J Antimicrob Chemother 2023; **78**: 2019–2027
https://doi.org/10.1093/jac/dkad200 Advance Access publication 30 June 2023

Journal of Antimicrobial Chemotherapy

In vitro activity of cefiderocol against MBL-producing Gram-negative bacteria collected in North America and Europe in five consecutive annual multinational SIDERO-WT surveillance studies (2014–2019)

Miki Takemura[1]*, Mark G. Wise[2], Meredith A. Hackel[2], Daniel F. Sahm[2] and Yoshinori Yamano[1]

[1]*Laboratory for Drug Discovery and Disease Research, Shionogi & Co., Ltd., Osaka, Japan;* [2]*International Health Management Associates, Inc., Schaumburg, IL, USA*

*Corresponding author. E-mail: miki.takemura@shionogi.co.jp

Received 27 January 2023; accepted 8 June 2023

Objectives: To evaluate the *in vitro* antibacterial activity of cefiderocol, a siderophore cephalosporin against MBL-producing clinical isolates.

Methods: MBL-producing strains were selected from clinical isolates of Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* complex collected in North America and Europe in five consecutive annual multinational SIDERO-WT surveillance studies from 2014 to 2019. MICs of cefiderocol and comparator agents were determined by the broth microdilution method according to the CLSI guideline.

Results: A total of 452 MBL-producing strains consisting of 200 Enterobacterales, 227 *P. aeruginosa* and 25 *A. baumannii* complex were identified. The highest number of MBL-producing Enterobacterales strains were detected in Greece. MBL-producing strains of both *P. aeruginosa* and *A. baumannii* complex were isolated most frequently in Russia. For Enterobacterales, 91.5% or 67.5% of MBL-producing strains had cefiderocol MIC values ≤4 mg/L (CLSI susceptibility breakpoint) or ≤2 mg/L (EUCAST susceptibility breakpoint), respectively. All MIC values of cefiderocol for MBL-producing *P. aeruginosa* strains were ≤4 mg/L (CLSI susceptibility breakpoint), and 97.4% of them had cefiderocol MIC values ≤2 mg/L (EUCAST susceptibility breakpoint). For *A. baumannii* complex, 60.0% or 44.0% of MBL-producing strains had cefiderocol MIC values ≤4 mg/L (CLSI susceptibility breakpoint) or ≤2 mg/L (EUCAST pharmacokinetic-pharmacodynamic susceptibility breakpoint), respectively. Against all types of MBL-producing strains, MIC distribution curves of cefiderocol were located in the lowest numerical values, compared with other β-lactams and β-lactam/β-lactamase inhibitor combinations tested and ciprofloxacin.

Conclusions: Although the types of MBL-producing strains isolated by country varied, cefiderocol showed potent *in vitro* activity against all types of MBL-producing Gram-negative bacteria regardless of the bacterial species.

Introduction

MBLs (e.g. IMP, VIM, NDM and GIM) cause serious clinical problems because they can inactivate most of the commonly used β-lactam antibiotics, including carbapenems.[1–3] Recently approved β-lactam/β-lactamase inhibitor combinations are not active against MBL-producing clinical isolates.[4]

Cefiderocol is a siderophore cephalosporin with activity against a wide variety of Gram-negative bacteria including carbapenem-resistant isolates and was approved in the USA in 2019 for the treatment of patients with complicated urinary tract infections, and in 2020 for nosocomial pneumonia (hospital-acquired bacterial pneumonia [HABP]/ventilator-associated bacterial pneumonia [VABP]) caused by Gram-negative bacteria.[5] In Europe, cefiderocol was approved in 2020 for the treatment of infections due to Gram-negative pathogens with limited treatment options.[6] Cefiderocol is stable against a wide variety of carbapenemases including MBLs such as IMP, VIM and NDM.[7–9] We conducted annual surveillance studies (SIDERO-WT) over five consecutive years, with approximately 46 000 Gram-negative clinical isolates collected in North America and Europe between 2014 and 2019.[10] Cefiderocol has shown potent antibacterial activity against clinical isolates of Enterobacterales and non-fermenters in these surveillance studies. In this study, we evaluated the antibacterial activity of cefiderocol and comparator agents against MBL-producing strains of Gram-negative bacteria collected in these five surveillance studies.

Materials and methods

Susceptibility testing

Susceptibility testing of cefiderocol (0.03–64 mg/L), ceftazidime/avibactam (0.12/4–16/4 mg/L), ceftolozane/tazobactam (0.12/4–16/4 mg/L), meropenem (0.06–16 mg/L), cefepime (0.12–16 mg/L), ciprofloxacin (0.12–8 mg/L) and colistin (0.25–8 mg/L) was conducted against clinical isolates collected from North America and 11 European countries in annual surveillance studies (SIDERO-WT; 2014–2019) conducted over five consecutive years. MICs of these agents were determined by the broth microdilution method according to the CLSI guidelines.[11] For MIC determination of cefiderocol, iron-depleted cation-adjusted Mueller–Hinton broth medium was used. All MIC measurements were conducted at International Health Management Associates, Inc. (IHMA, Schaumburg, IL, USA).[10]

Bacterial strains

In this study, Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* complex were targeted, and strains to be analysed were selected from the isolates collected in the SIDERO-WT surveillance studies (2014–2019). Bacterial identification was performed using MALDI-TOF MS (Bruker Daltonics, Billerica, MA, USA).[10] For the Enterobacterales, a total of 908 molecularly characterized meropenem-resistant strains (meropenem MIC ≥4 mg/L) (32 *Citrobacter freundii* complex, 1 *Citrobacter amalonaticus*, 2 *Citrobacter koseri*, 83 *Enterobacter cloacae* complex, 2 *Enterobacter bugandensis*, 33 *Escherichia coli*, 15 *Klebsiella aerogenes*, 16 *Klebsiella oxytoca*, 645 *Klebsiella pneumoniae*, 2 *Klebsiella variicola*, 2 *Proteus mirabilis*, 7 *Providencia rettgeri* and 68 *Serratia marcescens*) were selected from a total of 30 258 strains. For *P. aeruginosa*, a total of 1759 molecularly characterized meropenem-non-susceptible strains (meropenem MIC ≥4 mg/L) were selected from a total of 7700 strains. For *A. baumannii* complex, a total of 2809 molecularly characterized meropenem-non-susceptible strains (meropenem MIC ≥4 mg/L) were selected from a total of 5226 strains.

