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Activity of Cefiderocol Against Enterobacterales Carrying Multiple Carbapenemases, Collected as Part of the SENTRY Antimicrobial Surveillance Program

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BACKGROUND

- Carbapenemases are major determinants of resistance to carbapenems and other β-lactam antibiotics in Enterobacterales.
- They can be categorized as metallo-β-lactamases (MBLs; NDM, IMP, and VIM enzymes) or serine-based β-lactamases (KPC, OXA-48-like, and certain GES enzymes).
- Cefiderocol is a siderophore-conjugated cephalosporin with remarkable stability against β-lactamases, including all classes of carbapenemases, and it leverages the iron-uptake systems of bacteria to facilitate transportation into the cell.

OBJECTIVE

- The objective of this study was to elucidate the *in vitro* activity of cefiderocol and comparator agents against contemporary Enterobacterales isolates carrying multiple carbapenemases.

METHODS

- Isolates were collected from 2020 to 2023 in Europe and the USA as part of the SENTRY antimicrobial surveillance program.
- Minimum inhibitory concentrations (MICs) were determined according to Clinical and Laboratory Standards Institute (CLSI) methods using broth microdilution with cation-adjusted Mueller–Hinton broth (CAMHB) for comparator agents and iron-depleted CAMHB for cefiderocol.
- Isolates non-susceptible to meropenem or imipenem (excluding *Proteus mirabilis, P. penneri*, and indole-positive Proteaea) or extended-spectrum β-lactamase phenotypes were subject to whole-genome sequencing to determine β-lactamase content.
- Susceptibility was assessed according to 2024 European Committee on Antimicrobial Susceptibility Testing (EUCAST), CLSI, and US Food and Drug Administration (FDA) breakpoints.

RESULTS

- Of the 32,053 Enterobacterales collected, 82 (0.3%) carried multiple carbapenemase genes, the majority of which were found in *Klebsiella pneumoniae* (**Figure 1**).
- All isolates carried two carbapenemases, except for one *K. pneumoniae* isolate, which carried two MBLs (NDM-1, NDM-4) and an OXA-48-like enzyme.
  - The combination of MBL and OXA-48-like enzymes was the most frequently encountered, followed by combinations of MBL and KPC enzymes (**Table 1**).
- Cefiderocol showed good activity against isolates expressing multiple carbapenemases, with 63.4% and 81.7% of the isolates being susceptible according to EUCAST and CLSI/FDA breakpoints, respectively (**Table 2**).
  - Among MBL-producing isolates (n=78), cefiderocol displayed highest activity against VIM-producing isolates (n=18), with 88.9% and 94.4% of the isolates being susceptible according to EUCAST and CLSI/FDA breakpoints, respectively (**Table 1**).
- β-lactam–β-lactamase inhibitor combinations showed low susceptibility against isolates expressing multiple carbapenemases, suggesting a lack of cross resistance with cefiderocol (**Table 2**).
- Other comparator agents, with the exception of tigecycline (92.7% at the FDA breakpoint), also demonstrated limited activity for these resistant isolates (**Table 2**).

Figure 1: Isolates carrying multiple carbapenemase genes (n=82)

