAZ, ceftazidime; MIN, minocycline; SAM, ampicillin/sulbactam.

approximately 10^6 CFU/ml, per the CLSI guidelines. 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 completion MIC testing (MIC range 0.06 to 0.5 mg/liter). Cefiderocol at a concentration of ≤4 mg/liter inhibited the growth of 87% (130/150) of the *A. baumannii* isolates evaluated in the study. Of the 32 COL-resistant (COL-R) isolates evaluated, 94% (30/32) of the isolates were susceptible to CFDC. The MIC_{50} and MIC_{90} values reflected that CFDC presented with significantly lower MIC values compared to the other commonly used Gram-negative agents and, more specifically, when tested against carbapenem-resistant and COL-R *A. baumannii* isolates ($P < 0.001$). The MIC ranges for all of the agents are listed in Table 1.

Six isolates presented with elevated MICs (16 to 32 mg/liter) to CFDC. These isolates were submitted to whole-genome sequencing (WGS) and multilocus sequence typing (https://pubmlst.org/abaumannii/) for the identification and analysis of genes related to β-lactam resistance. The sequence types (ST) of these isolates were compared to *A. baumannii-calcoaceticus* species complex from the SENTRY Antimicrobial Surveillance Program. Isolates with the highest genetic similarity were susceptibility tested against CFDC and used as a control for the genetic analysis. Briefly, WGS was performed with total genomic DNA as input for a DNA library prepared using Nextera XT library construction protocol and index kit (Illumina, San Diego, CA, USA). Sequencing was conducted in a MiSeq using reagent kit v3 (600 cycle; Illumina).

FASTQ format files for each sample set were assembled independently using the *de novo* assembler SPAdes v3.11.1. An in-house-designed software used the target assembled sequences as queries to align against numerous β-lactam resistance determinants as part of a curated database (https://www.ncbi.nlm.nih.gov/pathogens/antimicrobial-resistance/). Other resistance genes we searched by reference-guided assembly. Whole-genome sequencing revealed extended-spectrum AmpC (ADC variants) and OXA-51-like-encoding genes, and the acquired OXA-23 and TEM-1 that were present in all six and two isolates, respectively. In addition, AdeB mutations are listed and were noted in comparison to CFDC-susceptible isolates from the same sequence type (ST). The sequencing results of the six isolates are shown in Table 2.

To assess the impact of the addition of beta-lactamase inhibitors (BLIs) on decreasing elevated CFDC MICs, we supplemented tazobactam (TAZ), sulbactam (SUL), avibactam

TABLE 2 Cefiderocol (CFDC) project isolates with CFDC MICs of 16 to 32 mg/liter[a]

Isolate no.	R no.	Species	Geographical location	Cefiderocol MIC (mg/liter)	CFDC+AVI MIC (mg/liter)	CFDC+SUL MIC (mg/liter)	CFDC+TAZ MIC (mg/liter)	CFDC+CLAV MIC (mg/liter)
1	11248	*A. baumannii*	Thailand	32	0.5	2	8	1
2	10141	*A. baumannii*	Thailand	32	1	32	32	32
3	9755	*A. baumannii*	Israel	32	1	0.5	4	1
4	11357	*A. baumannii*	Israel	16	1	1	1	1
5	11189	*A. baumannii*	Thailand	32	1	1	4	0.25
6	10053	*A. baumannii*	United States	32	8	4	32	4

[a]AVI, avibactam; SUL, sulbactam; TAZ, tazobactam; CLAV, clavulanic acid.

TABLE 3 Beta-lactam resistance mechanisms among the *A. baumannii* isolates with elevated CFDC MICs

R no.	MLST[a]	CFDC[a] MIC (mg/liter)	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; also observed in ST3 CFDC-susceptible isolates)	ADC-73, OXA-66, OXA-23, TEM-1
10053	2	32	AdeB (T674S)	ADC-172, OXA-82, OXA-23
9755	3	32	None detected	ADC-79, OXA-71, OXA-23
11357	3	16	None detected	ADC-6-like, OXA-71, OXA-23

[a]MLST, multilocus sequence type; CFDC, cefiderocol.

