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Activity of Cefiderocol and Comparator Agents Against Metallo-β-Lactamase Carrying *Acinetobacter baumannii-calcoaceticus* Complex Isolates Collected in the SENTRY Antimicrobial Surveillance Program

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Boudewijn L.M. DeJonge¹, Sean T. Nguyen¹, Joshua M. Maher², Rodrigo E. Mendes², Chris Longshaw³, Hidenori Yamashiro⁴, Yoshinori Yamano⁴

¹Shionogi Inc., Florham Park, New Jersey, USA, ²Element Iowa City (JMI Laboratories), North Liberty, Iowa, USA, ³Shionogi B.V., London, UK, ⁴Shionogi & Co., Ltd., Osaka, Japan

BACKGROUND

- Acinetobacter baumannii-calcoaceticus* species complex (*A. baumannii*) has become highly resistant to multiple antibiotics, especially isolates that carry metallo-β-lactamases (MBLs).
- Cefiderocol is a siderophore-conjugated cephalosporin and one of the few agents with activity against Gram-negative isolates carrying MBLs.
- In this study, the activity of cefiderocol and comparator agents was assessed against MBL-carrying *A. baumannii* collected in the SENTRY Antimicrobial Surveillance Program.

METHODS

- Twenty-nine clinical *A. baumannii* isolates, collected as part of the SENTRY Antimicrobial Surveillance Program between 2001 and 2022, were identified as carrying MBLs (Table 1).
 - Isolates originated from at least three different infection types and from 11 countries.
 - Most isolates carried NDM alleles (n=20), while eight carried IMP alleles and one carried a VIM allele.
- Minimum inhibitory concentrations (MICs) were determined by broth microdilution using Clinical and Laboratory Standards Institute (CLSI) protocols, with cation-adjusted Mueller-Hinton broth (CAMHB) for comparator agents and iron-depleted CAMHB for cefiderocol.
- Susceptibility was assessed according to 2024 CLSI, US Food and Drug Administration (FDA), and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints.

RESULTS

- MIC values for cefiderocol ranged from 0.06 µg/mL to 16 µg/mL, with IMP-carrying isolates showing lower values compared with NDM-carrying isolates (Figure 1).
- 82.8%, 69.0%, and 44.8% of the isolates showed susceptibility to cefiderocol according to CLSI, EUCAST, and FDA breakpoints, respectively, whereas β-lactam comparator agents, including sulbactam-durlobactam, all showed lower susceptibilities (<30%); minocycline and colistin were the only other active agents (Table 2).
- NDM-carrying isolates often co-carried additional β-lactamases, but no correlation between their carriage and cefiderocol MIC value could be delineated, indicating that additional factors, beyond MBL and other β-lactamase carriage, determines the activity of cefiderocol against *A. baumannii* (Table 1).

Table 1. Origin, cefiderocol MIC, and β-lactamase content for clinical *A. baumannii* isolates tested in this study (n=29)

Isolate	Year	Country	Infection	FDC MIC (µg/mL)	Class B (MBL) ^a			Class A ^a	Class C (AmpC) ^{a,b}						Class D ^a						BL per isolate	
					NDM-1	IMP-1	VIM-1	TEM-1	ADC-30	ADC-73	ADC-80	ADC-96	ADC-158	ADC-176	OXA-23	OXA-51 ^b	OXA-58	OXA-66 ^b	OXA-94 ^b	OXA-98 ^b	OXA-336 ^b	
143038	2001	Brazil	BSI	0.5		+			Not tested													1 ^a
143675	2001	Argentina	BSI	0.12		+																1 ^a
173803	2002	Brazil	SSSI	16		+																1 ^a
173804	2002	Brazil	SSSI	0.5		+																1 ^a
173805	2002	Brazil	SSSI	2		+																1 ^a
175139	2002	Brazil	PIHP	0.25		+																1 ^a
175640	2002	Argentina	PIHP	0.06		+																1 ^a
177190	2002	Argentina	BSI	0.5		+																1 ^a
203331	2003	Greece	BSI	16			+															1 ^a
357374	2006	India	BSI	2	+											+						2 ^a
406355	2007	India	PIHP	1	+																	1 ^a
598951	2010	India	PIHP	2	+			+							+	+						4 ^a
602690	2010	India	PIHP	1	+			+								+						3 ^a
602847	2010	India	SSSI	1	+			+							+	+						4 ^a
602862	2010	India	SSSI	0.06	+										+	+						3 ^a
1160843	2020	Germany	PIHP	1	+			+		+					+		+					5
1165688	2020	Belgium	BSI	2	+					+					+		+					4
1187252	2020	USA	SSSI	0.5	+								+				+			+		4
1193938	2021	USA	BSI	16	+				+						+		+					4
1195362	2021	Israel	PIHP	4	+			+		+					+		+					5
1217414	2021	Turkey	PIHP	4	+				+						+		+					4
1222299	2021	Israel	NR	2	+			+		+					+		+					5
1222306	2021	Israel	NR	4	+			+		+					+		+					5
1222346	2021	Israel	NR	1	+						+								+			3
1251040	2022	Czech Republic	SSSI	2	+			+		+					+		+					5
1251312	2022	Romania	PIHP	16	+					+					+						+	4
1261188	2022	Israel	PIHP	4	+			+		+					+		+					5
1261300	2022	Israel	PIHP	2	+			+		+					+		+					5
1261509	2022	Israel	BSI	8	+								+	+					+			4
Total					20	8	1	10	2	9	1	1	1	1	14	5	1	10	2	1	1	

