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SUSCEPTIBILITY

ARGONAUT-I: Activity of Cefiderocol (S-649266), a Siderophore Cephalosporin, against Gram-Negative Bacteria, Including Carbapenem-Resistant Nonfermenters and *Enterobacteriaceae* with Defined Extended-Spectrum β-Lactamases and Carbapenemases

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ABSTRACT The activity of the siderophore cephalosporin cefiderocol is targeted against carbapenem-resistant Gram-negative bacteria. In this study, the activity of cefiderocol against characterized carbapenem-resistant *Acinetobacter baumannii* complex, *Stenotrophomonas maltophilia*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae* strains was determined by microdilution in iron-depleted Mueller-Hinton broth. The MIC_{90}s against *A. baumannii*, *S. maltophilia*, and *P. aeruginosa* were 1, 0.25, and 0.5 mg/liter, respectively. Against *Enterobacteriaceae*, the MIC_{90} was 1 mg/liter for the group harboring OXA-48-like, 2 mg/liter for the group harboring KPC-3, and 8 mg/liter for the group harboring TEM/SHV ESBL, NDM, and KPC-2.

KEYWORDS *Enterobacteriaceae*, Gram-negative bacteria, S-649266, cefiderocol, cephalosporin, siderophore

The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) have designated that antibiotic resistance is a threat of enormous gravity to public health (1, 2). At least 2 million people in the United States acquire serious infections with bacteria that are resistant to the antibiotics that they are designed to treat, and more than 23,000 deaths from these infections occur each year. Novel agents and strategies are urgently required to combat this scourge.

This report is the first in a series of studies called ARGONAUT (Antibacterial Resistance Leadership Group [ARLG] Reference Group for the testing of Novel Therapeutics), supported by the ARLG (3). In this study, the in vitro activity of cefiderocol and comparator agents against reference collections of Gram-negative bacterial species

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(3–6), with an emphasis on carbapenem-resistant isolates, was determined to assess the spectrum of activity of this novel agent.

Cefiderocol is a siderophore cephalosporin under development and is targeted for activity against carbapenem and multidrug-resistant (MDR) Gram-negative species (7–9). This novel agent possesses a catechol moiety on the 3 position of the R2 side chain and binds primarily to PBP3 (10) (Fig. S1 in the supplemental material). The catechol moiety acts as a siderophore to form a chelating complex with ferric iron, which facilitates transport to the periplasmic space. Cefiderocol has been reported to be more stable against β-lactamases, such as KPC-3, VIM-2, L1 (the chromosomal metallo-type carbapenemase of *Stenotrophomonas maltophilia*), and NDM-1 carbapenemases than agents such as cefepime and meropenem (11). The human plasma protein binding of cefiderocol is 58% (12), and pharmacokinetic/pharmacodynamic (PK/PD) studies show that cefiderocol is an agent with time-dependent activity, with the fraction of the free drug concentration in plasma exceeding a MIC (fT_{MIC}) target of 75% of the dosing interval (13, 14). At the proposed dosing regimen for cefiderocol of 2 g infused over 3 h every 8 h, PK/PD modeling showed that this 75% fT_{MIC} target would be attained in >90% of patients for organisms with MICs of ≤4 mg/liter (15).

In this analysis, the MICs of cefiderocol and comparators were determined by broth microdilution according to the current Clinical and Laboratory Standards Institute (CLSI) guidelines (16, 17). Testing was performed using customized frozen 96-well trays provided by International Health Management Associates, Inc. (Schaumburg, IL). The range of concentrations of the agents tested and current MIC interpretative breakpoints are shown in Table S1 in the supplemental material. Cefiderocol was tested in iron-depleted cation-adjusted Mueller-Hinton (MH) broth, and MICs were read as the concentration in the first drug well in which the growth was significantly reduced (i.e., to a button of <1 mm or light/faint turbidity) relative to the growth observed in the growth control well containing the same medium; trailing endpoints were disregarded (16, 18). All other agents were tested in cation-adjusted MH broth. Appropriate quality control (QC) strains were tested on each day of testing using appropriate reference strains, including *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 for QC for cefiderocol (16).