(AVI), and clavulanic acid (CLAV) to CFDC and completed BMD susceptibility testing. CLAV, TAZ, and SUL were purchased through Sigma Chemical Company (St. Louis, MO) and AVI was purchased through Fisher Scientific (Pittsburgh, PA). The BLIs were supplemented in the following ratios to CFDC: 8:1 (TAZ) (15), 2:1 (SUL) (16), 4:1 (AVI) (17), and 4:1 (CLAV) (18). 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/liter) to ensure the induction of bacterial iron transporters per manufacturer standards (19).We observed a decline in the MIC values with the addition of the BLIs for each of the isolates. AVI produced the most frequent reduction in MIC values for all of the tested isolates, with an average 28-fold reduction in MIC values observed. The CFDC MICs of each of the isolates with the addition of the beta-lactamase inhibitors are provided in Table 3.

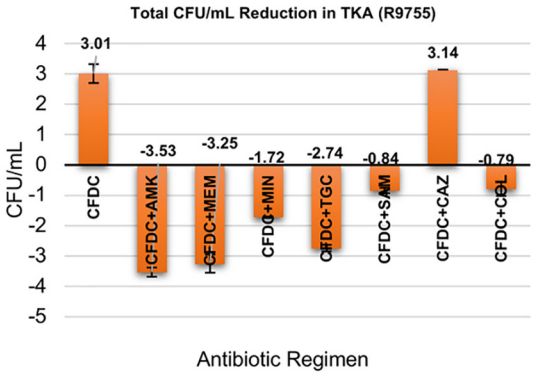
The six isolates with elevated MICs were further evaluated in TKA, with 24-well tissue culture plates utilizing ID-CAMHB as growth medium (supplied by IHMA, Inc.) to assess the potential for enhanced activity when combined with additional Gram-negative agents. All antimicrobials were tested at 0.5$\times$ MIC or the maximum concentration of free drug in serum (fC_{max}), whichever was lower. Synergistic activity was defined as a $\geq$2-$\log_{10}$ CFU/ml from the most active single agent; bactericidal activity was defined as a $\geq$3-$\log_{10}$ CFU/ml reduction from the starting inoculum; and bacterial growth of $\geq$1-log CFU/ml in either combination compared to single agent(s) was considered antagonistic activity. The TKA were conducted in duplicate to ensure reproducibility. Of the isolates that were evaluated, 5/6 had a CFDC MIC of 32 mg/liter, and the single remaining strain had a MIC of 16 mg/liter. We observed synergistic activity in 100% (6/6) of the isolates with the CFDC+MEM, CFDC+AMK, CFDC+TGC, CFDC+MIN, and CFDC+SAM combinations, and bactericidal activity was observed in several of these isolates with the CFDC+MIN, CFDC+TGC, CFDC+MEM, and CFDC+AMK combinations. CFDC+CAZ did not present with improved activity in any of the evaluated isolates, and, in the COL-R strains, the CFDC+COL combination did not reveal enhanced activity.

Of note, in 4/6 of the TKAs, the combinations of CFDC+AMK and CFDC+MEM resulted in the highest reductions in bacterial counts ($\log_{10}$ CFU/ml), despite the increased resistance to either agent ($P < 0.001$). The six TKAs are pictured in Fig. 1.

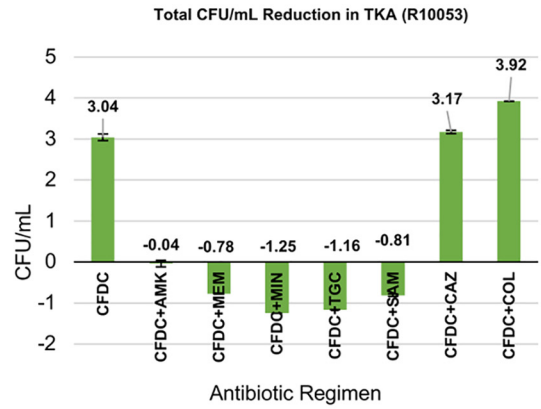
Acinetobacter baumannii-mediated infections are a leading cause of nosocomial infections, with MDR isolates increasing in prevalence. With respect to this, CFDC retains activity against a large percentage of highly resistant *A. baumannii* isolates. Nevertheless, the propensity for *A. baumannii* to develop mechanisms of resistance, and the potential for the emergence of CFDC resistance, calls for the exploration of alternative mitigating strategies.

