ECCMID 2023 | Poster #P0069

Activity of Cefiderocol and Comparator Agents against European Enterobacterales, Including Carbapenem-Resistant Isolates, From the SENTRY Antimicrobial Surveillance Program (2020–2022)

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Introduction

- Cefiderocol is a siderophore-conjugated cephalosporin with broad activity against Gram-negative bacteria (GNB).
- Cefiderocol was approved by the EMA for the treatment of infections caused by GNB in adult patients with limited treatment options and by the US FDA for complicated urinary tract infection (cUTI), hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia.
- Carbapenem-resistant Enterobacterales (CRE) isolates have disseminated worldwide and present a challenge to treatment.
- In this study, we analysed the susceptibility of cefiderocol and comparator agents against European Enterobacterales isolates, including CRE, collected in 2020–2022 as part of the SENTRY Antimicrobial Surveillance Program.

Materials and Methods

- A total of 9,644 Enterobacterales isolates were consecutively collected from 39 European hospitals in 18 countries during 2020–2022.
- Susceptibility testing was performed using the broth microdilution method with cation-adjusted Mueller-Hinton broth (CAMHB) for comparator agents and iron-depleted CAMHB for cefiderocol. CLSI/US FDA and EUCAST (2022) breakpoints were applied.
- Comparator agents included meropenem and imipenem (results not shown) as well as the newer β-lactam/β-lactamase inhibitor (BL/BLI) combinations ceftazidime-avibactam, imipenem-relebactam, and meropenem-vaborbactam.
- Isolates showing an MIC ≥4 mg/L to imipenem (not used for Proteaee) and/or meropenem were defined as CRE.

Results

- The majority of isolates were from bloodstream infections (*n*=3,799), followed by UTI (*n*=2,920), pneumonia (*n*=2,340), and intra-abdominal infections (*n*=564).
- The most common species was *Escherichia coli* (46.2%, *n*=4,454) followed by *Klebsiella pneumoniae* (20.9%, *n*=2,020).
- 3.0% (*n*=286) of the isolates were CRE, of which 89.2% (255/286) were *K. pneumoniae*.
- The susceptibilities of all tested agents against all isolates were >93% (Table 1).
- Against CRE, cefiderocol was the most active and had higher susceptibility (96.5/82.5%, CLSI/EUCAST) than any of the tested BL/BLI combinations, for which susceptibilities ranged from 57.7/62.2% for imipenem-relebactam to 77.3/77.3% for ceftazidime-avibactam (Figure 1, Table 1).
- Cefiderocol also showed good activity and high susceptibility against isolates resistant to the newer BL/BLI combinations (Table 1, Figure 2).

Conclusions

- Cefiderocol had good activity against contemporary European Enterobacterales isolates, including CRE and those resistant to approved BL/BLI combinations.
- These *in vitro* data suggest that cefiderocol is an important option for the treatment of infections caused by CRE and other BL/BLI-resistant Enterobacterales.

Acknowledgement

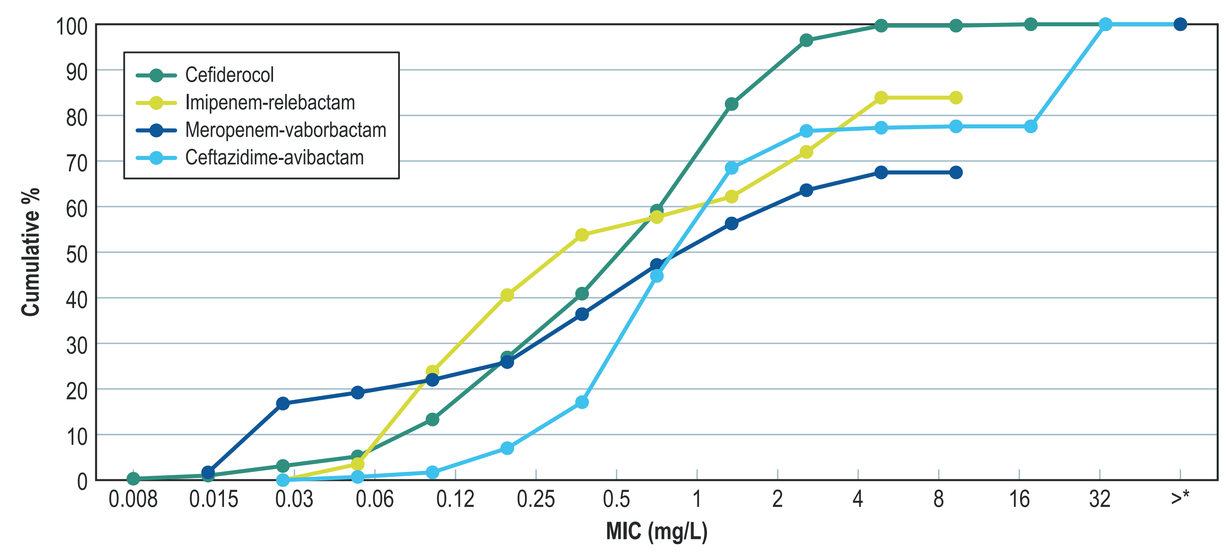
This research and poster presentation were sponsored by Shionogi & Co., LTD.

