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In Vitro Activity of Cefiderocol against IMP-Producing Enterobacterales Isolated in Japan

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INTRODUCTION

- Beta-lactam resistance is a major worldwide concern. Metallo-β-lactamases (MBLs) are a group of enzymes that can inactivate most commonly used β-lactam antibiotics including carbapenems and are not inhibited by commercially available diazabicyclooctane β-lactamase inhibitors such as avibactam and relebactam. Therefore, treating infections caused by MBL producing strains is difficult.
- Imipenemase (IMP) type MBLs are a family of acquired carbapenemases frequently found in non-fermenters such as *Pseudomonas aeruginosa* and rarely detected in Enterobacterales in the US and Europe, however, it has been detected and become a major therapeutic concern in clinical settings mainly in India and East Asia including Japan [1,2]. Detecting IMP enzymes by current diagnostic tests is unsatisfactory, and it could be suggested its prevalence is under-reported [3]. Intriguingly, unlike typical IMP type carbapenemase such as IMP-1, IMP-6 causes imipenem (IPM)-susceptible but meropenem (MEM)-resistant phenotype, which is concerned to be diagnosed as non-carbapenemase-producing pathogenic infections by antimicrobial susceptibility test using only IPM [4].
- Cefiderocol (CFDC) is an injectable siderophore cephalosporin antibiotic approved in the US and Europe with its potent activity against aerobic Gram-negative bacterial pathogens [5,6].
- We have revealed that CFDC shows potent activities against a wide variety of carbapenem resistant strains including both serine- and metallo-type carbapenemase-producers isolated from North America and Europe in 5 consecutive annual surveillance study [7-10]. However, there were no IMP-type carbapenemase-producing Enterobacterales in those studies.
- We evaluated *in vitro* activity of CFDC and comparator agents against IMP-producing Enterobacterales isolated in Japan.

MATERIALS AND METHODS

Bacterial strains

- A total of 150 IMP-producing strains consisting of 48 *Escherichia coli*, 34 *Klebsiella pneumoniae*, 29 *Klebsiella oxytoca*, 21 *Enterobacter cloacae*, 7 *Citrobacter freundii*, 7 *Serratia marcescens*, 2 *Providencia rettgeri*, 1 *Klebsiella aerogenes*, and 1 *Morganella morganii* were tested for antimicrobial susceptibility.
- The tested strains were provided from a tertiary hospital in Osaka (n=92), Study of Bacterial Resistance Kinki Region of Japan (SBRK, n=36), and Nagoya University (n=16). IMP-producing strains found in our nation-wide surveillance study (n=6) were also used as test strains.
- The 92 strains from a tertiary hospital in Osaka were identified to produce IMP-types by allele-specific PCR in our laboratory among 100 MBL-producing strains, isolated between 2010 and 2014, provided from the hospital [11]. The 36 IMP-producing strains from SBRK were selected from 139 IMP-producers determined by sequencing among their 142 carbapenemase-producing Enterobacterales (CPE) stocks isolated in Kinki-region between 2000 and 2018. The 16 strains from Nagoya University were also a part of their collection isolated in nation-wide Japan between 2007 and 2012. Among their 45 MBL-producing strains, 40 strains were found to be IMP-producing CPE by PCR in their laboratory. The provided information about IMP-type of each strain and clinical specimen where each strain isolated from were indicated in Table 1 if available.
- Our nation-wide surveillance studies conducted in 2014, 2016, and 2018 found 7 CPEs from 2,515 Enterobacterales strains (0.28%) isolated in 16 medical institutions in Japan followed by carbapenem MIC determination, and carbapenemase producibility detection using modified carbapenem inactivation method (mCIM) [12]. Carbapenemase genes in the CPEs were detected by PCR and identified by sequencing, and 1 NDM-1 producer (in 2018), 2 IMP-1 producers (in 2014), and 4 IMP-6 producers (two each in 2014 and 2018) were found. These 6 IMP-producers were used in this study.