A total of 1,086 Gram-negative clinical isolates were tested, including 834 *Enterobacteriaceae* isolates and 252 nonfermenters. The *Enterobacteriaceae* tested included *Klebsiella pneumoniae* ($n = 794$), *E. coli* ($n = 35$), *Citrobacter freundii* ($n = 1$), and *Enterobacter* species ($n = 4$); the resistance mechanisms present included bla_{KPC} in 737 isolates, bla_{NDM} in 28 isolates, $bla_{OXA\text{-}48\text{-}like}$ in 7 isolates, bla_{NDM} and $bla_{OXA\text{-}48\text{-}like}$ in 1 isolate, and extended-spectrum β-lactamases (ESBLs) or AmpCs in 43 isolates; 18 isolates lacked ESBLs or carbapenemases. The *Enterobacteriaceae* group included 700 recent, carbapenem-resistant, clinical isolates of *K. pneumoniae* from the Great Lakes region (19). In addition, there were 116 clinical strains of various enterobacterial species selected from a reference collection with various β-lactamases and included the 18 isolates without ESBLs or carbapenemases. The nonfermenter isolates tested were clinical isolates from a worldwide collection of *Acinetobacter baumannii* complex isolates ($n = 200$; 101 were resistant to at least one carbapenem), *S. maltophilia* ($n = 25$ with bla_{L1}), and *P. aeruginosa* ($n = 27$) isolates with bla_{VIM}, bla_{PDC}, and/or porin OprD deletions from hospitals in the Cleveland, OH, area (6, 20–22). All *A. baumannii* complex isolates and a subset of the *K. pneumoniae* isolates were sequenced by whole-genome sequencing (WGS) using paired-end NexteraXT libraries and an Illumina NextSeq sequencer (2× 150 bp) to ~100-fold coverage. Reads were assembled using SPAdes software (23), annotated using NCBI's PGAP pipeline (24), and deposited in the NCBI SRA and GenBank whole-genome sequencing (WGS) repositories (BioProject accession numbers PRJNA384060 and PRJNA384065). Resistance mechanisms in isolates whose whole genomes were not sequenced were characterized by PCR amplification and sequencing of the KPC β-lactamase genes, if present, as previously reported (4, 25). In addition, a modified carbapenemase multiplex PCR that detects bla_{IMP}, bla_{NDM}, $bla_{OXA\text{-}48\text{-}like}$, and bla_{VIM} was employed (26). The *P. aeruginosa* and *S. maltophilia* β-lactamase

TABLE 1 Activity of antimicrobial agents tested against *Enterobacteriaceae*[b]

Agent	MIC (mg/liter)			% susceptible
	Range	50%	90%	
Cefiderocol[a]	≤0.03 to >64	0.5	4	90.5
Amikacin	≤4 to >64	16	32	67.7
Ciprofloxacin	≤0.25 to >4	>4	>4	8.0
Colistin	≤0.5 to >8	0.5	4	89.3
Tigecycline	≤0.25 to >4	0.5	1	98.4
Aztreonam	≤0.5 to >32	>32	>32	3.2
Ceftolozane-tazobactam	0.06 to >64	64	>64	5.5
Cefepime	≤0.5 to >16	>16	>16	4.2
Ceftazidime	≤0.03 to >64	>64	>64	3.7
Ceftazidime-avibactam	≤0.03 to >64	0.5	2	96.6
Meropenem	≤0.03 to >64	8	>64	12.7

[a]Percent susceptible based on a provisional breakpoint of 4 mg/liter.
[b]A total of 834 *Enterobacteriaceae* were tested.

content was previously determined in other studies (20–22). In this manner, we identified the relevant β-lactamases for the entire collection of 1,086 Gram-negative clinical isolates. The results for each organism group are shown as MIC ranges, MIC_{50} and MIC_{90} values, and the percentage of isolates susceptible to each agent for cefiderocol and comparator agents in Tables 1 to 4.