Detection of MBL genes

Most meropenem-non-susceptible strains were screened for the carriage of genes encoding MBLs (IMP, VIM, NDM and GIM) by multiplex PCR using published primers followed by Sanger sequencing.[12] For all MBL genes sequenced, the deduced amino acid sequence was compared with NCBI databases (www.ncbi.nlm.nih.gov) to identify those variants. Isolates with elevated cefiderocol MICs [≥4 mg/L (in 2018) and ≥8 mg/L (in 2019)] were subjected to WGS instead of PCR and Sanger sequencing.[12] Genomic DNA from each bacterial sample was extracted using the DNeasy Ultraclean Microbial extraction kit (Qiagen) and WGS was performed on an Illumina HiSeq system as described previously.[12] All analyses were carried out using the CLC Genomics Workbench v. 20 (Qiagen). If the MBL genes had a match rate of less than 100% with a known nucleotide reference, those were translated to their deduced amino acid sequence and BLASTP search was performed against the Refseq database in Genbank dedicated to β-lactamase nomenclature (Bioproject 313047) to identify those variants.

Geographical analysis

MBL-producing strains were aggregated by MBL type and bacterial species to provide an epidemiological profile for each country. The percentages of MBL-producing strains among all isolated strains were calculated by country for Enterobacterales, *P. aeruginosa* and *A. baumannii* complex. In addition, the percentage of MBL-producing strains among meropenem-resistant Enterobacterales, meropenem-non-susceptible *P. aeruginosa* and meropenem-non-susceptible *A. baumannii* complex was also calculated.

Results

Identification of MBL-producing strains

Among 908 meropenem-resistant Enterobacterales strains (3.00% of all 30 258 strains), a total of 200 MBL-producing strains (0.66% of all 30 258 strains) consisting of 1 *C. amalonaticus*, 17 *C. freundii* complex, 42 *E. cloacae* complex, 7 *E. coli*, 5 *K. oxytoca*, 110 *K. pneumoniae*, 2 *P. mirabilis*, 1 *P. rettgeri* and 15 *S. marcescens* were identified (Table 1). Of the 200 strains of MBL-producing Enterobacterales, VIM-producing strains ($n = 104$) were the most common, with VIM-1 ($n = 63$) as the most prevalent variant, followed by NDM-producing strains ($n = 94$), with NDM-1 as the most common variant ($n = 81$); there were only two IMP-producing strains (Table 1 and Table S1, available as Supplementary data at *JAC* Online). Of the NDM-producing Enterobacterales strains, 77.7% (73/94) were *K. pneumoniae*. VIM was encountered in various Enterobacterales species such as *K. pneumoniae*, *E. cloacae* complex, *C. freundii* complex and *S. marcescens*.

Among 1759 meropenem-non-susceptible *P. aeruginosa* strains (22.8% of all 7700 strains), a total of 227 MBL-producing *P. aeruginosa* strains (2.95% of all 7700 strains) were identified

Table 1. Number of MBL-producing strains among meropenem-resistant Enterobacterales, meropenem-non-susceptible *P. aeruginosa* and *A. baumannii* complex strains collected in the SIDERO-WT surveillance programmes

	Number of strains					
	MEM-R[a] or MEM-NS[b]	MBL producers				
		Total	IMP	VIM	NDM	GIM
Enterobacterales	908	200	2	104	94	0
Citrobacter amalonaticus	1	1	0	1	0	0
Citrobacter freundii complex	32	17	0	14	3	0
Citrobacter koseri	2	0	0	0	0	0
Enterobacter cloacae complex	83	42	0	33	9	0
Enterobacter bugandensis	2	0	0	0	0	0
Escherichia coli	33	7	0	2	5	0
Klebsiella aerogenes	15	0	0	0	0	0
Klebsiella oxytoca	16	5	0	5	0	0
Klebsiella pneumoniae	645	110	0	37	73	0
Klebsiella variicola	2	0	0	0	0	0
Proteus mirabilis	2	2	1	1	0	0
Providencia rettgeri	7	1	1	0	0	0
Serratia marcescens	68	15	0	11	4	0
Non-fermenters						
Pseudomonas aeruginosa	1759	227	25	200	2	0
Acinetobacter baumannii complex	2809	25	2	0	21	2

[a]MEM-R, meropenem-resistant. For Enterobacterales, numbers of meropenem-resistant strains are shown.

[b]MEM-NS, meropenem-non-susceptible. For A. *baumannii* complex and *P. aeruginosa*, numbers of meropenem-non-susceptible strains are shown.

Table 2. Number of MBL-producing strains and percentage of MBL-producing strains among all and meropenem-resistant Enterobacterales strains by country

		Number of strains							MBL (%)	
				MBL producers						
Region	Country	All	MEM-R	Total	IMP	VIM	NDM	GIM	For all	For MEM-R
North America	Canada	1967	11	6	1	0	5	0	0.31	54.5
	USA	12 243	175	6	1	2	3	0	0.05	3.43
Europe	Czech Republic	1296	6	0	0	0	0	0	0.00	0.00
	France	1575	4	0	0	0	0	0	0.00	0.00
	Germany	1822	17	6	0	1	5	0	0.33	35.3
	Greece	1428	170	52	0	38	14	0	3.64	30.6
	Hungary	1050	12	5	0	5	0	0	0.48	41.7
	Italy	1883	198	35	0	34	1	0	1.86	17.7
	Russia	1719	131	38	0	0	38	0	2.21	29.0
	Spain	1865	59	19	0	18	1	0	1.02	32.2
	Sweden	580	1	0	0	0	0	0	0.00	0.00
	Turkey	1334	104	26	0	4	22	0	1.95	25.0
	UK	1496	20	7	0	2	5	0	0.47	35.0
Total		30 258	902	200	2	104	94	0	0.66	22.2

MEM-R, meropenem-resistant.

(Table 1). Of these, VIM-producing strains ($n = 200$) were the most common, with VIM-2 ($n = 158$) as the most prevalent variant; of the IMP-producing strains ($n = 25$), IMP-7 ($n = 22$) was the most common variant; and there were two NDM-1-producing strains (Table 1 and Table S2).

