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Activity of cefiderocol against carbapenem-resistant and molecularly characterized Enterobacterales isolates causing infections in hospitals in Europe and adjacent regions (2020–2023)

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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 is 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 organisms like carbapenem-resistant Enterobacterales (CRE).
- The activity of cefiderocol 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 activities of cefiderocol and comparator agents were evaluated against CRE characterized for β-lactamase content and collected from hospitals in European countries and adjacent regions during 2020–2023.

Materials and Methods

Bacterial organisms

- This study comprised a collection of 16,904 Enterobacterales collected from various clinical specimens from patients hospitalized in 42 centers in 17 European countries, Israel, and Turkey during 2020–2023. 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 Element Iowa City (JMI Laboratories; North Liberty, IA, USA) and contained cation-adjusted Mueller-Hinton broth (CAMHB) for comparator agents.
- Susceptibility testing for cefiderocol used broth microdilution panels containing iron-depleted CAMHB 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 (FDA breakpoints are the same as CLSI) criteria, whereas MIC values obtained for comparator agents were interpreted based on EUCAST criteria.
- Enterobacterales with MIC ≥4 mg/L (resistant by CLSI/EUCAST criteria) for imipenem (excluded for *P. mirabilis, P. penneri*, and indole-positive Proteeae) or meropenem were screened for β-lactamase genes by genome sequencing and *in silico* analysis.

Results

- A total of 3.7% (623/16,904) CRE isolates were detected among all participating medical sites (Table 1).
  - CRE isolates were observed in 9.3% and 1.6% of isolates originating from Eastern (including Israel and Turkey) and Western European countries, respectively (Table 1).
  - The highest rates of CRE were observed in Poland (20.5%), Greece (19.3%), and Slovakia (18.3%).
  - Countries in Western Europe had low prevalence of CRE (<2%), except for Italy (5.5%).
- Among CRE isolates, 89.7% (559/623) carried carbapenemase genes (Figure 1 and Table 2).
  - Class A genes (bla_{KPC}; 40.6%) prevailed, followed by class B (25.9%) and class D (bla_{OXA}; 20.2%) carbapenemases.
  - In addition, 13.2% of CRE had multiple carbapenemases.
- Cefiderocol (80.3/94.5% susceptible) had MIC_{50} of 1 mg/L and MIC_{90} of 4 mg/L against CRE, and carbapenemase-positive CRE isolates (Table 2).
  - Other agents had susceptibilities of <69% against these two resistant subsets.
- Cefiderocol (92.5/99.1% susceptible; EUCAST/FDA criteria) and β-lactam-β-lactamase inhibitor combinations (98.2–99.6% susceptible) were active against CRE carrying class A carbapenemases.
- Cefiderocol had the lowest MIC_{90} against isolates carrying class B genes ($MIC_{50/90}$, 2/4 mg/L; 63.4/90.0% susceptible)
  - MIC_{90} of >8 mg/L were obtained for comparators.
- Cefiderocol (90.3/99.1% susceptible) and ceftazidime-avibactam (100% susceptible) were active against CRE carrying class D genes.
- Cefiderocol ($MIC_{50/90}$, 2/8 mg/L; 60.8/81.1% susceptible) showed the lowest MIC_{90} value against isolates carrying multiple carbapenemases.
  - Other agents had limited activity (MIC_{90}, >8 mg/L).

Conclusions

- Cefiderocol showed consistent *in vitro* activity against CRE isolates carrying different carbapenemase genes causing infections in hospitals in European countries and adjacent regions.
- Notably, this consistent activity was most pronounced against CRE carrying class B and multiple carbapenemases, which comprised 39.2% of carbapenemase-carrying CRE.
- These *in vitro* data position cefiderocol as a critical option for the treatment of infections caused by these resistant pathogens.

Acknowledgments

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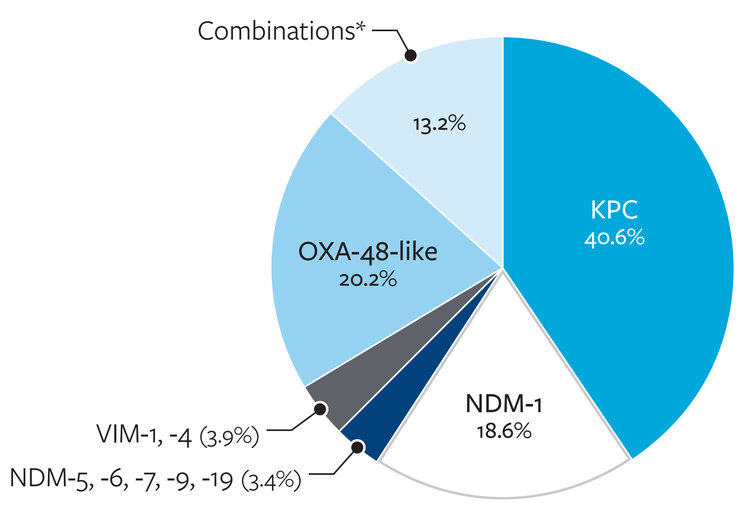
References

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.

