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Activity of cefiderocol against carbapenem-resistant *Pseudomonas aeruginosa*, including molecularly characterized clinical isolates, causing infections in hospitals in European and adjacent regions (2020–2023)

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Introduction

- *Pseudomonas aeruginosa* possess various intrinsic treatment-limiting resistance mechanisms, leading to decreased antibiotic permeability.
  - Isolates may acquire β-lactamase genes, such as those encoding class A carbapenemases and especially class B metallo-β-lactamases further decreasing susceptibility to numerous β-lactam agents.
- 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) 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, carbapenem-resistant and difficult-to-treat *P. aeruginosa*.
- In this study, the activity of cefiderocol and comparator agents was investigated against *P. aeruginosa* collected from hospitals in European countries, Israel and Turkey during 2020–2023, as part of the SENTRY Antimicrobial Surveillance Program.

Materials and Methods

Bacterial organisms

- This study comprised a collection of 5,172 *P. aeruginosa* collected from various clinical specimens in patients hospitalized in 43 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 (2024) 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 FDA/EUCAST/CLSI criteria, whereas MIC values obtained for comparator agents were interpreted based on EUCAST criteria.
- Isolates with imipenem and/or meropenem MIC ≥8 mg/L (resistant based on CLSI criteria) were subjected to genome sequencing and screening of β-lactamase genes.

Table 1. Distribution of carbapenem-resistant *P. aeruginosa* in European countries, Israel, and Turkey

Region Country (Number)	Number (%)
Eastern (1571)	455 (29.0)
Czech Republic (93)	22 (23.7)
Greece (173)	57 (32.9)
Hungary (155)	42 (27.1)
Israel (367)	71 (19.3)
Poland (179)	91 (50.8)
Romania (111)	32 (28.8)
Slovakia (19)	9 (47.4)
Slovenia (166)	27 (16.3)
Turkey (308)	104 (33.8)
Western (3601)	600 (16.6)
Belgium (99)	24 (24.2)
France (532)	80 (15.0)
Germany (654)	147 (22.5)
Ireland (120)	27 (22.5)
Italy (790)	114 (14.4)
Portugal (150)	20 (13.3)
Spain (700)	126 (18.0)
Sweden (133)	18 (13.5)
Switzerland (154)	16 (10.4)
UK (269)	28 (10.4)
Total (5172)	1055 (20.4)

Results

- A total of 20.4% (1,055/5,172) *P. aeruginosa* isolates were classified as carbapenem-resistant (Figure 1 and Table 1).
  - Most carbapenem-resistant *P. aeruginosa* originated from pneumonia patients (60%), whereas smaller percentages originated from bloodstream infections (14%), skin and skin structure infections (13%), and urinary tract infections (8%).
- A carbapenem resistance phenotype was observed in 29.0% and 16.6% of isolates originating from Eastern (includes Israel and Turkey) and Western European countries, respectively (Table 1).
  - Poland (51%), Slovakia (47%), Turkey (34%), and Greece (33%) showed highest percentages of carbapenem resistance among isolates from the Eastern European region.
  - Belgium (24%), Germany (23%), and Ireland (23%) showed highest percentages of carbapenem resistance among isolates from the Western region.
- Among carbapenem-resistant isolates, 21.1% (146/1,055) carried carbapenemases (Figure 1 and Table 2).
  - Carbapenemse genes were mostly represented by class B (85.5%; 125/146), where *bla*$_{VIM}$ consisted of 79.2% (99/125) of alleles.
  - Class A genes were detected in 14.5% (21/146) carbapenemase-positive isolates.
- Cefiderocol had MIC$_{50}$ and MIC$_{90}$ values of 0.12 mg/L and 0.5 mg/L, respectively, and susceptibilities of 95.3–98.9% against carbapenem-resistant *P. aeruginosa*, whereas β-lactam-β-lactamase inhibitor (BL-BLI) combinations had susceptibilities of 54.2–80.6% (Table 2).
- Cefiderocol had MIC$_{50/90}$ values of 0.12/0.25 mg/L against isolates carrying class A (100% susceptible) and MIC$_{50/90}$ of 0.25/2 mg/L against isolates with class B (83.2–94.4% susceptible) carbapenemases (Table 2).
  - Other comparators showed susceptibilities of <15% against both subsets, except for ceftazidime-avibactam against isolates carrying class A carbapenemases (90.5% susceptible).
- Cefiderocol (96.8–99.4% susceptible), imipenem-relebactam (90.5% susceptible), and ceftazidime-avibactam (91.0% susceptible) showed high susceptibilities against carbapenem-resistant, carbapenemase-negative isolates (Table 2).

Conclusions

- Cefiderocol was the most active agent tested *in vitro* against *P. aeruginosa* isolates causing infections in hospitals located in European countries, Israel and Turkey.
- Cefiderocol remained active against carbapenemase-producing subsets, where BL-BLI combinations and other agents were not active.
- These *in vitro* data suggest that cefiderocol is an important option for the treatment of infections caused by these resistant pathogens, for which antibiotic treatment options are limited.

