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In Vitro Activity of Cefiderocol Against Metallo-β-Lactamase-Producing Gram-Negative Bacteria Collected in North America and Europe Between 2014 and 2017: SIDERO-WT-2014–2016 Studies

Miki Takemura[1], Krystyna M. Kazmierczak[2], Meredith Hackel[2], Daniel F Sahm[2], Roger Echols[3], Yoshinori Yamano[1]

[1] Shionogi & Co., Ltd., Osaka, Japan, [2] International Health Management Associates, Inc. Schaumburg, IL, USA, [3] Infectious Disease Drug Development Consulting LLC, Easton, CT, USA

Contact information:
Miki Takemura
3-1-1, Futaba-cho, Toyonaka,
Osaka, 561-0825, Japan
Phone: +81-6-6331-8081
Fax: +81-6-6331-8612
Email: miki.takemura@shionogi.co.jp

Abstract (revised)

Background: Metallo-β-lactamases (MBLs; eg, NDM, VIM, and IMP) can inactivate most commonly-used β-lactam antibiotics, including carbapenems; therefore, infections caused by MBL-producers are difficult to treat. Cefiderocol (CFDC) is a siderophore cephalosporin antibiotic approved in the USA in 2019 and in the EU in 2020, with potent activity against carbapenem-resistant Gram-negative bacteria (GNB), including both serine- and metallo-carbapenemase-positive strains. We evaluated the *in vitro* activity of CFDC and comparator agents against MBL-producing strains of GNB collected from North America and Europe in the 3 consecutive years of surveillance studies (SIDERO-WT-2014, -2015, and -2016).

Methods: Susceptibility testing was performed for CFDC, ceftazidime-avibactam (CZA), ceftolozane-tazobactam (C/T), meropenem (MEM), cefepime (FEP), ciprofloxacin (CIP), and colistin (CST) by broth microdilution according to the CLSI guidance. CFDC was tested in iron-depleted medium. A total of 3691 Gram-negative bacteria consisting of MEM-nonsusceptible *Acinetobacter baumannii* complex, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, other *Klebsiella* spp., *Serratia marcescens*, *Enterobacter* spp., *Citrobacter* spp., and *Escherichia coli* collected in the 3 surveillance studies were molecularly characterized. A total of 275 MBL-producing strains consisting of 120 Enterobacterales (45 NDM; 75 VIM), 5 NDM-producing *A. baumannii*, and 150 *P. aeruginosa* (134 VIM; 16 IMP), identified as a result of molecular characterization were used for the analysis.

Results: The minimum inhibitory concentration (MIC) range and MIC_{90} for CFDC and comparators for each MBL-producing organism group are shown in the Table. Against NDM-producing Enterobacterales, of which 42% and 33% were isolated in Turkey and Russia, respectively, CFDC inhibited the growth of 84% of isolates tested at ≤4 μg/mL. CFDC MIC_{90} was 4 μg/mL for VIM-producing Enterobacterales (41% and 31% isolated in Greece and Italy, respectively), 1 μg/mL for VIM-producing *P. aeruginosa* (50% isolated in Russia), and 4 μg/mL for IMP-producing *P. aeruginosa* (88% isolated in Czech Republic). Other comparators (except for CST) were not active against these MBL-producers.

Conclusion: CFDC inhibited the growth of 100% of the collected MBL-positive GNB at ≤ 8 μg/mL and showed MIC_{90} of 4 μg/mL against all 275 MBL-producers, indicating that CFDC has a high potential for treating infections caused by these difficult-to-treat strains.

