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

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Introduction

- *Pseudomonas aeruginosa* and *A. baumannii-calcoaceticus* complex, especially multidrug-resistant (MDR) organisms, cause serious nosocomial infections, which bring therapeutic challenges and present a critical need for innovative antimicrobial agents.
- Cefiderocol is a novel siderophore-conjugated cephalosporin with broad activity against aerobic, Gram-negative bacteria. This new cephalosporin utilizes the bacterial iron transport system to gain access to the periplasmic space and reach its targets.
- Cefiderocol was approved by the Food and Drug Administration (FDA) for the treatment of complicated urinary tract infections and nosocomial pneumonia based on clinical trials demonstrating noninferiority to comparator agents.
- This study evaluated the activities of cefiderocol and comparator agents against molecularly characterized *A. baumannii* and *P. aeruginosa* recovered from hospitalized patients in US centers, as a part of the SENTRY Antimicrobial Surveillance Program.

Materials and Methods

Bacterial organisms

- This study included 248 *A. baumannii-calcoaceticus* complex (here referred as *A. baumannii*) and 1,069 *P. aeruginosa* consecutively collected during 2020 from 30 sites located in 9 US Census Divisions. 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 MALDI-TOF (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 (CA-MHB) for comparator agents. Cefiderocol susceptibility testing used broth microdilution panels containing iron-depleted media as per the 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 comparators and FDA breakpoints for cefiderocol and imipenem-relebactam.
- Isolates with imipenem and/or meropenem MIC ≥4 µg/mL, and/or ceftazidime and/or cefepime MIC ≥16 µg/mL were subjected to next-generation genome sequencing for screening of acquired extended-spectrum β-lactamase (ESBL) and carbapenemase genes.

Screening of β-lactamase genes

- 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 library construction.
- 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 Laboratories.
- FASTQ format sequencing files for each sample set were assembled independently using *de novo* assembler SPAdes 3.11.0. An in-house software was applied to align the assembled sequences against a comprehensive in-house database containing known β-lactamase genes. This database was originally based on the NCBI Bacterial Antimicrobial Resistance Reference Gene Database (https://www.ncbi.nlm.nih.gov/bioproject/PRJNA313047).

Results

- Among 1,069 *P. aeruginosa*, 353 (33.0%) met the MIC screening criteria and found to be either carbapenem-nonsusceptible or resistant to extended spectrum cephalosporins.
  - However, ESBL or carbapenemase genes were not detected among these isolates, except for 1 strain with bla_{IMP-1} (Table 1).
- Cefiderocol (99.4% and 100% susceptible based on FDA and CLSI criteria, respectively) inhibited all MIC screen-negative *P. aeruginosa* at ≤2 µg/mL (Tables 1 and 2, and Figure 1).
  - Several comparator agents were active (≥98.0 susceptible) against MIC screen-negative *P. aeruginosa*, and cefiderocol ($MIC_{50/90}$, 0.12/0.25 µg/mL) and imipenem-relebactam ($MIC_{50/90}$, 0.25/0.25 µg/mL) showed the lowest MIC values (Table 2).
- Similar MIC_{50} (0.12 µg/mL) and MIC_{90} (0.25-0.5 µg/mL) values for cefiderocol were obtained against MIC screen-positive and -negative *P. aeruginosa* populations (Table 1 and Figure 1).
  - Imipenem-relebactam ($MIC_{50/90}$, 0.12/0.25 µg/mL; 91.8% susceptible) and ceftazidime-avibactam (89.0% susceptible) had similar activity against MIC screen-positive *P. aeruginosa*.
  - An MIC of 1 µg/mL was noted for cefiderocol against the single bla_{IMP-1}-carrying *P. aeruginosa*, whereas other agents had MIC values >8 µg/mL (Tables 1 and 2).
- Among 248 *A. baumannii*, 124 (50%) met the MIC criteria for screening of acquired ESBL and carbapenemase genes (Table 1).
- Cefiderocol ($MIC_{50/90}$, 0.06/0.5 µg/mL) inhibited all but 1 MIC screen-negative *A. baumannii* at MIC of ≤1 µg/mL (Table 1 and Figure 2).
  - All agents tested showed activity (≥94.3 susceptible) against MIC screen-negative *A. baumannii*, with the lowest MIC_{90} noted for cefiderocol (MIC_{90}, 0.5 µg/mL), imipenem (MIC_{90}, 0.25 µg/mL) and imipenem-relebactam (MIC_{90}, 0.25 µg/mL) (Table 3).
- Among antimicrobial agents tested, cefiderocol ($MIC_{50/90}$, 0.25/2 µg/mL) had the lowest MIC against *A. baumannii* that met the MIC screening criteria (Table 3).
- Cefiderocol ($MIC_{50/90}$, 0.25/2 µg/mL; 86.7–96.7% susceptible) and imipenem-relebactam ($MIC_{50/90}$, 0.25/1 µg/mL; 90.0% susceptible) were the most active agents against *A. baumannii* where only the intrinsic bla_{OXA-51} and variant genes were noted (Table 3).
- Cefiderocol was the only agent active (93.9–100% susceptible; CLSI criteria) against *A. baumannii* carrying bla_{OXA-23} ($MIC_{50/90}$, 0.5/4 µg/mL) or bla_{OXA-24} ($MIC_{50/90}$, 0.25/1 µg/mL) (Table 3).
- All *A. baumannii* isolates carrying other carbapenemase genes were inhibited by cefiderocol at MIC of ≤2 µg/mL (Tables 1 and 3).

