IDWeek 2023
#2172

Activity of Cefiderocol and Comparator Agents Against Molecularly Characterized Multidrug-resistant Enterobacterales Clinical Isolates From United States Hospitals (2020–2022)

RE Mendes[1], JH Kimbrough[1], V Kantro[1], D Shortridge[1], HS Sader[1], M Castanheira[1]

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

Contact Information
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@element.com

SCAN ME

To obtain a PDF of this poster:
- Scan the QR code
- OR
- Visit https://www.jmilabs.com/data/posters/IDWeek2023_22-SHI-05_P7_Enterics.pdf

Charges may apply.
No personal information is stored.

SENTRY ANTIMICROBIAL SURVEILLANCE

Introduction

- Cefiderocol was approved by the US Food and Drug Administration (FDA) in 2019 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 increases 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 during 2020–2022.

Materials and Methods

Bacterial organisms

- This study comprised a collection of 11,882 Enterobacterales collected from various clinical specimens from patients hospitalized in 33 medical centers in all 9 US Census Divisions during 2020–2022. 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™ or Illumina DNA PrepTM library construction protocol (Illumina, San Diego, CA, USA) following the manufacturer's instructions and were sequenced on MiSeq or NextSeq 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 17.0% (1,339/7,881) of the carbapenem-susceptible *E. coli, K. pneumoniae,* and *P. mirabilis* isolates met the criteria for β-lactamase screening and 15.4% (1,215/7,881) carried ESBL (89.2% CTX-M) and/or plasmid AmpC (8.8% CMY, DHA and/or FOX) genes.
- Cefiderocol (99.8% susceptible), imipenem-relebactam (97.9% susceptible), meropenem-vaborbactam (100% susceptible), and ceftazidime-avibactam (100% susceptible) were all active against carbapenem-susceptible Enterobacterales that carried ESBL and/or AmpC genes (Figure 1 and Table 1).
  - The carbapenem agents, imipenem and meropenem were also active (98.1–100% susceptible) against this population (Table 2).
- A total of 1.4% (165/11,882) of all Enterobacterales isolates were not susceptible to imipenem and/or meropenem (Table 1).
  - Most isolates not susceptible to the carbapenems carried KPC (48.5%), followed by MBL (7.3%) and OXA-48-like (4.2%) (Figure 2).
- Cefiderocol ($MIC_{50/90}$, 0.5/4 mg/mL; 97.6% susceptible) and ceftazidime-avibactam ($MIC_{50/90}$, 1/8 mg/mL; 91.5% susceptible) were the most active agents against carbapenem-non-susceptible isolates (Tables 1 and 2), whereas imipenem-relebactam ($MIC_{50/90}$, 0.25/4 mg/mL; 81.2% susceptible) and meropenem-vaborbactam ($MIC_{50/90}$, 0.12/8 mg/mL; 87.9% susceptible) showed more limited activity (<90% susceptible).
- Compared to β-lactam-β-lactamase inhibitor combinations, cefiderocol was the only active agent against Enterobacterales carrying MBL genes ($MIC_{50/90}$, 2/4 mg/mL; 90.9% susceptible), and only cefiderocol (MIC, 0.5-2 mg/mL; 100% susceptible) and ceftazidime-avibactam (0.5-4 mg/mL; 100% susceptible) were active against isolates carrying only blaOXA-48-like (Table 1).
- Cefiderocol ($MIC_{50/90}$, 0.5/2 mg/mL), imipenem-relebactam ($MIC_{50/90}$, 0.12/0.5 mg/mL), meropenem-vaborbactam ($MIC_{50/90}$, 0.03/0.5 mg/mL), and ceftazidime-avibactam ($MIC_{50/90}$, 1/2 mg/mL) were all active against the KPC subset of isolates (98.8–100% susceptible) (Tables 1 and 2).

Conclusions

- Cefiderocol activity against Enterobacterales was consistent, regardless of isolate phenotypes or genotypes.
  - The cefiderocol activity was observed against isolates carrying serine and MBL carbapenemases, and also against OXA-48-like, where approved β-lactam/β-lactamase inhibitor combinations showed limited activity (Figure 1).
- These data emphasize cefiderocol as an important option for the treatment of infections caused by Enterobacterales and resistant subsets.

Acknowledgements

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. 2023. Performance standards for antimicrobial susceptibility testing. M100 33rd 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.

