ECCMID 2023 | Poster #P0104

Activity of Cefiderocol and Comparator Agents against US 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, including carbapenem-resistant isolates, which have disseminated worldwide and present a treatment challenge.
- Cefiderocol was approved by the EMA for the treatment of infections caused by Gram-negative bacteria 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.
- In this study, we analysed the susceptibility of cefiderocol and comparator agents against US Enterobacterales, including carbapenem-resistant (CRE) isolates, collected in 2020–2022 as part of the SENTRY Antimicrobial Surveillance Program.

Materials and Methods

- A total of 10,142 Enterobacterales isolates were consecutively collected from hospitalised patients in 32 US medical centres.
- 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.
- Isolates with an MIC ≥4 mg/L to meropenem and/or imipenem were defined as CRE, imipenem was only used to categorize CRE, data not shown. Imipenem was not used to characterize Proteaee.
- Comparator agents included the β-lactam/β-lactamase inhibitor (BL/BLI) combinations ceftazidime-avibactam (CZA), imipenem-relebactam (IMR), and meropenem-vaborbactam (MVB).

Results

- The majority of isolates were from UTI (*n*=3,522), followed by bloodstream infection (*n*=2,766), pneumonia (*n*=2,263), intra-abdominal infection (*n*=848), skin/soft tissue infection (*n*=665), and other sites (*n*=78).
- The most common organism was *Escherichia coli* (*n*=4,246) followed by *Klebsiella pneumoniae* (KPN, *n*=1,917); 1.0% (102/10,142) of the isolates were CRE, with 50.0% (*n*=51) being KPN.
- The susceptibilities of all tested agents were >94% against all isolates (Table 1).
- Against CRE, cefiderocol had susceptibilities of 98.0/87.3% (CLSI/EUCAST). The BL/BLI combinations had susceptibilities against CRE from 80.4/83.3% (IMR) to 89.2/89.2% (CZA; CLSI/EUCAST; Table 1 and Figure 1).
- Cefiderocol maintained good activity against the BL/BLI resistant phenotypes, with susceptibilities ranging from 80.0/53.3% (CLSI/EUCAST) for CZA-resistant isolates to 100/97.3% (CLSI/EUCAST) for IMR-resistant isolates (Table 1, Figure 2).

Conclusions

- Cefiderocol had broad activity against US Enterobacterales isolates, including those resistant to carbapenems and marketed BL/BLI combinations.
- These *in vitro* results suggest that cefiderocol is an important option for the treatment of infections caused by CRE and BL/BLI-resistant Enterobacterales.

Acknowledgements

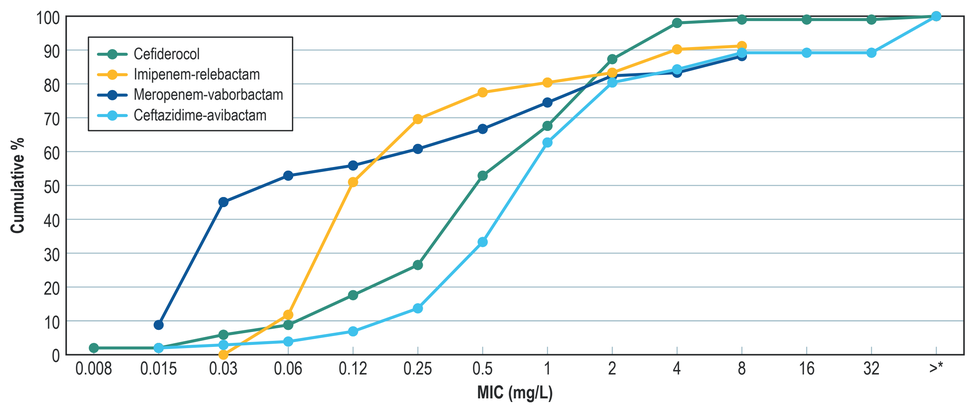
This research and poster presentation were sponsored by Shionogi & Co., LTD.

Table 1. Susceptibilities of cefiderocol and comparator agents tested against US Enterobacterales isolates collected as part of SENTRY 2020–2022, including resistant phenotypes

