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Activity of cefiderocol against carbapenem non-susceptible Enterobacterales, including molecularly characterized clinical isolates causing infection in hospitals in European and adjacent regions (2020–2022)

RE Mendes, CM Hubler, D Beekman, JM Maher, JH Kimbrough, HS Sader, M Castanheira
Element Iowa City (JMI Laboratories), North Liberty, Iowa, USA

Introduction

- Cefiderocol is approved in Europe for the treatment of infections in adult patients due to aerobic Gram-negative organisms, where limited treatment options are available.
  - Cefiderocol was also 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 activity of cefiderocol and comparators was investigated against Enterobacterales collected from hospitals in European countries and adjacent regions during 2020–2022.

Materials and Methods

Bacterial organisms

- This study comprised a collection of 12,200 Enterobacterales collected from various clinical specimens from patients hospitalized in 39 centers in 16 European countries, Israel, and Turkey during 2020–2022. Only consecutive isolates (1 per patient infection episode) responsible for documented infections according to local institutional 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, bacterial inoculum (colony counts), and testing CLSI-recommended quality control reference strains.
- Cefiderocol MIC results were interpreted according to EUCAST and FDA/CLSI criteria, whereas MIC values obtained for comparator agents were interpreted based on EUCAST criteria.
- *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 Prep™ 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.

Table 1. Activity of cefiderocol, β-lactam-β-lactamase inhibitor combinations, and comparator agents against Enterobacterales and resistant subsets

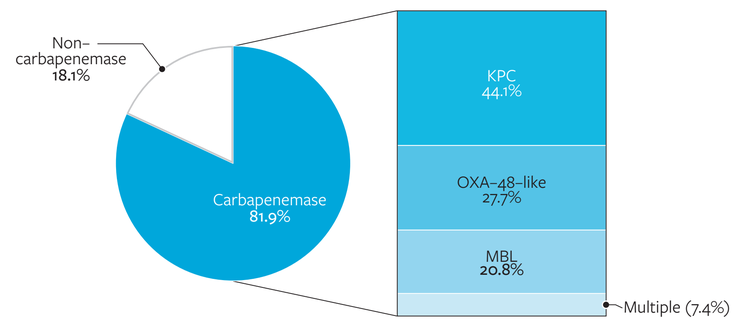
Phenotype/genotype[a] (No.)	MIC_{50}/MIC_{90} in mg/L (% susceptible by EUCAST/FDA criteria)[b]					
	CFDC	IMR	MEV	CZA	MER	COL
All (12,200)	0.06/0.5 (98.6/99.8)	0.12/1 (97.7)	0.03/0.06 (98.8)	0.12/0.25 (99.0)	0.03/0.06 (97.0)	0.25/>8 (83.7)
Carbapenem-non-S (463)	1/4 (82.3/95.0)	1/>8 (64.8)	1/>8 (67.8)	1/>32 (76.2)	32/>32 (21.2)	0.25/>8 (69.9)
Carbapenemase-positive[c] (379)	1/4 (81.5/95.5)	1/>8 (57.8)	2/>8 (60.9)	2/>32 (71.5)	32/>32 (15.0)	0.25/>8 (71.2)
Class A (167)	0.5/2 (91.0/98.2)	0.25/0.5 (100)	0.25/2 (98.8)	1/4 (98.8)	>32/>32 (6.0)	0.25/>8 (82.0)
Class B (79)	2/4 (63.3/91.1)	>8/>8 (3.8)	>8/>8 (20.3)	>32/>32 (2.5)	32/>32 (7.6)	0.25/>8 (62.0)
Class D (105)	0.5/4 (89.5/99.0)	4/8 (46.7)	>8/>8 (44.8)	1/2 (99.0)	16/>32 (39.0)	0.25/>8 (66.3)
Multiple (28)	4/8 (46.4/78.6)	>8/>8 (0.0)	>8/>8 (10.7)	>32/>32 (0.0)	>32/>32 (0.0)	2/>8 (50.0)
Carbapenemase-negative[d] (84)	1/4 (85.7/92.9)	0.5/2 (96.4)	0.5/4 (98.8)	1/4 (97.6)	4/16 (48.8)	0.25/>8 (64.2)

