IDWeek 2022 | Poster #P642

In Vitro Activity of Cefiderocol and Comparator Agents Against Molecularly Characterized Clinical Isolates of Enterobacterales Causing Infections in United States Hospitals (2020–2021)

RE Mendes, JH Kimbrough, V Kantro, D Shortridge, HS Sader, JM Streit, M Castanheira
JMI Laboratories, North Liberty, Iowa, USA

Introduction

- Cefiderocol is approved by the US Food and Drug Administration (FDA) for the treatment of complicated urinary tract infections, including pyelonephritis, as well as hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia.
- Cefiderocol is a siderophore cephalosporin with broad activity against Gram-negative bacteria, including multidrug-resistant (MDR) organisms like carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*.
- The activity of this molecule is due to its ability to achieve high periplasmic concentrations by hijacking the bacterial iron transport machinery, which in turn potentiates cell entry.
  - In addition, cefiderocol remains stable to hydrolysis by serine β-lactamases (ESBLs, KPCs, and OXA-type carbapenemases) and metallo-β-lactamases.
- In this study, the activities of cefiderocol and comparator agents were analyzed against Enterobacterales, including molecularly characterized isolates, as part of the SENTRY Antimicrobial Surveillance Program for USA.

Materials and Methods

Bacterial organisms

- This study comprised a collection of 8,328 Enterobacterales collected from various clinical specimens from patients hospitalized in 32 medical centers in all 9 US 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 comparators and FDA/CLSI breakpoints for cefiderocol (≤4/8/≥16 mg/L for susceptible, intermediate, and resistant).
- Imipenem-relebactam MIC interpretations used FDA breakpoints.
- *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* with ceftriaxone, ceftazidime, or aztreonam MIC values of ≥2 mg/L and any Enterobacterales displaying MIC values ≥2 mg/L for imipenem (excluded for *P. mirabilis, P. penneri*, and indole-positive Proteeae) or meropenem were subjected to genome sequencing and screening of β-lactamase 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 14.5% (793/5,451) of the carbapenem-susceptible *E. coli*, *K. pneumoniae*, and *P. mirabilis* isolates met the criteria for β-lactamase screening and carried ESBL and/or plasmid AmpC genes (Table 1).
  - The majority (87.0%; 690/793) of these isolates carried bla_{CTX-M} alone, followed by a smaller proportion of isolates carrying plasmid AmpC (6.4%; 51/793).
- Cefiderocol had MIC_{50} and MIC_{90} values of 0.5 mg/L and 2 mg/L, respectively, against the carbapenem-susceptible ESBL/AmpC and CTX-M groups of Enterobacterales, as well as against the group of isolates carrying multiple β-lactamase genes (Table 1 and Figure 1).
  - The cefiderocol MIC_{50} value of 0.06 mg/L and MIC_{90} value of 0.5 mg/L, noted against carbapenem-susceptible AmpC producers, were 4- to 8-fold lower than those values obtained against the CTX-M group ($MIC_{50/90}$, 0.5/2 mg/L) (Table 1 and Figure 1).
- All antimicrobial agents tested against non-ESBL, carbapenem-susceptible *E. coli*, *K. pneumoniae*, and *P. mirabilis* isolates showed activity (≥93.5% susceptible), except for the fluoroquinolones (Table 2).
  - In contrast, cefiderocol, ceftazidime-avibactam, the carbapenems, and the carbapenem combinations were active (≥99.4% susceptible) against carbapenem-susceptible, ESBL-AmpC *E. coli*, *K. pneumoniae*, and *P. mirabilis* producers.
- A total of 1.5% (125/8,328) of all Enterobacterales isolates were not susceptible to imipenem and/or meropenem (Table 1).
  - Most isolates not susceptible to the carbapenems carried KPC (52.0%), followed by MBL (7.2%) and OXA-48–like (4.8%).
  - Cefiderocol inhibited at ≤4 mg/L (98.4% susceptible) all but 2 of the Enterobacterales isolates not susceptible to carbapenems (Table 1).
- Cefiderocol ($MIC_{50/90}$, 0.5/4 mg/L; 98.4% susceptible) and ceftazidime-avibactam ($MIC_{50/90}$, 1/8 mg/L; 91.2% susceptible) were the most active agents against Enterobacterales not susceptible to carbapenems.
  - Imipenem-relebactam ($MIC_{50/90}$, 0.25/4 mg/L; 81.6% susceptible) and meropenem-vaborbactam ($MIC_{50/90}$, 0.12/8 mg/L; 86.4% susceptible) had suboptimal activity (Table 2).
- Cefiderocol ($MIC_{50/90}$, 0.5/2 mg/L), imipenem-relebactam ($MIC_{50/90}$, 0.12/0.5 mg/L), meropenem-vaborbactam ($MIC_{60/90}$, 0.03/0.5 mg/L), and ceftazidime-avibactam ($MIC_{50/90}$, 1/2 mg/L) were active (100% susceptible) against the KPC subset (Table 2).
- Cefiderocol (MIC, 0.06–4 mg/L; 100% susceptible) was also active against Enterobacterales carrying MBL genes (Table 1), whereas cefiderocol (MIC, 0.5–2 mg/L; 100% susceptible; Table 1) and ceftazidime-avibactam (1–4 mg/L; 100% susceptible) were active against isolates carrying bla_{OXA-48}–like (data not shown).

