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

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Introduction

- Cefiderocol is a novel siderophore-conjugated cephalosporin with broad activity against Gram-negative bacteria.
- Cefiderocol was recently approved by the EMA for the treatment of infections caused by Gram-negative bacteria in adult patients with limited treatment options and the FDA for complicated urinary tract infection (UTI), 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 analyzed the susceptibility of cefiderocol and comparators tested against European *Enterobacterales* isolates, including CRE, collected in 2020 as a part of the SENTRY Antimicrobial Surveillance Program.

Materials and Methods

- A total of 3,645 *Enterobacterales* isolates were consecutively collected from 32 European hospitals located in 18 countries during 2020.
- Susceptibility testing was performed using the broth microdilution method. Cefiderocol was tested in iron-depleted cation-adjusted Mueller-Hinton broth.
- CLSI/FDA and EUCAST (2021) breakpoints were used. Cefiderocol breakpoints for CLSI and FDA are ≤4/8/≥16 mg/L and EUCAST breakpoints are ≤2/-/>2 mg/L.
- CRE were identified as having an MIC >2 mg/L to meropenem or imipenem.
- Multi-drug resistant isolates (MDR) were defined as resistant to at least one drug in three or more drug classes. Extensively-drug resistant (XDR) isolates were defined as susceptible to ≤2 drug classes.
- Other antimicrobials tested included the β-lactam/β-lactamase inhibitor (BL/BLI) combinations ceftazidime-avibactam, imipenem-relebactam, and meropenem-vaborbactam as well as meropenem and imipenem.

Results

- The most common species was *Escherichia coli* (n=1,648) followed by *Klebsiella pneumoniae* (n=758; Figure 1).
  - Most isolates were either from bloodstream infection (n=1,287) or UTI (n=1,107).
- The susceptibilities and $MIC_{50/90}$ values of cefiderocol and comparators for all isolates and isolate groups are shown in Table 1. The cumulative percent MIC distributions are shown in Figure 2.
- The susceptibilities of all tested agents were >94% against all isolates.
- For isolates with the CRE phenotype, cefiderocol was the most active agent tested.
  - The CRE rate was 3.0% (108/3,645); 88% (95/108) of which were *K. pneumoniae*.
  - Cefiderocol had the highest percent susceptibility against CRE (97.2/88.9%, CLSI/EUCAST) compared to the BL/BLI combinations, for which susceptibilities ranged from 59.3/67.6% for imipenem-relebactam to 77.8/77.8% for ceftazidime-avibactam (Table 1).
- Cefiderocol maintained activity against isolates resistant to the BL/BLI combinations, including ceftazidime-avibactam-resistant isolates (Table 1).
  - 18 isolates were resistant to all 3 BL/BLI comparators; these isolates had a susceptibility to cefiderocol of 83.3/55.6% under CLSI/EUCAST criteria, respectively (Table 1).
- There were 15.4% MDR (n=563) and 2.7% XDR (n=99) isolates. The cumulative MIC distributions of MDR, and XDR isolates for cefiderocol and comparators are shown in Figures 3 and 4.
  - Cefiderocol susceptibility for MDR isolates was 99.1% (CLSI/FDA) and 95.2% (EUCAST).
  - Cefiderocol susceptibility for XDR isolates was 97.0% (CLSI/FDA) and 87.9% (EUCAST).

Figure 1. Prevalence of organisms with number of isolates tested in this study.

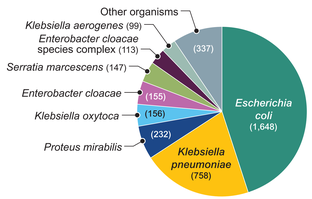
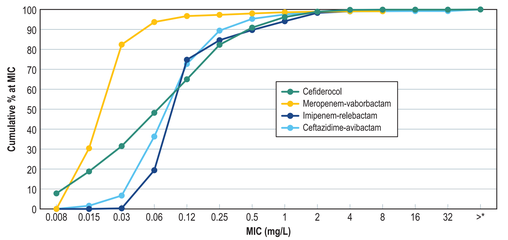
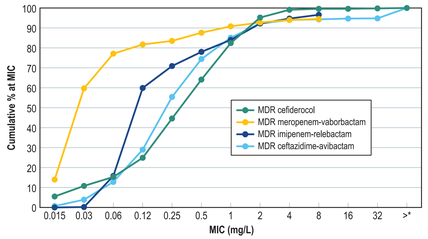