Abbreviations: CFDC, cefiderocol; IMR, imipenem-relebactam; MEV, meropenem-vaborbactam; CZA, ceftazidime-avibactam; MER, meropenem; COL, colistin.
[a] Carbapenem-non-S, isolates non-susceptible to imipenem (excluded for *P. mirabilis*, *P. penneri*, and indole-positive Proteeae) and/or meropenem based on CLSI criteria (MIC values ≥2 mg/L).
[b] Cefiderocol MIC results were interpreted according to EUCAST and FDA criteria (CLSI criteria are the same as FDA), whereas MIC values for comparator agents were interpreted based on EUCAST criteria.
[c] Includes the class A bla_{KPC-2} (71) and bla_{KPC-3} (96) genes; the class B bla_{NDM-1} (57), bla_{NDM-19} (1), bla_{NDM-5} (4), bla_{NDM-6} (1), bla_{NDM-7} (2), bla_{NDM-9} (2), bla_{VIM-1} (11), and bla_{VIM-4} (1) genes; the class D bla_{OXA-48} (60), $bla_{OXA-181}$ (8), $bla_{OXA-232}$ (34), and $bla_{OXA-244}$ (3) genes; and the combinations bla_{NDM-1} + bla_{KPC-2} (2), bla_{NDM-1} + bla_{KPC-3} (1), bla_{NDM-1} + bla_{OXA-48} (12), bla_{NDM-1} + $bla_{OXA-232}$ (3), bla_{VIM-1} + bla_{KPC-2} (5), bla_{VIM-1} + bla_{KPC-3} (4), and bla_{VIM-1} + bla_{OXA-48} (1).
[d] Carbapenemase genes were not detected in the following species: *Enterobacter cloacae* species complex (16), *Klebsiella aerogenes* (9), *K. pneumoniae* (44), *Serratia liquefaciens* (1), *S. marcescens* (14).

Results

- A total of 3.8% (463/12,200) of Enterobacterales clinical isolates were non-susceptible to carbapenems, and among these 81.9% (379/463) carried carbapenemase genes (Table 1 and Figure 1).
  - bla_{KPC} (44.1%) prevailed, followed by bla_{OXA-48} (27.7%) and class B carbapenemases (20.8%).
  - Turkey (23.8%), Italy (23.0%), and Greece (20.6%) contributed with 67.3% of carbapenemase-carrying isolates, followed by Spain (8.7%), Romania (5.5%), Poland (5.3%), Germany (4.2%), and 8 other countries (≤2.1%) contributing with less isolates (data not shown).
  - In addition, a total of 7.4% of Enterobacterales isolates carrying carbapenemases had 2 genes. These isolates originated from Turkey (35.7%), Romania (28.6%), Greece (21.4%), Italy (10.7%), and Spain (3.6%) (data not shown).
- Overall, cefiderocol, β-lactam/β-lactamase inhibitor combinations, and meropenem had susceptibility results of ≥97% when tested against all Enterobacterales.
- Cefiderocol (81.5–95.5% susceptible) had MIC_{50} of 1 mg/L and MIC_{90} of 4 mg/L against carbapenem-non-susceptible and carbapenemase-carrying isolates.
  - Other comparator agents had susceptibility results of 15.0–76.2%.
- Cefiderocol (91.0/98.2% susceptible) and β-lactam/β-lactamase inhibitor combinations (98.8–100% susceptible) were active against isolates carrying class A carbapenemases.
- Cefiderocol had the lowest MIC against isolates carrying class B genes ($MIC_{50/90}$, 2/4 mg/L; 63.3/91.1% susceptible).
- Cefiderocol (89.5/99.0% susceptible) and ceftazidime-avibactam (99.0% susceptible) were active against isolates carrying class D carbapenemase genes.
- Cefiderocol ($MIC_{50/90}$, 4/8 mg/L; 46.4/78.6% susceptible) showed the lowest MIC_{90} value against isolates carrying multiple carbapenemases, whereas other agents had limited activity (MIC_{90}, >8 mg/L).

Figure 1. Distribution of carbapenemase genes detected among carbapenem-non-susceptible Enterobacterales



Conclusions

- Cefiderocol was consistently *in vitro* active against carbapenem-non-susceptible Enterobacterales clinical isolates causing infections in hospitals in European countries and adjacent regions (2020–2022).
  - Cefiderocol was active against isolates carrying carbapenemases, including isolates with multiple carbapenemase genes emerging in some regions.
- These *in vitro* data suggest that cefiderocol is an important option for the treatment of infections caused by these resistant pathogens.

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Contact

Rodrigo E. Mendes, Ph.D.
Element Iowa City (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

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