Cefiderocol In vitro Activity Against Molecularly Characterized **Pseudomonas aeruginosa and Acinetobacter baumannii-calcoaceticus Complex Clinical Isolates Causing Infection in United States Hospitals** (2020 - 2021)

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Introduction

- Pseudomonas aeruginosa and Acinetobacter baumannii-calcoaceticus complex, especially multidrug-resistant (MDR) organisms, cause serious nosocomial infections.
- These pathogens may be resistant to many clinically available antimicrobial agents and bring therapeutic challenges.
- Cefiderocol is a siderophore-conjugated cephalosporin with broad activity against aerobic, Gram-negative bacteria. This cephalosporin utilizes the bacterial iron transport system to gain access to the periplasmic space and reach its targets.
- This siderophore cephalosporin possesses broad activity against Gramnegative bacteria, including MDR organisms like carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *P. aeruginosa*, and A. baumannii.
- This study evaluated the activities of cefiderocol and comparator agents against resistant and molecularly characterized Acinetobacter spp. and *P. aeruginosa* recovered from hospitalized patients in US centers as part of the SENTRY Antimicrobial Surveillance Program.

Materials and Methods

Bacterial organisms

- This study comprised a collection of 2,241 *P. aeruginosa* and 682 Acinetobacter spp. (588 A. baumannii-calcoaceticus complex and 94 isolates from 17 other species) consecutively collected from 63 US sites in all 9 Census Divisions during 2020–2021.
- Only consecutive isolates (1 per patient infection episode) responsible for documented infections according to local criteria were included.
- Bacterial identification was confirmed by standard algorithms supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) guidelines.
- Frozen-form broth microdilution panels were manufactured by JMI Laboratories (North Liberty, IA, USA) and contained cation-adjusted Mueller-Hinton broth for comparator agents.
- Susceptibility testing for cefiderocol used broth microdilution panels containing iron-depleted media per CLSI guidelines.
- Quality assurance was performed by sterility checks, colony counts, and testing CLSI-recommended quality control reference strains.
- MIC interpretations were performed using CLSI breakpoints for cefiderocol and comparators, with the exception that EUCAST breakpoints for meropenem-vaborbactam were used for P. aeruginosa and EUCAST breakpoints for imipenem-relebactam were used for Acinetobacter spp.
- P. aeruginosa and A. baumannii-calcoaceticus complex isolates with imipenem and/or meropenem MICs $\geq 4 \text{ mg/L}$ or ceftazidime and/or cefepime MICs ≥ 16 mg/L were subjected to next-generation genome sequencing for the screening of acquired carbapenemase genes.

Screening of β-lactamase genes

- library construction.
- Laboratories.

Results

Selected isolates had total genomic DNA extracted by the fully automated Thermo Scientific[™] KingFisher[™] Flex Magnetic Particle Processor (Cleveland, OH, USA), which was used as input material for

DNA libraries were prepared using the Nextera[™] library construction protocol (Illumina, San Diego, CA, USA) following the manufacturer's instructions and were sequenced on MiSeq Sequencer platforms at JMI

FASTQ format sequencing files for each sample set were assembled independently using *de novo* assembler SPAdes 3.15.3. An in-house software was applied to align the assembled sequences against a comprehensive in-house database containing known β-lactamase genes.

• A total of 31.6% (709/2,241) of *P. aeruginosa* met the MIC screening criteria and 16.9% (379/2,241) showed an MDR phenotype (Table 1). – A small proportion of *P. aeruginosa* (6/709; 0.8%) carried carbapenemase genes, all of which were class B carbapenemases, except for 1 isolate with bla_{GFS-5} (Table 1).

Cefiderocol had similar MIC values against P. aeruginosa that did not meet (MIC_{50/90}, 0.06/0.25 mg/L) and did meet (MIC_{50/90}, 0.12/0.5 mg/L) the MIC screening criteria, as well as against the MDR subset (MIC_{50/90}, 0.12/0.5 mg/L).

• High susceptibility rates (\geq 97.8%) were obtained for all agents tested against P. aeruginosa that did not meet the MIC screening criteria, except for colistin (99.7% intermediate; Table 2).

