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Activity of Cefiderocol and Comparator Agents Against European Enterobacterales, Including Carbapenem-Resistant Isolates, from the SENTRY Antimicrobial Surveillance Program (2020–2024)

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INTRODUCTION

- Carbapenem-resistant Enterobacterales (CRE) isolates represent a significant global healthcare threat and are recognised by the World Health Organization as critical priority pathogens.
- Cefiderocol, a siderophore cephalosporin, has broad activity against difficult-to-treat Gram-negative bacteria, including CRE and isolates that are resistant to recent beta-lactam–beta-lactamase inhibitor combinations (BL–BLIs).

OBJECTIVE

- In this study, we analysed the contemporary *in vitro* activity of cefiderocol and comparator agents against clinical CRE isolates collected from Europe, Turkey and Israel during 2020–2024 as part of the SENTRY Antimicrobial Surveillance Program.
- The surveillance study was designed to evaluate specifically *in vitro* activity according to major carbapenemase types, including metallo-beta-lactamases, and the activity of cefiderocol against isolates exhibiting cross-resistance to recent beta-lactam–beta-lactamase inhibitor combinations.

METHODS

- Gram-negative isolates responsible for documented infections were consecutively collected in European (n=38), Israeli (n=2) and Turkish (n=2) hospitals during 2020–2024 as part of the SENTRY Antimicrobial Surveillance Program.
- Minimum inhibitory concentrations were determined according to the Clinical and Laboratory Standards Institute (CLSI) methods using broth microdilution with cation-adjusted Mueller–Hinton broth (CAMHB) for comparator agents and iron-depleted CAMHB for cefiderocol.
- Resistance to carbapenems was based on European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for non-meningitis infections (meropenem >8 mg/L and/or imipenem >4 mg/L).
- Susceptibility to cefiderocol and comparators was assessed according to both EUCAST (v15) and CLSI/US Food and Drug Administration (FDA) (M100 ED35:2025) breakpoints.

RESULTS

- A total of **21,451** clinical isolates of Enterobacterales were tested, of which 3.4% (n=730) were defined as CRE by EUCAST criteria (**Table 1**).
  - The most prevalent CRE was *Klebsiella pneumoniae* (87.4%).
  - The most prevalent single carbapenemases were KPC (35%), NDM (21%) and OXA-48 type enzymes (17%); 14% of isolates carried both OXA-48 and metallo-beta-lactamases (MBLs) (**Figure 2**).
- Cefiderocol had potent activity against CRE (**Figure 1**) and showed the highest susceptibility rates by both EUCAST and CLSI/FDA breakpoint criteria (**Table 1**).
- High levels of cross-resistance were observed between the three BL–BLI combinations tested, whereas cefiderocol retained high activity against BL–BLI-resistant phenotypes (**Table 1**).
- Cefiderocol retained good activity against isolates carrying carbapenemases from different Ambler classes (**Figure 2**).

CONCLUSIONS

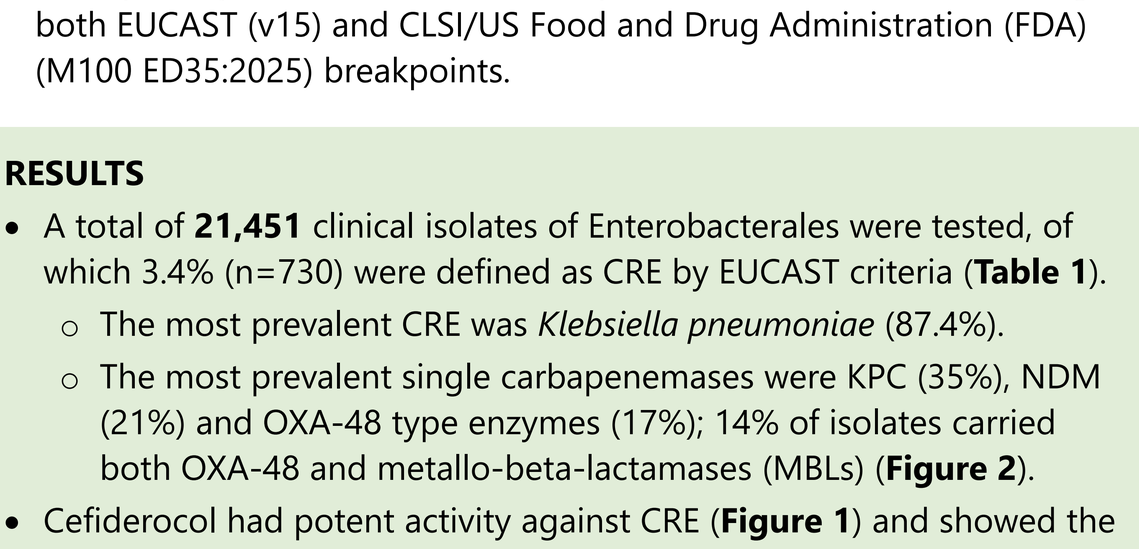
- Cefiderocol had potent activity against CRE isolates from Europe, including MBL-producing strains and the activity was retained against subsets cross-resistant to recent BL–BLI combinations.
- Cefiderocol should be considered as a treatment option when CRE, including those producing MBLs, are suspected or confirmed.

Table 1 Susceptibilities to cefiderocol and comparators tested against European Enterobacterales isolates, including resistant phenotypes.