Conclusions

- Acquired ESBL and carbapenemase genes remained rare among MDR *P. aeruginosa* in USA hospitals, whereas acquired bla_{OXA} carbapenemase were prevalent among *A. baumannii*.
- Cefiderocol showed potent activity against *P. aeruginosa* subsets, as well as across molecularly characterized subsets of *A. baumannii*, where treatment options were limited.

Acknowledgements

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Figure 1. MIC distribution for cefiderocol against MIC screen-negative and -positive *P. aeruginosa* clinical isolates

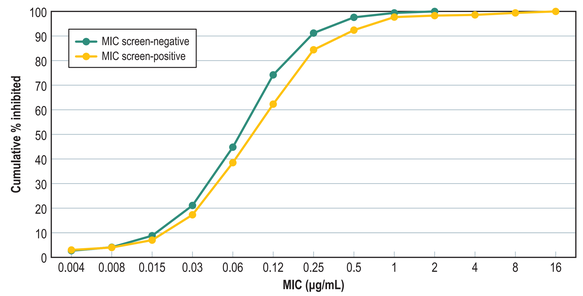

Figure 2. MIC distribution for cefiderocol against MIC screen-negative and -positive *A. baumannii* clinical isolates

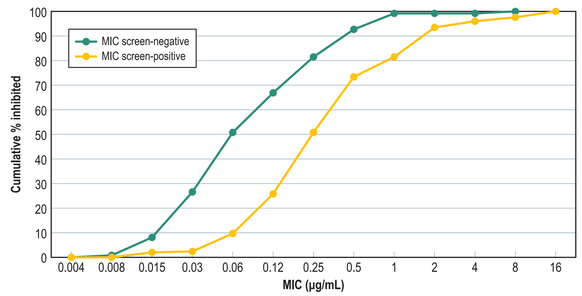

Table 1. MIC distribution of cefiderocol obtained against *P. aeruginosa* and *A. baumannii* from the USA

