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Short Communication

In vitro activity of cefiderocol, a siderophore cephalosporin, against a recent collection of clinically relevant carbapenem-non-susceptible Gram-negative bacilli, including serine carbapenemase- and metallo-β-lactamase-producing isolates (SIDERO-WT-2014 Study)

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ABSTRACT

Cefiderocol is a siderophore cephalosporin in development for treatment of infections caused by Gram-negative bacilli, including carbapenem-resistant and multidrug-resistant isolates. β-Lactamase carriage and in vitro activity of cefiderocol were determined against 1272 meropenem-non-susceptible isolates of Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* collected as part of the SIDERO-WT-2014 surveillance study. Minimum inhibitory concentration (MIC) values for cefiderocol were ≤4 μg/mL against 97.7% of tested isolates, including 100% of IMP-positive (range, 1-2 μg/mL), OXA-58-positive (MIC_{90}, 1 μg/mL), KPC-positive (MIC_{90}, 2 μg/mL), VIM-positive (MIC_{90}, 2 μg/mL), and OXA-48-like-positive (MIC_{90}, 4 μg/mL) isolates; 99.3% of carbapenemase-negative isolates (MIC_{90}, 1 μg/mL); 97.2% of OXA-23-positive isolates (MIC_{90}, 1 μg/mL); 95.2% of OXA-24-positive isolates (MIC_{90}, 1 μg/mL); 91.7% of GES-positive isolates (MIC_{90}, 4 μg/mL); and 64.3% of NDM-positive isolates (MIC_{90}, 8 μg/mL). A total of 29 isolates (2.3%; 15 OXA-23-producers, 6 OXA-24-producers, 5 NDM-producers, and 3 carbapenemase-negative isolates) exhibited cefiderocol MIC ≥8 μg/mL, confirming there was no clear correlation between carriage of β-lactamases included in the molecular testing algorithm and elevated cefiderocol MICs. Similarly, no correlation was observed between cefiderocol MICs and truncation or loss of porin proteins in meropenem-non-susceptible isolates of *E. coli* and *K. pneumoniae*. Cefiderocol MICs were also ≤4 μg/mL against 99.3% of 136 colistin-resistant Enterobacteriaceae collected as part of the SIDERO-WT-2014 study, including isolates carrying *mcr-1* (MIC_{90}, 2 μg/mL). Cefiderocol demonstrated potent in vitro activity against a collection of carbapenemase-producing and carbapenemase-negative meropenem-non-susceptible Gram-negative bacilli for which few treatment options are available, including the majority of metallo-β-lactamase producing isolates identified.

1. Introduction

Resistance to the β-lactams, one of the mainstays of therapy against Gram-negative bacilli, is mediated by the production of β-lactamases (broad-spectrum β-lactamases, extended-spectrum β-lactamases [ESBL], AmpC cephalosporinases and carbapenemases) and can be enhanced by reduced expression or loss of outer membrane pore-forming proteins and/or upregulation of efflux transport systems [1–6]. β-Lactamases differ in their mode of catalysis, substrate specificity and sensitivity to inhibitors, and are increasingly transmitted via plasmids in combination with determinants of resistance to other classes of antimicrobial agents [1,7]. Carbapenem-resistant isolates of Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, pathogens of critical priority that cause infections associated with significant morbidity

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Table 1
Species distribution of β-lactamase-positive meropenem-resistant Enterobacteriaceae and meropenem-non-susceptible *P. aeruginosa* and *A. baumannii* isolates collected as part of the SIDERO-WT-2014 surveillance study.

Organism (No. of isolates)	No. of isolates carrying the indicated β-lactamase[a]									
	KPC	GES[b]	IMP	VIM	NDM	OXA-23-type	OXA-24-type	OXA-48-like	OXA-58-type	Carbapenemase-negative meropenem-non-susceptible[c]
Citrobacter amalonaticus (1)				1						
Citrobacter freundii (7)[d]				7				3		
Enterobacter aerogenes (2)										2
Enterobacter cloacae (17)	3			7	1			4		2
Escherichia coli (4)								3		1
Klebsiella oxytoca (3)	1			1				1		
Klebsiella pneumoniae (105)[e]	65	1		8	11			21		5
Serratia marcescens (12)	6			3						3
Pseudomonas aeruginosa (353)		4	4	26						321
Acinetobacter baumannii (768)[f]		7			2	543	124		14	86
Total	75	12	4	53	14	543	124	32	14	420

