Activity of cefiderocol against NDM-producing *Enterobacterales* from a regional outbreak in the Tuscany region, Italy

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INTRODUCTION

Cefiderocol (FDC) is a novel siderophore-cephalosporin approved in Europe for the treatment of infections caused by Gram-negative bacteria with limited therapeutic options, including metallo-β-lactamase producing *Enterobacterales* (1).

Since late 2018, an outbreak of NDM-producing *Enterobacterales* emerged in Tuscany, mainly contributed by ST147 *K. pneumoniae,* where cefiderocol represented one of the few active therapies available (2). However, an outbreak of cefiderocol resistant NDM-producing *K. pneumoniae* strains has been recently described in a large University Hospital from the same region (3). FDC resistance was mainly contributed by alterations in the iron-uptake system (3).

The aim of this study was to evaluate the *in vitro* activity of FDC against a multicentric collection of NDM-producing *Enterobacterales* from Tuscany.

RESULTS

- 627 non-duplicate isolates of NDM-producing *Enterobacterales* (600 *Klebsiella pneumoniae*, 26 *Escherichia coli* and 1 *Citrobacter braakii*) were tested
- Overall, 78.9% of isolates were susceptible to FDC, showing $MIC_{50/90}$ values of 2/4 mg/L (Table 1)
- MIC_{90} values were higher for *E. coli* than *K. pneumoniae* (Table 1)
- 79.2% (475/600) of *K. pneumoniae* and 73.1% (19/26) of *E. coli* were inhibited at concentrations ≤ 2 mg/L (Table 2)
- FDC-resistant isolates were detected in 9/10 centers and 22 isolates (3.5%) showed a high-resistance level with MIC values >16 mg/L

	% S	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Collection (627)	78.9	2	4
K. pneumoniae (600)	79.2	2	4
E. coli (26)	73.1	2	8

Table 1. Percentage of susceptibility (% S) and $MIC_{50/90}$ values for NDM-producing strains

MATERIALS AND METHODS

Bacterial strains. Clinical isolates of NDM-producing *Enterobacterales* were collected in the period July-December 2022 from 10 centers in Tuscany (Figure 1).

Susceptibility testing. MICs of FDC were determined by broth microdilution using iron-depleted Müller-Hinton broth (4). Results were interpreted according to the EUCAST Clinical Breakpoints (v 13.0, 2023), considering the FDC susceptibility breakpoint of ≤ 2 mg/L.

CONCLUSIONS

FDC showed an overall good activity against NDM-producing *Enterobacterales*. The increasing number of resistant isolates underlines the need for FDC susceptibility testing in the clinical setting. The characterization of FDC resistance mechanisms is ongoing, and the adoption of additional infection control measures will be important in order to limit the spread of FDC resistant isolates.