Table. MIC range and MIC_{90} (μg/mL) for CFDC and comparators of MBL-producing organisms

	NDM-producing Enterobacterales (N=45)		VIM-producing Enterobacterales (N=75)		NDM-producing *A. baumannii* (N=5)		VIM-producing *P. aeruginosa* (N=134)		IMP-producing *P. aeruginosa* (N=16)	
Compounds	MIC range	MIC_{90}	MIC range	MIC_{90}	MIC range	MIC_{90}	MIC range	MIC_{90}	MIC range	MIC_{90}
CFDC	0.25–8	8	0.12–4	4	1–8	NC	0.008–4	1	0.12–4	4
CZA	1–>64	>64	4–>64	>64	>64	NC	2–>64	>64	>64	>64
C/T	>64	>64	32–>64	>64	>64	NC	0.5–>64	>64	>64	>64
MEM	4–>64	>64	2–>64	64	64–>64	NC	4–>64	>64	8–>64	>64
FEP	32–>64	>64	0.25–>64	>64	>64	NC	8–>64	>64	>64	>64
CST	≤0.25–8	1	≤0.25–>8	>8	≤0.25–0.5	NC	≤0.25–4	2	1–2	2
CIP	2–>8	>8	≤0.12–>8	>8	≤0.12–>8	NC	0.25–>8	>8	>8	>8

NC: MIC_{90} values were not calculated because the number of isolates was <10. IMP: imipenemase metallo-β-lactamase; NDM: New Delhi metallo-β-lactamase; VIM: Verona integron-encoded metallo-β-lactamase.

Introduction

Metallo-β-lactamases (MBLs; eg, NDM, VIM, and IMP) can inactivate most commonly-used β-lactam antibiotics, including carbapenems. Infections caused by MBL-producers are, therefore, difficult to treat. Recently approved β-lactam/β-lactamase inhibitor (BL/BLI) antibiotics do not have activity against metallo-β-lactamases producers.

Cefiderocol (CFDC) is a novel siderophore cephalosporin with activity against a wide variety of Gram-negative bacteria (GNB), including carbapenem-resistant (CR) Enterobacterales and non-fermenters. In the Phase 3 CREDIBLE-CR study, CFDC was effective against serious infections caused by CR pathogens [IDWeek2020 oral presentation #1271].

CFDC has been approved in the USA for the treatment of patients with complicated urinary tract infections (cUTI) and nosocomial pneumonia (HABP/VABP) caused by GNB in 2019-2020 and in Europe for the treatment of infections due to Gram-negative pathogens with limited treatment options in 2020 [1, 2]. We conducted 3-year-consecutive surveillance studies SIDERO-WT-2014–2016 with approximately 30,000 GNB collected in North America and Europe between 2014 and 2017 [3-5]. In this study, we evaluated the *in vitro* activity of CFDC and comparator agents against MBL-producing strains of GNB collected in these three surveillance studies.

Materials and Methods

Test Organisms

- A total of 3691 Gram-negative bacteria consisting of meropenem (MEM)-nonsusceptible *A. baumannii* complex, *P. aeruginosa, K. pneumoniae*, other *Klebsiella* spp., *Serratia marcescens*, *Enterobacter* spp., *Citrobacter* spp., and *Escherichia coli* collected in the 3 surveillance studies, ie, SIDERO-WT-2014 (Year 1: 2014–2015), SIDERO-WT-2015 (Year 2: 2015–2016), and SIDERO-WT-2016 (Year 3: 2016–2017), were molecularly characterized [3-5]. MEM-nonsusceptible strain was defined as MEM MIC ≥ 2 μg/mL for Enterobacterales, ≥ 4 μg/mL for non-fermenters.
- A total of 275 MBL-producing strains consisting of 120 Enterobacterales (45 NDM; 75 VIM), 5 NDM-producing *A. baumannii*, and 150 *P. aeruginosa* (134 VIM; 16 IMP), identified as a result of molecular characterization, were used for the analysis. The geographic source (country) for each isolate was identified to provide an epidemiological profile.

Detection of MBL genes

- Screening for the carriage of genes encoding carbapenemases and sequencing are described by Kazmierczak et al [6]. IMP, VIM, and NDM in *Acinetobacter* spp.; IMP, VIM, and NDM in *P. aeruginosa*; and IMP, VIM, and NDM in Enterobacterales were investigated to identify MBL-producing strains.
- All experiments were conducted at a central laboratory (International Health Management Associates, Inc. in Schaumburg, IL, USA), where the isolates were stored.