Enterobacteriaceae. Cefiderocol MICs ranged from ≤0.03 to >64 mg/liter, with the MIC_{90} being 4 mg/liter (Table 1). The rates of susceptibility of the comparator agents ranged from 3.7% (ceftazidime; MIC_{90}, >64 mg/liter) to 96.6% (ceftazidime-avibactam; MIC_{90}, 2 mg/liter) and 98.4% (tigecycline; MIC_{90}, 1 mg/liter). Analysis of these results based on β-lactam resistance mechanisms showed a cefiderocol MIC_{90} of ≤0.03 mg/liter for isolates without ESBLs or carbapenemases versus a cefiderocol MIC_{90} of from 1 to 8 mg/liter for isolates with ESBLs, carbapenemases, or AmpCs. There was no obvious association between the resistance mechanism and the MIC, although there was a bimodal MIC distribution, with peaks at 0.25 and 2 mg/liter (Table 2 and Fig. 1). In contrast, ceftazidime-avibactam susceptibility was related to β-lactam resistance mechanisms, with only 3/28 isolates (10.7%) with bla_{NDM} being susceptible and 735/738 isolates (99.6%) with bla_{KPC} being susceptible.

***A. baumannii* complex.** Cefiderocol MICs ranged from ≤0.03 to >64 mg/liter, with the overall MIC_{90} being 1 mg/liter, and there was little difference between the carbapenem-susceptible and -resistant groups (Table 3; Fig. 2 and 3). Other agents active against both groups were colistin (to which 90.0% of isolates were susceptible) and tigecycline (to which 93% of isolates were susceptible). Agents more active against

TABLE 2 Activity of cefiderocol against *Enterobacteriaceae* with characterized ESBLs and carbapenemases

β-Lactamase group[a]	No. of isolates	MIC (mg/liter)		
		Range	50%	90%
None	18	≤0.03 to 4	≤0.03	≤0.03
KPC-2	355	≤0.03 to 32	1	8
KPC-3	380	≤0.03 to 64	0.25	2
KPC-4 or KPC-4-like	2	0.5 to 16	0.5	16
NDM	28	0.25 to >64	2	8
OXA-48-like	7	≤0.03 to 1	0.25	1
NDM and OXA-48-like	1	1		
Other (TEM ESBL, SHV ESBL, CTX-M, PER, and/or AmpC)	43	≤0.03 to >64	2	8
All isolates	834	≤0.03 to >64	0.5	4

[a]The isolates included in the β-lactamase groups were as follows: none, *E. coli* (*n* = 10) and *K. pneumoniae* (*n* = 8); KPC-2, *K. pneumoniae* (*n* = 350), *E. coli* (*n* = 4), and *Enterobacter cloacae* (*n* = 1); KPC-3, *K. pneumoniae* (*n* = 378), *C. freundii* (*n* = 1), and *Enterobacter aerogenes* (*n* = 1); KPC-4 or KPC-4-like, *K. pneumoniae* (*n* = 2); NDM, *K. pneumoniae* (*n* = 19), *E. coli* (*n* = 7), and *E. cloacae* (*n* = 2); OXA-48-like, *K. pneumoniae* (*n* = 7); NDM and OXA-48-like, *K. pneumoniae* (*n* = 1); and other, *E. coli* (*n* = 14; 2 CMY, 1 TEM-5, 8 CTX-M, 3 not determined) and *K. pneumoniae* (*n* = 29; 1 CMY-2; 5 CTX-M; 1 CTX-M and SHV-2; 3 CTX-M and SHV-12; 2 PER; 1 SHV-2 and PER; 1 SHV-5 and PER; 10 SHV-2, -5, -7, or -12; 2 SHV-2 and TEM-10; 2 SHV-5 and TEM-10; 1 SHV-5; and TEM-26) (this group did not contain KPC, NDM, or OXA-48-like β-lactamases).