Cefiderocol (99.3% susceptible), imipenem-relebactam (91.1% susceptible), ceftazidime-avibactam (88.7% susceptible), and ceftolozane-tazobactam (92.2% susceptible) were the most active agents tested against *P. aeruginosa* that met the MIC screening criteria (Table 2).

- Cefiderocol (98.7% susceptible) had the greatest activity against the MDR subset of *P. aeruginosa*, whereas other agents tested showed susceptibility results <90% (Table 2).

• Among Acinetobacter spp., 42.5% (290/682) of isolates met the MIC screening criteria and 35.9% (245/682) had an MDR phenotype. - 64.1% (186/290) carried carbapenemase genes (all A. baumannii-

calcoaceticus complex).

- All carbapenemase genes detected belonged to class D β-lactamases, except for 2 isolates which both carried class B and D (Table 1).

• Cefiderocol demonstrated MIC_{50} results of 0.06 mg/L and MIC_{90} values of 0.5 mg/L when tested against Acinetobacter spp. that did not meet the MIC screening criteria (Table 1).

• MIC₉₀ values of 2 mg/L were obtained for cefiderocol against Acinetobacter spp. that met the MIC screening criteria and each subset, except against those carrying *bla*_{0XA-24}-like genes (MIC₉₀, 1 mg/L) (Table 1). • High susceptibility (94.5–100%) was obtained for all agents tested against Acinetobacter spp. that did not meet the MIC screening criteria and for which breakpoints are available (Table 3).

In contrast, only cefiderocol (MIC_{50/90}, 0.25–0.5/2 mg/L) was active against Acinetobacter spp. that met the MIC screening criteria and against the additional resistant subsets (Table 3).

Table 1. MIC distribution of cefiderocol obtained against *P. aeruginosa*, Acinetobacter spp., and resistant subsets from the USA

Organism/					No. and cumulative $\%$ of isolates inhibited at MIC (mg/L) of:				ng/L) of:							
Group (no. of isolates) ^a	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16	MIC ₅₀	MIC ₉₀
? aeruginosa (2,241)																
MIC screen-negative (1,532)	48 (3.1)	26 (4.8)	69 (9.3)	224 (24.0)	433 (52.2)	441 (81.0)	201 (94.1)	60 (98.0)	20 (99.3)	9 (99.9)	1 (100.0)				0.06	0.25
MIC screen-positive (709)	15 (2.1)	7 (3.1)	32 (7.6)	64 (16.6)	158 (38.9)	190 (65.7)	141 (85.6)	51 (92.8)	27 (96.6)	14 (98.6)	5 (99.3)	3 (99.7)	2 (100.0)		0.12	0.5
MDR (379)	10 (2.6)	5 (4.0)	12 (7.1)	29 (14.8)	78 (35.4)	101 (62.0)	82 (83.6)	31 (91.8)	15 (95.8)	7 (97.6)	4 (98.7)	3 (99.5)	2 (100.0)		0.12	0.5
Carbapenemase-positive ^b (6)					2 (33.3)	2 (66.7)	0 (66.7)	0 (66.7)	1 (83.3)	1 (100.0)					0.12	
cinetobacter spp. (682)																
MIC screen-negative (392)	1 (0.3)	1 (0.5)	31 (8.4)	83 (29.6)	121 (60.5)	69 (78.1)	36 (87.2)	30 (94.9)	16 (99.0)	1 (99.2)	2 (99.7)	1 (100.0)			0.06	0.5
MIC screen-positive (290)			4 (1.4)	9 (4.5)	35 (16.6)	47 (32.8)	63 (54.5)	60 (75.2)	28 (84.8)	26 (93.8)	8 (96.6)	3 (97.6)	3 (98.6)	4 (100.0)	0.25	2
MDR (245)			2 (0.8)	5 (2.9)	21 (11.4)	43 (29.0)	52 (50.2)	57 (73.5)	25 (83.7)	22 (92.7)	8 (95.9)	3 (97.1)	3 (98.4)	4 (100.0)	0.25	2
Carbapenemase ^c (186)			2 (1.1)	1 (1.6)	18 (11.3)	33 (29.0)	35 (47.8)	49 (74.2)	19 (84.4)	17 (93.5)	6 (96.8)	2 (97.8)	3 (99.5)	1 (100.0)	0.5	2
OXA-23-group (108)			1 (0.9)	1 (1.9)	9 (10.2)	16 (25.0)	23 (46.3)	24 (68.5)	14 (81.5)	11 (91.7)	5 (96.3)	1 (97.2)	2 (99.1)	1 (100.0)	0.5	2
OXA-24-group (58)					7 (12.1)	12 (32.8)	10 (50.0)	21 (86.2)	4 (93.1)	2 (96.6)	1 (98.3)	0 (98.3)	1 (100.0)		0.25	1
Other ^d (20)			1 (5.0)	0 (5.0)	2 (15.0)	5 (40.0)	2 (50.0)	4 (70.0)	1 (75.0)	4 (95.0)	0 (95.0)	1 (100.0)			0.25	2
No carbapenemases ^e (104)			2 (1.9)	8 (9.6)	17 (26.0)	14 (39.4)	28 (66.3)	11 (76.9)	9 (85.6)	9 (94.2)	2 (96.2)	1 (97.1)	0 (97.1)	3 (100)	0.25	2