Among 2809 meropenem-non-susceptible *A. baumannii* complex strains (53.8% of all 5226 strains), a total of 25 MBL-producing *A. baumannii* complex strains (0.48% of all 5226 strains) were identified (Table 1). Of these 25 strains, NDM-producing strains ($n = 21$; all NDM-1) were the most common. In addition, two IMP-61- and GIM-1-producing strains were detected (Table 1 and Table S3).

Geographical characteristics

For Enterobacterales, the percentage of MBL-producing strains among all isolates and meropenem-resistant strains in all regions was 0.66% and 22.2%, respectively (Table 2). MBL-producing strains were predominantly isolated in Greece ($n = 52$), Russia ($n = 38$), Italy ($n = 35$) and Turkey ($n = 26$). No MBL-producing Enterobacterales were detected in the Czech Republic, France and Sweden. The percentage of MBL-producing strains among all isolates was highest in Greece (3.64%), followed by Russia (2.21%), Turkey (1.95%) and Italy (1.86%). In Canada and Hungary, although the number of isolated MBL-producing strains was small, the percentage of MBL-producing strains amongst meropenem-resistant strains was high, at 54.6% and 41.7%, respectively (Table 2). Both strains of IMP-producing Enterobacterales were isolated from North America (Canada: $n = 1$, USA: $n = 1$). Greece ($n = 38$) had the highest number of VIM-producing Enterobacterales strains isolated, followed by Italy ($n = 34$) and Spain ($n = 18$) (Table 2). Of the 38 strains of VIM-producing Enterobacterales isolated in Greece, more than half, 24 strains, were *K. pneumoniae*, followed by *E. cloacae* complex ($n = 12$), and these two bacterial species accounted for 94.7% (36/38) of the total (Table S4). On the other hand, in Italy, the isolation of *E. cloacae* complex was the most common, accounting for 41.2% (14/34) of the total, but multiple isolates of other bacterial species such as *C. freundii*, *K. pneumoniae* and *S. marcescens* were also included (Table S4). For NDM-producing strains, the most common isolates were from Russia ($n = 38$), followed by Turkey ($n = 22$) and Greece ($n = 14$) (Table 2). All MBL-producing Enterobacterales isolated in Russia were NDM-producing strains. NDM-producing Enterobacterales from Russia, Turkey and Greece had cefiderocol MICs ranging from 0.25 to >64 mg/L, 0.25 to 2 mg/L, and 0.12 to 8 mg/L, respectively (data not shown). Three cefiderocol-resistant NDM-producing Enterobacterales strains have been isolated from Russia, and the MICs of cefiderocol against these strains were 16, >64 and >64 mg/L. Both strains with cefiderocol MICs >64 mg/L produced NDM-5 (Table S1).

For *P. aeruginosa*, the percentages of MBL-producing strains in all isolates and meropenem-non-susceptible strains in all regions were 2.95% and 12.9%, respectively (Table 3). MBL-producing strains were predominantly isolated in Russia ($n = 106$), Greece ($n = 30$), Czech Republic ($n = 21$) and Spain ($n = 21$). Countries with a high percentage of MBL-producing strains among all isolates collected and among meropenem-non-susceptible strains were similar to those with a high number of MBL-producing strains, with Russia having the highest percentage (20.4% for all, 50.0% for meropenem-non-susceptible), followed by Greece (9.87% for all, 44.1% for meropenem-non-susceptible), Czech Republic (6.29% for all, 21.0% for meropenem-non-susceptible) and Spain (4.36% for all, 17.1% for meropenem-non-susceptible) (Table 3). Russia

Table 3. Number of MBL-producing strains and percentage of MBL-producing strains among all and meropenem-non-susceptible *P. aeruginosa* strains by country

		Number of strains							MBL (%)	
				MBL producers						
Region	Country	All	MEM-NS	Total	IMP	VIM	NDM	GIM	For all	For MEM-NS
North America	Canada	461	87	2	1	0	1	0	0.43	2.30
	USA	3087	595	3	1	2	0	0	0.10	0.50
Europe	Czech Republic	334	100	21	21	0	0	0	6.29	21.0
	France	419	59	3	0	3	0	0	0.72	5.08
	Germany	473	110	6	1	5	0	0	1.27	5.45
	Greece	304	68	30	0	30	0	0	9.87	44.1
	Hungary	278	122	9	0	9	0	0	3.24	7.38
	Italy	463	118	14	1	13	0	0	3.02	11.9
	Russia	520	212	106	0	106	0	0	20.4	50.0
	Spain	482	123	21	0	21	0	0	4.36	17.1
	Sweden	124	10	1	0	1	0	0	0.81	10.0
	Turkey	369	103	10	0	9	1	0	2.71	9.71
	UK	386	52	1	0	1	0	0	0.26	1.92
Total		7700	1759	227	25	200	2	0	2.95	12.9

MEM-NS, meropenem-non-susceptible.

Table 4. Number of MBL-producing strains and percentage of MBL-producing strains among all and meropenem-non-susceptible *A. baumannii* complex strains by country

		Number of strains							MBL (%)	
				MBL producers						
Region	Country	All	MEM-NS	Total	IMP	VIM	NDM	GIM	For all	For MEM-NS
North America	Canada	243	20	1	0	0	1	0	0.41	5.00
	USA	1757	678	2	0	0	2	0	0.11	0.29
Europe	Czech Republic	213	28	0	0	0	0	0	0.00	0.00
	France	289	40	1	0	0	1	0	0.35	2.50
	Germany	265	51	4	2	0	0	2	1.51	7.84
	Greece	420	407	0	0	0	0	0	0.00	0.00
	Hungary	210	151	0	0	0	0	0	0.00	0.00
	Italy	505	432	4	0	0	4	0	0.79	0.93
	Russia	437	347	7	0	0	7	0	1.60	2.02
	Spain	336	238	1	0	0	1	0	0.30	0.42
	Sweden	10	6	0	0	0	0	0	0.00	0.00
	Turkey	432	391	2	0	0	2	0	0.46	0.51
	UK	109	20	3	0	0	3	0	2.75	15.0
Total		5226	2809	25	2	0	21	2	0.48	0.89

MEM-NS, meropenem-non-susceptible.

($n = 106$) had the highest number of VIM-producing *P. aeruginosa* strains isolated, followed by Greece ($n = 30$) and Spain ($n = 21$). Twenty-five IMP-producing strains were found, most of which were isolated in the Czech Republic ($n = 21$). Two NDM-producing strains were isolated in Canada and Turkey.

