Activity of Cefiderocol and Comparators against European Enterobacterales including Carbapenem-Resistant Isolates

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Objective

Cefiderocol is a siderophore-conjugated cephalosporin with broad activity against Gram-negative bacteria.

Cefiderocol was approved by the EMA for the treatment of infections caused by Gram-negative bacteria in adult patients with limited treatment options.

The objective of this study was to analyse the susceptibilities of cefiderocol, and comparators tested against European Enterobacterales isolates including CRE, collected in the SENTRY Surveillance Program.

Methods

- A total of 6,231 Enterobacterales isolates were consecutively collected from 35 hospitals located in 18 European countries during 2020-2021.
- Isolates from all infection types were included in the analysis.
- Susceptibility testing was performed using the CLSI broth microdilution method. Cefiderocol was tested in iron-depleted cation-adjusted Mueller-Hinton broth.
- CLSI/FDA and EUCAST (2022) breakpoints were applied. CRE were identified as having an MIC ≥4 mg/L to imipenem and/or meropenem (CLSI).
- Other agents tested included the beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations ceftazidime-avibactam, imipenem-relebactam, and meropenem-vaborbactam.

Results

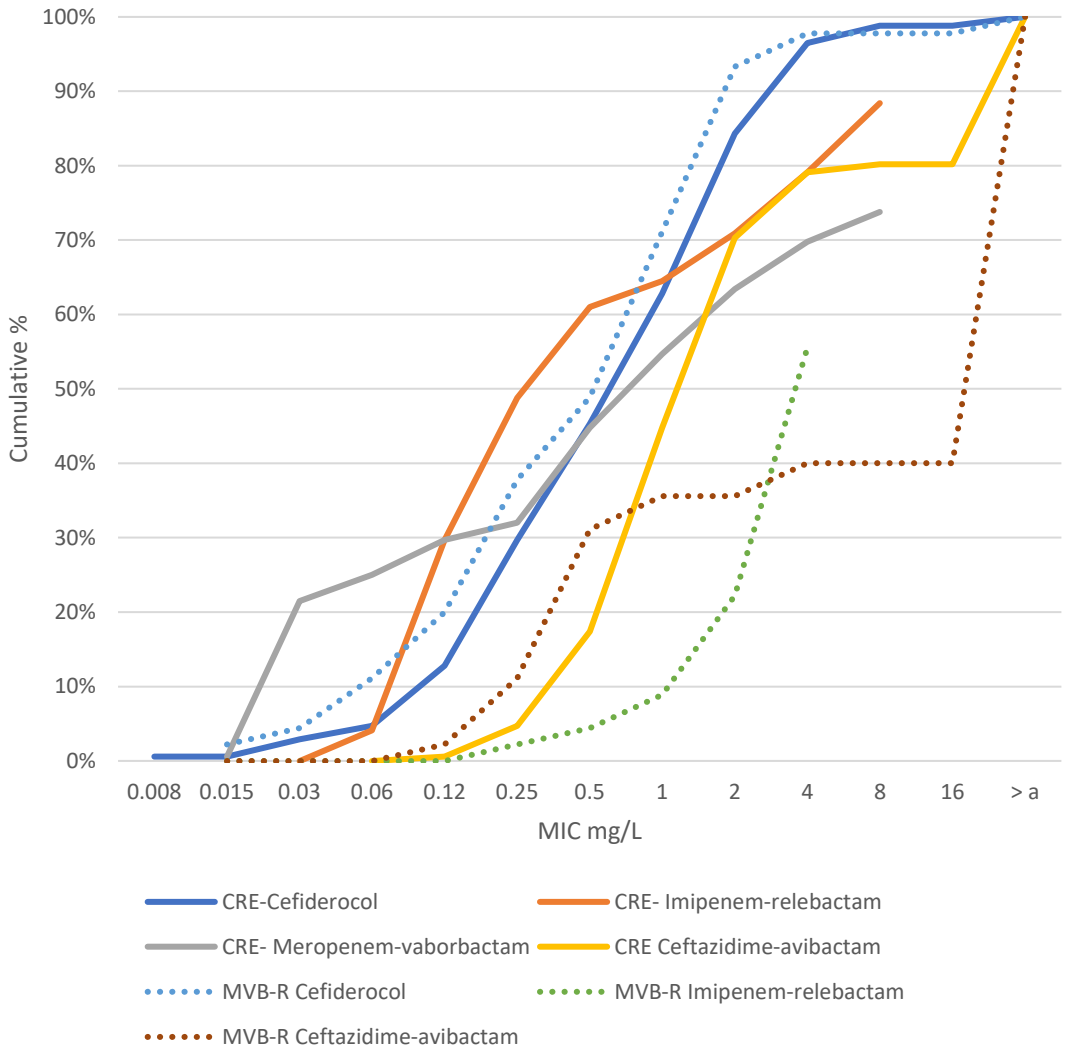
Table 1. Susceptibilities of European Enterobacterales and Resistant Subgroups