Susceptibility testing

- The minimum inhibitory concentrations (MICs) were determined for CFDC, ceftazidime-avibactam (CZA), ceftolozane-tazobactam (C/T), imipenem-relebactam (I-R), MEM, and amikacin (AMK) by broth microdilution according to CLSI guidelines. CFDC was tested in iron-depleted cation-adjusted Mueller-Hinton broth.
- MIC_{50}, MIC_{90}, and MIC range of CFDC and comparator agents were calculated. Susceptibility rate was determined by using CLSI breakpoints [12].

MATERIALS AND METHODS (continued)

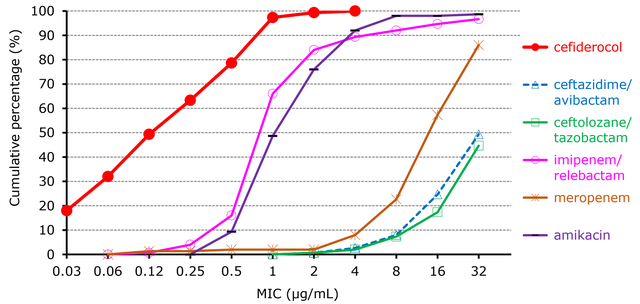
Table 1 Number of IMP-producing Enterobacterales strains isolated in Japan (N = 150)

	Type of specimen					Type of IMP			
species	Urine	Blood	Respiratory	Others	NA	IMP-1	IMP-6	IMP-11	IMP-type (not specified)
E. coli	3	0	0	28	17	2	46	0	0
K. pneumoniae	4	1	6	19	4	1	30	0	3
K. oxytoca	4	0	1	19	5	5	24	0	0
K. aerogenes	0	0	0	0	1	0	1	0	0
C. freundii	1	0	1	3	2	3	4	0	0
E. cloacae	4	1	2	12	2	5	14	0	2
M. morganii	0	0	0	0	1	1	0	0	0
P. rettgeri	0	0	0	0	2	2	0	0	0
S. marcescens	0	0	1	0	6	5	1	1	0

Others includes fecal, gastric, abdominal, drain, pus samples.
NA (not available) means no information provided.

RESULTS

Figure 1 Cumulative susceptibility curves of cefiderocol and comparator agents against IMP-producing Enterobacterales strains isolated in Japan (N = 150)



RESULTS (continued)

- Against 150 IMP-type MBL-producing Enterobacterales isolates, MIC_{50} and MIC_{90} of CFDC were 0.25 μg/mL and 1 μg/mL, respectively. MICs of CFDC for all tested strains ranged from ≤ 0.03 to 4 μg/mL, which showed all strains were susceptible to CFDC based on the CLSI breakpoint (≤ 4 μg/mL) (Table 2, Figure 1). On the other hand, MIC_{90}s of CZA, C/T, I-R, MEM, and AMK were > 32/4 μg/mL, > 32/4 μg/mL, 8/4 μg/mL, > 32 μg/mL, and 4 μg/mL, respectively. The susceptibilities were 98.0% for AMK, 66.0% for I-R, and <10% for CZA, C/T and MEM.
- Comparing IMP-1-producers (n=24) and IMP-6-producers (n=120), the susceptibility rates of CFDC and comparator agents were similar between the two types, except that I-R showed a large difference of 4.2% for IMP-1 and 81.7% for IMP-6 (Tables 2).

Table 2 *In vitro* susceptibility of cefiderocol and comparators to IMP-producing Enterobacterales isolated in Japan (N = 150)

