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In vitro Activity of Cefiderocol and Comparator Agents Against Global Enterobacterales Isolates from Hospitalized Patients with Pneumonia Collected as Part of the SENTRY Surveillance Program (2020–2022)

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BACKGROUND

- Infections caused by carbapenem-resistant (CR) Gram-negative bacteria and delays in appropriate therapy can lead to excess morbidity and mortality.[1]
- Cefiderocol is a siderophore conjugated cephalosporin with broad activity against Gram-negative bacteria, including multidrug-resistant (MDR) organisms.[2–4]
- Based on its unique structure and mode of cell entry, cefiderocol remains active against Gram-negative bacteria that employ mechanisms that commonly confer resistance to carbapenems.[2–4]
- In this study, the *in vitro* activity of cefiderocol and comparator agents was evaluated against Enterobacterales isolates collected from patients with pneumonia during 2020–2022 as part of the SENTRY Antimicrobial Surveillance Program.

METHODS

- 5793 Enterobacterales were collected from patients with pneumonia and tested for susceptibility (%S) using Clinical and Laboratory Standards Institute (CLSI) broth microdilution method with cation-adjusted Mueller-Hinton broth (CAMHB) or iron-depleted CAMHB for cefiderocol. 47% and 53% of isolates were from North America and Europe, respectively, and the most common genera were *Klebsiella*, *Escherichia*, *Serratia*, *Enterobacter*, *Proteus*, and *Citrobacter* **(Figure 1).**
- Comparator agents included β-lactam–β-lactamase inhibitor (BL–BLI) combinations ceftazidime-avibactam (CZA), ceftolozane-tazobactam (C/T), imipenem-relebactam (I/R), meropenem-vaborbactam (M/V), piperacillin-tazobactam, as well as meropenem (MEM), cefepime, and ceftazidime.
- Susceptibility was interpreted according to 2024 CLSI, US Food and Drug Administration (FDA), and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (**Figure 2**).
- CR Enterobacterales (CRE) was defined as resistant to imipenem and MEM.
- MDR Enterobacterales were defined as non-susceptible (NS) to ≥1 drug from ≥3 classes, and extensively drug-resistant (XDR) as susceptible to ≤2 classes per 2024 CLSI criteria.

RESULTS

- There was no discernible difference in cefiderocol MIC distributions when stratified by continent **(Figure 2)** or genera **(Table 1)**.
- Cefiderocol, MEM, CZA, I/R and M/V all showed high susceptibility against all Enterobacterales isolates (>94/>97 %S using CLSI|FDA/EUCAST breakpoints) **(Table 2)**.
- Cefiderocol (94.4/81.1 %S CLSI|FDA/EUCAST) was the only agent with appreciable activity against XDR isolates **(Table 2)**.
- Overall, against CRE, cefiderocol (99.7/83.5 %S CLSI|FDA/EUCAST) was the most active agent, while CZA was the second most active (74.7 %S CLSI|FDA and EUCAST) **(Table 3)**.
- Cefiderocol and CZA were the most active against CRE isolates harbouring $bla_{OXA-48-like}$, 100/86.4 %S CLSI|FDA/EUCAST and 100 %S CLSI|FDA/EUCAST, respectively **(Table 3).**
- Cefiderocol was the only tested agent with activity against CRE isolates with bla_{NDM} or bla_{VIM} (85.7/61.9 %S CLSI|FDA/EUCAST) **(Table 3)**.
- Among CRE isolates that were also non-susceptible to CZA or M/V, cefiderocol showed the highest *in vitro* activity, 86.0/62.8 %S CLSI|FDA/EUCAST and 89.6/70.1 %S CLSI|FDA/EUCAST, respectively **(Table 3)**.

Figure 1. Genus distribution

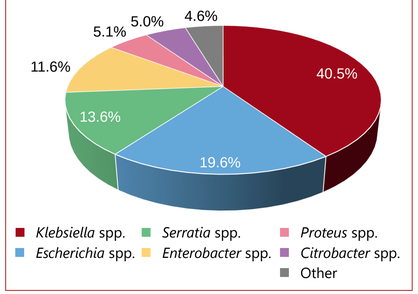

Figure 2. Cefiderocol MIC distribution against global Enterobacterales isolates from hospitalized patients with pneumonia (2020–2022) stratified by continent

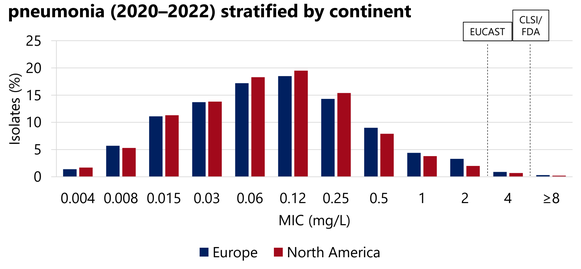

Table 1. Cumulative percentage distribution of cefiderocol MIC values against Enterobacterales isolated from patients with pneumonia, by genus

