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Activity of cefiderocol against carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex, 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 comparators was investigated against *A. baumannii-calcoaceticus* complex collected from hospitals in European countries and adjacent regions during 2020–2022.

Materials and Methods

Bacterial organisms

- This study comprised a collection of 1,504 *A. baumannii-calcoaceticus* complex 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).

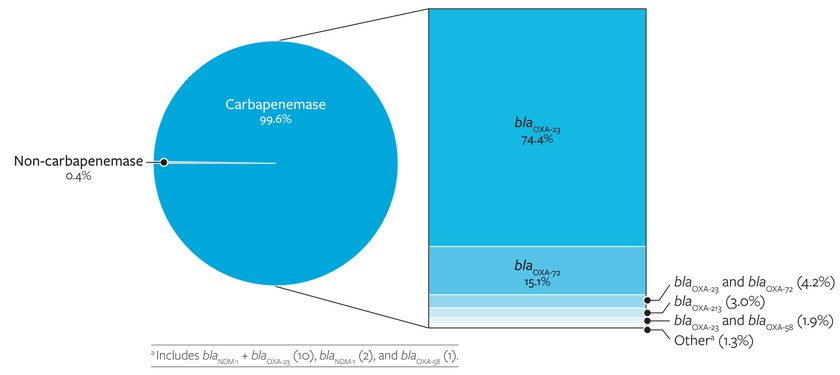
Susceptibility testing

- 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 the EUCAST/FDA (same as CLSI criteria) criteria, whereas MIC values obtained for comparator agents were interpreted based on EUCAST criteria, except for ampicillin-sulbactam and ceftazidime that used CLSI.
- 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 genes detected among carbapenem-nonsusceptible *A. baumannii-calcoaceticus* complex (66.2% of all isolates)



[a] Includes bla_{NDM-1} + bla_{OXA-23} (10), bla_{NDM-1} (2), and bla_{OXA-58} (1).

Table. Activity of cefiderocol, β-lactam-β-lactamase inhibitor combinations and comparator agents against *A. baumannii-calcoaceticus* complex and resistant subsets

Phenotype[a]/genotype (No.)	MIC_{50}/MIC_{90} in mg/L (% susceptible by EUCAST/CLSI criteria)[b]					
	CFDC	IMR	MER	A/S	CAZ	COL
All (1,504)	0.25/1 (96.2/97.6)	>8/>8 (35.9)	>32/>32 (35.8)	32/>64 (34.4)	>32/>32 (32.8)	0.5/>8 (85.4)
Carbapenem-nonS (996)	0.25/1 (94.4/96.5)	>8/>8 (0.2)	>32/>32 (0.0)	64/>64 (1.3)	>32/>32 (0.7)	0.5/>8 (77.9)
Carbapenemase-positive (992)	0.12/1 (94.5/96.6)	>8/>8 (3.0)	>32/>32 (2.9)	64/>64 (3.2)	>32/>32 (2.0)	0.5/>8 (78.5)
OXA-23 (738)	0.25/1 (95.5/97.4)	>8/>8 (0.1)	>32/>32 (0.1)	64/>64 (0.7)	>32/>32 (0.7)	0.5/>8 (75.2)
OXA-72 (150)	0.25/2 (96.7/99.3)	>8/>8 (0.7)	>32/>32 (0.7)	32/>64 (6.0)	>32/>32 (1.3)	0.5/>8 (84.7)
OXA-23 and OXA-72[c] (42)	0.25/16 (81.0/81.0)	>8/>8 (2.4)	>32/>32 (2.4)	>64/>64 (0.0)	>32/>32 (0.0)	0.25/0.5 (92.9)
OXA-213[d] (30)	0.12/0.5 (96.7/100)	0.25/>8 (86.7)	0.5/16 (86.7)	8/32 (60.0)	16/>32 (43.3)	0.5/1 (93.3)
OXA-23 and OXA-58 (19)	0.25/0.5 (100/100)	>8/>8 (5.3)	>32/>32 (0.0)	64/>64 (0.0)	>32/>32 (0.0)	0.5/2 (94.7)
Other[e] (13)	4/8 (38.5/53.8)	>8/>8 (0.0)	>32/>32 (0.0)	>64/>64 (0.0)	>32/>32 (0.0)	0.5/0.5 (92.3)

Abbreviations: CFDC, cefiderocol; IMR, imipenem-relebactam; MER, meropenem; A/S, ampicillin-sulbactam; CAZ, ceftazidime; COL, colistin.
[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, except for ampicillin-sulbactam and ceftazidime that used CLSI.
[c] One isolate includes $bla_{OXA-232}$.
[d] Includes *A. pittii* (24) and *A. calcoaceticus* (2), where $bla_{OXA-213}$-variants are intrinsic. Other species included *A. lactucae* (3) and *A. oleivorans* (1).
[e] Includes bla_{NDM-1} + bla_{OXA-23} (10), bla_{NDM-1} (2), and bla_{OXA-58} (1).

Results

- A total of 66.2% (996/1,504) *A. baumannii-calcoaceticus* complex isolates were non-susceptible to carbapenems, and among those virtually all (99.6%; 992/996) carried carbapenemases (Figure).
  - bla_{OXA-23} (74.4%) was among the most common carbapenemase gene detected, followed by bla_{OXA-72} (15.1%) (Figure and Table).
  - Other bla_{OXA} carbapenemases (12.2%) comprised a small number of genes; whereas 1.3% of isolates carried bla_{NDM} alone or in combination with bla_{OXA} carbapenemases.
- Cefiderocol (94.4–97.6% susceptible) had MIC_{50} of 0.25 mg/L and MIC_{90} of 1 mg/L against all isolates and the carbapenem non-susceptible subset, whereas comparators had susceptibilities of <85.5% (Table).
- Cefiderocol (94.5–96.6% susceptible) had MIC_{50} of 0.12 mg/L and MIC_{90} of 1 mg/L against *A. baumannii-calcoaceticus* complex carrying carbapenemases (Table).
  - Comparator agents (<79% susceptible) had activity against these isolates lower than cefiderocol (94.5–96.6% susceptible).
- Cefiderocol also retained activity against isolates showing different carbapenem resistance genes (MIC_{90}, 0.5–2 mg/L; 95.5–100% susceptible) (Table).
  - Higher MIC_{90} values were obtained for cefiderocol when tested against isolates carrying bla_{OXA-23} and bla_{OXA-72} or bla_{NDM-1} (MIC_{90}, 8–16 mg/L) with susceptibilities of 38.5–81.0%.
  - Only colistin (92.3–92.9% susceptible) was *in vitro* active against these isolates.

Conclusions

- Cefiderocol demonstrated *in vitro* activity against *A. baumannii-calcoaceticus* complex causing infections in hospitals located in European countries and adjacent regions (2020–2022).
- In general, this study demonstrated cefiderocol as the most active agent against carbapenem-non-susceptible *A. baumannii-calcoaceticus* complex, with activity across many different resistance genotypes where other agents had 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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