For *A. baumannii* complex, the percentage of MBL-producing strains in all isolates and in meropenem-resistant strains in all regions was 0.48% and 0.89%, respectively (Table 4). The number of isolates of MBL-producing strains was considerably lower than that of Enterobacterales and *P. aeruginosa*. Countries with relatively

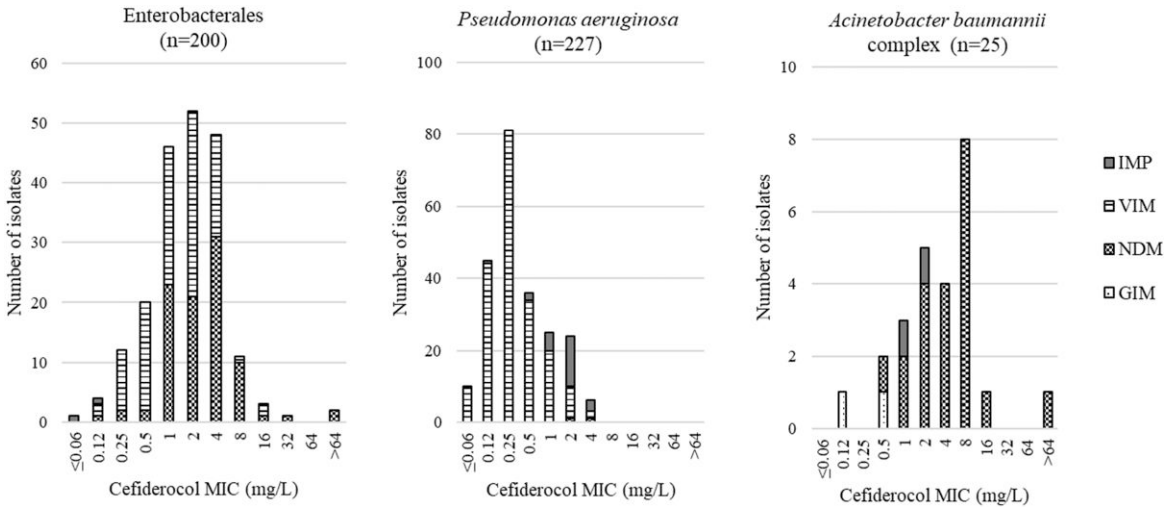

Figure 1. MIC distribution of cefiderocol for MBL-producing strains by MBL type.

high numbers of MBL-producing strains isolated were Russia ($n = 7$), Germany ($n = 4$) and Italy ($n = 4$). The percentage of MBL-producing strains among all isolates and meropenem-non-susceptible strains was the highest in the UK (2.75% for all, 15.0% for meropenem-nonsusceptible) although it should be noted that the number of MBL-producing strains in the UK was rather small ($n = 3$). Two IMP-producing strains and 2 GIM-producing strains were found, all of which were isolated in Germany (Table 4). NDM-producing strains were isolated in multiple countries, most in Russia ($n = 7$), followed by Italy ($n = 4$) and the UK ($n = 3$).

In vitro activity against MBL-producing strains

MIC distributions of cefiderocol against types of MBL-producing strains isolated in five SIDERO-WT surveillance studies (2014–2019) are shown in Figure 1. For Enterobacterales, 91.5% of MBL-producing strains showed MIC values ≤4 mg/L, which is the CLSI susceptibility breakpoint of cefiderocol, and 67.5% of MBL-producing strains showed MIC values ≤2 mg/L, which is the EUCAST susceptibility breakpoint of cefiderocol.[13,14] It should be noted that 73.0% of strains showed cefiderocol MICs of 1–4 mg/L, with a peak of 2 mg/L. Of the 17 cefiderocol-non-susceptible strains by CLSI criteria (>4 mg/L), 11 strains had an MIC of 8 mg/L (CLSI: intermediate) and the remaining 6 strains were resistant. Of the six strains that showed resistance to cefiderocol, one strain was an NDM-1 producer, three were NDM-5 producers, and two were VIM-1 producers (Figure 1). Activity of cefiderocol against isolates expressing different MBL variants was similar (e.g. MIC ranges against VIM-1-, VIM-2- and NDM-1-producing strains were 0.12–16, 0.25–4 and 0.12–16 mg/L, respectively; MIC_{90} values against VIM-1-, VIM-2- and NDM-1-producing strains were 4, 4 and 8 mg/L, respectively), with the possible exception of isolates that produced VIM-26, which showed lower MIC values (range 0.25–2 mg/L; MIC_{90} 1 mg/L), and NDM-5 producers, which showed higher MIC values (range 1 to >64 mg/L; MIC_{90} >64 mg/L) (Table S1). However, of all 104 strains producing VIM, only 10 strains produced VIM-26. Further studies are needed to confirm the susceptibility characteristics of cefiderocol against VIM-26-producing strains.

For *P. aeruginosa*, the MIC values of cefiderocol for all MBL-producing *P. aeruginosa* strains were ≤4 mg/L, which is the CLSI susceptibility breakpoint of cefiderocol, and 97.4% of MBL-producing *P. aeruginosa* strains showed MIC values ≤2 mg/L, which is the EUCAST susceptibility breakpoint of cefiderocol.[13,14] It should be noted that 71.4% of strains showed cefiderocol MICs of 1–4 mg/L, with a peak of 0.25 mg/L. IMP-producing *P. aeruginosa* strains tended to have relatively higher cefiderocol MIC values (range 0.12–4 mg/L; MIC_{90} 4 mg/L) than VIM-producing strains (range ≤0.06 to 4 mg/L; MIC_{90} 1 mg/L) (Figure 1). Strains producing VIM-2 and VIM-4 tended to have lower MICs (MIC_{90} values against VIM-2- and VIM-4-producing strains were both 1 mg/L) than strains producing other MBL variants (MIC_{90} values against IMP-7-producing strains and VIM-1-producing strains were 4 and 2 mg/L, respectively). Although only two NDM-producing strains were isolated, cefiderocol showed activity against these two strains, with MICs of 2 and 4 mg/L (Table S2).