Figure 1. Cumulative MIC distribution of cefiderocol against various subsets of Enterobacterales from the USA

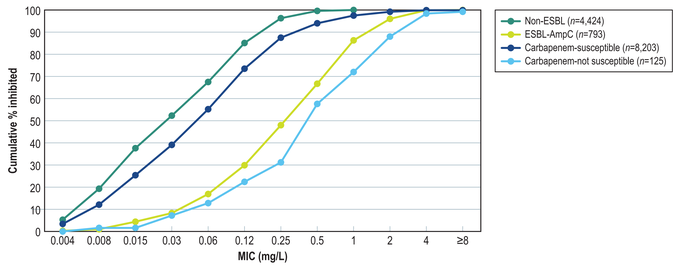

Table 1. MIC distribution of cefiderocol obtained against *Enterobacterales* and resistant subsets from the USA

Organism/ Group (no. of isolates)	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}	%S[h]
E. coli, K. pneumoniae, and *P. mirabilis*																	
Non-ESBL (4,424)[a]	235 (5.3)	618 (19.3)	810 (37.6)	652 (52.3)	670 (67.5)	780 (85.1)	495 (96.3)	146 (99.6)	18 (100.0)						0.03	0.25	100.0
ESBL/AmpC (793)[b]	2 (0.3)	6 (1.0)	27 (4.4)	31 (8.3)	68 (16.9)	103 (29.9)	144 (48.0)	148 (66.7)	155 (86.3)	77 (96.0)	31 (99.9)	1 (100.0)			0.5	2	99.9
CTX-M (690)[c]		5 (0.7)	21 (3.8)	21 (6.8)	53 (14.5)	86 (27.0)	127 (45.4)	132 (64.5)	144 (85.4)	72 (95.8)	28 (99.9)	1 (100.0)			0.5	2	99.9
AmpC (51)[d]	2 (3.9)	0 (3.9)	4 (11.8)	9 (29.4)	12 (52.9)	10 (72.5)	7 (86.3)	4 (94.1)	1 (96.1)	1 (98.0)	1 (100.0)				0.06	0.5	100.0
Multiple (26)[e]		1 (3.8)	1 (7.7)	0 (7.7)	2 (15.4)	2 (23.1)	5 (42.3)	6 (65.4)	5 (84.6)	2 (92.3)	2 (100.0)				0.5	2	100.0
All Enterobacterales																	
Carbapenem-S (8,203)[f]	278 (3.4)	714 (12.1)	1,094 (25.4)	1,121 (39.1)	1,319 (55.2)	1,502 (73.5)	1,146 (87.5)	538 (94.0)	289 (97.5)	139 (99.2)	52 (99.9)	9 (>99.9)	1 (>99.9)	1 (100.0)	0.06	0.5	99.9
Carbapenem-NS (125)[f]		2 (1.6)	0 (1.6)	7 (7.2)	7 (12.8)	12 (22.4)	11 (31.2)	33 (57.6)	18 (72.0)	20 (88.0)	13 (98.4)	1 (99.2)	0 (99.2)	1 (100.0)	0.5	4	98.4
KPC (65)		2 (3.1)	0 (3.1)	5 (10.8)	2 (13.8)	7 (24.6)	6 (33.8)	15 (56.9)	11 (73.8)	11 (90.8)	6 (100.0)				0.5	2	100.0
MBL (9)[g]					1 (11.1)	0 (11.1)	0 (11.1)	1 (22.2)	1 (33.3)	3 (66.7)	3 (100.0)				2	—	100.0
OXA-48–like (5)								2 (40.0)	2 (80.0)	1 (100.0)					1	—	100.0
Carbapenemase-negative (45)				2 (4.4)	4 (13.3)	5 (24.4)	5 (35.6)	14 (66.7)	4 (75.6)	5 (86.7)	4 (95.6)	1 (97.8)	0 (97.8)	1 (100.0)	0.5	4	95.6

