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

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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.
- The activity of cefiderocol and comparatodr agents was investigated against *P. aeruginosa* collected from hospitals in European countries and adjacent regions during 2020–2022.

Materials and Methods

Bacterial organisms

- This study comprised a collection of 3,926 *P. aeruginosa* collected from various clinical specimens from patients hospitalized in 40 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).

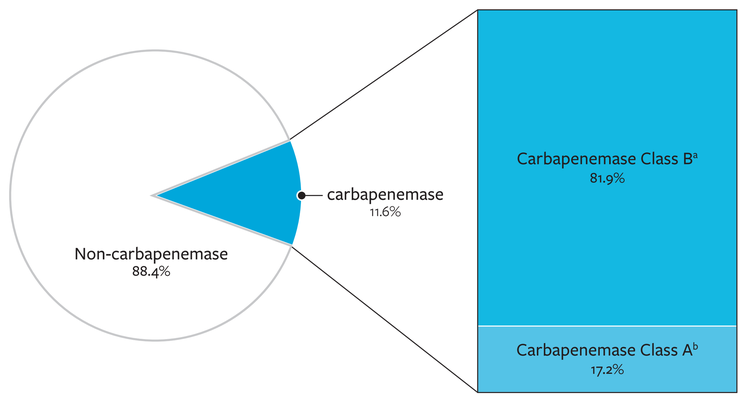
Susceptibility testing

- 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 the EUCAST/FDA (same as CLSI criteria) criteria, whereas MIC values obtained for comparator agents were interpreted based on EUCAST criteria.
- Isolates with imipenem and/or meropenem MIC ≥4 mg/L (non-susceptible based on CLSI criteria) 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.

Figure. Distribution of carbapenemase classes detected among carbapenem-nonsusceptible *P. aeruginosa*



[a] Includes bla_{IMP-13} (2), bla_{IMP-7} (4), bla_{NDM-1} (8), bla_{VIM-1} (8), bla_{VIM-1} and bla_{PER-1} (1), bla_{VIM-2} (65), bla_{VIM-20} (2), bla_{VIM-4} (4), bla_{VIM-43} (1).
[b] Includes bla_{GES-5} (16) and bla_{GES-6} (4).

Table. Activity of cefiderocol, β-lactam-β-lactamase inhibitor combinations and comparator agents against *P. aeruginosa* and resistant subsets

Phenotype/genotype[a] (No. tested)	MIC_{50}/MIC_{90} in mg/L (% susceptible by EUCAST/CLSI criteria)[b]					
	CFDC	IMR	MEV	MER	CZA	C/T
All (3,926)	0.12/0.25 (99.4/99.7)	0.25/1 (95.1)	0.5/8 (90.6)	0.5/8 (79.8)	2/4 (95.8)	0.5/2 (94.5)
Carbapenem-nonS (996)	0.12/0.5 (98.2/99.1)	1/>8 (80.8)	8/>8 (62.9)	8/32 (20.2)	4/32 (84.2)	1/>16 (80.2)
Carbapenemase-positive[c] (116)	0.12/2 (96.6/98.3)	>8/>8 (0.0)	>8/>8 (14.7)	>32/>32 (6.9)	32/>32 (19.0)	>16/>16 (0.0)
Class A[d] (20)	0.12/0.25 (100/100)	>8/>8 (0.0)	>8/>8 (0.0)	>32/>32 (0.0)	4/4 (4/4 (90.0)	8/>16 (0.0)
Class B[e] (95)	0.25/2 (95.8/97.9)	>8/>8 (0.0)	>8/>8 (17.9)	>32/>32 (8.4)	32/>32 (4.2)	>16/>16 (0.0)
Carbapenemase-negative (880)	0.12/0.5 (98.4/99.2)	1/2 (91.5)	8/>8 (69.2)	8/16 (21.9)	4/8 (92.8)	1/4 (90.8)

Abbreviations: CFDC, cefiderocol; IMR, imipenem-relebactam; MEV, meropenem-vaborbactam; MER, meropenem; CZA, ceftazidime-avibactam; C/T, ceftolozane-tazobactam.
[a] Carbapenem-nonS, isolates non-susceptible to imipenem and/or meropenem based on CLSI criteria (MIC values ≥4 mg/L).
[b] Cefiderocol MIC results were interpreted according to the EUCAST/CLSI criteria, whereas comparator agent MIC were interpreted based on EUCAST criteria.
[c] Includes bla_{GES-5} (16), bla_{GES-6} (4), bla_{IMP-13} (2), bla_{IMP-7} (4), bla_{NDM-1} (8), bla_{VIM-1} (8), bla_{VIM-1} and bla_{PER-1} (1), bla_{VIM-2} (65), bla_{VIM-2} + bla_{GES-5} (1), bla_{VIM-20} (2), bla_{VIM-4} (4), bla_{VIM-43} (1).
[d] Includes bla_{GES-5} (16) and bla_{GES-6} (4).
[e] Includes bla_{IMP-13} (2), bla_{IMP-7} (4), bla_{NDM-1} (8), bla_{VIM-1} (8), bla_{VIM-1} and bla_{PER-1} (1), bla_{VIM-2} (65), bla_{VIM-20} (2), bla_{VIM-4} (4), bla_{VIM-43} (1).

Results

- A total of 25.4% (996/3,926) *P. aeruginosa* isolates were not susceptible to carbapenems, and 11.6% (116/996) carried carbapenemases (Figure and Table).
  - Class B (81.9%) alleles were the most common carbapenemases detected, and mostly comprised by bla_{VIM} (85.3%).
  - A small number of isolates carried class A (17.2%) alleles.
- Cefiderocol and β-lactam/β-lactamase inhibitor (BL/BLI) agents had susceptibilities of >90% against all *P. aeruginosa* (Table).
- Cefiderocol had MIC_{50} and MIC_{90} of 0.12 mg/L and 0.5 mg/L, respectively, and susceptibilities of 98.2–99.1% against carbapenem-non-susceptible isolates (Table).
  - BL-BLI had susceptibilities of 62.9–84.2% against these groups.
- Cefiderocol remained active against isolates carrying carbapenemases (95.8–100% susceptible) (Table).
  - Other BL/BLI comparator agents showed susceptibilities of <20% against those isolates carrying carbapenemases, except for ceftazidime-avibactam against isolates carrying class A carbapenemases (90.0% susceptible).
- A great proportion (88.4%) of *P. aeruginosa* not susceptible to carbapenems did not carry carbapenemases (Figure and Table).
  - Cefiderocol had MIC_{50} and MIC_{90} of 0.12 mg/L and 0.5 mg/L, respectively, and susceptibilities of 98.4–99.2% against these isolates.
  - BL/BLI combinations tested were active against these isolates, except for meropenem-vaborbactam.

Conclusions

- Cefiderocol had consistent *in vitro* activity against *P. aeruginosa* isolates causing infections in hospitals located in European countries and adjacent regions (2020–2022).
- Cefiderocol remained active against carbapenemase-producing subsets, where most newer BL/BLI agents showed limited activity.
- These *in vitro* data suggest that cefiderocol is an important option for the treatment of infections caused by these resistant pathogens.

Acknowledgements

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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*. 74: 1303–1312.

6. Syed YY. 2021. Cefiderocol: A review in serious Gram-negative bacterial infections. *Drugs*. 24: 1–13.

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