For *A. baumannii* complex, 60.0% of MBL-producing strains showed MIC values ≤4 mg/L, which is the CLSI susceptibility breakpoint of cefiderocol, and 44.0% of MBL-producing strains showed MIC values ≤2 mg/L, which is the EUCAST pharmacokinetic-pharmacodynamic (PK-PD) susceptibility breakpoint of cefiderocol.[13,14] It should be noted that 72.0% of strains showed cefiderocol MICs of 1–8 mg/L, and the MIC value with the highest distribution number of strains was 8 mg/L. Of the 10 cefiderocol-non-susceptible strains, 8 had an MIC of 8 mg/L (CLSI: intermediate) whereas the remaining 2 were resistant. All cefiderocol-non-susceptible strains were NDM-1 producers (Figure 1). IMP- and GIM-producing *A. baumannii* complex strains showed lower MIC values (≤2 and ≤0.5 mg/L, respectively) compared with NDM-producing strains (range 0.5 to >64 mg/L), although the number of isolated IMP- and GIM-producing strains was small so it cannot be judged that there is a clear trend.

Cumulative percentage MIC distributions were plotted to compare the activity of cefiderocol and comparator agents against different types of MBL-producing strains (Figures 2–4). The MICs of cefiderocol were more distributed in the lower values, compared with other β-lactams and β-lactam/β-lactamase inhibitor

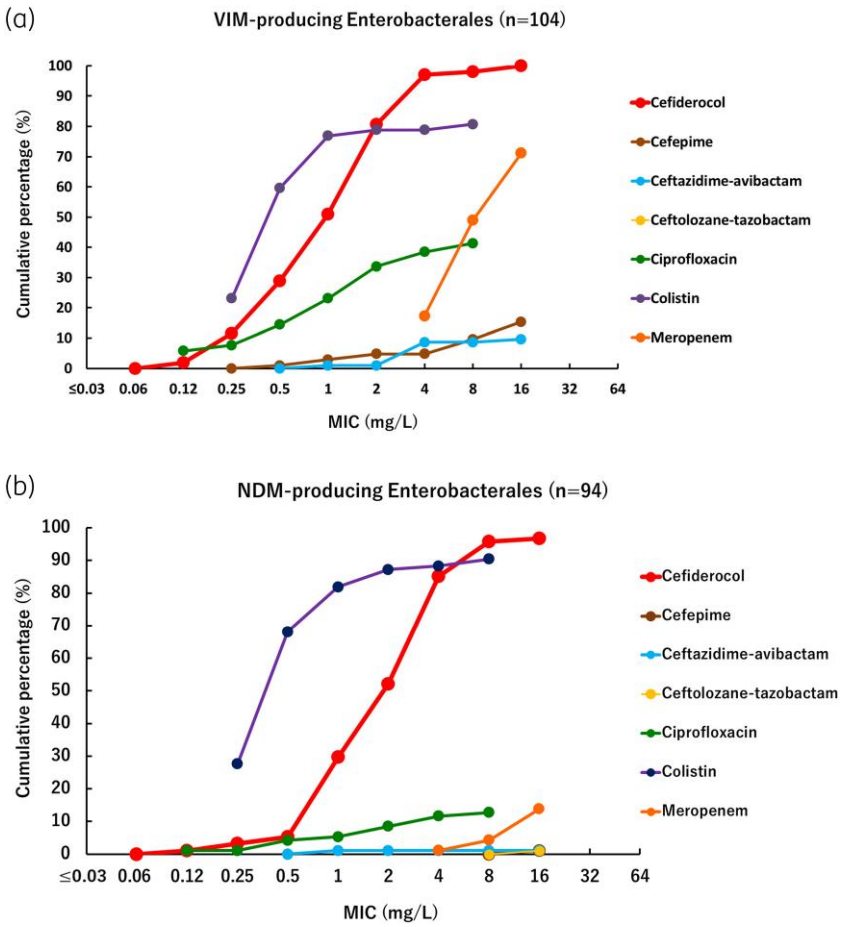

Figure 2. Cumulative percentage MIC distributions of cefiderocol and comparator agents against MBL-producing Enterobacterales strains. (a) VIM-producing Enterobacterales ($n = 104$). Data for strains above the upper end of the MIC measurement range are not plotted. Ceftolozane/tazobactam MIC values were >16 mg/L against all strains, so not plotted on graph. In the ciprofloxacin plot, the MIC value of 0.12 mg/L means ≤0.12 mg/L. In the colistin plot, the MIC value of 0.25 mg/L means ≤0.25 mg/L. VIM-producing Enterobacterales were screened among Enterobacterales with meropenem MICs ≥4 mg/L, so meropenem MICs are not plotted below 4 mg/L. (b) NDM-producing Enterobacterales ($n = 94$). Data for strains above the upper end of the MIC measurement range are not plotted. In the ciprofloxacin plot, the MIC value of 0.12 mg/L means ≤0.12 mg/L. In the colistin plot, the MIC value of 0.25 mg/L means ≤0.25 mg/L. NDM-producing Enterobacterales were screened among Enterobacterales with meropenem MICs ≥4 mg/L, so meropenem MICs are not plotted below 4 mg/L.

combinations tested (cefepime, meropenem, ceftazidime/avibactam and ceftolozane/tazobactam) and ciprofloxacin. Colistin was the only other agent that showed relatively good activity against MBL-producing strains, although some Enterobacterales strains demonstrated high MIC values (>2 mg/L). These results confirm that MBL-producing strains are MDR, for which only very few treatment options remain available.

Discussion

Cefiderocol is a parenteral siderophore cephalosporin that has a catechol moiety and behaves like a siderophore by chelating ferric iron, so it is efficiently taken up into the intracellular space of bacteria.[15] Cefiderocol is also characterized by its stability against a variety of β-lactamases, including MBLs.[7–9,16] This report describes the analysis of *in vitro* activity of cefiderocol against clinical isolates of MBL-producing Gram-negative bacteria collected in North America and European countries between 2014 and 2019 in SIDERO-WT surveillance studies (2014–2019).