Table 1. Distribution of CRE in European countries, Israel, and Turkey

Region Country (Number included)	Number (%) of CRE
Eastern (4533)	423 (9.3)
Czech Republic (346)	4 (1.2)
Greece (590)	114 (19.3)
Hungary (470)	0 (0.0)
Israel (649)	20 (3.1)
Poland (396)	81 (20.5)
Romania (269)	21 (7.8)
Slovakia (109)	20 (18.3)
Slovenia (691)	1 (0.1)
Turkey (1013)	162 (16.0)
Western (12371)	200 (1.6)
Belgium (535)	3 (0.6)
France (1690)	9 (0.5)
Germany (2738)	22 (0.8)
Ireland (597)	3 (0.5)
Italy (2212)	122 (5.5)
Portugal (535)	7 (1.3)
Spain (1665)	31 (1.9)
Sweden (657)	0 (0.0)
Switzerland (575)	0 (0.0)
UK (1167)	3 (0.3)
Total (16904)	623 (3.7)

Figure 1. Distribution of carbapenemase genes detected in CRE isolates included in this study



* Combination of 2 carbapenemase genes, as follows: bla_{KPC-2} + bla_{OXA-48} (4), bla_{NDM-1} + bla_{KPC-2} (6), bla_{NDM-1} + bla_{KPC-3} (3), bla_{NDM-1} + $bla_{OXA-181}$ (4), bla_{NDM-1} + bla_{OXA-48} (32), bla_{NDM-1} + $bla_{OXA-232}$ (4), bla_{NDM-5} + bla_{OXA-48} (7), bla_{NDM-5} + $bla_{OXA-181}$ (1), bla_{VIM-1} + bla_{KPC-2} (6), bla_{VIM-1} + bla_{KPC-3} (4), bla_{VIM-1} + bla_{GES-6} (1), and bla_{VIM-1} + bla_{OXA-48} (2)

Table 2. Activity of cefiderocol, β-lactam-β-lactamase inhibitor combinations and other comparator agents against CRE and molecular characterized subsets

Phenotype/genotype[a] (No.)	MIC_{50}/MIC_{90} in mg/L (% susceptible by EUCAST/FDA criteria)[b]					
	FDC	IMR	MEV	CZA	MER	COL
All (16,904)	0.06/0.5 (98.7/99.7)	0.12/1 (97.3)	0.03/0.06 (98.3)	0.12/0.5 (98.6)	0.03/0.06 (96.5)	0.25/>8 (83.1)
CRE (623)	1/4 (81.1/94.5)	2/>8 (53.5)	4/>8 (55.2)	2/>32 (65.3)	32/>32 (5.3)	0.25/>8 (68.6)
Carbapenemase-positive[c] (559)	1/4 (80.3/94.3)	4/>8 (48.3)	8/>8 (50.3)	2/>32 (61.7)	>32/>32 (5.2)	0.25/>8 (67.6)
Class A (227)	0.5/2 (92.5/99.1)	0.12/0.5 (99.6)	0.25/2 (98.2)	1/4 (99.1)	>32/>32 (2.6)	0.25/>8 (76.7)
Class B (145)	2/4 (63.4/90.0)	>8/>8 (2.1)	>8/>8 (18.6)	>32/>32 (1.4)	32/>32 (6.9)	0.25/>8 (70.3)
Class D (113)	1/2 (90.3/99.1)	4/>8 (31.9)	>8/>8 (19.5)	1/2 (100)	32/>32 (10.6)	2/>8 (50.4)
Multiple (74)	2/8 (60.8/81.1)	>8/>8 (6.8)	>8/>8 (12.2)	>32/>32 (6.8)	>32/>32 (1.4)	0.25/>8 (60.8)
Carbapenemase-negative[d] (64)	1/4 (87.5/96.9)	0.25/2 (98.4)	2/8 (98.4)	2/4 (96.9)	8/16 (6.2)	0.25/>8 (77.8)

Abbreviations: FDC, cefiderocol; IMR, imipenem-relebactam; MEV, meropenem-vaborbactam; CZA, ceftazidime-avibactam; MER, meropenem; COL, colistin.
[a] CRE, isolates resistant to imipenem (excluded for *P. mirabilis, P. penneri*, and indole-positive Proteeae) and/or meropenem based on CLSI criteria (MIC values ≥4 mg/L) or nonsusceptible based on EUCAST criteria.
[b] Cefiderocol MIC results were interpreted according to the EUCAST/FDA criteria (FDA are the same as CLSI criteria), whereas MIC for comparator agents were interpreted based on EUCAST criteria.
[c] Includes the class A bla_{KPC-2} (87), bla_{KPC-3} (139) and bla_{KPC-29} (1) genes; the class B bla_{NDM-1} (104), bla_{NDM-19} (1), bla_{NDM-5} (13), bla_{NDM-6} (1), bla_{NDM-7} (2), bla_{NDM-9} (2), bla_{VIM-1} (21), and bla_{VIM-4} (1) genes; the class D bla_{OXA-48} (50), $bla_{OXA-181}$ (5), $bla_{OXA-232}$ (55), and $bla_{OXA-244}$ (3) genes; and the combinations bla_{KPC-2} + bla_{OXA-48} (4), bla_{NDM-1} + bla_{KPC-2} (6), bla_{NDM-1} + bla_{KPC-3} (3), bla_{NDM-1} + $bla_{OXA-181}$ (4), bla_{NDM-1} + bla_{OXA-48} (32), bla_{NDM-1} + $bla_{OXA-232}$ (4), bla_{NDM-5} + bla_{OXA-48} (7), bla_{NDM-5} + $bla_{OXA-181}$ (1), bla_{VIM-1} + bla_{KPC-2} (6), bla_{VIM-1} + bla_{KPC-3} (4), bla_{VIM-1} + bla_{GES-6} (1), and bla_{VIM-1} + bla_{OXA-48} (2).
[d] Carbapenemase genes were not detected in the following species: *Enterobacter cloacae* species complex (6), *Klebsiella aerogenes* (5), and *K. pneumoniae* (53).

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