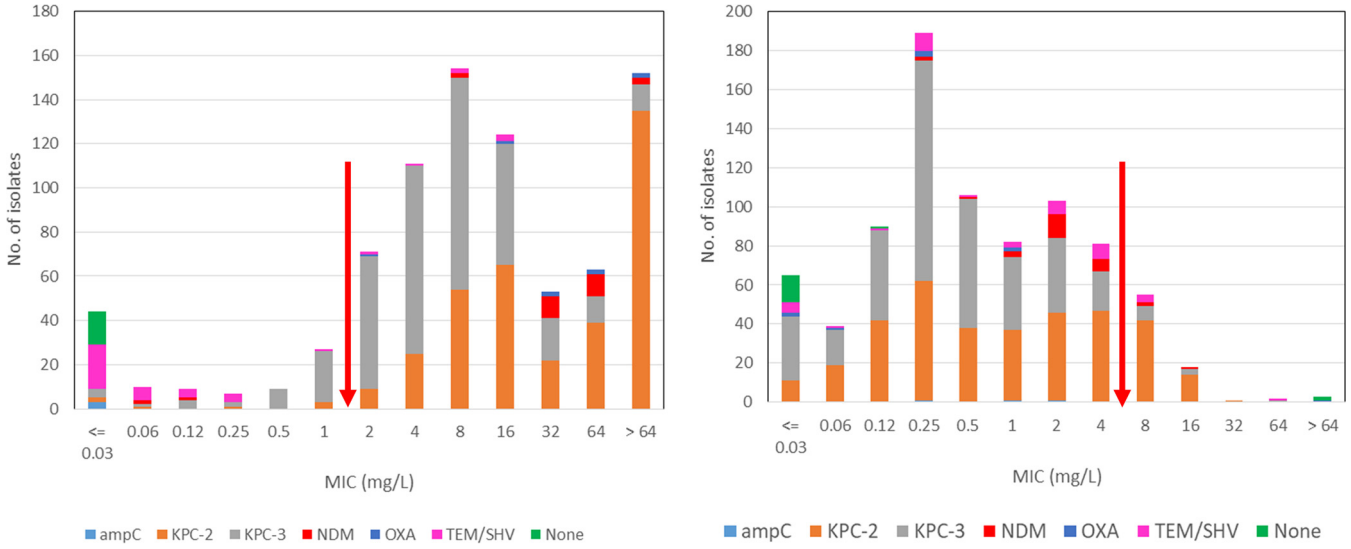

FIG 1 MIC distributions of meropenem (left) and cefiderocol (right) against *Enterobacteriaceae*. Arrows indicate the upper limit of susceptible and proposed susceptible MIC ranges for meropenem and cefiderocol, respectively. AmpC, CMY; OXA, OXA-48-like; TEM/SHV, TEM ESBL and/or SHV ESBL.

the carbapenem-susceptible group than against the carbapenem-resistant group included amikacin (94.9% versus 17.8%), ciprofloxacin (83.7% versus 0%), ceftazidime (86.9% versus 4.0%), ceftazidime-avibactam (64.6% versus 6.9%), and meropenem (100% versus 0%).

***P. aeruginosa*.** Cefiderocol MICs ranged from ≤0.03 to 1 mg/liter, with the MIC_{90} being 0.5 mg/liter (Table 4 and Fig. 4). Notably, the MICs against isolates with bla_{VIM} ranged from 0.06 to 1 mg/liter, with the MIC_{90} being 0.5 mg/liter. Colistin was the only comparator tested with good activity (96.3% of isolates were susceptible), while amikacin was active against 48.1% of isolates, aztreonam 22.2%, and ceftolozane-tazobactam 25.9%, and <10% of isolates were susceptible to ciprofloxacin, cefepime, ceftazidime, ceftazidime-avibactam, or meropenem.

***S. maltophilia*.** Cefiderocol MICs ranged from ≤0.03 to 0.25 mg/liter, with the MIC_{90} being 0.25 mg/liter (Table 4 and Fig. 4). Colistin was active against 68.0% of isolates, while the MIC_{90} of tigecycline was 2 mg/liter. Amikacin and the other β-lactam agents tested had little activity, as expected, against this intrinsically aminoglycoside- and carbapenem-resistant species.