MBLs are categorized into Ambler's class B and require Zn^{2+} metal as a cofactor.[3] MBL-producing strains have spread globally and can inactivate most commonly used β-lactam antibiotics, including carbapenems, as well as β-lactam/serine-type β-lactamase inhibitor combinations, such as ceftazidime/avibactam and ceftolozane/tazobactam.[1–3,17–20] The polymyxin antibiotics (colistin and polymyxin B) remain active against MBL-producing strains, with 92.6% of MBL-producing Enterobacterales reported as susceptible to colistin using the EUCAST breakpoint (MIC ≤2 mg/L).[21] In the analysis we conducted here, only 82.0% of the MBL-producing Enterobacterales had a colistin MIC ≤2 mg/L. In addition, although polymyxin antibiotics can still be used as a therapeutic agent for infections caused by MBL-producing strains, there is grave concern about the development of nephrotoxicity, necessitating the need for safer and better agents to combat MBL-producing bacteria.[22]

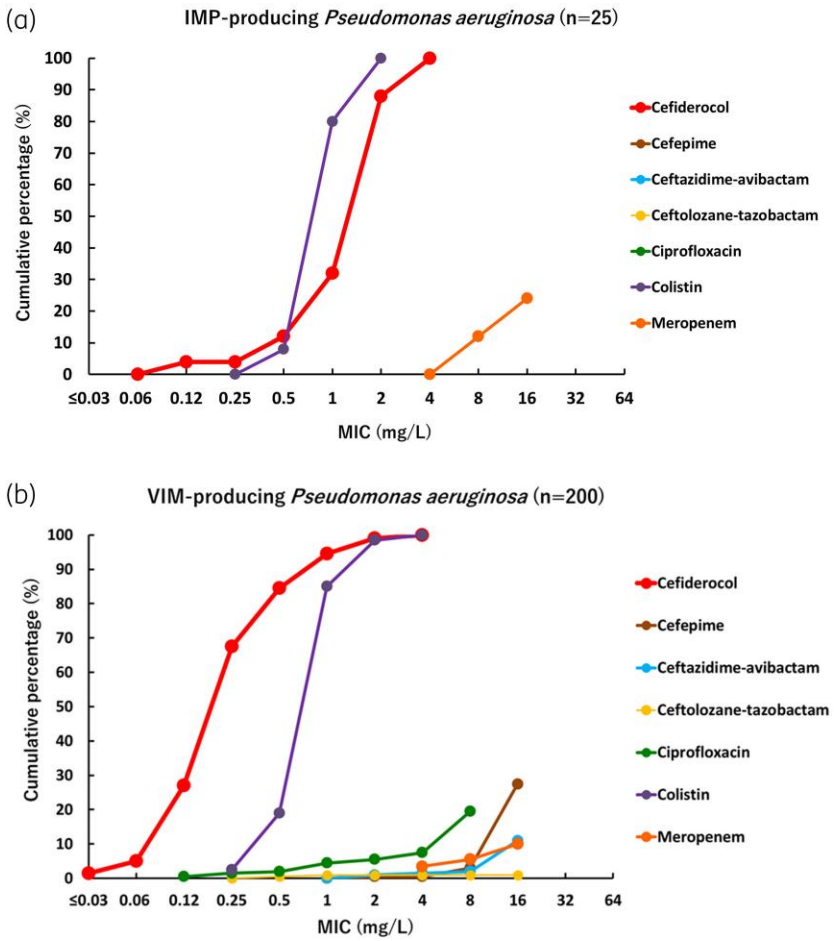

Figure 3. Cumulative percentage MIC distributions of cefiderocol and comparator agents against MBL-producing *P. aeruginosa* strains. (a) IMP-producing *P. aeruginosa* ($n = 25$). Data for strains above the upper end of the MIC measurement range are not plotted. Cefepime MIC values were >16 mg/L against all strains, so not plotted on graph. Ceftazidime/avibactam MIC values were >16 mg/L against all strains, so not plotted on graph. Ceftolozane/tazobactam MIC values were >16 mg/L against all strains, so not plotted on graph. Ciprofloxacin MIC values were >8 mg/L against all strains, so not plotted on graph. In the colistin plot, the MIC value of 0.25 mg/L means ≤0.25 mg/L. IMP-producing *P. aeruginosa* were screened among *P. aeruginosa* with meropenem MICs ≥4 mg/L, so meropenem MICs are not plotted below 4 mg/L. (b) VIM-producing *P. aeruginosa* ($n = 200$). Data for strains above the upper end of the MIC measurement range are not plotted. In the ciprofloxacin plot, the MIC value of 0.12 mg/L means ≤0.12 mg/L. In the colistin plot, the MIC value of 0.25 mg/L means ≤0.25 mg/L. VIM-producing *P. aeruginosa* were screened among *P. aeruginosa* with meropenem MICs ≥4 mg/L, so meropenem MICs are not plotted below 4 mg/L.

In our analysis 100% or 97.4% of MBL-producing *P. aeruginosa* were susceptible to cefiderocol when using CLSI (≤4 mg/L) or EUCAST (≤2 mg/L) breakpoints, respectively, confirming high susceptibility for cefiderocol against clinical MBL-producing isolates of this species. Activity against MBL-producing clinical isolates of Enterobacterales was lower, with susceptibility at 91.5% or 67.5%, using the CLSI or EUCAST breakpoints, respectively. The large difference in susceptibility percentages using EUCAST and CLSI breakpoints is the result of the high percentage of strains with MIC values of 4 mg/L among MBL-producing Enterobacterales (Figure 1). For MBL-producing *A. baumannii* complex, 60.0% or 44.0% of MBL-producing strains were susceptible to cefiderocol using CLSI or EUCAST PK-PD breakpoints, respectively. The lower susceptibility percentages for Enterobacterales and *A. baumannii* complex compared with *P. aeruginosa* may be due to the high ratio of NDM-producing strains to MBL-producing strains in those species. Cefiderocol showed relatively higher MIC values against a subset of NDM-producing strains compared with other subsets of MBL-producing strains. For example, MIC_{90} values of cefiderocol against VIM-producing and NDM-producing Enterobacterales were 4 and 8 mg/L, respectively (Figure 2), and the MIC values of IMP- and GIM-producing *A. baumannii* complex strains were much lower (≤2 mg/L; Figure 1) compared with the NDM-producing isolates ($MIC_{90} = 8$ mg/L; Figure 2b) although only two of each were collected. It has been previously reported that some NDM-producing strains are highly resistant to cefiderocol, and the results of this analysis are consistent with previous reports.[23–25] Considering that the MIC_{90} values of cefiderocol against all Enterobacterales, *P. aeruginosa* and *A.*