Acknowledgments

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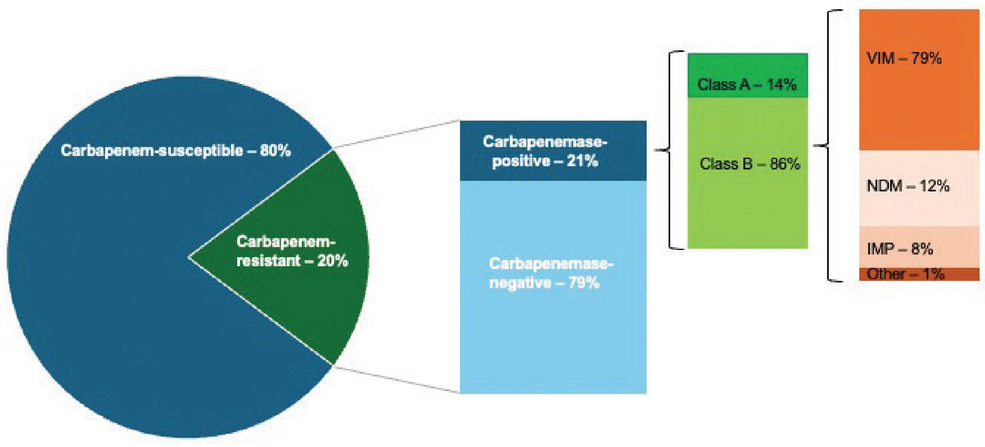
Figure 1. Distribution of phenotypes and genotypes[a] observed among *P. aeruginosa*



[a] Additional information related to the carbapenemase genes detected is described in the footnotes of Table 2.

Table 2. Activity of cefiderocol, β-lactam-β-lactamase inhibitor combinations and meropenem against *P. aeruginosa* and carbapenem-resistant subsets from European countries, Israel, and Turkey

Phenotype/genotype[a] (No. tested)	MIC$_{50}$/MIC$_{90}$ in mg/L (% susceptible by FDA/EUCAST/CLSI criteria)[b]					
	FDC	IMR	MEV	CZA	C/T	MER
All (5,172)	0.12/0.5 (98.6/99.4/99.7)	0.25/1 (95.5)	0.5/8 (90.7)	2/4 (95.6)	0.5/2 (94.7)	0.5/8 (79.6)
Carbapenem-resistant (1,055)	0.12/0.5 (95.3/97.8/98.9)	1/>8 (78.0)	8/>8 (54.2)	4/32 (80.6)	1/>16 (77.2)	8/>32 (9.7)
Carbapenemase-positive[c] (146)	0.25/2 (85.6/93.2/95.2)	>8/>8 (0.0)	>8/>8 (12.3)	32/>32 (16.4)	>16/>16 (0.0)	>32/>32 (5.5)
Class A[d] (21)	0.12/0.25 (100/100/100)	>8/>8 (0.0)	>8/>8 (0.0)	4/4 (90.5)	8/>16 (0.0)	>32/>32 (0.0)
Class B[e] (125)	0.25/2 (83.2/92.0/94.4)	>8/>8 (0.0)	>8/>8 (14.4)	>32/>32 (4.0)	>16/>16 (0.0)	>32/>32 (6.4)
Carbapenemase-negative (909)	0.12/0.5 (96.8/98.6/99.4)	1/2 (90.5)	8/>8 (60.9)	4/8 (91.0)	1/8 (89.6)	8/32 (10.3)

Abbreviations: FDC, cefiderocol; IMR, imipenem-relebactam; MEV, meropenem-vaborbactam; CZA, ceftazidime-avibactam; C/T, ceftolozane-tazobactam; MER, meropenem.
[a] Carbapenem-resistant, isolates resistant to imipenem and/or meropenem based on CLSI criteria (MIC values ≥8 mg/L).
[b] Cefiderocol MIC results were interpreted according to the FDA/EUCAST/CLSI criteria, whereas comparator agent MIC were interpreted based on EUCAST criteria.
[c] Includes *bla*$_{GES-5}$ (17), *bla*$_{GES-6}$ (4), *bla*$_{FIM-1}$ (1), *bla*$_{IMP-1}$ (1), *bla*$_{IMP-7}$ (5), *bla*$_{IMP-8}$ (1), *bla*$_{IMP-10}$ (1), *bla*$_{IMP-13}$ (2), *bla*$_{NDM-1}$ (15), *bla*$_{VIM-1}$ (9), *bla*$_{VIM-2}$ (77), *bla*$_{VIM-4}$ (8), *bla*$_{VIM-5}$ (1), *bla*$_{VIM-20}$ (2), *bla*$_{VIM-43}$ (1), *bla*$_{VIM-2}$ + *bla*$_{GES-5}$ (1).
[d] Includes *bla*$_{GES-5}$ (17) and *bla*$_{GES-6}$ (4).
[e] Includes *bla*$_{FIM-1}$ (1), *bla*$_{IMP-1}$ (1), *bla*$_{IMP-7}$ (5), *bla*$_{IMP-8}$ (1), *bla*$_{IMP-10}$ (1), *bla*$_{IMP-13}$ (2), *bla*$_{NDM-1}$ (15), *bla*$_{VIM-1}$ (9), *bla*$_{VIM-2}$ (77), *bla*$_{VIM-4}$ (8), *bla*$_{VIM-5}$ (1), *bla*$_{VIM-20}$ (2), *bla*$_{VIM-43}$ (1), *bla*$_{VIM-2}$ + *bla*$_{GES-5}$ (1).