Organism/	Number (cumulative %) of isolates inhibited at MIC (µg/mL) of:														
Phenotype/Genotype[a] (no.)	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	MIC_{50}	MIC_{90}
P. aeruginosa															
MIC screen-negative (716)	19 (2.7)	10 (4.1)	34 (8.8)	88 (21.1)	170 (44.8)	210 (74.2)	122 (91.2)	46 (97.6)	13 (99.4)	4 (100.0)				0.12	0.25
MIC screen-positive[b] (353)	9 (2.5)	5 (4.0)	12 (7.4)	35 (17.3)	75 (38.5)	84 (62.3)	78 (84.4)	28 (92.4)	19 (97.7)	2 (98.3)	1 (98.6)	3 (99.4)	2 (100.0)	0.12	0.5
A. baumannii															
MIC screen-negative (124)		1 (0.8)	9 (8.1)	23 (26.6)	30 (50.8)	20 (66.9)	18 (81.5)	14 (92.7)	8 (99.2)	0 (99.2)	0 (99.2)	1 (100.0)		0.06	0.5
MIC screen-positive (124)			2 (1.6)	1 (2.4)	9 (9.7)	20 (25.8)	31 (50.8)	28 (73.4)	10 (81.5)	15 (93.5)	3 (96.0)	2 (97.6)	3 (100.0)	0.25	2
OXA-51-group[c] (30)				1 (3.3)	4 (16.7)	2 (23.3)	12 (63.3)	3 (73.3)	4 (86.7)	3 (96.7)	0 (96.7)	1 (100.0)		0.25	2
OXA-23-group (49)			1 (2.0)	0 (2.0)	2 (6.1)	9 (24.5)	11 (46.9)	11 (69.4)	3 (75.5)	6 (87.8)	3 (93.9)	1 (95.9)	2 (100.0)	0.5	4
OXA-24-group (36)					3 (8.3)	8 (30.6)	7 (50.0)	13 (86.1)	2 (91.7)	2 (97.2)	0 (97.2)	0 (97.2)	1 (100.0)	0.25	1
Other[d] (9)			1 (11.1)	0 (11.1)	0 (11.1)	1 (22.2)	1 (33.3)	1 (44.4)	1 (55.6)	4 (100.0)				1	—

[a] MIC screen negative, includes isolates with imipenem and meropenem MIC values ≤2 µg/mL and ceftazidime and cefepime MIC ≤8 µg/mL; MIC screen positive, includes isolates with imipenem and/or meropenem MIC values ≥4 µg/mL, and/or ceftazidime and/or cefepime MIC ≥16 µg/mL.
[b] Acquired ESBL and carbapenemase genes were not detected, except for 1 *P. aeruginosa* carrying bla_{IMP-1}, against which cefiderocol showed an MIC of 1 µg/mL.
[c] Includes those *A. baumannii* that met the MIC screening criteria, but acquired ESBL and carbapenemase genes were not detected, except for 1 isolate with a bla_{SHV-12}.
[d] Includes 5 isolates with $bla_{OXA-213}$, 2 isolates with bla_{OXA-23} and bla_{OXA-24}, 1 isolate with bla_{NDM-1} and bla_{OXA-58}, and 1 isolate with $bla_{OXA-213}$ and bla_{OXA-24}.

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

Antimicrobial agent	MIC (µg/mL)			CLSI[a]		
	50%	90%	Range	%S	%I	%R
MIC screen-negative (716)						
Cefiderocol	0.12	0.25	≤0.004 to 2	99.4/100 [b]	0.6/0.0	0.0/0.0
Imipenem-relebactam	0.25	0.25	≤0.03 to 2	100.0 [b]	0.0	0.0
Meropenem-vaborbactam	0.25	1	≤0.015 to 4	—	—	—
Ceftazidime-avibactam	2	2	0.25 to 8	100.0	—	—
Ceftazidime	2	4	0.06 to 8	100.0	0.0	0.0
Cefepime	2	8	0.12 to 8	100.0	0.0	0.0
Piperacillin-tazobactam	4	8	≤0.06 to 64	98.0	2.0	0.0
Meropenem	0.25	1	≤0.015 to 2	100.0	0.0	0.0
Imipenem	1	1	≤0.12 to 2	100.0	0.0	0.0
MIC screen-positive[c] (353)						
Cefiderocol	0.12	0.5	≤0.004 to 16	97.7/98.6 [b]	0.6/0.8	1.7/0.6
Imipenem-relebactam	0.5	2	0.06 to >8	91.8 [b]	5.4	2.8
Meropenem-vaborbactam	4	>8	≤0.015 to >8	—	—	—
Ceftazidime-avibactam	4	16	0.12 to >32	89.0	—	—

[a] Criteria as published by CLSI (2021) unless otherwise indicated; "—", breakpoint not available.
[b] Using FDA/CLSI breakpoints for cefiderocol and FDA breakpoints for imipenem-relebactam.
[c] Acquired ESBL and carbapenemase genes were not detected, except for 1 *P. aeruginosa* carrying bla_{IMP-1}, against which cefiderocol showed an MIC of 1 µg/mL; imipenem-relebactam, meropenem-vaborbactam, and ceftazidime-avibactam MIC values were >8 µg/mL, >8 µg/mL, and >32 µg/mL, respectively.

