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Activity of Cefiderocol Against Metallo-β-Lactamase-Carrying Enterobacterales, Stratified by Allele, Collected as Part of the SENTRY Antimicrobial Surveillance Program

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BACKGROUND

- Cefiderocol is a siderophore-conjugated cephalosporin and one of the few agents with activity against Gram-negative isolates carrying metallo-β-lactamases.
- Activity of cefiderocol and comparator agents was analyzed against contemporary Enterobacterales isolates carrying metallo-β-lactamases.

METHODS

- 32,053 Enterobacterales isolates were collected as part of the SENTRY antimicrobial surveillance program in 2020–2023 in Europe and the USA.
- 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. Susceptibility was assessed according to CLSI, European Committee on Antimicrobial Susceptibility Testing (EUCAST), and US Food and Drug Administration (FDA) breakpoints.
- Isolates non-susceptible to meropenem or imipenem were subject to whole-genome sequencing to determine the presence of β-lactamases.

RESULTS

- 771 (2.4%) Enterobacterales non-susceptible to meropenem or imipenem were identified, and 252 of these (0.8% of total) carried metallo-β-lactamase genes, the majority of which were *Klebsiella pneumoniae* (**Figure 1**).
- 87.7% of 252 isolates carrying a metallo-β-lactamase genes were susceptible to cefiderocol when CLSI/FDA breakpoints were applied (susceptible ≤4 µg/mL) (**Table 1**); susceptibility was lower (63.9%) when EUCAST breakpoints were applied (susceptible ≤2 µg/mL), but cefiderocol still remained more potent than most comparator agents reported (**Table 1**).
- bla_{NDM-1} was the most prevalent allele identified (65.9%), followed by bla_{VIM-1} and bla_{NDM-5}. One isolate carried a bla_{IMP} enzyme (bla_{IMP-4}) and six carried multiple metallo-β-lactamase genes (**Figure 2** and **Table 2**).
- bla_{NDM}-carrying isolates showed more elevated MIC values compared with bla_{VIM}-carrying and all Enterobacterales isolates, but 85.3% of the bla_{NDM}-carrying isolates remained susceptible to cefiderocol using CLSI/FDA breakpoints, compared with 97.9% and 99.8% of bla_{VIM}-carrying and all Enterobacterales, respectively; susceptibilities were lower when EUCAST breakpoints were applied (**Table 2**).
- Cefiderocol showed similar activity against isolates carrying different bla_{NDM} alleles, and this also applied to isolates carrying different bla_{VIM} alleles (**Table 2**).

Figure 1: Enterobacterales isolates non-susceptible to meropenem or imipenem carrying metallo-β-lactamase genes (n=252)