Several studies on the *in vitro* activity of cefiderocol against carbapenem-resistant species have recently been published, and our findings are in general agreement with the findings of these studies (10, 21–24, 28). However, overall, cefiderocol MIC_{90}s against *Enterobacteriaceae* were lower (≤1 mg/liter) in two studies: (i) in the study of Kohira et al. against a 2009 to 2011 global collection of 617 *Enterobacteriaceae* isolates, although the MICs were up to 4 mg/liter against 226 of 233 strains (97.0%) with characterized β-lactamases, including 116 isolates with bla_{KPC}, bla_{SME}, or bla_{NDM} (27), and (ii) in the study of Hackel et al. (29) against a U.S. and European collection of 6,087 *Enterobacteriaceae* isolates collected between 2014 and 2016, although the MIC_{90} was 4 mg/liter against 169 meropenem-nonsusceptible *Enterobacteriaceae* isolates.

Our findings on the *in vitro* activity of cefiderocol are in alignment with those in the publications discussed above for *Enterobacteriaceae* (MIC_{90}, 4 mg/liter), *P. aeruginosa* (MIC_{90}, 0.5 mg/liter), and *S. maltophilia* (MIC_{90}, 0.25 mg/liter). Uniquely, our analysis also provides a correlation between the activity of cefiderocol and β-lactam resistance mechanisms; the activity against *Enterobacteriaceae* was affected by various β-lactamases, while the activity against nonfermenters was independent of the presence of β-lactamases, including carbapenemases. The wide distribution of MIC values for *Enterobacteriaceae* found here has been observed in other studies and is independent of the medium used, including iron-depleted-cation-adjusted (CA) MH broth

TABLE 3 Activity of antimicrobial agents tested against carbapenem-susceptible and -resistant *Acinetobacter baumannii* complex isolates[a]

	Carbapenem-susceptible isolates ($n = 99$)[b]				Carbapenem-resistant isolates ($n = 101$)[c]				All isolates ($n = 200$)			
	MIC (mg/liter)											
Agent	Range	50%	90%	% susceptible	Range (mg/liter)	50%	90%	% susceptible	Range	50%	90%	% susceptible
Cefiderocol[d]	≤0.03 to >64	0.12	0.5	97.9	≤0.03 to >64	0.25	1	96.0	≤0.03 to >64	0.12	1	97.0
Amikacin	≤4 to >64	≤4	8	94.9	≤4 to >64	>64	>64	17.8	≤4 to >64	≤4	>64	56.0
Ciprofloxacin	≤0.25 to >4	≤0.25	>4	83.8	4 to >4	>4	>4	0.0	≤0.25 to >4	>4	>4	41.5
Colistin	≤0.5 to >8	≤0.5	1	97.0	≤0.5 to >8	1	>8	83.2	≤0.5 to >8	≤0.5	2	90.0
Tigecycline	≤0.25 to >4	≤0.25	1	97.0	0.5 to >4	1	4	89.1	≤0.25 to >4	1	2	93.0
Aztreonam	2 to >32	32	>32		1 to >32	>32	>32		1 to >32	>32	>32	
Ceftolozane-tazobactam	0.06 to >64	0.25	4		0.25 to >64	32	>64		0.06 to >64	8	>64	
Cefepime	≤0.5 to >16	2	16		1 to >16	>16	>16		≤0.5 to >16	16	>16	
Ceftazidime	0.5 to >64	4	16	86.9	4 to >64	>64	>64	4.0	0.25 to >64	64	>64	45.0
Ceftazidime-avibactam	0.5 to >64	16	32	64.6	8 to >64	64	>64	6.9	0.25 to >64	16	>64	35.5
Meropenem	0.06 to >64	0.25	1	100.0	4 to >64	64	>64	0.0	0.06 to >64	2	>64	49.5

[a]All carbapenem-resistant isolates were *A. baumannii sensu stricto* ($n = 101$). The carbapenem-susceptible group contained *A. baumannii* ($n = 54$), *A. pittii* ($n = 37$), *A. nosocomialis* ($n = 5$), and a few mixed cultures ($n = 3$). Species identification within the *A. baumannii* complex was determined by WGS and other molecular methods (i.e., *gyrB* sequencing and identification of the intrinsic oxacillinases).

