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Real-World Efficacy of Cefiderocol for Treatment of Infections Caused by Metallo-Beta-Lactamase-Producing Enterobacterales in Spain

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BACKGROUND

- Carbapenem-resistant (CR) Gram-negative bacterial infections, particularly those caused by metallo-beta-lactamase (MBL)-producing CR Enterobacterales (CRE), are associated with increased mortality and morbidity and have limited treatment options [1–3]. Among newer antibiotic agents with *in vitro* activity against MBL-producing Enterobacterales, cefiderocol [4,5] and aztreonam-avibactam [6,7] are approved for clinical use.
- The objectives of the retrospective CIRCE study were to evaluate the clinical outcomes of cefiderocol treatment in patients with confirmed MBL-CRE infections.

METHODS

- CIRCE was a retrospective, observational, descriptive, multicentre study in Spain (January 2023–April 2025) investigating the clinical outcomes in adult patients with confirmed MBL-producing CRE infections, who received cefiderocol for ≥72 hours.
- Patients were excluded if they had concurrent non-MBL Gram-negative infections that were cefiderocol resistant by European Committee on Antimicrobial Susceptibility Testing criteria; cefiderocol use within 28 days before current cefiderocol initiation; receipt of other investigational agent; or MBL infections with cefiderocol minimum inhibitory concentrations >8 µg/mL.
- The main outcomes were clinical cure and clinical response at Day 14, all-cause mortality and survival at days 14 and 28.
  - Clinical cure at Day 14: resolution of all signs and symptoms of infection such that no antibiotic therapy was required to treat the infection caused by the MBL-CRE pathogen and where no additional Gram-negative antibiotic was administered to supplement the antibiotic regimen from >96 hours after cefiderocol initiation to Day 14.
  - Clinical response at Day 14: patients who had either complete resolution of signs and symptoms of infection OR showed clinical improvement but not complete resolution, and where no additional Gram-negative antibiotic was administered to supplement the antibiotic regimen from >96 hours after cefiderocol initiation to Day 14.
- Among data collected, patients' baseline demographics, clinical characteristics, baseline Gram-negative pathogen and susceptibilities, MBL status, and cefiderocol use, and adverse events associated with cefiderocol treatment were evaluated.
- The analyses were mainly descriptive, and no formal sample size calculation was performed.

RESULTS

Demographics and baseline characteristics

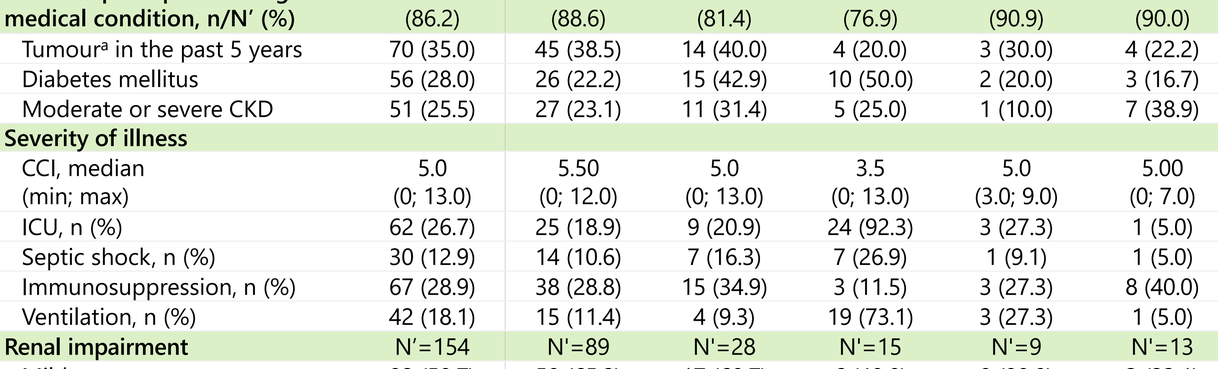
- A total of 232 patients were treated with cefiderocol for MBL-producing CRE infections (**Table 1**). There were 120 NDM producers and 106 VIM producers (**Figure 1**). Additionally, six patients had ≥2 MBLs (NDM + VIM [n=3]; IMP + VIM [n=1]; NDM + GIM [n=1]; NDM + VIM + OXA-48 [n=1]). Of the overall population, 34.1% (n=79) of patients had a different carbapenemase other than an MBL enzyme, mostly OXA-48.
- *K. pneumoniae* and *Enterobacter* spp. were the most frequent NDM-producing and VIM-producing CREs, respectively (**Figure 1**).
- Almost 40% of NDM-producing CRE infections originated from the urinary tract, whereas more than half of the VIM-producing CRE infections originated from the respiratory tract (28.3%) or the urinary tract (23.6%; **Figure 2**).
- Among patients with VIM-producing CRE infections, significantly more patients were admitted to the intensive care unit (ICU) and had septic shock at initiation of cefiderocol treatment compared with NDM-producing CRE infections (**Table 2**).
- Cefiderocol was administered as targeted therapy or empirical therapy in approximately half of patients in both NDM-producing (51.7% and 45.0%, respectively) and VIM-producing (48.1% and 50.9%, respectively) CRE infections.