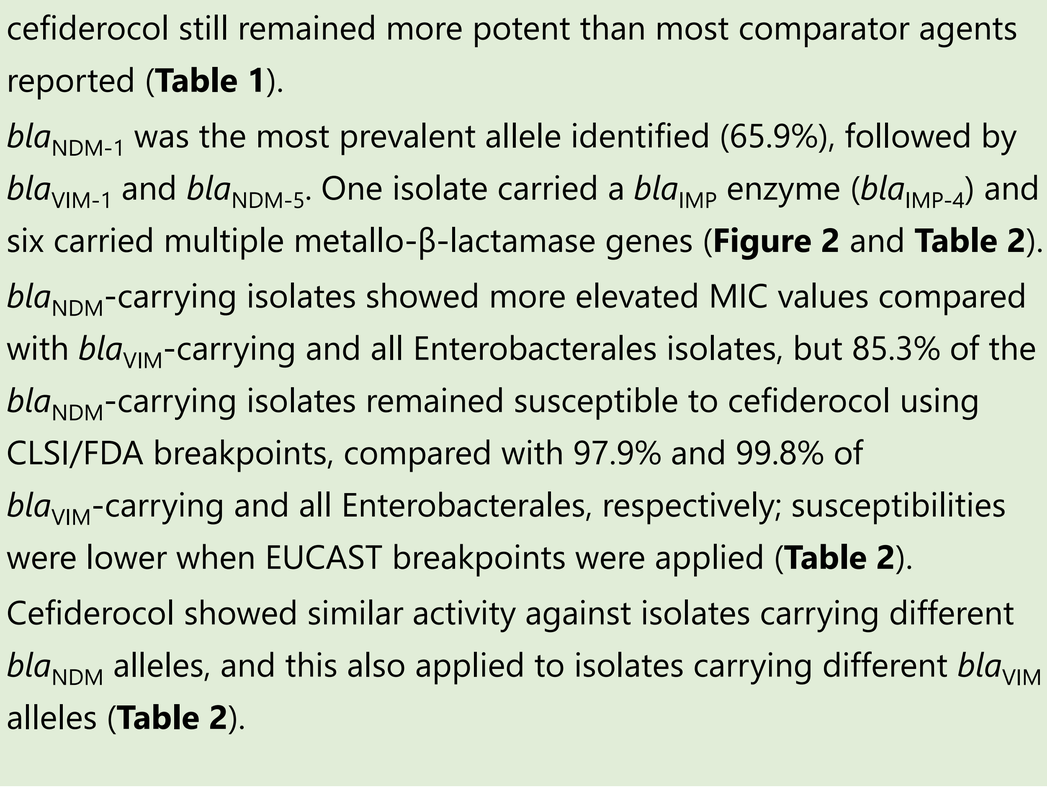

Figure 2: Metallo-β-lactamase genes encountered in Enterobacterales isolates non-susceptible to meropenem or imipenem carrying metallo-β-lactamase genes (n=252)

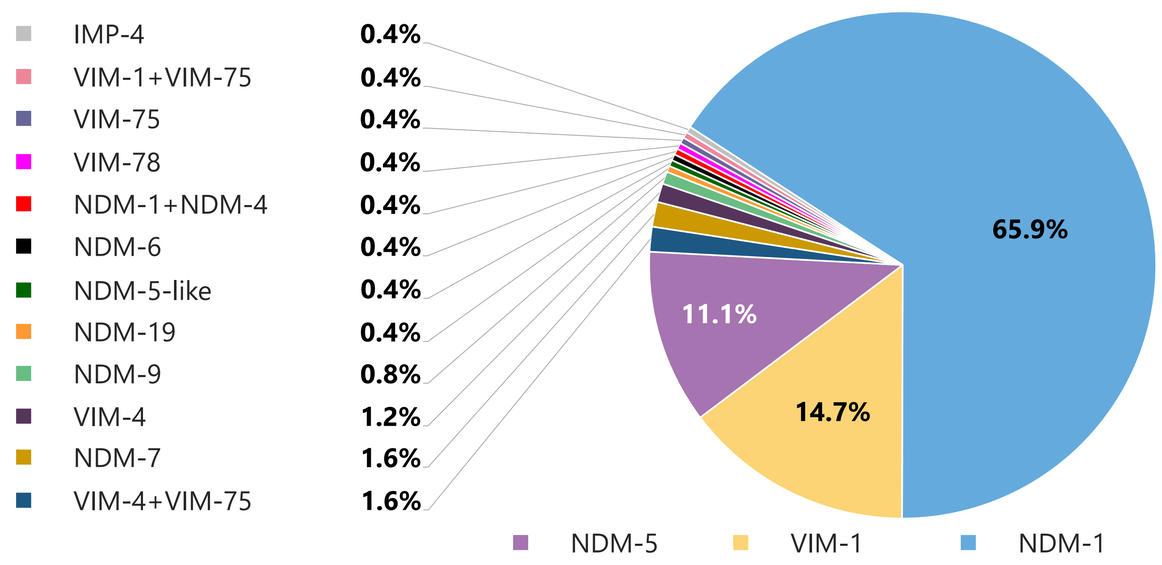

Table 1: Activity of cefiderocol and comparator agents against 252 metallo-β-lactamase-carrying Enterobacterales