^b Includes bla_{VIM_2} (2 isolates). $bla_{GES,5}$ (1). bla_{IMP_1} (1). $bla_{IMP_{13}}$ (1). and bla_{NDM_1} (1)

Includes $bla_{0XA-134}$ (4), $bla_{0XA-213}$ (7), $bla_{0XA-229}$ (1), bla_{0XA-23} and bla_{0XA-24} (5), bla_{NDM-1} and bla_{0XA-23} (1), bla_{NDM-1} and bla_{0XA-58} (1), and bla_{0XA-24} and $bla_{0XA-213}$ -like (1). Includes isolates in which acquired carbapenemase genes were not detected. These isolates carried the intrinsic OXA-51-like- and ADC-encoding genes, except for 4 isolates with an additional SHV-12.

Table 2. Antimicrobial activity of cefiderocol and comparator agents tested against P. aeruginosa from the USA

Antimicrobial agent	MIC (mg/L)			CLSI ^a			
Antimicrobial agent	50 %	90%	Range	% S	%	% R	
MIC screen-negative ^b (1,532)							
Cefiderocol	0.06	0.25	≤0.004 to 4	100.0	0.0	0.0	
Imipenem-relebactam	0.25	0.25	≤0.03 to 2	100.0	0.0	0.0	
Meropenem-vaborbactam	0.25	1	≤0.015 to 4	100.0		0.0	
Ceftazidime-avibactam	2	2	0.03 to 16	99.9		0.1	
Ceftolozane-tazobactam	0.5	1	≤0.12 to 4	100.0	0.0	0.0	
Ceftazidime	2	4	0.06 to 8	100.0	0.0	0.0	
Cefepime	2	4	0.12 to 8	100.0	0.0	0.0	
Piperacillin-tazobactam	4	8	≤0.06 to 64	97.8	2.2	0.0	
Meropenem	0.25	1	≤0.015 to 2	100.0	0.0	0.0	
Colistin	1	1	≤0.06 to >8		99.7	0.3	
MIC screen-positive ^b (709)							
Cefiderocol	0.12	0.5	≤0.004 to 16	99.3	0.4	0.3	
Imipenem-relebactam	1	2	≤0.03 to >8	91.1	6.1	2.8	
Meropenem-vaborbactam	4	>8	≤0.015 to >8	69.5		30.5	
Ceftazidime-avibactam	4	16	0.12 to >32	88.7		11.3	
Ceftolozane-tazobactam	1	4	≤0.12 to >16	92.2	3.5	4.2	
Ceftazidime	16	>32	0.25 to >32	46.7	12.1	41.2	
Cefepime	8	32	0.5 to >32	52.0	31.2	16.8	
Piperacillin-tazobactam	32	>128	0.12 to >128	39.0	26.8	34.2	
Meropenem	4	32	0.06 to >32	37.1	16.8	46.1	
Colistin	1	1	0.12 to >8		99.6	0.4	
MDR ^b (379)							
Cefiderocol	0.12	0.5	≤0.004 to 16	98.7	0.8	0.5	
Imipenem-relebactam	1	4	≤0.03 to >8	84.7	10.6	4.7	
Meropenem-vaborbactam	8	>8	0.03 to >8	52.5		47.5	
Ceftazidime-avibactam	8	16	0.5 to >32	79.7		20.3	
Ceftolozane-tazobactam	2	8	0.5 to >16	86.8	5.8	7.4	
Ceftazidime	32	>32	1 to >32	31.7	13.7	54.6	
Cefepime	16	32	2 to >32	27.7	43.0	29.3	
Piperacillin-tazobactam	64	>128	1 to >128	16.9	35.6	47.5	
Meropenem	8	32	0.06 to >32	19.3	12.4	68.3	
Colistin	1	1	0.12 to >8		99.2	0.8	