Table 1. Activity of cefiderocol and β-lactam-β-lactamase inhibitor combinations against Enterobacterales and resistant subsets from the USA

Phenotype/genotype (No. of isolates)	Cefiderocol	Imipenem-relebactam	Meropenem-vaborbactam	Ceftazidime-avibactam
All (11,882)	0.06/0.5 (99.8)	0.12/0.5 (94.8)	0.03/0.06 (99.8)	0.12/0.25 (99.8)
Non-ESBL (6,542)[b]	0.03/0.25 (100)	0.12/0.5 (93.5)	0.03/0.06 (100)	0.12/0.25 (100)
ESBL (1,215)[c]	0.25/2 (99.8)	0.12/0.25 (97.9)	0.03/0.03 (100)	0.12/0.5 (100)
Carbapenem-nonS (165)	0.5/4 (97.6)	0.25/4 (81.2)	0.12/8 (87.9)	1/8 (91.5)
Non-carbapenemase (64)[d]	0.5/4 (95.3)	0.25/2 (82.8)	0.25/2 (93.8)	0.5/8 (96.9)
Carbapenemase (101)[e]	0.5/4 (99.0)	0.12/8 (80.2)	0.03/>8 (84.2)	1/>32 (88.1)
KPC (80)[f]	0.5/2 (100)	0.12/0.5 (100)	0.03/0.5 (98.8)	1/2 (100)
MBL (11)[g]	2/4 (90.9)	>8/>8 (0.0)	>8/>8 (18.2)	>32/>32 (0.0)
OXA-48-like (6)[h]	0.5/- (100)	4/- (16.7)	>8/- (16.7)	1/- (100)
Other (4)[i]	0.06/- (100)	>8/- (0.0)	0.06/- (75.0)	0.25/- (75.0)

[a] MIC interpreted according to the CLSI M100 criteria (2023); cefiderocol used equivalent FDA/CLSI breakpoints.
[b] Non-ESBL includes 4,095 *E. coli*, 1,796 *K. pneumoniae*, and 651 *P. mirabilis* (carbapenem-susceptible) isolates that did not meet the MIC criteria for screening for β-lactamases.
[c] Includes carbapenem-susceptible *E. coli* (845), *K. pneumoniae* (336), and *P. mirabilis* (34; meropenem only for *P. mirabilis*) isolates that met the MIC criteria for screening of β-lactamases and carried ESBL and/or plasmid AmpC genes.
[d] Includes carbapenem-nonsusceptible isolates from the following species: *Citrobacter freundii* species complex (2), *Enterobacter cloacae* species complex (15), *Escherichia coli* (5), *Hafnia alvei* (1), *Klebsiella aerogenes* (18), *K. pneumoniae* (8), *Serratia liquefaciens* complex (1), *S. marcescens* (12), *Yokenella regensburgei* (1) and *Raoultella* spp. (1).
[e] Includes carbapenem-nonsusceptible isolates from the following species: *Citrobacter freundii* species complex (3), *Enterobacter cloacae* species complex (12), *Escherichia coli* (6), *Klebsiella aerogenes* (2), *K. oxytoca* (9), *K. pneumoniae* (53), *Providencia rettgeri* (2), *Serratia marcescens* (10), and *Raoultella* spp. (4). These isolates carried the following main genes: bla_{KPC} (80), bla_{NDM}-48-like (6), MBL (11), bla_{IMI} (3) and a *K. pneumoniae* with both bla_{KPC}- and $bla_{OXA-181}$ (1).
[f] Includes the following genes: bla_{KPC-2} (54), bla_{KPC-3} (44), and bla_{KPC-4} (2).
[g] Includes the following genes: bla_{NDM-1} (7), bla_{NDM-5} (2), bla_{NDM-7} (1), and bla_{VIM-1} (1). Excludes one *K. pneumoniae* that possessed bla_{NDM-1} and $bla_{OXA-181}$.
[h] Includes the following genes: $bla_{OXA-181}$ (2), $bla_{OXA-232}$ (2), and bla_{OXA-48} (3). Excludes one *K. pneumoniae* that possessed bla_{NDM-1} and $bla_{OXA-181}$.
[i] Includes the following genes: bla_{IMI} (3), and the combination bla_{NDM-1} and $bla_{OXA-181}$ (1).

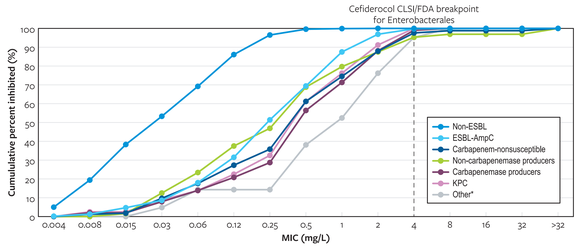
Table 2. Antimicrobial activity of cefiderocol and comparator agents tested against Enterobacterales and resistant subsets from the USA