[a] Isolates that carried more than one carbapenemase or GES-type β-lactamase are listed in each relevant category of analysis. Enzyme groups were composed of the following subtypes: KPC [KPC-2 (n=40), KPC-3 (n=35)]; GES [GES-1 (n=2), GES-5 (n=2), GES-6 (n=1), GES-11 (n=6), GES-12 (n=1)]; IMP [IMP-7 (n=4)]; VIM [VIM-1 (n=26), VIM-2 (n=14), VIM-4 (n=6), VIM-5 (n=1), VIM-19 (n=1), VIM-20 (n=2), VIM-31 (n=3)]; NDM [NDM-1 (n=14)]; OXA-48-like [OXA-48 (n=28), OXA-162 (n=2), OXA-181 (n=1), OXA-244 (n=1)].
[b] Included GES-type β-lactamases with carbapenemase activity (GES-5, GES-6) and those with only ESBL activity (GES-1, GES-11, GES-12).
[c] Included two *P. aeruginosa* and seven *A. baumannii* carrying GES-type β-lactamases with ESBL activity.
[d] Included three isolates carrying OXA-48-like and VIM-type carbapenemases.
[e] Included one isolate carrying KPC- and GES-type carbapenemases, three isolates carrying KPC- and VIM-type carbapenemases, and two isolates carrying OXA-48-like and NDM-type carbapenemases.
[f] Included one isolate carrying OXA-23-type and OXA-58-type carbapenemases, one isolate carrying an OXA-23-type carbapenemase and a GES-type ESBL, and two isolates carrying OXA-24-type carbapenemases and GES-type ESBLs.

and mortality, are frequently multidrug-resistant and challenging to treat [8]. In addition to plasmid-mediated carbapenemase expression, chromosomal β-lactamases, such as AmpC in *P. aeruginosa* and *Enterobacter* species and L1 and L2 in *Stenotrophomonas maltophilia*, provide mechanisms for intrinsic carbapenem resistance [3,4,9].

Cefiderocol (previously S-649266) is a novel catechol-substituted siderophore cephalosporin with broad spectrum activity against isolates of clinically-relevant Gram-negative species that are often multidrug resistant, including the ESKAPE pathogens *Klebsiella pneumoniae, A. baumannii, P. aeruginosa*, and *Enterobacter* spp., as well as *Escherichia coli*, the Proteeae, *Serratia* spp., *Burkholderia* spp., *S. maltophilia*, and *Elizabethkingia meningoseptica* [10–13]. Cefiderocol binds ferric iron and is actively transported across the bacterial outer membrane via iron-siderophore uptake systems [11,14]. Cefiderocol is more stable to hydrolysis by both serine β-lactamases (ESBLs, KPC and OXA-type carbapenemases) and metallo-β-lactamases (NDM, IMP, VIM, L1) than ceftazidime and meropenem [15–17].

The in vitro antimicrobial activity of cefiderocol and comparator agents was determined against 9205 recent clinical isolates collected in Europe and North America from November 2014 through October 2015 as part of the SIDERO-WT-2014 surveillance study. In that study, the cefiderocol MIC_{90} values against meropenem-non-susceptible (MIC ≥2 μg/mL) Enterobacteriaceae isolates from Europe and North America were 4 and 1 μg/mL, respectively; for meropenem-non-susceptible (MIC ≥4 μg/mL) *P. aeruginosa* they were 1 and 0.5 μg/mL, respectively; and for meropenem-non-susceptible (MIC ≥4 μg/mL) *A. baumannii* they were 1 μg/mL for isolates from both regions [12]. In the current study, meropenem-resistant and colistin-resistant isolates of Enterobacteriaceae and meropenem-non-susceptible isolates of *P. aeruginosa* and *A. baumannii* identified as part of the SIDERO-WT-2014 study were screened for the presence of genes encoding β-lactamases, outer membrane protein (porin) defects, and plasmid-mediated colistin resistance to further define the spectrum of activity of cefiderocol against these challenging Gram-negative bacteria. The SIDERO-WT-2014 study also identified the potent activity of cefiderocol against *S. maltophilia* isolates (100% of isolates inhibited by ≤4 μg/mL cefiderocol; MIC_{90}, 0.25 μg/mL) [12]. However, the carriage of acquired carbapenemases in *S. maltophilia* was not investigated in this study as the presence of chromosomal β-lactamases L1 and L2 is known to contribute to the intrinsic carbapenem-resistance of this organism [9].

2. Materials and Methods

Isolate collection, antimicrobial susceptibility testing, screening for the carriage of genes encoding β-lactamases and transmissible colistin resistance, and screening for the presence of porin gene disruptions are described in the Supplementary material.

3. Results

A total of 1272 isolates testing with meropenem MIC ≥4 μg/mL (151 meropenem-resistant Enterobacteriaceae isolates, 267 meropenem-resistant and 86 meropenem-intermediate *P. aeruginosa*, and 758 meropenem-resistant and 10 meropenem-intermediate *A. baumannii*) were molecularly characterized for the presence of β-lactamase genes. The distribution of carbapenemases found in these isolates is summarized in Table 1. Ten isolates carrying two carbapenemases (KPC and GES-type, KPC and VIM, VIM and OXA-48-like, NDM and OXA-48-like, OXA-23-type and OXA-58-type) were identified (Table 1). No isolates carrying IMI/NMC-A, SPM, or GIM carbapenemases were found. Additional acquired β-lactamases (ESBLs, predominantly CTX-M-1-type and SHV-type, and plasmid-mediated AmpCs, predominantly CMY-2-like) were detected in 53% of carbapenemase-positive Enterobacteriaceae and 3% of carbapenemase-positive *A. baumannii* isolates (data not shown). Acquired ESBLs and AmpC β-lactamases were also detected in 31%, 5% and 1% of carbapenemase-negative isolates of Enterobacteriaceae, *A. baumannii* and *P. aeruginosa*, respectively. The majority of meropenem-resistant Enterobacteriaceae isolates (76.9% [20/26] of North American isolates and 94.4% [118/125] of European isolates) carried carbapenemases, with KPC-type enzymes comprising the majority in both regions but metallo-β-lactamases (VIM- and NDM-type) found predominantly and OXA-48-like enzyme found exclusively in isolates collected in Europe.