[b]OXA β-lactamases present in 99 carbapenem-susceptible isolates: OXA-100 or -100-like ($n = 5$), OXA-106 ($n = 1$), OXA-121 ($n = 4$), OXA-208 ($n = 1$), OXA-217 or -217-like ($n = 2$), OXA-223 ($n = 1$), OXA-263 ($n = 1$), OXA-270-like ($n = 1$), OXA-273 ($n = 1$), OXA-314 ($n = 4$), OXA-338-like ($n = 2$), OXA-340 ($n = 1$), OXA-421 or -421-like ($n = 4$), OXA-429-like ($n = 1$), OXA-500 or -500-like ($n = 26$), OXA-502-like ($n = 1$), OXA-506 ($n = 5$), OXA-51 or -51-like ($n = 2$), OXA-63 ($n = 3$), OXA-64 ($n = 4$), OXA-66 ($n = 5$), OXA-66 and -437-like ($n = 1$), OXA-68 ($n = 2$), OXA-69 ($n = 1$), OXA-71 ($n = 1$), OXA-78 ($n = 1$), OXA-90 ($n = 4$), OXA-94 ($n = 3$), OXA-98 ($n = 4$), and no OXA or unknown ($n = 7$).

[c]OXA β-lactamase combinations present in 101 carbapenem-resistant isolates: OXA-23, -24/40, and -65 ($n = 1$); OXA-23 and -64 ($n = 1$); OXA-23 and -66 ($n = 54$); OXA-23, -66, and -72 ($n = 2$); OXA-23 and -68 ($n = 2$); OXA-23 and -69 ($n = 1$); OXA-23 and -71 ($n = 2$); OXA-23 and -82 ($n = 12$); OXA-23 and -407 ($n = 3$); OXA-24/40 and -65 ($n = 4$); OXA-24/40 and -71 ($n = 1$); OXA-58 and -66 ($n = 1$); OXA-58 and -100 ($n = 1$); OXA-66 ($n = 1$); OXA-72 and -66 ($n = 4$); OXA-82 ($n = 5$); OXA-82 and -167 ($n = 1$); OXA-172 ($n = 2$); OXA-223 ($n = 1$); OXA-223 and -72 ($n = 1$); and OXA-338-like ($n = 1$).

[d]Percent susceptible based on a provisional breakpoint of 4 mg/liter.

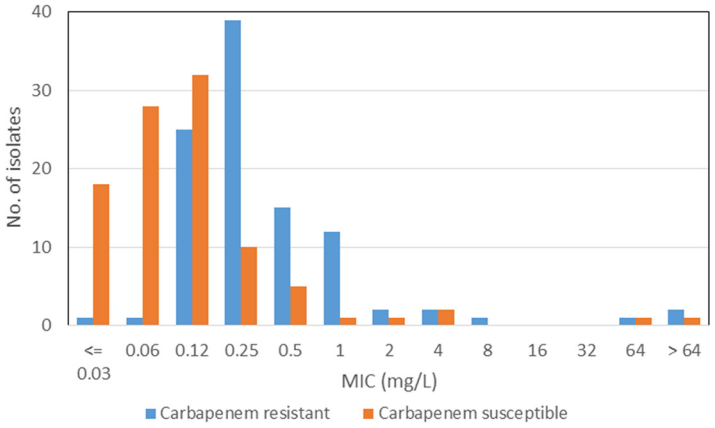

FIG 2 MIC distributions of cefiderocol against carbapenem-susceptible and -resistant *A. baumannii* complex isolates.

