IDWeek 2022 | Poster #P643

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

RE Mendes[1], CM Hubler[1], V Kantro[1], D Shortridge[1], HS Sader[1], JM Streit[1], M Castanheira[1]

[1] JMI Laboratories, North Liberty, Iowa, USA

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 Gram-negative 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 ≥4 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

- 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 3.15.3. An in-house software was applied to align the assembled sequences against a comprehensive in-house database containing known β-lactamase genes.

Results

- 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_{GES-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 (≥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).
- MIC_{90} 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_{OXA-24}-like genes (MIC_{90}, 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/ Group (no. of isolates)[a]	No. and cumulative % of isolates inhibited at MIC (mg/L) of: ≤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}
P. 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	—
Acinetobacter 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)	3 (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

[a] MIC screen negative, including isolates with imipenem and/or meropenem MIC values ≤2 mg/L or ceftazidime and/or cefepime MICs ≤8 mg/L; MIC screen positive, including isolates with imipenem and/or meropenem MIC values ≥4 mg/L or ceftazidime and/or cefepime MICs ≥16 mg/L; MDR, multidrug-resistant isolate (resistant to ≥3 classes).
[b] Includes bla_{IMP-1} (2 isolates), bla_{GES-5} (1), bla_{NMC-1} (1), and bla_{NMC-2} (1), and bla_{NMC-3} (1).
[c] All *A. baumannii-calcoaceticus* species complex, includes bla_{OXA-23}-like (108), bla_{OXA-24}-like (58), bla_{OXA-51}-like (7), bla_{OXA-58} and bla_{OXA-64} (5), $bla_{OXA-134}$-like (4), $bla_{OXA-235}$ and $bla_{OXA-253}$-like (1), and $bla_{OXA-421}$-like (1).
[d] Includes $bla_{OXA-143}$ (4), $bla_{OXA-237}$ (1), $bla_{OXA-239}$ (1), $bla_{OXA-253}$ and $bla_{OXA-421}$ (5), $bla_{OXA-421}$ and $bla_{OXA-253}$ (1), $bla_{OXA-421}$ and bla_{OXA-58} (1), and bla_{OXA-64} and $bla_{OXA-253}$-like (1).
[e] 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) 50%	90%	Range	%S	CLSI[a] %I	%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.

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

Antimicrobial agent	MIC (mg/L) 50%	90%	Range	%S	CLSI[a] %I	%R
MIC screen-negative (392)						
Cefiderocol	0.06	0.5	≤0.004 to 8	99.7	0.3	0.0
Imipenem-relebactam	0.12	0.25	≤0.03 to 1	100.0		0.0
Meropenem-vaborbactam	0.25	1	0.03 to 4			
Ceftazidime-avibactam	4	16	≤0.015 to 32			
Ceftolozane-tazobactam	≤0.12	2	≤0.12 to 8			
Ampicillin-sulbactam	2	4	≤0.5 to 64	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			
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[c] (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		95.2
Meropenem-vaborbactam	>8	>8	0.25 to >8			
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[c] (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

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

Conclusions

- 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.

Funding

This research and poster presentation were sponsored by Shionogi & Co., LTD.

Acknowledgements

Authors would like to thank all medical centers participating in the SENTRY Antimicrobial Surveillance Program for providing surveillance isolates.

References

1. CLSI. 2018. M07Ed11. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Wayne, PA, USA.
2. CLSI. 2021. M100Ed31. Performance standards for antimicrobial susceptibility testing. Wayne, PA, USA.
3. EUCAST. 2021. Version 11.0. Breakpoint tables for interpretation of MICs and zone diameters.
4. McCreary EK, Heil EL, Tamma PD. 2021. New perspectives on antimicrobial agents: Cefiderocol. *Antimicrob Agents Chemother*. 65 (8): e0217120.
5. Mendes RE, Jones RN, Woosley LN, Cattoir V, Castanheira M. 2019. Application of next-generation sequencing for characterization of surveillance and clinical trial isolates: Analysis of the distribution of β-lactamase resistance genes and lineage background in the United States. *Open Forum Infect. Dis.* 6 (Suppl. 1): S69–S78.
6. Ong'uti S, Czech M, Robilotti E, Holubar M. 2021. Cefiderocol: A new cephalosporin stratagem against multidrug resistant Gram-negative bacteria. *Clin. Infect. Dis*. 74(7): 1203–1312.
7. Syed YY. 2021. Cefiderocol: A review in serious Gram-negative bacterial infections. *Drugs*. 24: 1–13.

Contact

Rodrigo E. Mendes, Ph.D.
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, Iowa 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: rodrigo-mendes@jmilabs.com

To obtain a PDF of this poster:

Scan the QR code or visit https://www.jmilabs.com/data/posters/IDWeek2022_CefiderocolVsPaeruginosa.pdf

SCAN ME

No personal information is stored.