The majority of meropenem-non-susceptible *P. aeruginosa* isolates, including all isolates collected in North America, did not carry acquired β-lactamases; however, 16% of European isolates carried a VIM-, IMP- or GES-type carbapenemase. Among meropenem-non-susceptible *A. baumannii*, OXA-23-type carbapenemases were most common in both regions, followed by OXA-24-type carbapenemases. Isolates carrying OXA-58-type carbapenemases were only detected in Europe (Figure S1).

Table 2 shows the distribution of cefiderocol MIC values against these carbapenemase-producing and carbapenemase-negative isolates and the cumulative percentage of isolates inhibited at each MIC value. Cefiderocol MICs ranged from ≤0.002 μg/mL to 64 μg/mL against the overall collection of meropenem-non-susceptible isolates. The MIC_{90} value of cefiderocol was 1 μg/mL against OXA-23-positive, OXA-24-positive, and OXA-58-positive isolates, 2 μg/mL against KPC-positive isolates and the overall collection of VIM-positive isolates, 4 μg/mL against OXA-48-like-positive isolates, and 8 μg/mL against NDM-positive isolates. Although the number of isolates was small, cefiderocol MICs ranged between 0.12 to 8 μg/mL against isolates carrying GES carbapenemases or GES-type β-lactamases with ESBL activity, and between 1 to 2 μg/mL against IMP-positive isolates (Table 2). The MIC_{90} was 1 μg/mL against the overall collection of meropenem-non-susceptible carbapenemase-negative isolates, and 0.5 μg/mL, 2 μg/mL, and 2 μg/mL against the subsets of carbapenemase-negative *P. aeruginosa, A. baumannii*, and Enterobacteriaceae isolates, respectively (Table 2 and Table 3). A total of 97.7% (1243/1272) isolates tested had MIC values ≤4 μg/mL, including all KPC-positive, IMP-positive, VIM-positive, OXA-48-like-positive, and OXA-58-positive isolates, 99.3% of carbapenemase-negative isolates, 97.2% of OXA-23-positive isolates, 95.2% of OXA-24-positive isolates, 91.7% of GES-positive isolates, and 64.3% of NDM-positive isolates. All but five isolates (99.6%; 1267/1272) were inhibited by ≤8 μg/mL cefiderocol (Table 2).

Table 3 summarizes the in vitro activity of cefiderocol and comparator agents against carbapenemase-producing isolates and carbapenemase-negative isolates of meropenem-resistant Enterobacteriaceae and meropenem-non-susceptible *P. aeruginosa* and *A. baumannii*. The MIC_{90} value of cefiderocol against all meropenem-resistant Enterobacteriaceae isolates was 4 μg/mL, compared with MIC_{90}s of >64 μg/mL for meropenem, cefepime, ceftolozane-tazobactam, and ceftazidime-avibactam, and >8 μg/mL for ciprofloxacin and colistin. Against individual subsets of carbapenemase-positive and meropenem-resistant carbapenemase-negative Enterobacteriaceae, cefiderocol MIC_{90}s (range, 2-8 μg/mL) and MIC values for subsets of 10 or fewer isolates were lower than the corresponding values of all other tested agents, except ceftazidime-avibactam, in all cases. Ceftazidime-avibactam showed MIC_{90} values equal to or only 2- to 4-fold greater than those of cefiderocol against KPC-positive, OXA-48-like-positive, and meropenem-resistant carbapenemase-negative isolates but was inactive against VIM- and NDM-positive isolates. The modestly decreased activity of ceftazidime-avibactam observed against the subsets of KPC-positive and OXA-48-like-positive Enterobacteriaceae (96.0% and 90.6% susceptible, respectively) reflected the presence of isolates co-carrying a metallo-β-lactamase insensitive to inhibition by avibactam. The majority of other tested comparator agents showed reduced activity (0-84% susceptible) against all subsets of serine carbapenemase-positive isolates, metallo-β-lactamase-positive isolates and carbapenemase-negative isolates (Table 3). The genes encoding major outer membrane porins *ompF* and *ompC* (*E. coli*) and *ompK35* and *ompK36* (*K. pneumoniae*) were sequenced in 109 meropenem-resistant isolates (4 *E. coli* and 105 *K. pneumoniae*) identified in this study, including 61 KPC-positive, 22 OXA-48-like-positive, 9 NDM-positive, and 5 VIM-positive isolates, 3 isolates carrying VIM and KPC, 2 isolates carrying OXA-48 and NDM, 1 isolate carrying KPC and a GES-type carbapenemase, and 6 carbapenemase-negative isolates. Of these, 85 isolates harbored a deletion of, or insertion or frameshift mutation within, one or both porin-encoding genes. No correlation was observed between cefiderocol MIC values and the presence of different combinations of intact and disrupted porin genes (data not shown).