Minimum inhibitory concentration (MIC) data

- MIC data reported in the SIDERO-WT studies were used [3-5]. MICs of CFDC, ceftazidime-avibactam (CZA), ceftolozane-tazobactam (C/T), MEM, cefepime (FEP), ciprofloxacin (CIP), and colistin (CST) were determined using the broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. For MIC determination of CFDC, iron-depleted cation-adjusted Mueller–Hinton broth (ID-CAMHB) medium was used.

Results

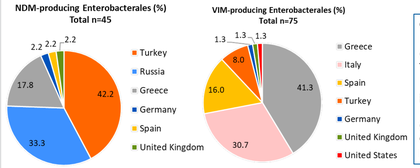
Table 1. Number of isolates of MBL-producing Gram-negative bacteria by species and MBL type

MBL-producing isolates (Total number of isolates)	Number of Isolates		
	NDM	VIM	IMP
Enterobacterales (n=120)	**45**	**75**	**-**
Enterobacter cloacae (n=29)	3	26	-
Escherichia coli (n=2)	1	1	-
Klebsiella pneumoniae (n=64)	41	23	-
Klebsiella aerogenes (n=2)	-	2	-
Klebsiella oxytoca (n=2)	-	2	-
Serratia marcescens (n=10)	-	10	-
Citrobacter freundii (n=10)	-	10	-
Citrobacter amalonaticus (n=1)	-	1	
Non-fermenters (n=155)	**5**	**134**	**16**
Acinetobacter baumannii (n=5)	5	-	-
Pseudomonas aeruginosa (n=150)	-	134	16

Of the 45 Enterobacterales in which NDM was detected, 41 were *K. pneumoniae*. All 5 MBL-producing *A. baumannii* were NDM-producing strains. VIM was detected in various types of Enterobacterales and *P. aeruginosa*. IMP was detected only in *P. aeruginosa*.

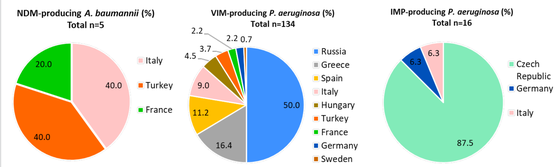
Results

Figure 1. Distribution of MBL-producing Enterobacterales by country



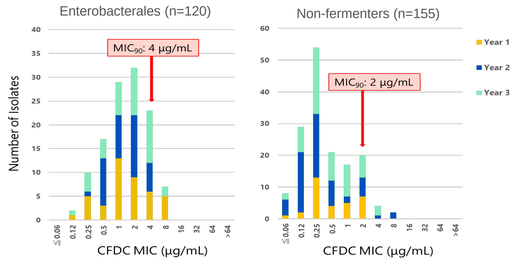
Of the 45 NDM-producing Enterobacterales, 19 (42.2%) were isolated in Turkey and 15 (33.3%) in Russia. Of the 75 VIM-producing Enterobacterales, 31 (41.3%) were isolated in Greece and 23 (30.7%) in Italy.

Figure 2. Distribution of MBL-producing *A. baumannii* and *P. aeruginosa* by country



5 NDM-producing *A. baumannii* were isolated in Italy, Turkey, and France. Of the 134 VIM-producing *P. aeruginosa*, 67 (50.0%) were isolated in Russia and 22 (16.4%) in Greece. Most of the IMP-producing *P. aeruginosa* (14/16: 87.5%) were isolated in the Czech Republic.

Figure 3. CFDC MIC distribution in MBL-producing isolates



・CFDC maintained potent *in vitro* activity against MBL-producing strains isolated in Year 1, 2, and 3 of SIDERO-WT. MIC_{90} of CFDC against MBL-producing Enterobacterales and non-fermenters were 4 and 2 μg/mL, respectively in the data pooled for 3 years of SIDERO-WT data.

・CFDC showed MIC_{90} of 4 μg/mL against total 275 MBL-producers.