Overall, the addition of each of the BLIs decreased the elevated MICs of the six evaluated isolates. This is likely attributed to the fact that multiple classes of beta-lactamases (class A, class C, and class D) and efflux genes associated with decreased cephalosporin activity (adeB) were simultaneously present in the isolates (20). Thus, to some extent, the addition of each of the BLIs to CFDC improved its activity. Further, upon the genetic analysis completed in our study, we observed that each of the six *A. baumannii* isolates had extended-spectrum AmpC beta-lactamases present (ADC variants), which have the potential to severely impact extended-spectrum cephalosporin activity (21, 22). Nevertheless, studies have shown that AVI has activity against ADC variants in Gram-negative organisms, which could possibly attribute to the increased susceptibility of CFDC in the *A. baumannii* isolates observed with AVI use (23).

R9755	
Antibiotic (concentration utilized in TKA) *indicates biological free peak utilized)	MIC (mg/L)
CFDC (16 mg/L)	32
COL (0.25 mg/L)	0.5
MIN (0.5 mg/L)	1
TGC* (1.5 mg/L)(25)	16
SAM (4/8 mg/L)	16/8
AMK*(60 mg/L)(26)	256
MEM (16 mg/L)	32
CAZ* (39 mg/L)(27)	>256



R10053	
Antibiotic (concentration utilized in TKA) *indicates biological free peak utilized)	MIC (mg/L)
CFDC (16 mg/L)	32
COL (0.25 mg/L)	0.5
MIN (4 mg/L)	8
TGC* (1.5 mg/L)(25)	16
SAM (32/16)	64/32
AMK* (60 mg/L)(26)	>256
MEM* (30mg/L)(28)	64
CAZ* (39 mg/L)(27)	>256



R11189	
Antibiotic (concentration utilized in TKA) *indicates biological free peak utilized)	MIC (mg/L)
CFDC (16 mg/L)	32
COL (0.25 mg/L)	0.5
MIN (4mg/L)	8
TGC* (1.5 mg/L)(25)	16
SAM (32/16)	64/32
AMK* (60 mg/L)(26)	>256
MEM*(30 mg/L)(28)	64
CAZ* (39 mg/L)(27)	>256

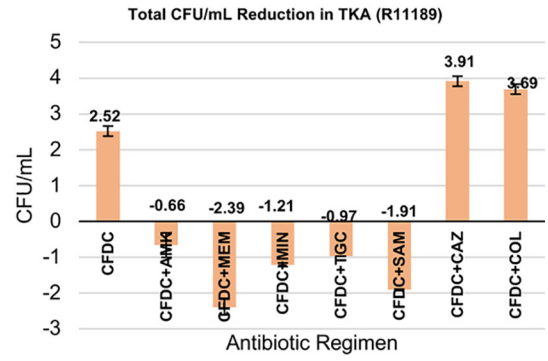
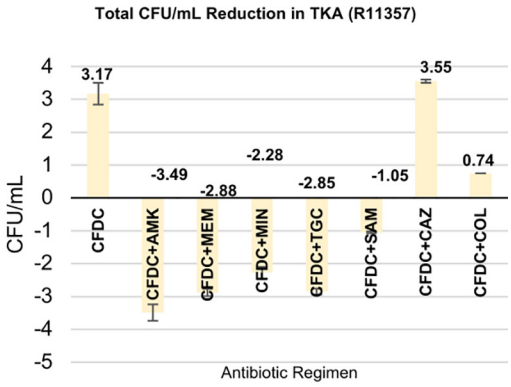


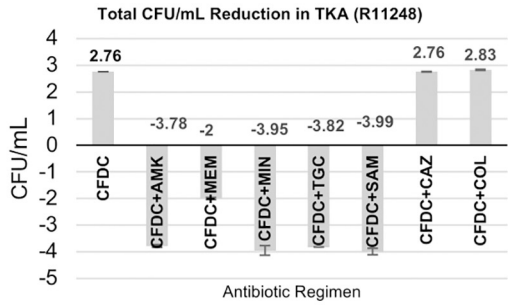
FIG 1 Six isolates with elevated CFDC MICs tested alone and in combination with other Gram-negative agents in TKA.

