Comparison Analysis of *In vitro* Activity of Cefiderocol and Comparator Agents against Molecularly Characterized Carbapenem-resistant *Enterobacterales* Clinical Isolates Causing Infections in Europe and Surrounding Regions (2020)

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Objective

- The cefiderocol and comparator activities were analysed against *Enterobacterales*, including molecularly characterized carbapenem-resistant isolates (CRE) as part of the SENTRY Antimicrobial Surveillance Program for Europe and adjacent regions.

Methods

- A total of 3,994 *Enterobacterales* were collected from 34 medical sites in 15 European countries, Israel, and Turkey during 2020.
- Isolates were tested for susceptibility by broth microdilution method.
  - Cefiderocol was tested in iron-depleted media.
  - MIC interpretation used EUCAST and CLSI breakpoints.
- Isolates displaying MIC values ≥4 mg/L for imipenem (excluding *Proteus mirabilis, P. penneri*, and indole-positive *Proteus*) or meropenem were subjected to genome sequencing and screening of β-lactamase genes.

Results

Table Activity of cefiderocol and main comparators against *Enterobacterales* and molecularly characterized clinical isolates from Europe and adjacent regions

Phenotype/genotype (No. isolates)	MIC_{50}/MIC_{90} in mg/L (% susceptible by EUCAST/CLSI criteria)[a]				
	Cefiderocol	IMR	MEV	CZA	Meropenem
Enterobacterales (3,994)	0.12/0.5 (98.9/99.8)	0.12/1 (98.2/94.0)	0.03/0.06 (99.0/98.9)	0.12/0.5 (99.1)	0.03/0.06 (96.9)
Non-CRE[b] (3,861)	0.12/0.5 (99.3/99.9)	0.12/0.5 (99.3/95.2)	0.03/0.06 (100/100)	0.12/0.25 (99.8)	0.03/0.06 (100)
CRE[b] (133)	1/4 (88.0/98.5)	0.5/>8 (66.9/67.7)	1/>8 (71.4/67.7)	2/>32 (78.2)	32/>32 (8.3)
KPC[c] (64)	0.5/2 (100/100)	0.25/0.5 (100/98.4)	0.06/2 (98.4/98.4)	2/4 (100)	32/>32 (4.7)
OXA-48-like[d] (21)	0.5/1 (100/100)	4/8 (23.8/0.0)	>8/>8 (28.6/23.8)	1/1 (100)	16/>32 (23.8)
MBL[e] (19)	2/4 (57.9/94.7)	>8/>8 (5.3/0.0)	>8/>8 (26.3/26.3)	>32/>32 (0.0)	32/>32 (10.5)
Other[f] (8)	2/- (50.0/87.5)	8/- (0.0/0.0)	>8/- (25.0/0.0)	>32/- (0.0)	>32/- (0.0)
Non-carbapenemases[g] (21)	1/4 (81.0/100)	0.5/2 (90.5/76.2)	2/8 (90.5/81.0)	1/4 (90.5)	8/16 (4.8)

[a] EUCAST/CLSI interpretation were used for cefiderocol, imipenem/relebactam (IMR), and meropenem-vaborbactam (MEV); ceftazidime-avibactam (CZA) and meropenem MIC interpreted according to EUCAST criteria (2021)

[b] Non-CRE, includes isolates with imipenem and/or meropenem MIC ≤2 mg/L; CRE, defined as isolates with imipenem (excluded for *P. mirabilis, P. penneri* and indole-positive *Proteus*) and/or meropenem MIC ≥4 mg/L

[c] Includes 20 isolates carrying bla_{KPC-2} and 44 bla_{KPC-3}

[d] Includes 16 isolates carrying bla_{OXA-48}, 3 $bla_{OXA-232}$ and 2 $bla_{OXA-181}$

[e] Includes 15 isolates carrying bla_{NDM-1} and 4 bla_{VIM-1}

[f] Includes isolates with multiple genes. 4 bla_{KPC-3} and bla_{VIM-1}; 2 bla_{OXA-48} and bla_{NDM-1}; 1 bla_{KPC-2} and bla_{NDM-1}; and 1 bla_{OXA-48} and bla_{VIM-1}

[g] Includes CRE with no known carbapenemase genes detected

Results

- A total of 133 (3.3%) CRE were detected and were represented mostly by isolates carrying *bla*$_{KPC}$ (48.1%; 64/133).
  - Other carbapenemases found were *bla*$_{OXA-48}$-like (15.8%; 21/133) and metallo-β-lactamase (MBL) genes (14.3%; 19/133).
- Cefiderocol, imipenem-relebactam, meropenem-vaborbactam, ceftazidime-avibactam, and meropenem were active (94.0-100% susceptible) against all isolates and the non-CRE subset.
- Only cefiderocol (MIC$_{50/90}$, 1/4 mg/L; 88-98.5% susceptible) had on-scale MIC$_{90}$ results against all CRE.
- All comparator agents but meropenem were active (98.4-100% susceptible) against isolates carrying *bla*$_{KPC}$.
- Cefiderocol (MIC$_{50/90}$, 0.5/1 mg/L) and ceftazidime-avibactam (MIC$_{50/90}$, 1/1 mg/L) were fully active against those isolates carrying *bla*$_{OXA-48}$-like genes.
- All but 2 isolates (MIC, 8 mg/L) carrying MBL or multiple carbapenemase genes were inhibited by cefiderocol at ≤4 mg/L.
- Finally, cefiderocol (MIC$_{50/90}$, 1/4 mg/L), imipenem-relebactam (MIC$_{50/90}$, 0.5/2 mg/L), and ceftazidime-avibactam (MIC$_{50/90}$, 1/4 mg/L) were the most active agent against CRE, where no known carbapenemase genes were detected.

Conclusions

- Cefiderocol showed potent activity against this collection of isolates carrying an heterogeneous array of carbapenemase genes.
- The activity of cefiderocol was consistent against various genotypes, where approved β-lactam/β-lactamase inhibitor combinations showed limited activity.
- These data confirm cefiderocol as an important option for the treatment of infections caused by *Enterobacterales* and resistant subsets.

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