	MIC distributions (μg/mL)												MIC (μg/mL)						
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}	MIC range			%S	%R
IMP-producers (N=150)																			
cefiderocol	27	21	26	21	23	28	3	1					0.25	1	≤0.03	-	4	100	0
ceftazidime/avibactam							1	3	8	25	37	76	>32/4	>32/4	2/4	-	>32/4	8.0	92.0
ceftolozane/tazobactam							1	2	8	15	41	83	>32/4	>32/4	2/4	-	>32/4	0.7	98.0
imipenem/relebactam			1	5	18	75	27	8	4	4	3	5	1/4	8/4	0.12/4	-	>32/4	66.0	16.0
meropenem			2		1			9	22	52	43	21	16	>32	0.12	-	>32	2.0	98.0
amikacin					14	59	41	24	9		1	2	2	4	0.5	-	>32	98.0	1.3
IMP-1-producers (N=24)																			
cefiderocol	3	3		4	6	5	2	1					0.5	2	≤0.03	-	4	100	0
ceftazidime/avibactam								1	1	1		21	>32/4	>32/4	4/4	-	>32/4	8.3	91.7
ceftolozane/tazobactam										1	1	22	>32/4	>32/4	16/4	-	>32/4	0	100
imipenem/relebactam					1		6	4	4	2	3	4	8/4	>32/4	0.5/4	-	>32/4	4.2	70.8
meropenem			1					5	4	5	2	7	>32	>32	0.12	-	>32	4.2	95.8
amikacin					2	8	7	4	1			2	2	8	0.5	-	>32	91.7	8.3
IMP-6-producers (N=120)																			
cefiderocol	24	18	24	16	16	21	1						0.12	1	≤0.03	-	2	100	0
ceftazidime/avibactam							1	2	7	24	37	49	32/4	>32/4	2/4	-	>32/4	8.3	91.7
ceftolozane/tazobactam							1	2	8	14	40	55	32/4	>32/4	2/4	-	>32/4	0.8	97.5
imipenem/relebactam			1	5	17	75	19	2		1			1	2	0.12/4	-	16/4	81.7	2.5
meropenem			1		1			3	15	46	41	13	16	>32	0.12	-	>32	1.7	98.3
amikacin					10	48	34	20	8				2	4	0.5	-	8	100	0

Percent susceptible (%S) and resistance (%R) are based on the CLSI criteria; cefiderocol, S ≤ 4, R ≥ 16 μg/mL; ceftazidime/avibactam, S ≤ 8/4, R ≥ 16/4 μg/mL; ceftolozane/tazobactam, S ≤ 2/4, R ≥ 8/4 μg/mL; imipenem/relebactam, S ≤ 1/4, R ≥ 4/4 μg/mL; meropenem, S ≤ 1, R ≥ 4 μg/mL; amikacin, S ≤ 16, R ≥ 64 μg/mL.

CONCLUSIONS

- CFDC had potent *in vitro* activity against IMP-producing Enterobacterales collected from Japan, indicating CFDC has high potential for treating infections caused by these difficult-to-treat strains.

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REFERENCES

1. Logan, LK. et al., J Infect Dis. 2017 Feb 15;215(suppl 1):S28-S36.
2. Indian Council of Medical Research. Annual report January 2021 to December 2021 - Antimicrobial Resistance Research and Surveillance Network. AMR surveillance Network, Indian Council of Medical Research, 2021.
3. Lowe, CF. et al., J Clin Microbiol. 2020;58(4):e01094-19.
4. Shigemoto, N. et al., Diagn Microbiol Infect Dis. 2012;72:109-112.
5. Fetroja® (cefiderocol) injection for intravenous use. Prescribing Information. Shionogi Inc., Florham Park, NJ, USA; 2019.
6. Fectroja® (cefiderocol). 1 g powder for concentrate for solution for infusion. Summary of Product Characteristics. Shionogi B.V., Kingsfordweg 151, 1043 GR, Amsterdam, Netherlands. 2020.
7. Hackel, MA. et al., Antimicrob Agents Chemother. 2017;61(9):e00093-17.
8. Karlowsky, JA. et al., Int J Antimicrob Agents. 2019;53(4):456-466.
9. Kohira, N. et al., J Glob Antimicrob Res. 2020;22:738-741.
10. Karlowsky, JA. et al., Antimicrob Agents Chemother. 2022;66(2):e01990-21.
11. Kayama, S. et al., J Microbiol Methods. 2012;88:182-184.
12. CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 32nd ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2022.