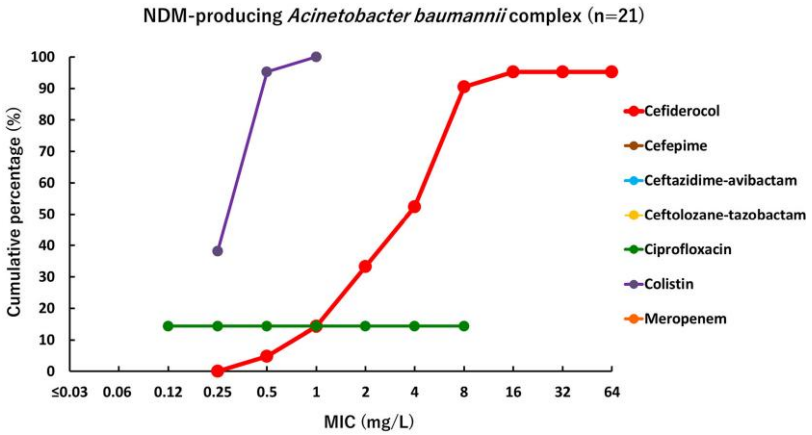

Figure 4. Cumulative percentage MIC distributions of cefiderocol and comparator agents against MBL-producing *A. baumannii* complex strains. Data for strains above the upper end of the MIC measurement range are not plotted. Cefepime MIC values were >16 mg/L against all strains, so not plotted on graph. Ceftazidime/avibactam MIC values were >16 mg/L against all strains, so not plotted on graph. Ceftolozane/tazobactam MIC values were >16 mg/L against all strains, so not plotted on graph. In the ciprofloxacin plot, the MIC value of 0.12 mg/L means ≤0.12 mg/L. In the colistin plot, the MIC value of 0.25 mg/L means ≤0.25 mg/L. NDM-producing *A. baumannii* complex were screened among *A. baumannii* complex with meropenem MICs ≥4 mg/L and meropenem MIC values were >16 mg/L against all strains, so not plotted on graph.

baumannii complex strains isolated in SIDERO-WT studies were 1, 0.5 and 1 mg/L, respectively, MBL-producing strains, and NDM-producing isolates in particular, showed higher cefiderocol MIC values.[10] NDM-5-producing *E. coli* isolated in China have been reported to exhibit high resistance to cefiderocol, though these NDM-5 producers also had a four-amino acid insertion into penicillin-binding protein 3 (PBP3) and mutations in the siderophore receptor gene *cirA*.[26]

The largest MBL-producing subset in this analysis was VIM-producing *P. aeruginosa* ($n = 200$), which were detected in all countries except Canada and the Czech Republic (Tables 1 and 3). Our analysis revealed that more than half (106/200) of the VIM-producing *P. aeruginosa* were isolated in Russia and all of them were VIM-2-producing strains (data not shown). In Russia, VIM-2-producing ST235 *P. aeruginosa* has been reported to spread rapidly, and according to a report by Edelstein *et al.*,[27] 96.5% of MBL-positive *P. aeruginosa* strains isolated in Russia between 2002 and 2010 were ST235, and 99.6% of them were VIM-2-producing strains. Cefiderocol showed high activity against VIM-producing *P. aeruginosa*, regardless of VIM variants, and showed MIC values ≤4 mg/L against all VIM-producing *P. aeruginosa* strains. Interestingly, 84.0% (21/25) of IMP-producing *P. aeruginosa* were isolated in the Czech Republic (Table 3). All of them were IMP-7-producing strains (data not shown). In another surveillance study of *P. aeruginosa* strains isolated in the Czech Republic in 2015, among 136 carbapenemase-producing *P. aeruginosa* strains, 117 IMP-producing strains [IMP-7 ($n = 116$) and IMP-1 ($n = 1$)] were found. One hundred and fifteen of the 116 IMP-7-producing strains were ST357, which was the most dominant ST among carbapenemase-producing *P. aeruginosa*.[28]

Although there are still few reports on the use of cefiderocol for MBL-producing strains in clinical practice, in the Phase 3 studies of cefiderocol (CREDIBLE-CR and APEKS-NP), there were multiple cases of use in patients infected with MBL-producing strains, and a higher clinical cure rate was observed in the cefiderocol group than in the best available therapy group and high-dose meropenem group.[29] The most frequently isolated MBL in CREDIBLE-CR and APEKS-NP was NDM (15 NDM-1 and 1 NDM-5), with cefiderocol MICs of 4 mg/L reported in 9 of 22 cases.[29]

These clinical data and non-clinical data obtained by our analysis suggest that cefiderocol has potential for the treatment of infections caused by MBL-producing strains.

Acknowledgements

We thank all members of Shionogi & Co., Ltd, Shionogi TechnoAdvance Research & Co., Ltd and IHMA Inc. who were involved in obtaining the data.

Funding

This study was supported by internal funding from Shionogi & Co., Ltd.

Transparency declarations

All authors have no declarations other than those provided below. M.T. and Y.Y. report being employed by and owning stock in Shionogi & Co., Ltd. M.G.W., M.A.H. and D.F.S. are employees of IHMA Inc.

Supplementary data

Tables S1–S4 are available as Supplementary data at *JAC* Online.

References

1 Nordmann P, Naas T, Poirel L. Global spread of carbapenemase-producing Enterobacteriaceae. *Emerg Infect Dis* 2011; **17**: 1791–8. https://doi.org/10.3201/eid1710.110655

2 Mojica MF, Rossi MA, Vila AJ *et al.* The urgent need for metallo-β-lactamase inhibitors: an unattended global threat. *Lancet Infect Dis* 2022; **22**: e28–34. https://doi.org/10.1016/S1473-3099(20)30868-9

3 Boyd SE, Livermore DM, Hooper DC *et al*. Metallo-β-lactamases: structure, function, epidemiology, treatment options, and the development pipeline. *Antimicrob Agents Chemother* 2020; **64**: e00397-20. https://doi.org/10.1128/AAC.00397-20

4 Yahav D, Giske CG, Grāmatniece A *et al*. New β-lactam-β-lactamase inhibitor combinations. *Clin Microbiol Rev* 2020; **34**: e00115-20. https://doi.org/10.1128/CMR.00115-20

5 Shionogi Inc. *Fetroja (cefiderocol) for injection, for intravenous use. Prescribing information*. Shionogi Inc., 2019.

6 Shionogi BV. *Fetcroja (cefiderocol). 1 g powder for concentrate for solution for infusion. Summary of product characteristics*. Shionogi BV, 2020.