Table 1. Baseline demographics, clinical characteristics and antibiotic use in patients with MBL-producing CRE infections

	Overall N=232	*K. pneumoniae* N=132	*Enterobacter* spp. N=43	*Serratia* spp. N=26	*E. coli* N=11	Other N=20
Sex (male), n (%)	161 (69.4)	95 (72.0)	27 (62.8)	18 (69.2)	8 (72.7)	13 (65.0)
Age (years), median (min; max)	66.0 (19.0; 93.0)	62.5 (28.0; 93.0)	68.0 (19.0; 89.0)	62.0 (21.0; 80.0)	71.0 (49.0; 80.0)	65.5 (20.0; 82.0)
Most frequent pre-existing medical condition, n/N' (%)	N'=200 (86.2)	N'=117 (88.6)	N'=35 (81.4)	N'=20 (76.9)	N'=10 (90.9)	N'=18 (90.0)
Tumour[a] in the past 5 years	70 (35.0)	45 (38.5)	14 (40.0)	4 (20.0)	3 (30.0)	4 (22.2)
Diabetes mellitus	56 (28.0)	26 (22.2)	15 (42.9)	10 (50.0)	2 (20.0)	3 (16.7)
Moderate or severe CKD	51 (25.5)	27 (23.1)	11 (31.4)	5 (25.0)	1 (10.0)	7 (38.9)
Severity of illness						
CCI, median (min; max)	5.0 (0; 13.0)	5.50 (0; 12.0)	5.0 (0; 13.0)	3.5 (0; 13.0)	5.0 (3.0; 9.0)	5.00 (0; 7.0)
ICU, n (%)	62 (26.7)	25 (18.9)	9 (20.9)	24 (92.3)	3 (27.3)	1 (5.0)
Septic shock, n (%)	30 (12.9)	14 (10.6)	7 (16.3)	7 (26.9)	1 (9.1)	1 (5.0)
Immunosuppression, n (%)	67 (28.9)	38 (28.8)	15 (34.9)	3 (11.5)	3 (27.3)	8 (40.0)
Ventilation, n (%)	42 (18.1)	15 (11.4)	4 (9.3)	19 (73.1)	3 (27.3)	1 (5.0)
Renal impairment	N'=154	N'=89	N'=28	N'=15	N'=9	N'=13
Mild	92 (59.7)	58 (65.2)	17 (60.7)	6 (40.0)	8 (88.9)	3 (23.1)
Moderate	34 (22.1)	17 (19.1)	5 (17.9)	6 (40.0)	1 (11.1)	5 (38.5)
Severe	17 (11.0)	6 (6.7)	6 (21.4)	2 (13.3)	0 (0.0)	3 (23.1)
End-stage renal disease	11 (7.1)	8 (9.0)	0 (0.0)	1 (6.7)	0 (0.0)	2 (15.4)
Prior antibiotic treatment, n (%)	152 (65.5)	86 (65.2)	34 (79.1)	7 (26.9)	10 (90.9)	15 (75.0)
Duration of prior antibiotics (days), median (min; max)	3.0 (0; 111.0)	3.5 (0; 76.0)	6.5 (0; 111.0)	0.0 (0; 34.0)	4.0 (0; 46.0)	13.0 (0; 85.0)
Use of cefiderocol, n (%)[c]						
Targeted therapy	114 (49.1)	70 (53.0)	15 (34.9)	12 (46.2)	4 (36.4)	13 (65.0)
Empirical therapy	113 (48.7)	59 (44.7)	28 (65.1)	14 (53.9)	5 (45.5)	7 (35.0)
Unsure if targeted or empirical	5 (2.2)	3 (2.3)	0 (0)	0 (0)	2 (18.2)	0 (0)
Treatment duration (days), median (min; max)	8.0 (2.3; 91.2)	7.8 (2.3; 44.5)	10.0 (3.0; 91.2)	7.7 (3.5; 37.9)	9.7 (3.1; 13.1)	9.5 (3.3; 83.8)
Combination therapy, n (%)	44 (19.0)	24 (18.2)	10 (23.3)	3 (11.5)	3 (27.3)	4 (20.0)
Monotherapy, n (%)	188 (81.0)	108 (81.8)	33 (76.7)	23 (88.5)	8 (72.7)	16 (80.0)