(approved by CLSI), iron-depleted medium using the chelator ApoT, and non-iron-depleted CA MH broth (11, 12). This wide distribution is believed to be due to variations in iron transport channel expression, the primary mechanism for cell entry of siderophore antibiotic conjugates, which varies by species and within species (7, 11, 15).

For *A. baumannii* our MIC_{90} of 1 mg/liter was in agreement with the MIC_{90} values of 1 and 2 mg/liter, respectively, reported by Ito et al. (10) and Hackel et al. (29), while a later publication by Hackel et al. reported a higher MIC_{90} value of 8 mg/liter (30). The reason for this difference in activity against *A. baumannii* may be associated with regional differences in the resistance mechanisms of this species. Overall, our study showed the potent activity of cefiderocol against all isolates of *P. aeruginosa* and *S. maltophilia* tested and activity against most isolates of the *Acinetobacter baumannii*

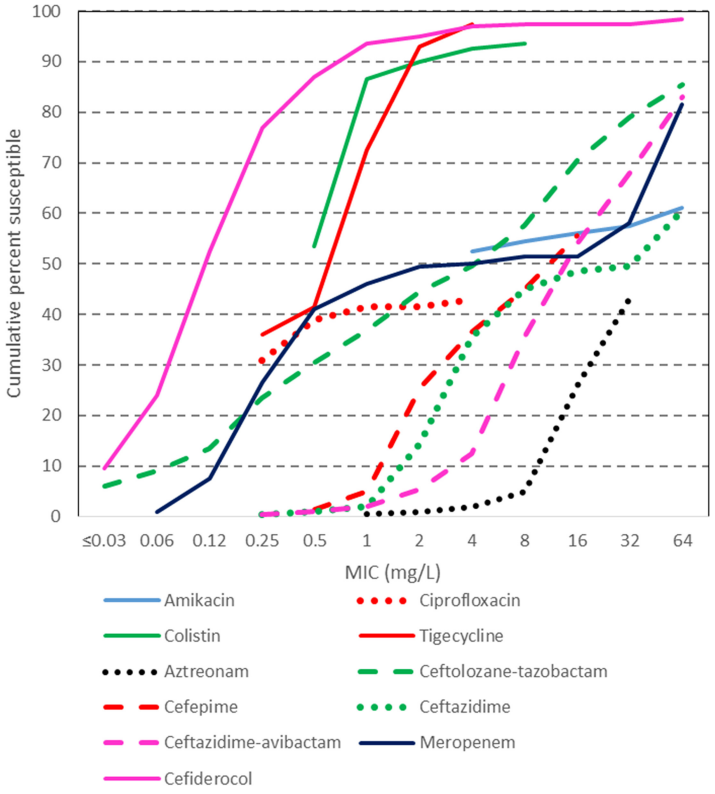

FIG 3 Cumulative MICs of cefiderocol and comparator agents against *A. baumannii* complex isolates.

TABLE 4 Activity of antimicrobial agents tested against carbapenem-resistant *P. aeruginosa*[a] and *S. maltophilia*[b]

Agent	MIC (mg/liter)			% susceptible
	Range	50%	90%	
P. aeruginosa				
Cefiderocol[c]	≤0.03 to 1	0.25	0.5	100
Amikacin	≤4 to >64	64	>64	48
Ciprofloxacin	2 to >4	>4	>4	0
Colistin	≤0.5 to >8	1	1	96
Tigecycline	1 to >4	>4	>4	22
Aztreonam	4 to >32	32	>32	22
Ceftolozane-tazobactam	1 to >64	>64	>64	26
Cefepime	8 to >16	>16	>16	7
Ceftazidime	16 to >64	64	>64	0
Ceftazidime-avibactam	1 to >64	64	>64	8
Meropenem	2 to >64	32	64	4
S. maltophilia				
Cefiderocol[c]	≤0.03 to 0.25	0.06	0.25	100
Amikacin	≤4 to >64	>64	>64	—[d]
Ciprofloxacin	0.5 to >4	2	>4	—
Colistin	≤0.5 to >8	1	8	68
Tigecycline	≤0.25 to >4	0.5	2	—
Aztreonam	>32	>32	>32	—
Ceftolozane-tazobactam	1 to >64	>64	>64	—
Cefepime	8 to >16	>16	>16	—
Ceftazidime	2 to >64	>64	>64	8
Ceftazidime-avibactam	0.25 to >64	64	>64	16