^aβ-lactamases were identified through whole genome sequencing for isolates collected between 2020 and 2022; for earlier isolates, targeted polymerase chain reaction was used but not all isolates were tested with all indicated Class A and D primers ^bIntrinsic β-lactamase gene in *Acinetobacter* spp. **ADC**, *Acinetobacter*-derived cephalosporinase; **AmpC**, chromosomal cephalosporinase; **BL**, β-lactamase; **BSI**, blood stream infection; **FDC**, cefiderocol; **MBL**, metallo-beta-lactamase; **NR**, not reported; **OXA**, oxacillinase; **PIHP**, pneumonia in hospitalized patients; **SSSI**, skin and skin structure infection; **TEM**, Temoneira extended-spectrum β-lactamase; **VIM**, Verona integron-encoded metallo-β-lactamase.

CONCLUSION

- Cefiderocol remained one of the few agents with *in vitro* activity against MBL-carrying *A. baumannii* and should be considered as a component of combination therapy when infections caused by these multidrug-resistant isolates are encountered.

Figure 1. Cefiderocol MIC distribution of metallo-β-lactamase-producing *A. baumannii* isolates from the SENTRY collection (n=29)

Table 2. Antimicrobial activity of cefiderocol and comparator agents tested against metallo-β-lactamase-producing *A. baumannii* isolates from the SENTRY collection (n=29)

Antimicrobial agent	MIC (µg/mL)			CLSI ^a			EUCAST ^a			FDA ^a		
	MIC ₅₀	MIC ₉₀	MIC range	%S	%I	%R	%S	%I	%R	%S	%I	%R
Cefiderocol	2	16	0.06 to 16	82.8	3.4	13.8	69.0 ^b		31.0 ^b	44.8	24.1	31.0
Sulbactam-durlobactam	>32	>32	2 to >32	27.6	0.0	72.4				27.6	0.0	72.4
Ampicillin-sulbactam	>64	>64	4 to >64	10.3	0.0	89.7				10.3	0.0	89.7
Imipenem-relebactam	>16	>16	1 to >16							3.4	0.0	96.6
Meropenem	>32	>32	4 to >32	0.0	3.4	96.6	0.0	3.4	96.6	0.0	3.4	96.6
Imipenem	>8	>8	>8	0.0	0.0	100	0.0	0.0	100	0.0	0.0	100
Ceftazidime	>32	>32	>32	0.0	0.0	100				0.0	0.0	100
Minocycline	2	32	0.12 to 32	82.8	0.0	17.2				82.8	0.0	17.2
Colistin	0.25	0.5	0.12 to 8		96.6	3.4	96.6		3.4			

^aCriteria as published by CLSI (2024), EUCAST (2024), and US FDA (2024).
^bThere are insufficient clinical data to determine a clinical breakpoint, but isolates with MIC values >2 µg/mL will likely be resistant.
FDA, United States Food and Drug Administration; **CLSI**, Clinical and Laboratory Standards Institute; **EUCAST**, European Committee on Antimicrobial Susceptibility Testing; **I**, intermediate; **MIC**, minimum inhibitory concentration; **R**, resistant; **S**, susceptible

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Conflicts of interest
BLMD, STN, CL, HY, and YY are employees of Shionogi.