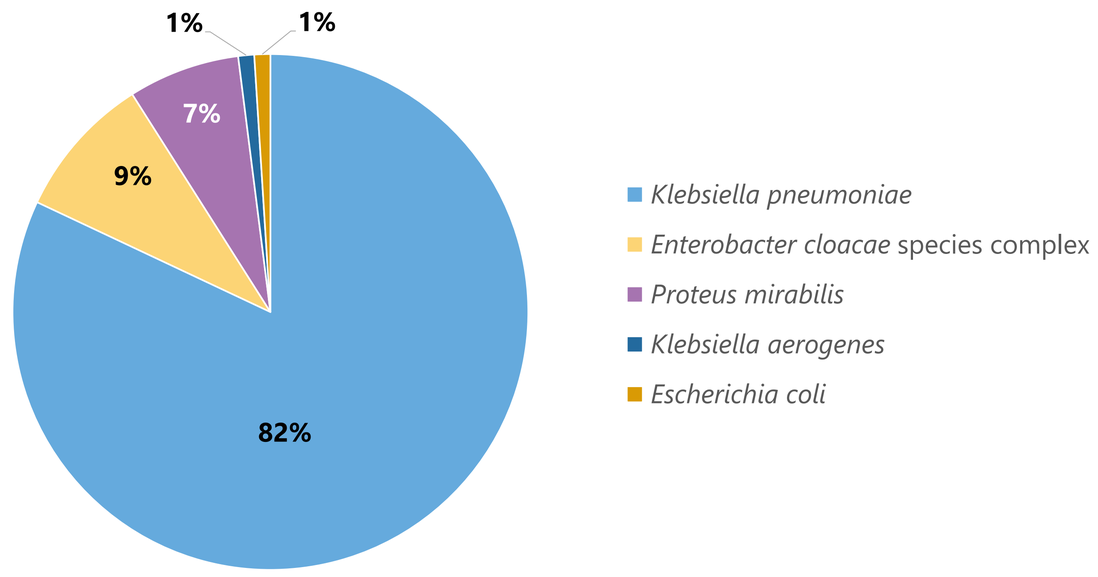

Table 1: Cefiderocol MIC frequency distribution for isolates with multiple carbapenemases (n=82)

Carbapenemase combinations	MIC (µg/mL)											Total
	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	
MBL + OXA-48-like	**0**	**0**	**1**	**2**	**0**	**2**	**22**	**13**	**9**	**2**	**1**	**52**
NDM-1, OXA-48						2	11	11	5	2	1	32
NDM-5, OXA-48				1			6					7
NDM-1, OXA-181				1			1		3			5
NDM-1, OXA-232			1				1	1	1			4
VIM-1, OXA-48							2					2
NDM-5, OXA-181								1				1
NDM-1, NDM-4, OXA-232 KPN							1					1
MBL + KPC	**0**	**0**	**1**	**0**	**6**	**0**	**8**	**2**	**2**	**1**	**0**	**20**
NDM-1, KPC-2							5	1				6
VIM-1, KPC-2			1		3		1		1			6
VIM-1, KPC-3					3			1				4
NDM-1, KPC-3							2		1			3
NDM-5, KPC-65										1		1
MBL + MBL	**1**	**2**	**0**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**5**
VIM-4, VIM-75		2		1	1							4
VIM-1, VIM-75	1											1
KPC + OXA-48-like	**0**	**1**	**1**	**2**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**4**
KPC-2, OXA-48		1	1	2								4
MBL + GES	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**1**
VIM-1, GES-6						1						1

Table 2: Activity of cefiderocol and comparator agents against Enterobacterales carrying multiple carbapenemases (n=82)

Agent*	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC range (µg/mL)	% Susceptibility		
				CLSI	EUCAST	FDA
Cefiderocol	2	8	0.03 to 32	81.7	63.4	81.7
Imipenem-relebactam	>8	>8	0.5 to >8	3.7	6.1	3.7
Meropenem-vaborbactam	>8	>8	0.25 to >8	13.4	17.1	13.4
Ceftazidime-avibactam	>32	>32	0.5 to >32	6.1	6.1	6.1
Ceftolozane-tazobactam	>16	>16	8 to >16	0.0	0.0	0.0
Aztreonam	>16	>16	0.12 to >16	20.7	12.2	20.7
Ciprofloxacin	>4	>4	0.5 to >4	0.0	0.0	0.0
Levofloxacin	32	>32	0.5 to >32	1.2	1.2	1.2
Amikacin	>32	>32	2 to >32	18.3	19.5	37.8
Gentamicin	>16	>16	0.25 to >16	17.1	17.1	18.3
Trimethoprim-sulfamethoxazole	>4	>4	0.25 to >4	22.0	22.0	22.0
Tigecycline	0.5	2	0.12 to 8			92.7
Minocycline	4	32	0.5 to >32	69.5		69.5
Colistin	0.25	>8	0.12 to >8		57.3	

*Susceptibility to cephalosporins, carbapenems, and piperacillin-tazobactam were all <10%.

CONCLUSIONS

- Cefiderocol showed good *in vitro* activity against Enterobacterales carrying multiple carbapenemases that are often multidrug resistant.
- No correlation between MIC value and carbapenemase content was observed, suggesting that other additional factors play a role in cefiderocol susceptibility.
- Cefiderocol should be considered as a treatment option when Enterobacterales isolates carrying multiple carbapenemases are encountered.

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