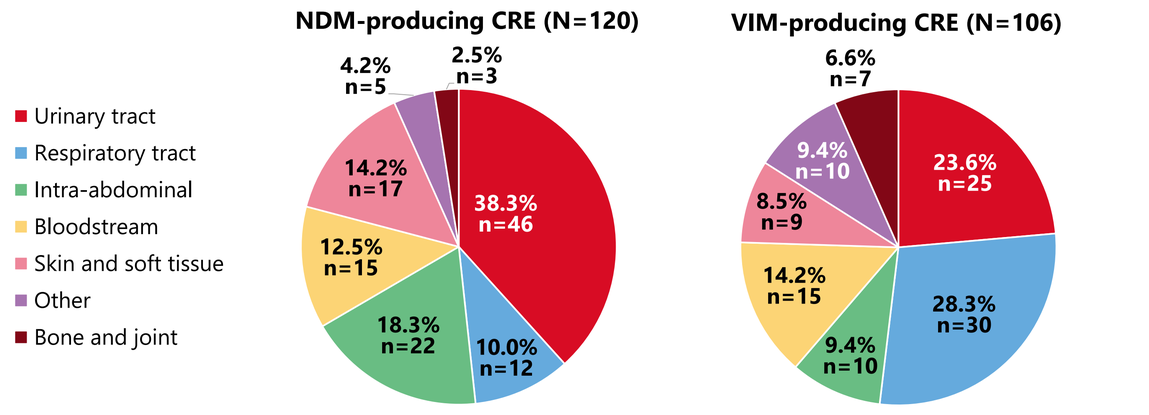
CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; CRE, carbapenem-resistant Enterobacterales; ICU, intensive care unit; MBL, metallo-beta-lactamase. [a]Solid or haematological.

Figure 1. Distribution of Gram-negative bacterial species in NDM- or VIM-producing CRE infections



CRE, carbapenem-resistant Enterobacterales; MBL, metallo-beta-lactamase; NDM, New-Delhi MBL; VIM, Verona integron-encoded MBL.

Figure 2. Distribution of infection sites for patients infected by NDM- or VIM-producing CRE



CRE, carbapenem-resistant Enterobacterales; MBL, metallo-beta-lactamase; NDM, New-Delhi MBL; VIM, Verona integron-encoded MBL.

Table 2. Severity of illness in patients infected by NDM- or VIM-producing CRE

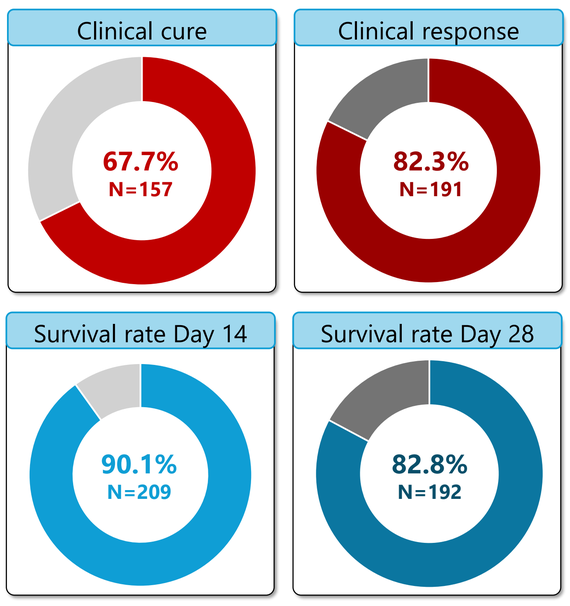
	NDM (N=120)	VIM (N=106)	*P* value[a]
ICU status, n (%)			
No	102 (85.0)	65 (61.3)	0.0001
Yes	18 (15.0)	41 (38.7)	
Presence of septic shock, n (%)			
No	111 (92.5)	86 (81.1)	0.0158
Yes	9 (7.5)	20 (18.9)	

CRE, carbapenem-resistant Enterobacterales; ICU, intensive care unit; MBL, metallo-beta-lactamase; NDM, New-Delhi MBL; VIM, Verona integron-encoded MBL. [a]Fisher's exact test.