Agent	CLSI[a]			EUCAST[a]			US FDA[a]		
	%S	%I	%R	%S	%I	%R	%S	%I	%R
Cefiderocol	87.7	8.7	3.6	63.9		36.1	87.7	8.7	3.6
Imipenem-relebactam	0.8	2.4	96.8[b]	3.2		96.8[b]	0.8	2.4	96.8[c]
Meropenem-vaborbactam	13.9	6.3	79.8	20.2		79.8	13.9	6.3	79.8
Ceftazidime-avibactam	2.4		97.6	2.4		97.6	2.4		97.6
Ceftolozane-tazobactam	0.4	0.0	99.6	0.4		99.6	0.4	0.0	99.6
Aztreonam	24.2	2.0	73.8	16.3	7.9	75.8	24.2	2.0	73.8
Ciprofloxacin	7.9	3.2	88.9	7.9	3.2	88.9[d]	7.9	3.2	88.9
Levofloxacin	11.2	6.8	82.1	11.2	6.8	82.1	11.2	6.8	82.1
Amikacin	27.4	7.9	64.7	35.3		64.7[e]	55.6	8.7	35.7
Gentamicin	34.1	4.8	61.1	34.1		65.9[e]	38.9	1.6	59.5
Trimethoprim-sulfamethoxazole	20.2		79.8	20.2	3.2	76.6	20.2		79.8
Tigecycline							92.1	6.7	1.2
Minocycline	67.9	13.5	18.7				67.9	13.5	18.7
Colistin		65.1	34.9	65.1		34.9			

I, intermediate; R, resistant; S, susceptible.
Susceptibilities for cephalosporins (ceftriaxone, ceftazidime, cefepime), carbapenems (imipenem, meropenem), ampicillin-sulbactam, and piperacillin-tazobactam were <10%.
[a]Criteria as published by CLSI (2024), EUCAST (2024), and US FDA (2024). [b]All Enterobacterales species were included in the analysis, but CLSI and EUCAST exclude organisms from the family Morganellaceae. [c]CLSI M100 standard is recognized. All Enterobacterales species were included in the analysis, but CLSI and EUCAST exclude organisms from the family Morganellaceae. [d]Using non-meningitis breakpoints. [e]For infections originating from the urinary tract. For systemic infections, aminoglycosides must be used in combination with other active therapy. Organisms included: *Enterobacter cloacae* species complex (33), *Escherichia coli* (17), *Klebsiella aerogenes* (3), *K. oxytoca* (2), *K. pneumoniae* (172), *Morganella morganii* (1), *Proteus mirabilis* (13), *Providencia rettgeri* (3), *P. stuartii* (4), *Serratia marcescens* (4).

Table 2: Activity of cefiderocol against metallo-β-lactamase-carrying Enterobacterales

	Allele	n	Number of isolates with MIC (µg/mL) of													MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	% Susceptibility	
			≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64			CLSI/FDA	EUCAST
All isolates		32053	11602	5497	5798	4437	2312	1369	712	249	53	10	7	2	5	0.06	0.5	99.8	99.0
Carbapenem-NS		771	20	27	60	84	113	143	185	99	27	5	3	2	3	1	4	94.8	82.0
MBL	**All**	252	3	6	6	8	17	34	87	60	22	4	2	2	1	2	8	87.7	63.9
	NDM-all	204		3	2	4	7	28	76	54	21	4	2	2	1	2	8	85.3	58.8
	NDM-1	166		2	2	3	5	25	59	47	15	3	2	2	1	2	8	86.2	58.1
	NDM-5	28		1	0	1	2	1	14	5	3	1				2	8	85.7	67.9
	NDM-7	4						1	1	1	1					-	-	-	-
NDM	**NDM-9**	2							1	1						-	-	-	-
	NDM-5-like	1						1								-	-	-	-
	NDM-6	1									1					-	-	-	-
	NDM-19	1									1					-	-	-	-
	NDM-1+NDM-4	1							1							-	-	-	-
	VIM-all	47	3	3	4	4	10	6	10	6	1					0.5	4	97.9	85.1
	VIM-1	37	1	0	2	3	8	6	10	6	1					1	4	97.4	81.6
	VIM-4	3	0	1	2											-	-	-	-
VIM	**VIM-75**	1					1									-	-	-	-
	VIM-78	1	1													-	-	-	-
	VIM-4+VIM-75	4		2		1	1									-	-	-	-
	VIM-1+VIM-75	1	1													-	-	-	-
IMP	**IMP-4**	1							1							-	-	-	-

IMP, imipenemase metallo-β-lactamase; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; NS, non-susceptible; VIM, Verona integron-encoded metallo-β-lactamase.

CONCLUSIONS

- Higher cefiderocol MIC values compared with those of wild-type isolates were observed for contemporary metallo-β-lactamase-carrying Enterobacterales, regardless of the allele encountered, but most of these multidrug-resistant isolates, especially those carrying VIM alleles, remained susceptible to cefiderocol.
- Cefiderocol should be considered as a treatment option when infections caused by metallo-β-lactamase-carrying Enterobacterales are encountered.

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