	MIC (mg/L)									
Genus	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**≥16**
Enterobacterales (=5793)	32	49.8	68.7	83.5	**92.0**	96.2	98.9	99.7	>99.9	100
Klebsiella spp. (n=2347)	33.9	51.6	68.7	81.9	**90.0**	95.0	98.4	99.6	100	
Escherichia spp. (n=1134)	38.3	54.3	73.6	86.9	**92.9**	97.3	99.6	100		
Serratia spp. (n=788)	18.9	53.6	82.4	**93.5**	98.1	99.2	99.7	99.9	100	
Enterobacter spp. (n=673)	7.0	16.9	37.6	64.6	84.2	**91.2**	96.9	99.1	99.7	100
Proteus spp. (n=298)	83.2	**91.3**	97.0	99.0	99.7	99.7	100			
Citrobacter spp. (n=292)	18.5	28.4	50.0	84.2	**95.2**	99.0	99.7	100		
Other (n=261)[a]	49.4	63.2	75.1	83.5	**95.8**	98.5	99.6	99.6	100	

n, number of isolates.
Bold indicates MIC_{90}.
[a]Organisms include *Cronobacter sakazakii* (3), *Hafnia alvei* (47), *H. alvei/H. paralvei* (2), *Kluyvera cryocrescens* (1), *Kosakonia cowanii* (1), *Morganella morganii* (79), *Pantoea agglomerans* (2), *P. calida* (1), *P. dispersa* (1), *P. piersonii* (1), *Phytobacter diazotrophicus* (1), *Pluralibacter gergoviae* (6), *Providencia rettgeri* (17), *P. stuartii* (27), *Rahnella aquatilis* (3), *Raoultella ornithinolytica* (34), *R. planticola* (5), unspeciated *Pantoea* (2), unspeciated *Providencia* (2), unspeciated *Raoultella* (24), unspeciated *Yersinia* (not *Yersinia pestis*) (1), and *Yokenella regensburgei* (1).

Table 2. *In vitro* activity of cefiderocol and comparators against global Enterobacterales isolates from patients with pneumonia, 2020–2022

Phenotype/antimicrobial agent	$MIC_{50/90}$ mg/L	MIC Range mg/L	CLSI/FDA %S	EUCAST %S
Enterobacterales, n=5793				
Cefiderocol	0.12/0.5	≤0.004 to 16	99.7	98.9
Cefepime[a]	0.06/32	≤0.03 to >32	84.7	82.8
Ceftazidime	0.25/>32	0.03 to >32	79.8	76.2
Meropenem	0.03/0.06	≤0.015 to >32	96.6	97.0
Piperacillin-tazobactam	2/64	≤0.06 to >128	79.3	79.3
Ceftazidime-avibactam	0.12/0.5	≤0.015 to >32	99.1	99.1
Ceftolozane-tazobactam	0.25/4	≤0.12 to >16	89.1	89.1
Imipenem-relebactam[b]	0.12/1	≤0.03 to >8	94.3	97.9
Meropenem-vaborbactam	0.03/0.06	≤0.015 to >8	98.8	99.0
MDR Enterobacterales, n=1621				
Cefiderocol	0.25/2	≤0.004 to 16	99.0	95.9
Cefepime[a]	4/>32	≤0.03 to >32	48.9	42.4
Ceftazidime	32/>32	0.06 to >32	31.5	23.5
Meropenem	0.03/4	≤0.015 to >32	87.8	89.1
Piperacillin-tazobactam	32/>128	0.12 to >128	31.1	31.1
Ceftazidime-avibactam	0.25/1	≤0.015 to >32	96.8	96.8
Ceftolozane-tazobactam	1/>16	≤0.12 to >16	61.5	61.5
Imipenem-relebactam[b]	0.12/0.5	≤0.03 to >8	93.2	94.8
Meropenem-vaborbactam	0.03/0.25	≤0.015 to >8	95.9	96.4
XDR Enterobacterales, n=90				
Cefiderocol	1/4	0.008 to 8	94.4	81.1
Cefepime[a]	>32/>32	4 to >32	0.0	0.0
Ceftazidime	>32/>32	4 to >32	1.1	0.0
Meropenem	32/>32	1 to >32	1.1	4.4
Piperacillin-tazobactam	>128/>128	128 to >128	0.0	0.0
Ceftazidime-avibactam	2/>32	0.03 to >32	61.1	61.1
Ceftolozane-tazobactam	>16/>16	16 to >16	0.0	0.0
Imipenem-relebactam[b]	4/>8	≤0.06 to >8	35.6	40.0
Meropenem-vaborbactam	>8/>8	≤0.015 to >8	37.8	45.6

n, number of isolates.
[a]Intermediate is interpreted as susceptible, dose-dependent.
[b]All Enterobacterales species were included in the analysis, but CLSI excludes *Morganella*, *Proteus*, and *Providencia* species, and EUCAST excludes Morganellaceae.