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

Organism/organism group Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S CLSI/FDA[a]	%S EUCAST[a]
All Enterobacterales (*n*=9,644)				
Cefiderocol	0.12	0.5	99.8	98.7
Meropenem	0.03	0.06	96.9	97.2
Meropenem-vaborbactam	0.03	0.06	98.9	99.0
Imipenem-relebactam[b]	0.12	1	93.9	97.9
Ceftazidime-avibactam	0.12	0.25	99.2	99.2
CRE[c] (*n*=286)				
Cefiderocol	1	4	96.5	82.5
Meropenem	32	>32	2.8	5.9
Meropenem-vaborbactam	2	>8	63.6	67.5
Imipenem-relebactam[b]	0.5	>8	57.7	62.2
Ceftazidime-avibactam	2	>32	77.3	77.3
Meropenem-vaborbactam MIC >8 mg/L (*n*=93)				
Cefiderocol	2	4	93.5	72.0
Meropenem	32	>32	0.0	0.0
Meropenem-vaborbactam	>8	>8	0.0	0.0
Imipenem-relebactam[b]	8	>8	2.2	5.4
Ceftazidime-avibactam	>32	>32	46.2	46.2
Imipenem-relebactam MIC >2 mg/L (*n*=201)				
Cefiderocol	0.25	4	97.0	86.1
Meropenem	2	>32	47.8	50.2
Meropenem-vaborbactam	2	>8	53.7	56.2
Imipenem-relebactam[b]	4	>8	0.0	0.0
Ceftazidime-avibactam	1	>32	65.2	65.2
Ceftazidime-avibactam MIC >8 mg/L (*n*=75)				
Cefiderocol	2	8	88.0	64.0
Meropenem	32	>32	16.0	18.7
Meropenem-vaborbactam	>8	>8	29.3	33.3
Imipenem-relebactam[b]	>8	>8	5.3	6.7
Ceftazidime-avibactam	>32	>32	0.0	0.0

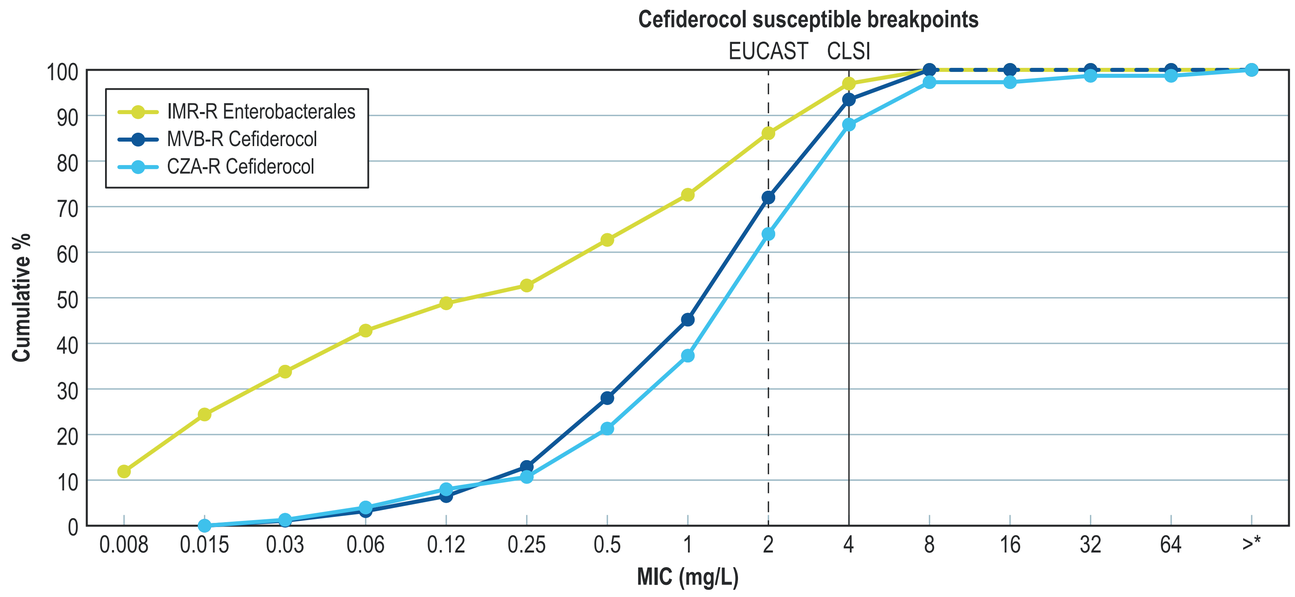
[a] Criteria as published by CLSI, EUCAST, and the US FDA (2022).
[b] All Enterobacterales species were included in the analysis, but CLSI excludes *Morganella*, *Proteus,* and *Providencia* species while EUCAST excludes *Morganellaceae.*
[c] CRE, carbapenem-resistant Enterobacterales are defined as having an MIC ≥4 mg/L to meropenem and/or imipenem. CRE include: *Citrobacter freundii* species complex (2), *Enterobacter cloacae* species complex (16), *Escherichia coli* (2), *Klebsiella aerogenes* (5), *K. oxytoca* (3), *K. pneumoniae* (255), *Proteus mirabilis* (1), *Providencia rettgeri* (1), and *P. stuartii* (1).

Figure 1. MIC distributions of CRE isolates tested against cefiderocol, or β-lactam/β-lactamase combinations in this study



*Greater than the highest concentration tested.
CRE, carbapenem-resistant Enterobacterales; MVB-R, meropenem-vaborbactam-resistant.

Figure 2. Cefiderocol MIC distributions of ceftazidime-avibactam-resistant, imipenem-relebactam-resistant, and meropenem-vaborbactam-resistant isolates



* Greater than the highest concentration tested.
CZA-R, ceftazidime-avibactam-resistant; IMR-R, imipenem-relebactam-resistant, MVB-R, meropenem-vaborbactam-resistant.

References

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