Table 3. Antimicrobial activity of cefiderocol and comparator agents tested against *A. baumannii* from the USA

Antimicrobial agent	MIC (µg/mL)			CLSI[a]		
	50%	90%	Range	%S	%I	%R
MIC screen-negative (124)						
Cefiderocol	0.06	0.5	0.008 to 8	99.2/99.2 [b]	0.0/ 0.8	0.8/0.0
Imipenem-relebactam	0.12	0.25	0.06 to 0.5	100.0 [b]	0.0	0.0
Meropenem-vaborbactam	0.25	1	0.06 to 2	—	—	—
Ceftazidime-avibactam	4	16	0.5 to 32	—	—	—
Ceftazidime	4	8	0.5 to 8	100.0	0.0	0.0
Cefepime	4	8	0.25 to 8	100.0	0.0	0.0
Piperacillin-tazobactam	≤0.06	16	≤0.06 to >128	94.3	2.5	3.3
Meropenem	0.25	1	0.06 to 2	100.0	0.0	0.0
Imipenem	0.25	0.25	≤0.12 to 0.5	100.0	0.0	0.0
MIC screen-positive (124)						
Cefiderocol	0.25	2	0.015 to 16	81.5/96.0 [b]	12./1.6	6.5/2.4
Imipenem-relebactam	>8	>8	0.12 to >8	25.8 [b]	0.0	74.2
Meropenem-vaborbactam	>8	>8	0.25 to >8	—	—	—
Ceftazidime-avibactam	16	>32	2 to >32	—	—	—
OXA-51-group[c] (30)						
Cefiderocol	0.25	2	0.03 to 8	86.7/96.7 [b]	10.0/3.3	3.3/0.0
Imipenem-relebactam	0.25	1	0.12 to >8	90.0 [b]	0.0	10.0
Meropenem-vaborbactam	1	>8	0.25 to >8	—	—	—
Ceftazidime-avibactam	32	>32	4 to >32	—	—	—
OXA-23-group (49)						
Cefiderocol	0.5	4	0.015 to 16	75.5/93.9 [b]	12.2/2.0	12.2/4.1
Imipenem-relebactam	>8	>8	>8 to >8	0.0 [b]	0.0	100.0
Meropenem-vaborbactam	>8	>8	>8 to >8	—	—	—
Ceftazidime-avibactam	32	>32	2 to >32	—	—	—
OXA-24-group (36)						
Cefiderocol	0.25	1	0.06 to 16	91.7/97.2 [b]	5.6/0.0	2.8/2.8
Imipenem-relebactam	>8	>8	>8 to >8	0.0 [b]	0.0	100.0
Meropenem-vaborbactam	>8	>8	>8 to >8	—	—	—
Ceftazidime-avibactam	16	>32	4 to >32	—	—	—
Other[d] (9)						
Cefiderocol	1	—	0.015 to 2	55.6/100 [b]	44.4/0.0	0.0/0.0
Imipenem-relebactam	0.25	—	0.12 to >8	55.6 [b]	0.0	44.4
Meropenem-vaborbactam	1	—	0.5 to >8	—	—	—
Ceftazidime-avibactam	16	—	8 to >32	—	—	—

[a] Criteria as published by CLSI (2021) unless otherwise indicated; "—", breakpoint not available.
[b] Using FDA/CLSI breakpoints for cefiderocol and FDA breakpoints for imipenem-relebactam.
[c] Includes those *A. baumannii* that met the MIC screening criteria, but acquired ESBL and carbapenemase genes were not detected, except for 1 isolate with a bla_{SHV-12}.
[d] Includes 5 isolates with $bla_{OXA-213}$, 2 isolates with bla_{OXA-23} and bla_{OXA-24}, 1 isolate with bla_{NDM-1} and bla_{OXA-58}, and 1 isolate with $bla_{OXA-213}$ and bla_{OXA-24}.