Table 3. *In vitro* activity of cefiderocol and comparators against global carbapenem-resistant Enterobacterales isolates from patients with pneumonia, 2020–2022

Phenotype/antimicrobial agent	$MIC_{50/90}$ mg/L	MIC range mg/L	CLSI/FDA %S	EUCAST %S
CRE n=170				
Cefiderocol	0.12/0.5	0.008 to 8	99.7	83.5
Ceftazidime-avibactam	0.12/0.5	0.03 to >32	74.7	74.7
Ceftolozane-tazobactam	0.25/4	0.5 to >16	2.9	2.9
Imipenem-relebactam[a]	0.12/1	0.06 to >8	58.2	61.2
Meropenem-vaborbactam	0.03/0.06	≤0.015 to >8	60.6	65.3
CRE, bla_{KPC} n=88[b]				
Cefiderocol	0.5/2	0.008 to 8	98.9	93.2
Ceftazidime-avibactam	1/2	0.03 to 8	100.0	100.0
Ceftolozane-tazobactam	>16/>16	16 to >16	0.0	0.0
Imipenem-relebactam[a]	0.12/0.5	0.06 to 1	100.0	100.0
Meropenem-vaborbactam	0.06 to 1	≤0.015 to >16	98.9	98.9
CRE, $bla_{OXA-48-like}$ n=22[c]				
Cefiderocol	1/4	0.015 to 4	100.0	86.4
Ceftazidime-avibactam	1/2	0.06 to 2	100.0	100.0
Ceftolozane-tazobactam	>16/>16	1 to >16	4.5	4.5
Imipenem-relebactam[a]	4/>8	2 to >8	0.0	9.1
Meropenem-vaborbactam	>8/>8	8 to >8	0.0	4.5
CRE, MBL n=42[d]				
Cefiderocol	2/8	0.06 to 8	85.7	61.9
Ceftazidime-avibactam	>32/>32	>32 to >32	0.0	0.0
Ceftolozane-tazobactam	>16/>16	>16 to >16	0.0	0.0
Imipenem-relebactam[a]	>8/>8	4 to >8	0.0	0.0
Meropenem-vaborbactam	>8/>8	4 to >8	4.8	14.3
CRE, CZA-NS n=43				
Cefiderocol	2/8	0.06 to 8	86.0	62.8
Ceftazidime-avibactam	>32/>32	>32 to >32	0.0	0.0
Ceftolozane-tazobactam	>16/>16	>16 to >16	0.0	0.0
Imipenem-relebactam[a]	>8/>8	4 to >8	0.0	0.0
Meropenem-vaborbactam	>8/>8	4 to >8	4.7	14.0
CRE, M/V-NS n=67				
Cefiderocol	1/8	0.015 to 8	89.6	70.1
Ceftazidime-avibactam	>32/>32	0.06 to >32	38.8	38.8
Ceftolozane-tazobactam	>16/>16	1 to >16	1.5	1.5
Imipenem-relebactam[a]	>8/>8	1 to >8	4.5	9.0
Meropenem-vaborbactam	>8/>8	8 to >8	0.0	0.0

n, number of isolates.
[a]All Enterobacterales species were included in the analysis, but CLSI excludes *Morganella*, *Proteus*, and *Providencia* species, and EUCAST excludes Morganellaceae; [b]Excluded 9 isolates coharboring metallo-β-lactamase (MBL); [c]Excluded 3 isolates coharboring an MBL; [d]MBLs included bla_{NDM} (n=33; 4 isolates had dual carbapenemases; 1 bla_{KPC}, 3 $bla_{OXA-48-like}$) and bla_{VIM} (n=9; 8 isolates had dual carbapenemases with bla_{KPC}).

CONCLUSIONS

- Cefiderocol demonstrated high *in vitro* activity against a global collection of Enterobacterales isolates from hospitalized patients with pneumonia, including CRE, MDR, and XDR isolates.
- Susceptibility to comparator agents, comprising BL–BLI combinations, was generally lower for isolates with CRE and XDR phenotypes.
- The data support cefiderocol as an important treatment option for patients with pneumonia caused by Enterobacterales with presumed or defined MDR, XDR, or CRE phenotypes, including subsets of CRE harboring bla_{KPC}, bla_{OXA}, bla_{NDM}, bla_{VIM}, or those NS to CZA or M/V.

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