7 Ito-Horiyama T, Ishii Y, Ito A *et al*. Stability of novel siderophore cephalosporin S-649266 against clinically relevant carbapenemases. *Antimicrob Agents Chemother* 2016; **60**: 4384–6. https://doi.org/10.1128/AAC.03098-15

8 Poirel L, Kieffer N, Nordmann P. Stability of cefiderocol against clinically significant broad-spectrum oxacillinases. *Int J Antimicrob Agents* 2018; **52**: 866–7. https://doi.org/10.1016/j.ijantimicag.2018.11.005

9 Zhanel GG, Golden AR, Zelenitsky S *et al*. Cefiderocol: a siderophore cephalosporin with activity against carbapenem-resistant and multidrug-resistant gram-negative bacilli. *Drugs* 2019; **79**: 271–89. https://doi.org/10.1007/s40265-019-1055-2

10 Karlowsky JA, Hackel MA, Takemura M *et al*. *In vitro* susceptibility of gram-negative pathogens to cefiderocol in five consecutive annual multinational SIDERO-WT surveillance studies, 2014 to 2019. *Antimicrob Agents Chemother* 2022; **66**: e0199021. https://doi.org/10.1128/AAC.01990-21

11 CLSI. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically—Eleventh Edition: M07*. 2018.

12 Wise MG, Karlowsky JA, Hackel MA *et al*. *In vitro* activity of cefiderocol against meropenem-nonsusceptible gram-negative bacilli with defined β-lactamase carriage: SIDERO-WT surveillance studies, 2014–2019. *Microb Drug Resist* 2023. https://doi.org/10.1089/mdr.2022.0279

13 CLSI. *Performance Standards for Antimicrobial Susceptibility Testing—Thirty-Second Edition: M100*. 2022.

14 The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters, version 12.0, 2022.

15 Sato T, Yamawaki K. Cefiderocol: discovery, chemistry, and in vivo profiles of a novel siderophore cephalosporin. *Clin Infect Dis* 2019; **69**: S538–43. https://doi.org/10.1093/cid/ciz826

16 Yamano Y. In vitro activity of cefiderocol against a broad range of clinically important gram-negative bacteria. *Clin Infect Dis* 2019; **69**: S544–51. https://doi.org/10.1093/cid/ciz827

17 Tan X, Kim HS, Baugh K *et al*. Therapeutic options for metallo-β-lactamase-producing enterobacterales. *Infect Drug Resist* 2021; **14**: 125–42. https://doi.org/10.2147/IDR.S246174

18 Yoon EJ, Jeong SH. Mobile carbapenemase genes in *Pseudomonas aeruginosa*. *Front Microbiol* 2021; **12**: 614058. https://doi.org/10.3389/fmicb.2021.614058

19 Hirsch EB, Brigman HV, Zucchi PC *et al*. Ceftolozane-tazobactam and ceftazidime-avibactam activity against β-lactam-resistant *Pseudomonas aeruginosa* and extended-spectrum β-lactamase-producing enterobacterales clinical isolates from U.S. medical centres. *J Glob Antimicrob Resist* 2020; **22**: 689–94. https://doi.org/10.1016/j.jgar.2020.04.017

20 Abboud MI, Damblon C, Brem J *et al*. Interaction of avibactam with class B metallo-β-lactamases. *Antimicrob Agents Chemother* 2016; **60**: 5655–62. https://doi.org/10.1128/AAC.00897-16

21 Bradford PA, Kazmierczak KM, Biedenbach DJ *et al*. Correlation of β-lactamase production and colistin resistance among Enterobacteriaceae isolates from a global surveillance program. *Antimicrob Agents Chemother* 2015; **60**: 1385–92. https://doi.org/10.1128/AAC.01870-15

22 Javan AO, Shokouhi S, Sahraei Z. A review on colistin nephrotoxicity. *Eur J Clin Pharmacol* 2015; **71**: 801–10. https://doi.org/10.1007/s00228-015-1865-4

23 Poirel L, de la Rosa JM O, Sakaoglu Z *et al*. NDM-35-producing ST167 *Escherichia coli* highly resistant to β-lactams including cefiderocol. *Antimicrob Agents Chemother* 2022; **66**: e0031122. https://doi.org/10.1128/aac.00311-22

24 Coppi M, Antonelli A, Niccolai C *et al*. Nosocomial outbreak by NDM-1-producing *Klebsiella pneumoniae* highly resistant to cefiderocol, Florence, Italy, August 2021 to June 2022. *Euro Surveill* 2022; **27**: 2200795. https://doi.org/10.2807/1560-7917.ES.2022.27.43.2200795

25 Mushtaq S, Sadouki Z, Vickers A *et al*. *In vitro* activity of cefiderocol, a siderophore cephalosporin, against multidrug-resistant gram-negative bacteria. *Antimicrob Agents Chemother* 2020; **64**: e01582-20. https://doi.org/10.1128/AAC.01582-20

26 Wang Q, Jin L, Sun S *et al*. Occurrence of high levels of cefiderocol resistance in carbapenem-resistant *Escherichia coli* before its approval in China: a report from China CRE-network. *Microbiol Spectr* 2022; **10**: e0267021.

27 Edelstein MV, Skleenova EN, Shevchenko OV *et al*. Spread of extensively resistant VIM-2-positive ST235 *Pseudomonas aeruginosa* in Belarus, Kazakhstan, and Russia: a longitudinal epidemiological and clinical study. *Lancet Infect Dis* 2013; **13**: 867–76. https://doi.org/10.1016/S1473-3099(13)70168-3

28 Papagiannitsis CC, Medvecky M, Chudejova K *et al*. Molecular characterization of carbapenemase-producing *Pseudomonas aeruginosa* of Czech origin and evidence for clonal spread of extensively resistant sequence type 357 expressing IMP-7 metallo-β-lactamase. *Antimicrob Agents Chemother* 2017; **61**: e01811-17. https://doi.org/10.1128/AAC.01811-17

29 Timsit JF, Paul M, Shields RK *et al*. Cefiderocol for the treatment of infections due to metallo-B-lactamase-producing pathogens in the CREDIBLE-CR and APEKS-NP phase 3 randomized studies. *Clin Infect Dis* 2022; **75**: 1081–4. https://doi.org/10.1093/cid/ciac078