The MIC_{90} value of cefiderocol against the overall collection of meropenem-non-susceptible *P. aeruginosa* isolates was 1 μg/mL, compared with MIC_{90}s of ≥32 μg/mL for meropenem, cefepime, ceftolozane-tazobactam, and ceftazidime-avibactam and >8 μg/mL for ciprofloxacin; only colistin tested with a low MIC_{90} identical to that of cefiderocol. Cefiderocol MIC_{90}s (0.5 and 2 μg/mL) and MIC values for subsets of fewer than 10 isolates were also comparable to those of colistin against β-lactamase-producing (GES, IMP, VIM) and meropenem-non-susceptible carbapenemase-negative isolates and were at least 8-fold lower than those observed for other tested β-lactam agents. With the exception of colistin, the comparator agents showed reduced activity against subsets of serine β-lactamase (GES)-positive isolates, metallo-β-lactamase-positive isolates, and carbapenemase-negative isolates (0-86% susceptible) (Table 3).

Similarly, the MIC_{90} value of cefiderocol against all meropenem-non-susceptible *A. baumannii* isolates was 1 μg/mL, compared with MIC_{90}s of >64 μg/mL for meropenem, cefepime, ceftazidime-avibactam, and ceftolozane-tazobactam and >8 μg/mL for ciprofloxacin and colistin. Cefiderocol displayed MIC_{90}s (range, 1-2 μg/mL) and MIC values for subsets of fewer than 10 isolates similar to those of colistin against β-lactamase-producing and meropenem-non-susceptible carbapenemase-negative *A. baumannii* isolates, except for the subset of OXA-23 producers, against which the cefiderocol MIC_{90} value was >8-fold lower than that of colistin. Cefiderocol MIC_{90}s were at least 8-fold lower than those of other tested comparator agents against most subsets of *A. baumannii* examined, including NDM-positive isolates. Meropenem, cefepime and ciprofloxacin showed reduced activity against the various subsets of carbapenemase-producing and carbapenemase-negative isolates (0-50% susceptible), as observed for *P. aeruginosa* (Table 3).

A total of 136 colistin-resistant isolates of Enterobacteriaceae, excluding Proteeae and *Serratia* spp., which are naturally colistin-resistant, were screened for the presence of the transmissible colistin resistance determinant, *mcr-1*. These isolates were composed of 101 meropenem-susceptible and 35 meropenem-resistant isolates, including 22 KPC-positive, 6 OXA-48-positive and 2 NDM-positive isolates, 2 isolates co-carrying KPC-2 and VIM-1, and 1 isolate co-carrying NDM-1 and OXA-48. The MIC_{90} of cefiderocol against the overall set of colistin-resistant isolates was 2 μg/mL, compared with ≥64 μg/mL for meropenem, cefepime, ceftazidime-avibactam, and ceftolozane-tazobactam and >8 μg/mL for ciprofloxacin; 99.3% (135/136) of the isolates tested had cefiderocol MIC values of ≤4 μg/mL. Although no *mcr*-positive meropenem-resistant isolates were identified, two meropenem-susceptible *E. coli* isolates, collected in Germany and Russia, were found to carry *mcr-1* and tested with cefiderocol MICs of 0.03 and 0.06 μg/mL and colistin MICs of 4 and 8 μg/mL, respectively (Table S1).

4. Discussion

In the current study, cefiderocol showed potent in vitro activity against the majority of meropenem-non-susceptible Enterobacteriaceae, *P. aeruginosa* and *A. baumannii* isolates (96.7%, 100% and 96.9% inhibited at a cefiderocol MIC of ≤4 μg/mL, respectively; 100%, 100% and 99.3% inhibited at an MIC of ≤8 μg/mL) collected during one year of the SIDERO-WT surveillance program. Isolates included serine- and metallo-carbapenemase-producers and complex isolates possessing multiple resistance mechanisms, such

Table 2
Cefiderocol MIC distributions against meropenem-resistant Enterobacteriaceae and meropenem-non-susceptible *P. aeruginosa* and *A. baumannii* isolates producing various β-lactamases.

β-lactamase (N)[a]	Value	Number (N) and cumulative percent (Cum Pct, %) of isolates inhibited at an MIC (μg/mL) of:[b]															
		≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64
KPC (75)[c,d]	N					1	1	8	15	11	16	16	7				
	Cum Pct					1.3	2.7	13.3	33.3	48.0	69.3	**90.7**	100				
GES carbapenemase (3)[c]	N								3								
	Cum Pct								100								
GES-type ESBL (9)[e,f]	N							2	1	3	1		1	1			
	Cum Pct							22.2	33.3	66.7	77.7		88.9	100			
IMP (4)	N										1	3					
	Cum Pct										25.0	100					
VIM (53)[d,g]	N			1				3	18	7	10	11	3				
	Cum Pct			1.9				7.5	41.5	54.7	73.6	**94.3**	100				
NDM (14)[h]	N										4	2	3	5			
	Cum Pct										28.6	42.9	64.3	**100**			
OXA-23-type (543)[e,i]	N	1	2	1	6	12	177	154	63	40	55	10	7	13	2		
	Cum Pct	0.2	0.6	0.7	1.8	4.1	36.6	65.0	76.6	84.0	**94.1**	95.9	97.2	99.6	100		
OXA-24-type (124)[f]	N		1	2	1	6	26	39	10	13	14	5	1	3	1	1	1
	Cum Pct		0.8	2.4	3.2	8.1	29.0	60.5	68.5	79.0	**90.3**	94.4	95.2	97.6	98.4	99.2	100
OXA-48-like (32)[g,h]	N					1	2	4	5	5	4	6	5				
	Cum Pct					3.1	9.4	21.9	37.5	53.1	65.6	84.4	**100**				
OXA-58-type (14)[i]	N						7	2		3	2						
	Cum Pct						50.0	64.3		85.7	**100**						
Carbapenemase-negative, meropenem-NS (420)[j]	N	5	7	22	15	16	103	81	65	46	39	10	8	3			
	Cum Pct	1.2	2.9	8.1	11.7	15.5	40.0	59.3	74.8	85.7	**95.0**	97.4	99.3	100			