Additionally, we observed synergy with the other Gram-negative agents in 100% of the evaluated isolates. Of note, synergy, as well as bactericidal activity, was most often displayed with CFDC+AMK and CFDC+MEM dual therapies, although all isolates evaluated were resistant to MEM and AMK. This may potentially be attributed to increased CFDC permeability induced by an AMK-mediated disruption of the *A. baumannii* outer membrane, and the complementary binding of PBP2 by MEM and PBP3 binding by CFDC, with the CFDC+AMK and CFDC+MEM combinations, respectively. Notably, synergy was not observed in any of the six resistant isolates when tested in the TKA against the CFDC+CAZ combination. The structure of CFDC is closely related to that of CAZ, with each antimicrobial binding to PBP1a, PBP1b, PBP2, and PBP3 (11, 24). Therefore, it is possible that the saturation of target binding sites eliminates the ability of CAZ to bind to the PBPs to potentiate action and ultimately synergize with CFDC.

R11357	
Antibiotic (concentration utilized in TKA) *indicates biological free peak utilized)	MIC (mg/L)
CFDC (8 mg/L)	16
COL (0.5 mg/L)	1
MIN (0.25 mg/L)	0.5
TGC* (1.5 mg/L)(25)	8
SAM (32/16)	64/32
AMK* (60 mg/L)(26)	>256
MEM* (30mg/L)(28)	64
CAZ* (39 mg/L)(27)	>256



R11248	
Antibiotic (concentration utilized in TKA) *indicates biological free peak utilized)	MIC (mg/L)
CFDC (16 mg/L)	32
COL (2 mg/L)	4
MIN (2 mg/L)	4
TGC* (1.5 mg/L)(25)	8
SAM (32/16)	64/32
AMK* (60 mg/L)(26)	>256
MEM (16 mg/L)	16
CAZ* (39 mg/L)(27)	>256



R10141	
Antibiotic (concentration utilized in TKA) *indicates biological free peak utilized)	MIC (mg/lL)
CFDC (16 mg/L)	32
COL* (2mg/L)(29)	32
MIN (2 mg/L)	4
TGC• (1.5 mg/L)(25)	8
SAM (16/8)	32/16
AMK* (60 mg/L)(26)	>256
MEM* (30 mg/L)(28)	64
CAZ* (39 mg/L)(27)	>256

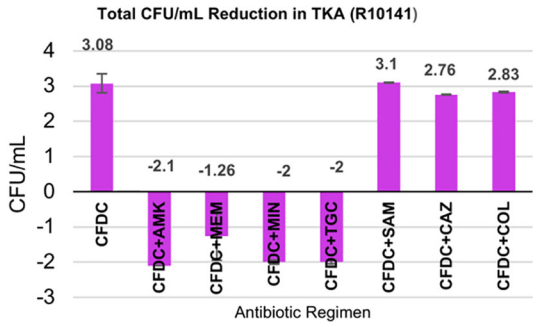


FIG 1 (Continued).

Although our study did present with positive findings for CFDC, both MIC testing as well as TKA are short in duration and use static concentrations, thus presenting a limitation when considering clinical applicability. Also, all 150 of the isolates included were not investigated for detailed phenotypes and genotypes regarding specific mechanisms of resistance, which may also limit the application of these findings in clinical settings.

Overall, CFDC presented with high susceptibility compared to other commonly utilized Gram-negative agents against MDR, including COL-R *A. baumannii* isolates. This study also investigated and revealed that CFDC is capable of producing synergy with other agents, despite increased MICs to either drug. The characteristics of CFDC indicate that it may be a promising agent, given either as a monotherapy or in combination with other commonly utilized antimicrobials. Further research is warranted to solidify the positioning of CFDC as an antibiotic for use against MDR *A. baumannii*.

Data availability. Whole-genome sequence data have been deposited in NCBI under BioProject no. PRJNA735707.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.2 MB.

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