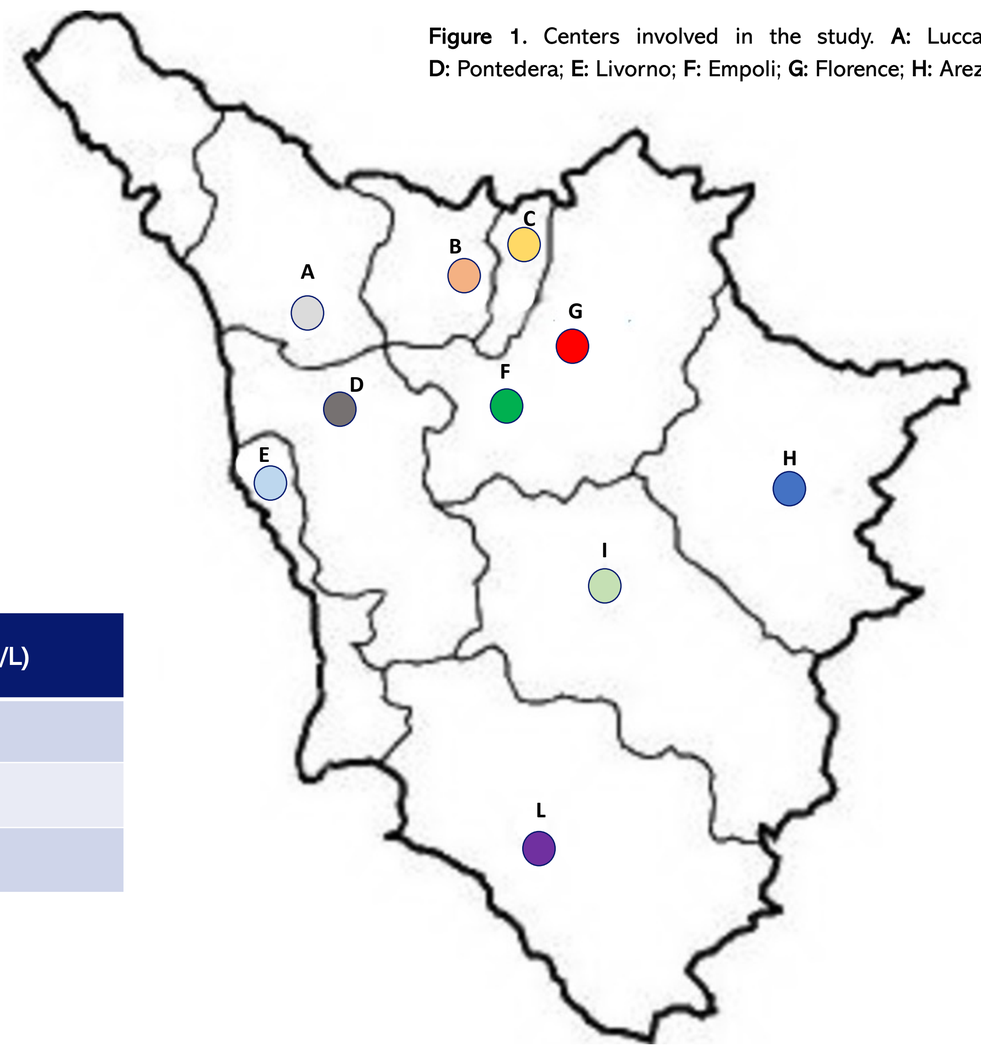

Figure 1. Centers involved in the study. **A:** Lucca; **B:** Pistoia; **C:** Prato; **D:** Pontedera; **E:** Livorno; **F:** Empoli; **G:** Florence; **H:** Arezzo; **I:** Siena; **L:** Grosseto.

Organism	Value	MIC (mg/L)												
		≤0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	>64
Enterobacterales (627)	N (%) at MIC	3 (0.5)	2 (0.3)	2 (0.3)	3 (0.5)	25 (3.9)	144 (23)	316 (50.4)	84 (13.4)	23 (3.7)	3 (0.5)	3 (0.5)	7 (1.1)	12 (1.9)
	Cum. % at MIC	0.5	0.8	1.1	1.6	5.5	28.5	78.9	92.3	96	96.5	97	98.1	100
K. pneumoniae (600)	N (%) at MIC	3 (0.5)	2 (0.3)	2 (0.3)	3 (0.5)	23 (3.9)	134 (22.4)	308 (51.3)	81 (13.5)	22 (3.7)	3 (0.5)	3 (0.5)	5 (0.8)	11 (1.8)
	Cum. % at MIC	0.5	0.8	1.1	1.6	5.5	27.9	79.2	92.7	96.4	96.9	97.4	98.2	100
E. coli (26)	N (%) at MIC	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.8)	10 (38.5)	8 (30.8)	3 (11.6)	1 (3.8)	0 (0)	0 (0)	2 (7.7)	1 (3.8)
	Cum. % at MIC	0	0	0	0	3.8	42.3	73.1	84.7	88.5	88.5	88.5	96.2	100

Table 2. Cefiderocol MIC distributions, for *Enterobacterales* overall and by organism

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