[a] Isolates that carried more than one carbapenemase or GES-type β-lactamase were included in each relevant category of analysis. ESBL, extended-spectrum β-lactamase; NS, non-susceptible.
[b] The MIC_{90} is in bold type for each MIC distribution. The MIC_{90} was not calculated for <10 isolates.
[c] Included one isolate carrying KPC- and GES-type carbapenemases.
[d] Included three isolates carrying KPC- and VIM-type carbapenemases.
[e] Included one isolate carrying an OXA-23-type carbapenemase and a GES-type ESBL.
[f] Included two isolates carrying OXA-24-type carbapenemases and GES-type ESBLs.
[g] Included three isolates carrying VIM-type and OXA-48-like carbapenemases.
[h] Included two isolates carrying NDM-type and OXA-48-like carbapenemases.
[i] Included one isolate carrying OXA-23-type and OXA-58-type carbapenemases.
[j] Included nine isolates carrying GES-type ESBLs.

Table 3
In vitro activity of cefiderocol and comparator antimicrobial agents against meropenem-resistant Enterobacteriaceae and meropenem-non-susceptible *P. aeruginosa* and *A. baumannii* isolates producing various β-lactamases.

Organism/β-lactamase carriage (No. of isolates)[a]	Antimicrobial agent[b]	MIC (μg/mL)[c]			MIC interpretation[d,e]		
		Range	MIC_{50}	MIC_{90}	% Susceptible	% Intermediate	% Resistant
Enterobacteriaceae							
All meropenem-resistant (MIC ≥4 μg/mL) (151)	Cefiderocol	0.008–8	1	4	NA	NA	NA
	Meropenem	4–>64	16	>64	0	0	100
	Cefepime	0.25–>64	>64	>64	4.6	4.6	90.8
	Ceftazidime-avibactam	0.12–>64	1	>64	75.5	NA	24.5
	Ceftolozane-tazobactam	0.5–>64	>64	>64	4.6	2.7	92.7
	Ciprofloxacin	≤0.12–>8	>8	>8	12.6	4.6	82.8
	Colistin	≤0.25–>8	1	>8	69.5	NA	30.5
KPC-positive (75)[f,g]	Cefiderocol	0.03–4	1	2	NA	NA	NA
	Meropenem	4–>64	64	>64	0	0	100
	Cefepime	4–>64	>64	>64	0	6.7	93.3
	Ceftazidime-avibactam	0.12–>64	1	4	96.0	NA	4.0
	Ceftolozane-tazobactam	4–>64	64	>64	0	2.7	97.3
	Ciprofloxacin	≤0.12–>8	>8	>8	5.3	4.0	90.7
	Colistin	≤0.25–>8	1	>8	60.0	NA	40.0
GES carbapenemase-positive (1)[f]	Cefiderocol	0.25	–	–	NA	NA	NA
	Meropenem	>64	–	–	0	0	100
	Cefepime	64	–	–	0	0	100
	Ceftazidime-avibactam	1	–	–	100	NA	0
	Ceftolozane-tazobactam	32	–	–	0	0	100
	Ciprofloxacin	8	–	–	0	0	100
	Colistin	0.5	–	–	100	NA	0
VIM-positive (27)[g,h]	Cefiderocol	0.12–4	1	4	NA	NA	NA
	Meropenem	4–>64	16	64	0	0	100
	Cefepime	0.5–>64	64	>64	14.8	0	85.2
	Ceftazidime-avibactam	4–>64	>64	>64	11.1	NA	88.9
	Ceftolozane-tazobactam	>64–>64	>64	>64	0	0	100
	Ciprofloxacin	≤0.12–>8	>8	>8	25.9	7.4	66.7
	Colistin	≤0.25–>8	0.5	>8	81.5	NA	18.5
NDM-positive (12)[i]	Cefiderocol	1–8	4	8	NA	NA	NA
	Meropenem	16–>64	64	>64	0	0	100
	Cefepime	32–>64	>64	>64	0	0	100
	Ceftazidime-avibactam	>64–>64	>64	>64	0	NA	100
	Ceftolozane-tazobactam	>64–>64	>64	>64	0	0	100
	Ciprofloxacin	>8–>8	>8	>8	0	0	100
	Colistin	0.5–>8	0.5	>8	75.0	NA	25.0
OXA-48-like positive (32)[h,i]	Cefiderocol	0.03–4	0.5	4	NA	NA	NA
	Meropenem	4–>64	8	64	0	0	100
	Cefepime	0.25–>64	>64	>64	12.5	0	87.5
	Ceftazidime-avibactam	0.12–>64	1	4	90.6	NA	9.4
	Ceftolozane-tazobactam	2–>64	>64	>64	3.1	3.1	93.8
	Ciprofloxacin	≤0.12–>8	>8	>8	3.1	0	96.9
	Colistin	≤0.25–>8	0.5	>8	78.1	NA	21.9
Carbapenemase-negative, meropenem-resistant (13)	Cefiderocol	0.008–4	0.12	2	NA	NA	NA
	Meropenem	4–>64	16	64	0	0	100
	Cefepime	0.5–>64	16	>64	15.4	15.4	69.2
	Ceftazidime-avibactam	0.5–8	2	8	100	NA	0
	Ceftolozane-tazobactam	0.5–>64	4	>64	46.2	7.6	46.2
	Ciprofloxacin	≤0.12–>8	1	>8	53.8	15.4	30.8
	Colistin	≤0.25–>8	1	>8	69.2	NA	30.8
Pseudomonas aeruginosa							
All meropenem-non-susceptible (353)	Cefiderocol	≤0.002–8	0.12	1	NA	NA	NA
	Meropenem	4–>64	8	64	0	24.4	75.6
	Cefepime	1–>64	8	64	50.2	19.8	30.0
	Ceftazidime-avibactam	0.5–>64	4	32	77.9	NA	22.1
	Ceftolozane-tazobactam	0.25–>64	1	64	77.0	5.4	17.6
	Ciprofloxacin	≤0.12–>8	4	>8	38.5	8.2	53.3
	Colistin	≤0.25–4	1	1	99.2	NA	0.8
GES-positive (4)[j]	Cefiderocol	0.12–0.25	–	–	NA	NA	NA
	Meropenem	8–>64	–	–	0	0	100
	Cefepime	8–32	–	–	25.0	25.0	50.0
	Ceftazidime-avibactam	2–16	–	–	50.0	NA	50.0
	Ceftolozane-tazobactam	8–64	–	–	0	50.0	50.0
	Ciprofloxacin	>8–>8	–	–	0	0	100
	Colistin	1–1	–	–	100	NA	0