^a Criteria as published by CLSI (2021), except for EUCAST breakpoints for meropenem-vaborbactam ^b See footnotes of Table 1 for additional information.

All A. baumannii-calcoaceticus species complex, includes bla_{0XA-23} -like (108), bla_{0XA-24} -like (7), bla_{0XA-23} and bla_{0XA-23} and bla_{0XA-23} (1), bla_{0XA-23} (1), bla_{0XA-23} (1), bla_{0XA-29} -like (1), and bla_{0XA-24} and bla_{0XA-24} -like (2), bla_{0XA-23} (1), bla_{0XA-23} (1), bla_{0XA-23} (1), bla_{0XA-29} -like (1), and bla_{0XA-24} and bla_{0XA-24} -like (2), bla_{0XA-23} (1), bla_{0XA-23} (1), bla_{0XA-23} (1), bla_{0XA-23} -like (2), bla_{0XA-23} -like (2), bla_{0XA-23} -like (2), bla_{0XA-23} (2), bla_{0XA-23} (2), bla_{0XA-23} (2), bla_{0XA-23} -like (2), bla_{0XA-23} -like (2), bla_{0XA-23} -like (2), bla_{0XA-23} (2), bla_{0XA-23} (2), bla_{0XA-23} -like (3), bla_{0XA-23} -like (4), bla_{0XA-23} -like (2), bla_{0XA-23} -like (2), bla_{0XA-23} -like (2), bla_{0XA-23} -like (3), bla_{0XA-23} -like (4), bla_{0XA-23} -like (3), bla_{0XA-23} -like (4), bla_{0XA-23} -like (2), bla_{0XA-23} -like (2), bla_{0XA-23} -like (3), bla_{0XA-23} -like (4), bla_{0XA-23} -like (2), bla_{0XA-23} -like (3), bla_{0XA-23} -like (4), bla_{0XA-23} -like (4

Table 3. Antimicrobial activity of cefiderocol and comparator agents tested against Acinetobacter snn from the USA