[a]Data are for 27 *P. aeruginosa* isolates. Resistance mechanisms included VIM plus PDC ($n = 12$) and PDC alone ($n = 4$).
[b]Data are for 25 *S. maltophilia* isolates. All isolates contained L1 and L2 β-lactamases.
[c]Percent susceptible based on a provisional breakpoint of 4 mg/liter.
[d]—, no breakpoint is available.

complex, with little difference between carbapenem-susceptible and -resistant isolates. Cefiderocol shows higher MICs against isolates with ESBLs (including the bla_{TEM} ESBL, the bla_{SHV} ESBL, and bla_{CTX-M}) and carbapenemases (including bla_{KPC}, bla_{NDM}, and $bla_{OXA-48-like}$) than against isolates of *Enterobacteriaceae* without ESBLs or carbapenemases.

Based on the proposed dosing regimen of cefiderocol and the PK/PD target attained at this dosing regimen, our findings support the *in vivo* activity of this agent against carbapenem-resistant Gram-negative nonfermenters and most carbapenem-resistant *Enterobacteriaceae*. Based on studies performed to date, cefiderocol may prove to be a

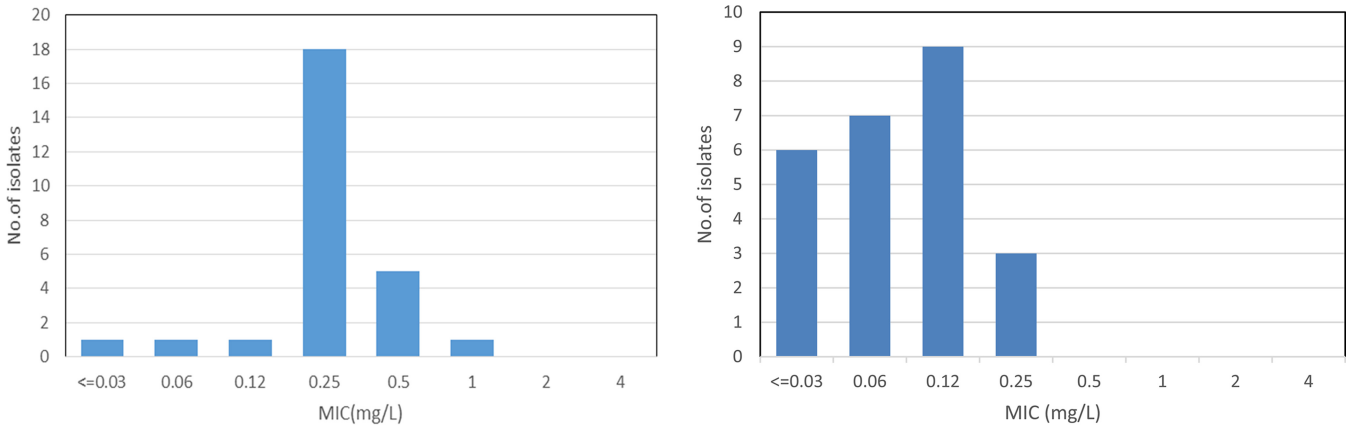

FIG 4 MIC distribution of cefiderocol against *P. aeruginosa* (left) and *S. maltophilia* (right).

particularly valuable addition to our limited armamentarium for combating infections caused by carbapenem-resistant Gram-negative nonfermenters.

Accession number(s). The reads obtained in this study have been deposited in the NCBI Sequence Read Archive and GenBank WGS repositories under BioProject accession numbers PRJNA384060 and PRJNA384065.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.01801-18.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

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