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Table 3 (*continued*)

Organism/β-lactamase carriage (No. of isolates)[a]	Antimicrobial agent[b]	MIC (μg/mL)[c]			MIC interpretation[d,e]		
		Range	MIC_{50}	MIC_{90}	% Susceptible	% Intermediate	% Resistant
IMP-positive (4)	Cefiderocol	1–2	–	–	NA	NA	NA
	Meropenem	>64–>64	–	–	0	0	100
	Cefepime	>64–>64	–	–	0	0	100
	Ceftazidime-avibactam	>64–>64	–	–	0	NA	100
	Ceftolozane-tazobactam	>64–>64	–	–	0	0	100
	Ciprofloxacin	>8–>8	–	–	0	0	100
	Colistin	1–2	–	–	100	NA	0
VIM-positive (26)	Cefiderocol	0.008–2	0.25	2	NA	NA	NA
	Meropenem	4–>64	>64	>64	0	3.8	96.2
	Cefepime	8–>64	32	>64	3.8	30.8	65.4
	Ceftazidime-avibactam	16–>64	64	>64	0	NA	100
	Ceftolozane-tazobactam	64–>64	>64	>64	0	0	100
	Ciprofloxacin	1–>8	>8	>8	11.5	0	88.5
	Colistin	≤0.25–4	1	2	96.2	NA	3.8
Carbapenemase-negative, meropenem-non-susceptible (319)	Cefiderocol	≤0.002–4	0.12	0.5	NA	NA	NA
	Meropenem	4–>64	8	16	0	26.6	73.4
	Cefepime	1–>64	8	64	54.9	19.1	26.0
	Ceftazidime-avibactam	0.5–>64	4	16	85.6	NA	14.4
	Ceftolozane-tazobactam	0.25–>64	1	8	85.3	5.3	9.4
	Ciprofloxacin	≤0.12–>8	2	>8	41.7	9.1	49.2
	Colistin	≤0.25–4	1	1	99.4	NA	0.6
Acinetobacter baumannii							
All meropenem-non-susceptible (768)	Cefiderocol	≤0.002–64	0.12	1	NA	NA	NA
	Meropenem	4–>64	64	>64	0	1.3	98.7
	Cefepime	4–>64	64	>64	5.6	17.7	76.7
	Ceftazidime-avibactam	1–>64	32	>64	NA	NA	NA
	Ceftolozane-tazobactam	0.5–>64	16	>64	NA	NA	NA
	Ciprofloxacin	≤0.12–>8	>8	>8	0.5	0	99.5
	Colistin	≤0.25–>8	1	>8	84.6	NA	15.4
GES-type ESBL-positive (7)[k,l]	Cefiderocol	0.25-8	–	–	NA	NA	NA
	Meropenem	8–64	–	–	0	0	100
	Cefepime	>64–>64	–	–	0	0	100
	Ceftazidime-avibactam	32–>64	–	–	NA	NA	NA
	Ceftolozane-tazobactam	>64–>64	–	–	NA	NA	NA
	Ciprofloxacin	>8–>8	–	–	0	0	100
	Colistin	0.5–1	–	–	100	NA	0
NDM-positive (2)	Cefiderocol	1–1	–	–	NA	NA	NA
	Meropenem	64–>64	–	–	0	0	100
	Cefepime	>64–>64	–	–	0	0	100
	Ceftazidime-avibactam	>64–>64	–	–	NA	NA	NA
	Ceftolozane-tazobactam	>64–>64	–	–	NA	NA	NA
	Ciprofloxacin	≤0.12–>8	–	–	50.0	0	50.0
	Colistin	≤0.25–0.5	–	–	100	NA	0
OXA-23-positive (543)[k,m]	Cefiderocol	≤0.002–16	0.12	1	NA	NA	NA
	Meropenem	4–>64	64	>64	0	0.2	99.8
	Cefepime	4–>64	64	>64	1.7	11.0	87.3
	Ceftazidime-avibactam	1–>64	32	>64	NA	NA	NA
	Ceftolozane-tazobactam	1–>64	16	>64	NA	NA	NA
	Ciprofloxacin	8–>8	>8	>8	0	0	100
	Colistin	≤0.25–>8	1	>8	79.6	NA	20.4
OXA-24-positive (124)[l]	Cefiderocol	0.004–64	0.12	1	NA	NA	NA
	Meropenem	8–>64	>64	>64	0	0	100
	Cefepime	4–>64	32	>64	11.3	25.8	62.9
	Ceftazidime-avibactam	4–>64	16	>64	NA	NA	NA
	Ceftolozane-tazobactam	0.5–>64	8	>64	NA	NA	NA