Figure 2. Cumulative percent MIC distribution of cefiderocol and comparators for 3,645 European isolates of *Enterobacterales*



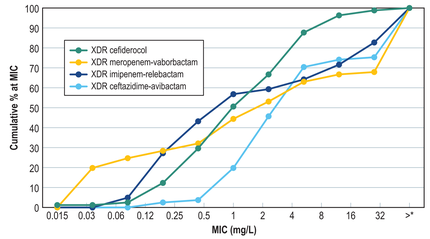
*MIC value greater than the highest dilution tested

Figure 3. Cumulative percent MIC distribution for cefiderocol and comparators against *Enterobacterales* with MDR (n=563) phenotype



*MIC value greater than the highest dilution tested
MDR, multidrug-resistant

Figure 4. Cumulative percent MIC distribution for cefiderocol and comparators against Enterobacterales with XDR (n=81) phenotype



*MIC value greater than the highest dilution tested
XDR, extensively drug-resistant

Table 1. Susceptibilities of cefiderocol and comparators tested against *Enterobacterales* isolates and resistant phenotypes

Organism/Antimicrobial agent	No. of isolates	MIC (mg/L) MIC_{50}	MIC (mg/L) MIC_{90}	CLSI/FDA[a] %S	EUCAST[a] %S
All *Enterobacterales*					
Cefiderocol	3,645	0.12	0.5	99.8 [b]	98.9
Meropenem-vaborbactam	3,640	0.03	0.06	99.1	99.1
Imipenem-relebactam	3,645	0.12	1	94.1 [c]	98.3
Ceftazidime-avibactam	3,644	0.12	0.5	99.1	99.1
CRE[d]					
Cefiderocol	108	0.5	4	97.2 [b]	88.9
Meropenem-vaborbactam	108	1	>8	68.5	71.3
Imipenem-relebactam	108	0.5	>8	59.3 [c]	67.6
Ceftazidime-avibactam	108	2	>32	77.8	77.8
Meropenem-vaborbactam R					
Cefiderocol	31	1	4	90.3 [b]	74.2
Meropenem-vaborbactam	31	>8	>8	0.0	0.0
Imipenem-relebactam	31	8	>8	3.2 [c]	9.7
Ceftazidime-avibactam	31	>32	>32	41.9	41.9
Imipenem-relebactam R					
Cefiderocol	61	0.25	4	95.1 [b]	83.6
Meropenem-vaborbactam	61	4	>8	50.8	54.1
Imipenem-relebactam	61	8	>8	0.0 [c]	0.0
Ceftazidime-avibactam	61	1	>32	55.7	55.7
Ceftazidime-avibactam-R					
Cefiderocol	32	2	8	87.5 [b]	59.4
Meropenem-vaborbactam	32	>8	>8	40.6	43.8
Imipenem-relebactam	32	>8	>8	6.2 [c]	15.6
Ceftazidime-avibactam	32	>32	>32	0.0	0.0
BL/BLI-R					
Cefiderocol	18	2	8	83.3 [b]	55.6
Meropenem-vaborbactam	18	>8	>8	0.0	0.0
Imipenem-relebactam	18	>8	>8	0.0	0.0
Ceftazidime-avibactam	18	>32	>32	0.0	0.0

[a] Criteria as published by CLSI/FDA and EUCAST (2021).
[b] FDA breakpoints were published on 2020SEP25.
[c] Imipenem-relebactam FDA breakpoints were published on 2020JUN04, and have been applied to all *Enterobacterales* other than *Morganella*, *Proteus*, and *Providencia*.
[d] CRE, carbapenem-resistant *Enterobacterales*. Organisms include: *Citrobacter freundii* species complex (2), *Enterobacter cloacae* species complex (4), *Escherichia coli* (3), *Klebsiella aerogenes* (2), *K. oxytoca* (2), and *K. pneumoniae* (95).

Conclusions

- Cefiderocol had excellent activity against *Enterobacterales* isolates from Europe, including CRE, and those resistant to 1 or more of the recently approved BL/BLI combinations.
- Cefiderocol also had excellent activity against MDR and XDR isolates.
- These data suggest that cefiderocol is an important option for the treatment of infections caused by CRE and other drug resistant pathogens.

Acknowledgements

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