Conclusions

- Most of the MBL-producing GNB were isolated mainly in European countries, particularly in Russia and Greece.
- MIC_{90} of CFDC against MBL-producing Enterobacterales and non-fermenters collected in the 3 surveillance studies were 4 and 2 μg/mL, respectively.
- CFDC inhibited the growth of 100% of the isolates of MBL-positive GNB at ≤ 8 μg/mL.
- These results indicate that CFDC has a high potential for treating infections caused by these difficult-to-treat strains.

Table 2. MIC range, MIC_{50}, and MIC_{90} of CFDC and comparators against MBL-producing GNB

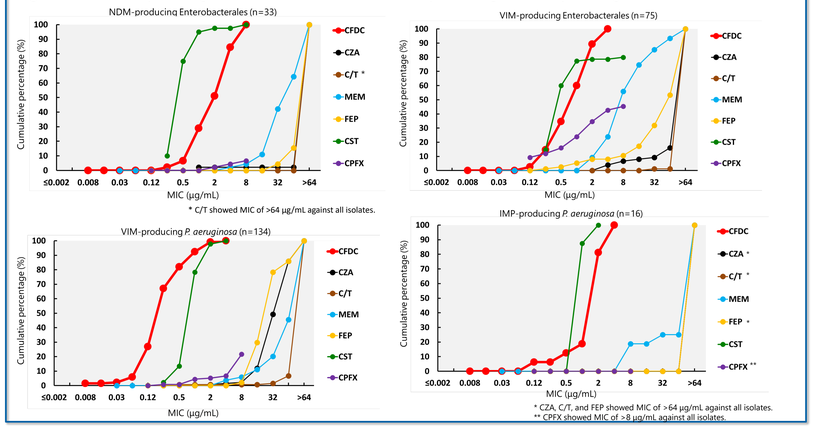
	NDM-producing Enterobacterales (n=45)			VIM-producing Enterobacterales (n=75)		
	MIC range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	MIC range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)
CFDC	0.25-8	2	8	0.12-4	1	4
CZA	1->64	>64	>64	4->64	>64	>64
C/T	>64	>64	>64	32->64	>64	>64
MEM	4->64	64	>64	2->64	8	64
FEP	32->64	>64	>64	0.25->64	64	>64
CST	≤0.25-8	0.5	1	≤0.25->8	0.5	>8
CPFX	2->8	>8	>8	≤0.12->8	>8	>8

Against NDM-producing Enterobacterales, CFDC inhibited the growth of 84% of isolates tested at ≤ 4 μg/mL. CFDC MIC_{90} was 4 μg/mL for VIM-producing Enterobacterales, 1 μg/mL for VIM-producing *P. aeruginosa*, and 4 μg/mL for IMP-producing *P. aeruginosa*.
As expected, the BL/BLI combination antibiotics (CZA, C/T) did not have useful activity against MBL-producing organisms.

	NDM-producing *A. baumannii* (n=5)			VIM-producing *P. aeruginosa* (n= 134)			IMP-producing *P. aeruginosa* (n=16)		
	MIC range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	MIC range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	MIC range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)
CFDC	1-8	NC	NC	0.008-4	0.5	1	0.12-4	2	4
CZA	>64	NC	NC	2->64	64	>64	>64	>64	>64
C/T	>64	NC	NC	0.5->64	>64	>64	>64	>64	>64
MEM	64->64	NC	NC	4->64	>64	>64	8->64	>64	>64
FEP	>64	NC	NC	8->64	32	>64	>64	>64	>64
CST	≤0.25-0.5	NC	NC	≤0.25-4	1	2	1-2	1	2
CPFX	≤0.12->8	NC	NC	0.25->8	>8	>8	>8	>8	>8

NC: MIC_{50} and MIC_{90} values were not calculated because the number of isolates was <10.
IMP: imipenemase metallo-β-lactamase; NDM: New Delhi metallo-β-lactamase; VIM: Verona integron-encoded metallo-β-lactamase.

Figure 4. Cumulative percentage MIC distributions of CFDC and comparators against MBL-producing GNB



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