	Ciprofloxacin	8–>8	>8	>8	0	0	100
	Colistin	≤0.25–>8	0.5	1	96.8	NA	3.2
OXA-58-positive (14)[m]	Cefiderocol	0.06–1	0.06	1	NA	NA	NA
	Meropenem	4–64	8	16	0	21.4	78.6
	Cefepime	16–>64	16	>64	0	64.3	35.7
	Ceftazidime-avibactam	8–>64	64	>64	NA	NA	NA
	Ceftolozane-tazobactam	8–>64	16	>64	NA	NA	NA
	Ciprofloxacin	>8–>8	>8	>8	0	0	100
	Colistin	0.5–>8	1	1	92.9	NA	7.1

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Table 3 (*continued*)

Organism/β-lactamase carriage (No. of isolates)[a]	Antimicrobial agent[b]	MIC (μg/mL)[c]			MIC interpretation[d,e]		
		Range	MIC_{50}	MIC_{90}	% Susceptible	% Intermediate	% Resistant
Carbapenemase-negative, meropenem-non-susceptible (86)	Cefiderocol	0.008–8	0.25	2	NA	NA	NA
	Meropenem	4–>64	16	64	0	7.0	93.0
	Cefepime	4–>64	16	>64	23.3	40.7	36.0
	Ceftazidime-avibactam	4–>64	32	>64	NA	NA	NA
	Ceftolozane-tazobactam	0.5–>64	16	>64	NA	NA	NA
	Ciprofloxacin	0.25–>8	>8	>8	3.5	0	96.5
	Colistin	≤0.25–>8	0.5	1	97.7	NA	2.3

[a] Included isolates co-carrying extended-spectrum β-lactamases, original-spectrum β-lactamases (e.g. TEM-1, SHV-1, SHV-11), and chromosomal- and plasmid-mediated AmpC cephalosporinases. Isolates that carried more than one carbapenemase or GES-type β-lactamase were included in each relevant category of analysis.
[b] Ceftazidime-avibactam was tested with 4 μg/mL avibactam; ceftolozane-tazobactam was tested with 8 μg/mL tazobactam.
[c] MIC_{50} and MIC_{90} were not calculated for <10 isolates.
[d] Clinical and Laboratory Standards Institute 2018 breakpoints were used for all antimicrobial agents tested against all organisms except for the Enterobacteriaceae, for which EUCAST 2018 breakpoints for colistin were applied because no CLSI breakpoints for this agent/organism combination have been defined. For cefepime, the intermediate category is replaced by the susceptible dose dependent category.
[e] NA, no breakpoint available.
[f] Included one isolate carrying KPC and GES carbapenemases.
[g] Included three isolates carrying KPC and VIM carbapenemases.
[h] Included three isolates carrying VIM-type and OXA-48-like carbapenemases.
[i] Included two isolates carrying NDM-type and OXA-48-like carbapenemases.
[j] GES-positive included isolates carrying GES with carbapenemase activity (n=2) and GES with only ESBL activity (n=2).
[k] One isolate co-carried a GES-type ESBL and an OXA-23-type carbapenemase.
[l] Two isolates co-carried a GES-type ESBL and an OXA-24-type carbapenemase.
[m] One isolate carried both OXA-23-type and OXA-58 type carbapenemases.