	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S EUCAST[a]	%S CLSI/FDA[a]
All Enterobacterales (n=21,451)				
Cefiderocol	0.06	0.5	98.8	99.7
Meropenem	0.03	0.06	96.4	96.1
Meropenem-vaborbactam	0.03	0.06	98.1	97.9
Imipenem-relebactam[b]	0.12	1	97.1	92.7
Ceftazidime-avibactam	0.12	0.5	98.4	98.4
CRE: Meropenem MIC >8 mg/L and/or imipenem >4 mg/L (n=730)[c]				
Cefiderocol	1	4	82.6	94.6
Meropenem	>32	>32	4.1	3.6
Meropenem-vaborbactam	>8	>8	43.9	40.7
Imipenem-relebactam[b]	4	>8	44.2	37.7
Ceftazidime-avibactam	2	>32	58.4	58.4
Meropenem-vaborbactam MIC >8 mg/L (n=412)				
Cefiderocol	2	4	73.5	91.0
Meropenem	>32	>32	0.0	0.0
Meropenem-vaborbactam	>8	>8	0.0	0.0
Imipenem-relebactam[b]	>8	>8	12.4	3.4
Ceftazidime-avibactam	>32	>32	33.5	34.0
Imipenem-relebactam MIC >2 mg/L (n=402) excluding Morganellaceae				
Cefiderocol	2	4	72.6	90.8
Meropenem	>32	>32	5.2	2.2
Meropenem-vaborbactam	>8	>8	11.7	7.5
Imipenem-relebactam	8	>8	0.0	0.0
Ceftazidime-avibactam	>32	>32	25.4	25.4
Ceftazidime-avibactam MIC >8 mg/L (n=336)				
Cefiderocol	2	8	68.5	88.1
Meropenem	>32	>32	8.3	6.3
Meropenem-vaborbactam	>8	>8	18.5	12.8
Imipenem-relebactam[b]	>8	>8	4.5	2.7
Ceftazidime-avibactam	>32	>32	0.0	0.0

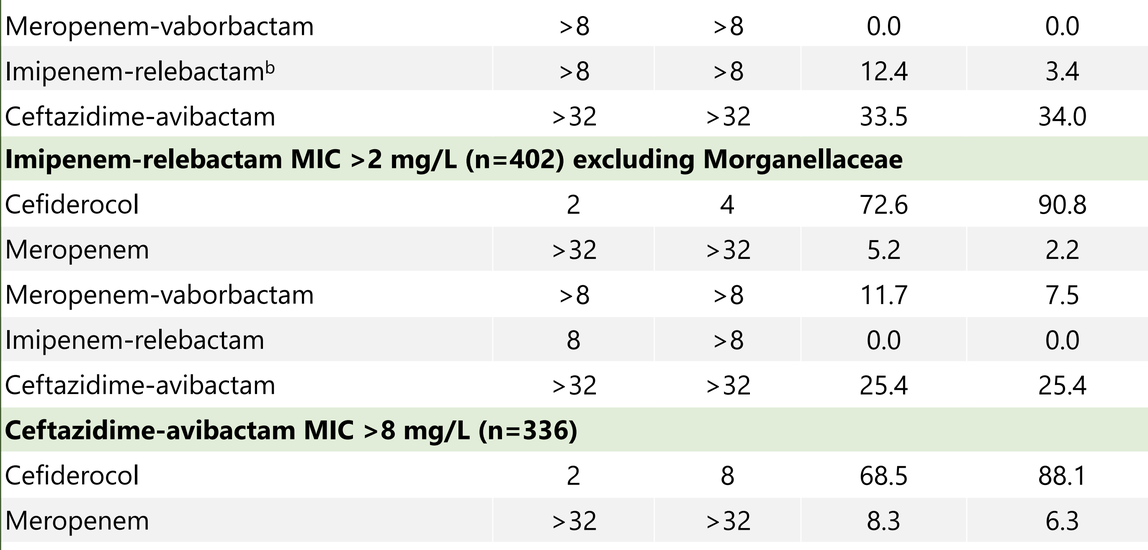
CLSI, Clinical and Laboratory Standards Institute; CRE, carbapenem-resistant Enterobacterales; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; MIC, minimum inhibitory concentration; S, susceptible.
[a]Criteria as published by EUCAST, CLSI and FDA (2025).
[b]All Enterobacterales species were included in the analysis, but CLSI and EUCAST breakpoints for imipenem-relebactam exclude Morganellaceae.
[c]CRE included *Enterobacter cloacae* species complex (30), *Escherichia coli* (12), *Klebsiella aerogenes* (4), *K. oxytoca* (4), *K. pneumoniae* (638), *Morganella morganii* (2), *Proteus mirabilis* (29), *P. penneri* (1), *Providencia rettgeri* (1), *P. stuartii* (5) and *Serratia marcescens* (4).

Figure 1 MIC distributions of European CRE isolates tested against cefiderocol or BL-BLI combinations.



BL–BLI, beta-lactam–beta-lactamase inhibitor; CRE, carbapenem-resistant Enterobacterales; MIC, minimum inhibitory concentration.

Figure 2 MIC distributions of European CRE isolates tested against cefiderocol by carbapenemase type.



CLSI, Clinical and Laboratory Standards Institute; CRE, carbapenem-resistant Enterobacterales; EUCAST, European Committee on Antimicrobial Susceptibility Testing; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-beta-lactamase; NDM, New-Delhi MBL; OXA, oxacillinase; VIM, Verona integron-encoded MBL; MIC, minimum inhibitory concentration.

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Conflict of interest

CL, HY and YY are employees of the SHIONOGI Group.

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