Acinetobacter spp. from the USA							
Antimicrobial agent		MIC (m		0/ 🔿	CLSI ^a	0/ D	
	50%	90%	Range	% S	%	% R	
MIC screen-negative (392) Cefiderocol	0.06	0.5	≤0.004 to 8	99.7	0.3	0.0	
Imipenem-relebactam	0.00	0.25	≤0.004 to 8	100.0	0.5	0.0	
Meropenem-vaborbactam	0.12	1	0.03 to 4	100.0		0.0	
Ceftazidime-avibactam	4	16	≤0.015 to 32				
Ceftolozane-tazobactam	≤0.12	2	≤ 0.013 to 32				
Ampicillin-sulbactam	2	4	≤0.12 to 8	97.4	2.0	0.5	
Ceftazidime	4	8	0.25 to 8	100.0	0.0	0.0	
Cefepime	2	8	0.12 to 8	100.0	0.0	0.0	
Piperacillin-tazobactam	≤0.06	16	≤0.06 to >128	94.5	2.9	2.6	
Meropenem	0.25	1	0.03 to 2	100.0	0.0	0.0	
Colistin	0.5	1	≤0.06 to >8		95.9	4.1	
MIC screen-positive ^b (290)							
Cefiderocol	0.25	2	0.015 to >64	96.6	1.0	2.4	
Imipenem-relebactam	>8	>8	≤0.03 to >8	32.1		67.9	
Meropenem-vaborbactam	>8	>8	0.06 to >8				
Ceftazidime-avibactam	16	>32	0.5 to >32				
Ceftolozane-tazobactam	16	>16	≤0.12 to >16				
Ampicillin-sulbactam	32	64	≤0.5 to >64	30.0	12.8	57.2	
Ceftazidime	>32	>32	2 to >32	21.7	14.8	63.4	
Cefepime	32	>32	1 to >32	11.4	19.0	69.7	
Piperacillin-tazobactam	>128	>128	≤0.06 to >128	15.9	10.0	74.1	
Meropenem	32	>32	0.06 to >32	29.0	2.1	69.0	
Colistin	0.5	2	0.12 to >8		92.7	7.3	
MDR ^b (245)							
Cefiderocol	0.25	2	0.015 to >64	95.9	1.2	2.9	
Imipenem-relebactam	>8	>8	0.06 to >8	20.0		80.0	
Meropenem-vaborbactam	>8	>8	0.25 to >8				
Ceftazidime-avibactam	32	>32	0.5 to >32				
Ceftolozane-tazobactam	16	>16	≤0.12 to >16	10.0		07.0	
Ampicillin-sulbactam	32	64	1 to >64	18.0	14.3	67.8	
Ceftazidime	>32	>32	4 to >32	19.6	10.6	69.8	
Cefepime	>32	>32	4 to >32	6.1	16.3	77.6	
Piperacillin-tazobactam	>128	>128	≤0.06 to >128	5.3	10.2	84.5	
Meropenem	>32	>32	0.25 to >32	16.3	2.4	81.2	
Colistin	0.5	2	0.12 to >8	_	92.2	7.8	
Carbapenemase ^b (186) Cefiderocol	0.5	2	0.015 to >64	96.8	1 1	2.2	
Imipenem-relebactam	>8	 >8	0.12 to >8	4.8	1.1	95.2	
Meropenem-vaborbactam	>8	>8	0.12 to >8	4.0		95.2	
Ceftazidime-avibactam	32	>32	0.5 to >32				
Ceftolozane-tazobactam	16	>16	1 to >16				
Ampicillin-sulbactam	32	64	2 to >64	8.1	13.4	78.5	
Ceftazidime	>32	>32	4 to >32	22.0	9.1	68.8	
Cefepime	>32	>32	2 to >32	4.3	12.4	83.3	
Piperacillin-tazobactam	>128	>128	8 to >128	2.2	3.2	94.6	
Meropenem	>32	>32	0.25 to >32	4.8	0.0	95.2	
Colistin	0.5	2	0.12 to >8		92.4	7.6	
Non-carbapenemase ^b (104)							
Cefiderocol	0.25	2	0.015 to >64	96.2	1.0	2.9	
Imipenem-relebactam	0.25	8	≤0.03 to >8	80.8		19.2	
Meropenem-vaborbactam	1	>8	0.06 to >8				
Ceftazidime-avibactam	16	>32	2 to >32				
Ceftolozane-tazobactam	8	>16	≤0.12 to >16				
Ampicillin-sulbactam	8	32	≤0.5 to >64	69.2	11.5	19.2	
Ceftazidime	32	>32	2 to >32	21.2	25.0	53.8	
Cefepime	16	>32	1 to >32	24.0	30.8	45.2	
Piperacillin-tazobactam	32	>128	≤0.06 to >128	40.4	22.1	37.5	
Meropenem	1	16	0.06 to >32	72.1	5.8	22.1	
Colistin	0.5	2	0.12 to >8		94.2	5.8	

Criteria as published by CLSI (2021), except for EUCAST breakpoints for imipenem-relebactam See Table 1 footnotes for additional information

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- Many P. aeruginosa (31.6%) met the MIC screening criteria but rarely acquired carbapenemase genes (0.8%).
- In contrast, many Acinetobacter spp. (42.5%) met the MIC screening criteria, as well as showed a resistance phenotype (35.9%).
- In addition, the presence of carbapenemase genes was high among Acinetobacter spp.
- Cefiderocol showed potent in vitro activity against P. aeruginosa and Acinetobacter spp. causing infections in US hospitals, including across resistant and molecularly characterized subsets, where treatment options were limited.

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