as carbapenemase-, ESBL-, or plasmidic or chromosomal AmpC-producing Gram-negative isolates known or assumed to harbor porin defects and/or upregulated efflux transport [2–6]. Cefiderocol activity, as represented by MIC_{50} and MIC_{90} values, was comparable to that of ceftazidime-avibactam against metallo-β-lactamase-negative Enterobacteriaceae isolates and superior to all tested comparators against NDM-positive and VIM-positive Enterobacteriaceae. Similarly, cefiderocol activity exceeded that of all tested comparators except colistin against meropenem-non-susceptible isolates of *P. aeruginosa* and *A. baumannii*. Comparable results were reported by others in early studies utilizing cation-adjusted Mueller-Hinton broth (CAMHB) supplemented with 20 μM apo-transferrin [15,17]. In a study by Dobias and colleagues testing the activity of cefiderocol in Chelex-treated iron-depleted CAMHB against a set of well-characterized global isolates, the MIC_{90}s of carbapenemase-producing isolates of Gram-negative bacilli were determined to be 2 μg/mL for KPC-producing Enterobacteriaceae (n=127), OXA-48-producing Enterobacteriaceae (n=154), and carbapenemase (IMP, KPC, VIM, SPM, GIM)-producing *P. aeruginosa* (n=30), and 4 μg/mL for IMP-, VIM-, or NDM-producing Enterobacteriaceae (n=134) and OXA carbapenemase-producing *A. baumannii* (n=85). In that set of isolates, only 24 of 753 isolates exhibited a cefiderocol MIC ≥8 μg/mL and, of these, 45% were NDM-producers and 30% were OXA-23 producers [18].

In this study, we found that some (5 of 14, 35.7%) NDM-positive isolates were not inhibited by ≤4 μg/mL cefiderocol, the provisional susceptible breakpoint recently set by the Clinical and Laboratory Standards Institute [19]. These isolates were *K. pneumoniae* with cefiderocol MICs of 8 μg/mL that carried NDM-1 and a CTX-M-1-type ESBL and were collected from one participating hospital in Turkey. Porin gene sequencing revealed that one isolate had lost OmpK35 and three others were expected to produce truncated OmpK36 proteins of different lengths; however, the strain relatedness of the isolates was not determined. Twenty-four additional meropenem-non-susceptible isolates with cefiderocol MIC ≥8 μg/mL, all *A. baumannii*, included isolates carrying OXA-23-type (n=15) or OXA-24-type (n=6) β-lactamases and 3 carbapenemase-negative isolates, of which one carried a GES-type ESBL. Molecular characterization of meropenem-non-susceptible Enterobacteriaceae, *P. aeruginosa* and *A. baumannii* isolates with cefiderocol MIC ≥8 μg/mL collected as part of the SIDERO-WT-2014 study confirmed that there was no clear correlation between carriage of the β-lactamases included in the screening algorithm and elevated cefiderocol MICs (Table 2). The mechanisms conferring elevated MICs to cefiderocol in these isolates is currently under study. Recent work by Ito et al. demonstrated that disruption of the iron transport proteins PiuA in *P. aeruginosa* and CirA and Fiu in *E. coli* resulted in a 16-fold increase in cefiderocol MICs. Loss of the *K. pneumoniae* porins OmpK35 and OmpK36 or *P. aeruginosa* OprD, or upregulation of the pseudomonal efflux transporter MexAB-OprM, resulted in only 2- to 4-fold increases in cefiderocol MIC that did not significantly impact its activity [11].

5. Conclusions

The current study examined the activity of cefiderocol, a promising parenteral siderophore cephalosporin in late-stage clinical development for treatment of infections caused by Gram-negative pathogens, including carbapenem-resistant and multidrug-resistant isolates, against carbapenemase-producing and carbapenemase-negative, meropenem-non-susceptible isolates of Enterobacteriaceae, *P. aeruginosa* and *A. baumannii* collected as part of a global surveillance program. The distribution of carbapenemase types varied among isolates collected in Europe and North America, underscoring the importance of knowing the local incidence of different resistance mechanisms when evaluating treatment options. Cefiderocol demonstrated potent in vitro activity against carbapenemase-producing isolates, including those that co-carried additional ESBL and AmpC β-lactamases, regardless of species, and was insensitive to the presence of porin defects. Cefiderocol was also active against colistin-resistant isolates of Enterobacteriaceae, including isolates carrying the transmissible colistin resistance determinant, *mcr-1*, as reported by others [18,20].

Cefiderocol represents a promising addition to the limited pool of existing antimicrobial agents available for treatment of infections caused by problematic drug-resistant Gram-negative bacilli.

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Declarations

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Competing Interests

K.M.K., M.W.G., M.A.H., and D.F.S. are employees of IHMA, Inc. M.T. and Y.Y. are employees of Shionogi & Co. R.E. is a consultant to Shionogi and was compensated for supporting this research. The IHMA authors do not have personal financial interests in the sponsor of this paper (Shionogi & Co., Ltd.).

Ethical Approval

Not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2018.10.007.

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