[a] Includes 2,736 *E. coli*, 1,233 *K. pneumoniae*, and 455 *P. mirabilis* isolates that did not meet the MIC criteria for β-lactamase screening (i.e., ceftriaxone, ceftazidime, or aztreonam MICs ≤1 mg/L).
[b] Includes 575 *E. coli*, 209 *K. pneumoniae*, and 9 *P. mirabilis* (carbapenem-susceptible) isolates that met the MIC criteria for β-lactamase screening and carried ESBL and/or AmpC genes (i.e., ceftriaxone, ceftazidime, or aztreonam MICs ≥2 mg/L).
[c] Includes 512 *E. coli*, 173 *K. pneumoniae*, and 5 *P. mirabilis* (carbapenem-susceptible) isolates that met the MIC criteria for β-lactamase screening and carried bla_{CTX-M} as the sole ESBL gene.
[d] Includes 43 *E. coli*, 6 *K. pneumoniae*, and 2 *P. mirabilis* (carbapenem-susceptible) isolates that met the MIC criteria for β-lactamase screening and carried bla_{DHA-1}, bla_{CMY-2}, or bla_{FOX} genes without other extended-spectrum β-lactamases.
[e] Includes 17 *E. coli* and 9 *K. pneumoniae* (carbapenem-susceptible) isolates that met the MIC criteria for β-lactamase screening and carried multiple combinations of ESBL or ESBL and AmpC genes.
[f] Enterobacterales susceptible to carbapenems were defined as isolates with imipenem and/or meropenem MICs ≤1 mg/L while those Enterobacterales classified as not susceptible were those with imipenem (excluding *P. mirabilis, P. penneri,* and indole-positive Proteeae) and/or meropenem MICs ≥2 mg/L.
[g] Includes the following genes: bla_{IMP} (7), bla_{VIM} (1), and bla_{NDM} (1).
[h] % of isolates inhibited at the FDA/CLSI breakpoint of ≤4 mg/L.

Table 2. Antimicrobial activity of cefiderocol tested against Enterobacterales and resistant subsets from the USA