Overall clinical outcomes

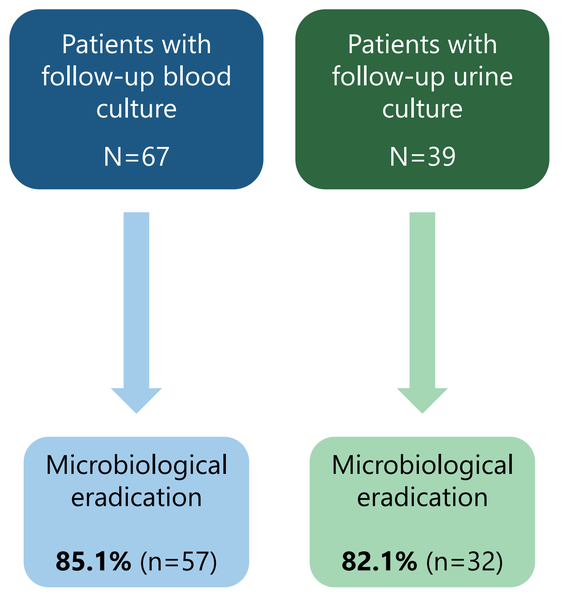
- Overall clinical cure and clinical response rates were 67.7% and 82.3%, respectively (**Figure 3**). Overall rates of survival at days 14 and 28 were 90.1% and 82.8%, respectively.
- Among patients with follow-up blood or urine samples, the microbiological eradication rates were high (i.e., >80%; **Figure 4**).

Figure 3. Overall clinical outcomes in MBL-producing CRE[a] infections in the CIRCE study (N=232)



CRE, carbapenem-resistant Enterobacterales; MBL, metallo-beta-lactamase. [a]Six patients had two MBL enzymes: NDM + VIM (n=3); IMP + VIM (n=1); NDM + GIM (n=1); NDM + VIM + OXA-48 (n=1).

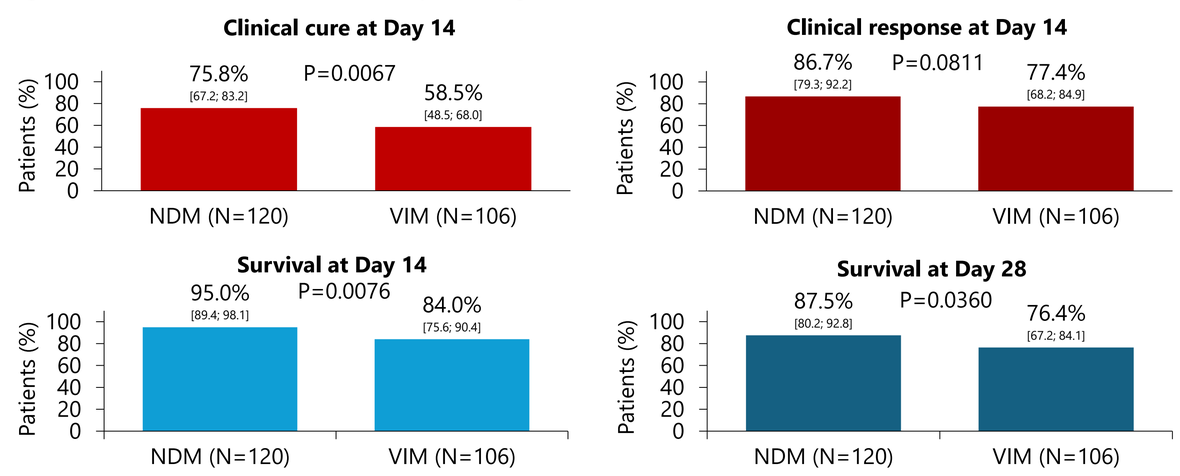
Figure 4. Microbiological eradication from blood in bloodstream infections and from urine in complicated urinary tract infections



Clinical outcomes by type of MBL

- At Day 14, 75.8% and 58.5% of patients with NDM- and VIM-producing CRE infections, respectively, achieved clinical cure, with clinical response rates of 86.7% and 77.4%, and survival rates of 95.0% and 84.0%, respectively (**Figure 5**).
  - Treatment-emergent resistance was found in 0.8% (n=1) and 1.9% (n=2) of NDM- and VIM-producing CRE isolates, respectively.
- Survival rates at Day 28 were 87.5% and 76.4%, respectively (**Figure 5**).

Figure 5. Outcomes for NDM- or VIM-producing CRE infections



CRE, carbapenem-resistant Enterobacterales; GIM, German imipenemase MBL; IMP, imipenemase MBL; MBL, metallo-beta-lactamase; NDM, New-Delhi MBL; OXA, oxacillinase; VIM, Verona integron-encoded MBL. P values were based on Fisher's exact test. Data are shown as % [95% confidence interval].

CONCLUSIONS

- The results of this real-world study showed that cefiderocol treatment for infections caused by MBL-producing Enterobacterales achieved good clinical outcomes, particularly in infections caused by NDM-producing CRE.
- The less favourable clinical outcomes observed in patients with VIM-producing CRE infections were most likely due to the significantly higher prevalence of septic shock and longer ICU stays.

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Conflict of interest

LG, CL and JGC are employees of the Shionogi Group.

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