Organism/organism group Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S CLSI/FDA[a]	%S EUCAST[a]
All (*n*=10,142)				
Cefiderocol	0.06	0.5	99.9	99.2
Meropenem	0.03	0.06	98.9	99.2
Meropenem-vaborbactam	0.03	0.06	99.8	99.9
Imipenem-relebactam[b]	0.12	0.5	94.6	98.9
Ceftazidime-avibactam	0.12	0.25	99.9	99.9
CRE[c] (*n*=102)				
Cefiderocol	0.5	4	98.0	87.3
Meropenem	8	>32	4.9	16.7
Meropenem-vaborbactam	0.06	>8	83.3	88.2
Imipenem-relebactam[b]	0.12	4	80.4	83.3
Ceftazidime-avibactam	1	>32	89.2	89.2
Meropenem-vaborbactam MIC >8 mg/L (*n*=12)[d]				
Cefiderocol	2	4	100.0	83.3
Meropenem	32	>32	0.0	0.0
Meropenem-vaborbactam	>8	>8	0.0	0.0
Imipenem-relebactam[b]	>8	>8	0.0	0.0
Ceftazidime-avibactam	2	>32	50.0	50.0
Imipenem-relebactam MIC >2 mg/L (*n*=112)[e]				
Cefiderocol	0.015	0.5	100.0	97.3
Meropenem	0.12	16	85.7	85.7
Meropenem-vaborbactam	0.12	>8	86.6	89.3
Imipenem-relebactam[b]	4	8	0.0	0.0
Ceftazidime-avibactam	0.06	2	91.1	91.1
Ceftazidime-avibactam MIC >8 mg/L (*n*=15)[f]				
Cefiderocol	2	16	80.0	53.3
Meropenem	8	>32	33.3	40.0
Meropenem-vaborbactam	8	>8	40.0	60.0
Imipenem-relebactam[b]	4	>8	20.0	33.3
Ceftazidime-avibactam	>32	>32	0.0	0.0

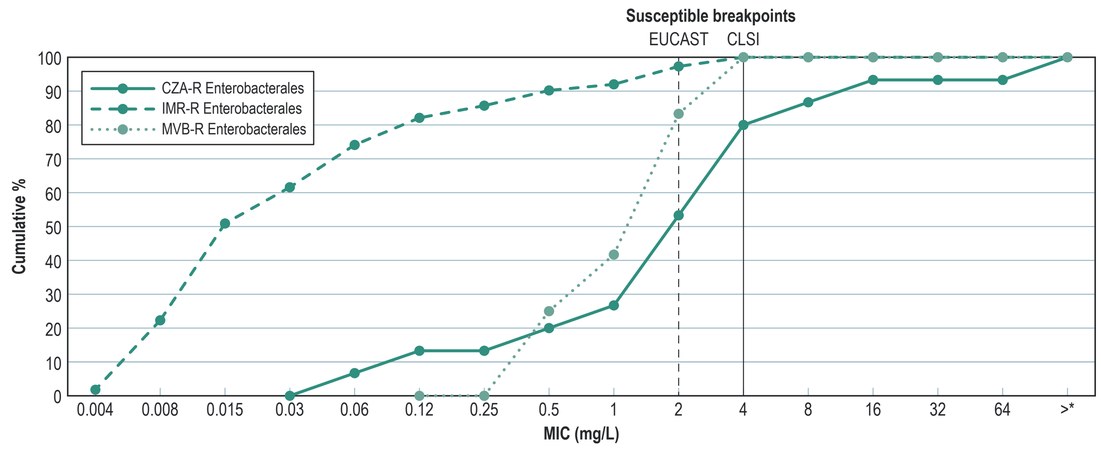
Abbreviations: CRE, carbapenem-resistant Enterobacterales.
[a] Criteria as published by CLSI, EUCAST, and the US FDA (2022).
[b] All Enterobacterales species were included in the analysis, but CLSI excludes *Morganella*, *Proteus*, and *Providencia* species while EUCAST excludes *Morganellaceae*.
[c] CRE are defined as having an MIC ≥4 mg/L to meropenem and/or imipenem. CRE include: *Citrobacter freundii* species complex (3), *Enterobacter cloacae* species complex (11), *Escherichia coli* (6), *Hafnia alvei* (1), *Klebsiella aerogenes* (9), *K. oxytoca* (7), *K. pneumoniae* (51), *Providencia rettgeri* (2), *Raoultella ornithinolytica* (1), *Serratia marcescens* (8), and unspeciated *Raoultella* (3).
[d] Meropenem-vaborbactam–resistant organisms include *Enterobacter cloacae* species complex (3), *Klebsiella aerogenes* (1), *K. pneumoniae* (7), and *Providencia rettgeri* (1).
[e] Imipenem-relebactam organisms include: *Enterobacter cloacae* species complex (3), *Escherichia coli* (1), *Klebsiella aerogenes* (1), *K. pneumoniae* (9), *Morganella morganii* (4), *Proteus hauseri* (1), *P. mirabilis* (79), *P. penneri* (1), *P. vulgaris* (5), *P. vulgaris* group (3), *Providencia rettgeri* (2), *P. stuartii* (1), *Serratia marcescens* (1), unspeciated *Providencia* (1).
[f] Ceftazidime-avibactam–resistant organisms include *Enterobacter cloacae* species complex (6), *Escherichia coli* (1), *Klebsiella aerogenes* (1), *K. oxytoca* (1), *K. pneumoniae* (4), and *Providencia rettgeri* (2).

Figure 1. MIC distributions of CRE to cefiderocol and β-lactam/β-lactamase inhibitors comparators



Abbreviations: CRE, carbapenem-resistant Enterobacterales
*Greater than the highest concentration tested.

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



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

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