Antimicrobial agent	MIC (mg/L) 50%	90%	Range	CLSI[a] %S	%I	%R
Non-ESBL[b] (4,424)						
Cefiderocol[c]	0.03	0.25	≤0.004 to 1	100.0	0.0	0.0
Imipenem-relebactam[c]	0.12	0.5	≤0.03 to 8	93.5[b]	5.4	1.1
Meropenem-vaborbactam	0.03	0.06	≤0.015 to 1	100.0	0.0	0.0
Ceftazidime-avibactam	0.12	0.25	≤0.015 to 0.5	100.0		0.0
Piperacillin-tazobactam	2	4	≤0.06 to >128	96.8	1.8	1.4
Aztreonam	0.06	0.12	≤0.03 to 1	100.0	0.0	0.0
Ceftriaxone	≤0.06	0.12	≤0.06 to 1	100.0	0.0	0.0
Ceftazidime	0.12	0.5	≤0.015 to 1	100.0	0.0	0.0
Cefepime	0.06	0.12	≤0.03 to 32	99.8[d]	0.1	<0.1
Meropenem	≤0.015	0.06	≤0.015 to 1	100.0	0.0	0.0
Imipenem	≤0.12	0.5	≤0.12 to 4	93.6	5.7	0.8
Ciprofloxacin	0.03	>4	≤0.008 to >4	84.0	2.9	13.0
Levofloxacin	0.06	8	≤0.015 to >32	86.0	2.1	11.9
Amikacin	2	4	≤0.25 to >32	99.9	0.1	<0.1
Gentamicin	0.5	1	≤0.12 to >16	94.9	0.3	4.8
ESBL-AmpC[b] (793)						
Cefiderocol[c]	0.5	2	≤0.004 to 8	99.9	0.1	0.0
Imipenem-relebactam[c]	0.12	0.12	≤0.03 to 8	99.4[b]	0.3	0.4
Meropenem-vaborbactam	0.03	0.03	≤0.015 to 0.5	100.0	0.0	0.0
Ceftazidime-avibactam	0.12	0.5	≤0.015 to 4	100.0		0.0
Piperacillin-tazobactam	4	32	0.12 to >128	71.4	12.9	15.7
Aztreonam	>16	>16	0.12 to >16	9.5	11.3	79.2
Ceftriaxone	>8	>8	0.12 to >8	1.4	0.6	98.0
Ceftazidime	16	>32	0.25 to >32	16.3	12.9	70.9
Cefepime	>32	>32	≤0.03 to >32	12.0[e]	9.1	78.9
Meropenem	0.03	0.06	≤0.015 to 1	100.0	0.0	0.0
Imipenem	≤0.12	0.25	≤0.12 to 8	99.4	0.3	0.4
Ciprofloxacin	>4	>4	≤0.008 to >4	15.4	6.3	78.3
Levofloxacin	8	32	≤0.015 to >32	23.9	7.5	68.6
Amikacin	4	8	≤0.25 to >32	97.5	1.4	1.1
Gentamicin	1	>16	≤0.12 to >16	61.7	1.8	36.5
Carbapenem-susceptible[b] (8,203)						
Cefiderocol[c]	0.06	0.5	≤0.004 to 32	99.9	0.1	<0.1
Imipenem-relebactam[c]	0.12	0.5	≤0.03 to 8	94.9[b]	4.2	0.8
Meropenem-vaborbactam	0.03	0.06	≤0.015 to 1	100.0	0.0	0.0
Ceftazidime-avibactam	0.12	0.25	≤0.015 to >32	>99.9		<0.1
Piperacillin-tazobactam	2	16	≤0.06 to >128	88.4	3.8	7.8
Aztreonam	0.12	>16	≤0.03 to >16	84.9	1.8	13.3
Ceftriaxone	≤0.06	>8	≤0.06 to >8	81.6	0.9	17.5
Ceftazidime	0.25	16	≤0.015 to >32	85.6	1.9	12.5
Cefepime	0.06	8	≤0.03 to >32	88.7[d]	2.2	9.1
Meropenem	0.03	0.06	≤0.015 to 1	100.0	0.0	0.0
Imipenem	≤0.12	1	≤0.12 to 8	93.9	5.2	0.9
Ciprofloxacin	0.03	>4	≤0.008 to >4	78.9	3.1	18.0
Levofloxacin	0.06	8	≤0.015 to >32	81.2	3.0	15.8
Amikacin	2	4	≤0.25 to >32	99.6	0.3	0.1
Gentamicin	0.5	2	≤0.12 to >16	91.9	0.6	7.5
Carbapenem-nonsusceptible[b] (125)						
Cefiderocol[c]	0.5	4	0.008 to >64	98.4	0.8	0.8
Imipenem-relebactam[c]	0.25	4	0.06 to >8	81.6[b]	4.8	13.6
Meropenem-vaborbactam	0.12	8	≤0.015 to >8	86.4	4.0	9.6
Ceftazidime-avibactam	1	8	≤0.015 to >32	91.2		8.8
Piperacillin-tazobactam	>128	>128	1 to >128	8.0	1.6	90.4
Aztreonam	>16	>16	≤0.03 to >16	13.6	0.8	85.6
Ceftriaxone	>8	>8	0.12 to >8	8.0	0.8	91.2
Ceftazidime	>32	>32	0.12 to >32	14.4	2.4	83.2
Cefepime	32	>32	≤0.03 to >32	16.8[d]	23.2	60.0
Meropenem	8	>32	0.03 to >32	19.2	16.0	64.8
Imipenem	8	>8	0.5 to >8	4.0	21.6	74.4
Ciprofloxacin	2	>4	≤0.008 to >4	32.0	4.8	63.2
Levofloxacin	2	>32	≤0.015 to >32	35.2	8.8	56.0
Amikacin	4	32	≤0.25 to >32	82.4	10.4	7.2
Gentamicin	1	>16	≤0.12 to >16	63.2	12.8	24.0

[a] Criteria as published by CLSI (2021) unless otherwise indicated; "—", breakpoint not available.
[b] See footnotes on Table 1 for additional information.
[c] Using CLSI/FDA breakpoints for cefiderocol. Imipenem-relebactam breakpoints were applied to all organisms, including *Morganella* spp., *Proteus* spp., and *Providencia* spp., where breakpoints are not available.

Conclusions

- Cefiderocol *in vitro* activity (98.4% susceptible) was consistent against various subsets, including against Enterobacterales carrying carbapenemase genes other than bla_{KPC}, against which approved β-lactam/β-lactamase inhibitor combinations showed limited activity.
- These data reinforce cefiderocol as an important option for the treatment of serious infections caused by Enterobacterales and resistant subsets in patients hospitalized in US medical centers.

Acknowledgments

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

References

1. Clinical and Laboratory Standards Institute. 2018. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. *M07 11th Edition*. Wayne, PA, USA.
2. Clinical and Laboratory Standards Institute. 2022. Performance standards for antimicrobial susceptibility testing. *M100 32nd Edition*. Wayne, PA, USA.
3. FDA Susceptibility Test Interpretive Criteria: https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria. Accessed April 2022.
4. 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: S69-S78.
5. Ong'uti S, Czech M, Robilotti E, Holubar M. 2021. Cefiderocol: A new cephalosporin stratagem against multidrug resistant Gram-negative bacteria. *Clin Infect Dis. In press.*
6. 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_CefiderocolVsMolecularEnteros.pdf

SCAN ME

No personal information is stored.