Antimicrobial agent	mg/L		CLSI/FDA[a]	EUCAST[a]
	MIC_{50}	MIC_{90}	%S	%S
All (*n*=6,231)				
Cefiderocol	0.12	0.5	99.8	98.8
Meropenem	0.03	0.06	97.1	97.4
Meropenem-vaborbactam	0.03	0.06	99.2	99.3
Imipenem-relebactam	0.12	0.5	94.6 [b]	98.5
Ceftazidime-avibactam	0.12	0.25	99.3	99.3
CRE [c] (*n*=172)				
Cefiderocol	1	4	96.5	84.3
Meropenem	32	>32	4.1	7.0
Meropenem-vaborbactam	1	>8	69.8	73.8
Imipenem-relebactam	0.5	>8	64.5 [b]	70.9
Ceftazidime-avibactam	2	>32	80.2	80.2
Meropenem-vaborbactam MIC >8 mg/L (*n*=45)				
Cefiderocol	2	4	93.3	71.1
Meropenem	32	>32	0.0	0.0
Meropenem-vaborbactam	>8	>8	0.0	0.0
Imipenem-relebactam	8	>8	4.4 [b]	8.9
Ceftazidime-avibactam	>32	>32	40.0	40.0
Imipenem-relebactam MIC >2 mg/L (*n*=96)				
Cefiderocol	0.25	4	96.9	84.4
Meropenem	1	>32	50.0	52.1
Meropenem-vaborbactam	1	>8	54.2	57.3
Imipenem-relebactam	4	>8	0.0 [b]	0.0
Ceftazidime-avibactam	1	>32	59.4	59.4
Ceftazidime-avibactam MIC >8 mg/L (*n*=42)				
Cefiderocol	2	8	88.1	59.5
Meropenem	32	>32	23.8	23.8
Meropenem-vaborbactam	>8	>8	31.0	35.7
Imipenem-relebactam	>8	>8	4.8 [b]	7.1
Ceftazidime-avibactam	>32	>32	0.0	0.0

[a] Criteria as published by CLSI/FDA and EUCAST (2022).
[b] All Enterobacterales species were included in the analysis, but CLSI excludes *Morganella*, *Proteus*, and *Providencia* species and EUCAST excludes *Morganellaceae*.
[c] CRE, carbapenem-resistant Enterobacterales with an MIC ≥4 mg/L to meropenem and/or imipenem. Organisms include: *Citrobacter freundii* species complex (2), *Enterobacter cloacae* species complex (10), *Escherichia coli* (1), *Klebsiella aerogenes* (3), *K. oxytoca* (2), *K. pneumoniae* (153), and *Providencia rettgeri* (1).