Antimicrobial agent	MIC (mg/L)			CLSI[a]		
	50%	90%	Range	%S	%I	%R
All[b] (11,882)						
Cefiderocol	0.06	0.5	≤0.004 to >64	99.8	0.1	0.1
Imipenem-relebactam[c]	0.12	0.5	≤0.03 to >8	94.8	4.2	1.0
Meropenem-vaborbactam	0.03	0.06	≤0.015 to >8	99.8	0.1	0.1
Ceftazidime-avibactam	0.12	0.25	≤0.015 to >32	99.8	—	0.2
Piperacillin-tazobactam	2	16	≤0.06 to >128	87.8	3.5	8.7
Aztreonam	0.12	>16	≤0.03 to >16	84.5	1.7	13.8
Ceftriaxone	≤0.06	>8	≤0.06 to >8	81.5	0.9	17.7
Ceftazidime	0.25	32	≤0.015 to >32	85.1	1.8	13.1
Cefepime[d]	0.06	8	≤0.03 to >32	88.1	2.5	9.4
Meropenem	0.03	0.06	≤0.015 to >32	98.9	0.2	0.9
Imipenem	≤0.12	1	≤0.12 to >8	92.9	5.2	1.9
Ciprofloxacin	0.03	>4	≤0.008 to >4	79.1	2.9	18.0
Levofloxacin	0.06	8	≤0.015 to >32	81.2	2.9	15.9
Amikacin	2	4	≤0.25 to >32	93.7	4.8	1.4
Gentamicin	0.5	2	≤0.12 to >16	91.1	0.6	8.3
ESBL[b] (1,215)						
Cefiderocol	0.25	2	≤0.004 to 16	99.8	0.1	0.1
Imipenem-relebactam[c]	0.12	0.25	≤0.03 to 8	97.9	1.6	0.5
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	64	0.12 to >128	71.5	11.4	17.1
Aztreonam	>16	>16	≤0.03 to >16	11.9	11.3	76.8
Ceftriaxone	>8	>8	≤0.06 to >8	1.9	1.1	97.0
Ceftazidime	16	>32	0.06 to >32	18.3	12.6	69.1

Antimicrobial agent	MIC (mg/L)			CLSI[a]		
	50%	90%	Range	%S	%I	%R
Cefepime[d]	>32	>32	≤0.03 to >32	12.6	10.5	76.9
Meropenem	0.03	0.06	≤0.015 to 1	100.0	0.0	0.0
Imipenem	≤0.12	0.25	≤0.12 to 8	98.1	1.2	0.7
Ciprofloxacin	>4	>4	≤0.008 to >4	16.8	6.6	76.6
Levofloxacin	8	32	≤0.015 to >32	25.3	7.3	67.4
Amikacin	4	8	≤0.25 to >32	78.9	14.0	7.1
Gentamicin	1	>16	≤0.12 to >16	62.5	0.7	36.8
Carbapenem-nonsusceptible[b] (165)						
Cefiderocol	0.5	4	0.008 to >64	97.6	1.2	1.2
Imipenem-relebactam[c]	0.25	4	0.06 to >8	81.2	6.1	12.7
Meropenem-vaborbactam	0.12	8	≤0.015 to >8	87.9	3.6	8.5
Ceftazidime-avibactam	1	8	≤0.015 to >32	91.5	—	8.5
Piperacillin-tazobactam	>128	>128	1 to >128	12.7	1.8	85.5
Aztreonam	>16	>16	≤0.03 to >16	16.4	0.6	83.0
Ceftriaxone	>8	>8	≤0.06 to >8	12.1	1.2	86.7
Ceftazidime	>32	>32	0.12 to >32	18.2	1.8	80.0
Cefepime[d]	32	>32	≤0.03 to >32	20.6	21.8	57.6
Meropenem	8	>32	0.03 to >32	22.4	15.8	61.8
Imipenem	8	>8	0.5 to >8	5.5	23.6	70.9
Ciprofloxacin	2	>4	≤0.008 to >4	38.8	4.8	56.4
Levofloxacin	1	>32	≤0.015 to >32	43.0	7.3	49.7
Amikacin	2	32	≤0.25 to >32	70.9	10.3	18.8
Gentamicin	1	>16	≤0.12 to >16	62.4	6.1	31.5

[a] Criteria as published by CLSI (2023); cefiderocol used equivalent FDA/CLSI breakpoints; "—", breakpoint not available.
[b] See footnotes on Table 1 for additional information.
[c] Imipenem-relebactam analyses excludes *Morganella* spp., *Proteus* spp., and *Providencia* spp., where breakpoints are not available.
[d] Intermediate can be interpreted as susceptible-dose dependent.

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



* Other includes isolates carrying the following genes: bla_{NDM-1} (7), bla_{NDM-5} (3), bla_{VIM-1} (1), $bla_{OXA-181}$ (2), $bla_{OXA-232}$ (2), bla_{OXA-48} (4), and bla_{NDM-5} + $bla_{OXA-181}$ (1). See footnotes on Table 1 for additional information.

Figure 2. Distribution of carbapenemase genes detected among carbapenem-nonsusceptible Enterobacterales