Results

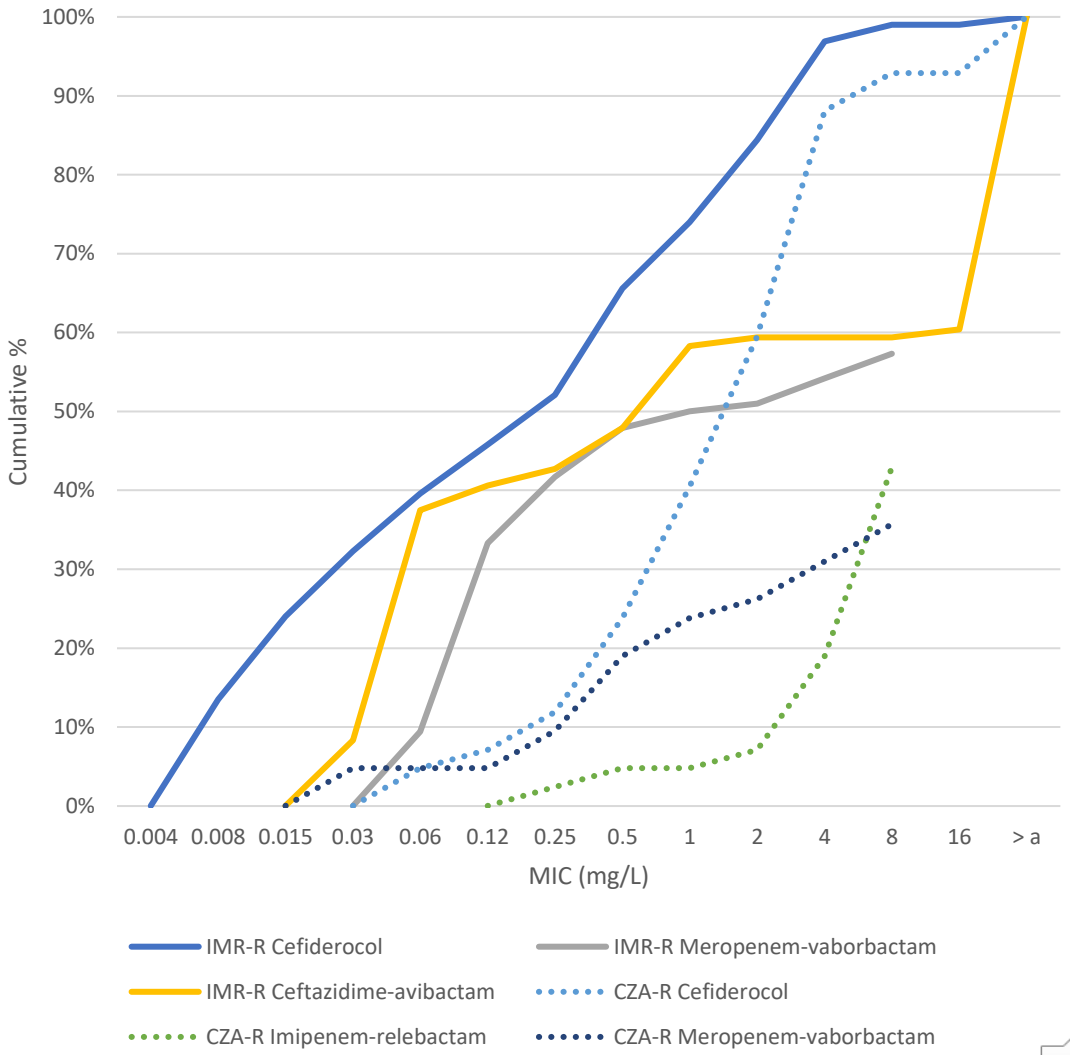
Figure 1. CRE and MVB-R MIC Distributions



MVB-R, meropenem-vaborbactam resistant

> a, MIC greater than highest dilution tested.

Figure 2. IMR-R and CZA-R MIC Distributions



IMR-R, imipenem-relebactam resistant; CZA-R, ceftazidime-avibactam resistant

Results

- Most isolates were from bloodstream infections (*n*=2,483), followed by urinary tract infections (*n*=1,851) and patients hospitalized with pneumonia (*n*=1,480).
  - The most common species was *Escherichia coli* (*n*=2,895) followed by *Klebsiella pneumoniae* (*n*=1,279).
- Against CRE, cefiderocol had higher susceptibility (96.5/84.3%, CLSI/EUCAST) than the BL/BLI combinations (Table 1).
- Cefiderocol maintained activity against isolates resistant to the BL/BLI combinations, including ceftazidime-avibactam-resistant isolates (Table 1, Figure 2).

Conclusions

- Cefiderocol had broad activity against European Enterobacterales isolates, including those resistant to approved BL/BLI combinations.
- These data suggest that cefiderocol is an important option for the treatment of serious infections caused by CRE and BL/BLI-resistant Gram-negative pathogens that have limited treatment options.

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