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Categorisation of Routine Cefiderocol Susceptibility by EUCAST Zone Diameter Breakpoints Has Low Predictability of Clinical Outcome for Metallo-Beta-Lactamase-Producing Enterobacterales

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INTRODUCTION

- Cefiderocol susceptibility testing by disk diffusion is approved by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [1]. Cefiderocol has good *in vitro* activity against most metallo-beta-lactamase (MBL)-producing carbapenem-resistant Enterobacterales (CRE) species [2].
- Cefiderocol is approved in Europe for the treatment of serious Gram-negative bacterial infections caused by susceptible bacteria with limited treatment options [3]. It is recommended as a preferred agent for the treatment of MBL-positive infections by the Infectious Diseases Society of America and conditionally recommended for MBL-CRE infections in the European Society of Clinical Microbiology and Infectious Diseases guidelines [4,5].

OBJECTIVES

- We aimed to evaluate how well the current EUCAST interpretive criteria for cefiderocol susceptibility testing by the disk diffusion method in daily routine in microbiology laboratories predicted the clinical outcomes of patients treated with cefiderocol for MBL-CRE infections.

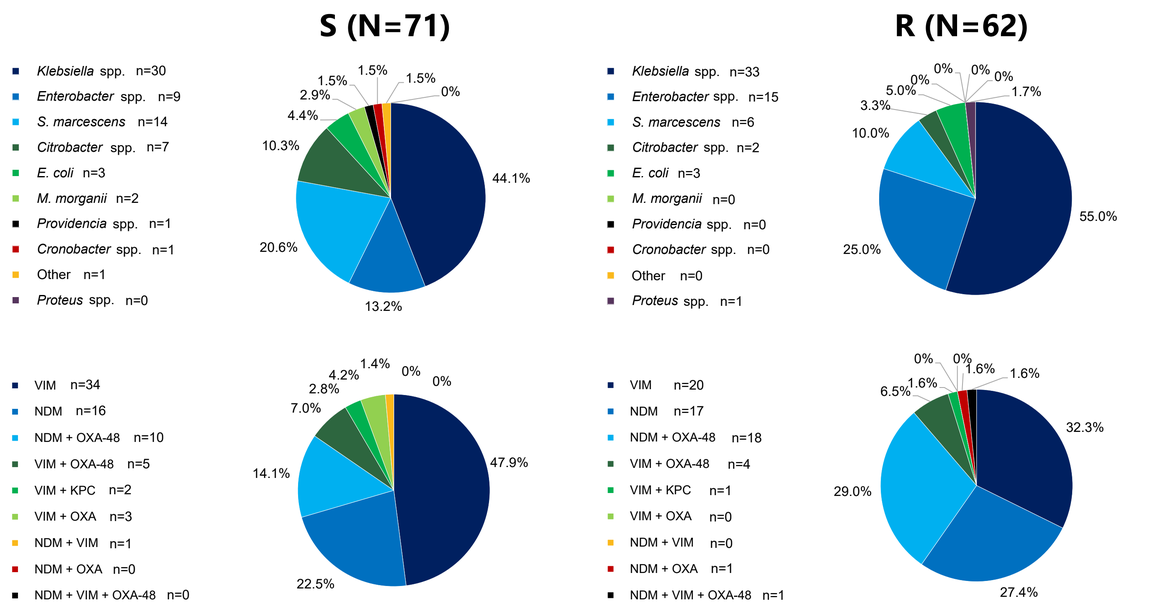
METHODS

- Data were collected in the observational, multicentre CIRCE study performed in Spain (January 2023–April 2025) investigating the clinical outcomes of adult hospitalised patients with MBL-CRE infections, who received cefiderocol for ≥72 hours (**Table 1**).
- The following data were collected from the patients' medical charts: demographics and baseline clinical characteristics, medical history, infection site, Enterobacterales species, susceptibility status to antibiotics, prior and concomitant antibiotics, cefiderocol use, clinical outcomes, vital status and adverse drug reactions [6].
- Cefiderocol susceptibility was determined by each participating laboratory with disk diffusion according to EUCAST recommendations [1]. The current study analysed results for patients who had local susceptibility data available by disk diffusion. Identification of an MBL enzyme was based on the following methods:
  - Lateral flow test (CARBA-5 [NG Biotech] or OKNVI-RESIST-5 [Coris])
  - Nucleic acid amplification test (NAAT)/polymerase chain reaction (PCR) (e.g. Xpert CARBA-5 [Cepheid])
  - Multiplex PCR test (BioFire Film Array)
  - Other tests
- Clinical response and clinical cure rates were determined at Day 14 by the treating physician and evaluated according to zone inhibition category.
- Interpretive criteria for disk zone diameters were based on EUCAST breakpoint table v15 [1]: susceptible (S) ≥23 mm, area of technical uncertainty (ATU) 21–23 mm, and resistant (R) <23 mm.
- Only descriptive statistics were utilised.

RESULTS

- Among 232 patients with MBL-producing CRE infections enrolled into the CIRCE study [6], 133 patients had information on cefiderocol susceptibility obtained from the disk diffusion method performed in the local laboratory. 71 patients (53.4%) had infections involving MBL-CRE categorised as S to cefiderocol, and 62 patients (46.6%) had MBL-CRE categorised as R based on EUCAST criteria (**Table 1**).
- Baseline demographics and clinical characteristics were similar between patients with S and R CRE isolates and were largely consistent with the wider population, apart from significantly more frequent tumours observed among patients with R isolates (**Table 1**). Numerically more patients with R isolates had combination therapy and were treated empirically than those with S isolates (**Table 1**).
- *Klebsiella* spp. was the most frequent MBL-producing CRE (**Figure 1**) among both S and R isolates. *Enterobacter* spp. was found approximately twice as often in R as in S isolates, while *Serratia marcescens* were more frequent among S isolates than R isolates (**Figure 1**).
- VIM enzyme was most frequent in both S and R isolates. NDM enzyme alone was found in about a quarter of S and R isolates, but it was found in combination with OXA-48 in 29.0% of R isolates and 14.1% of S isolates (**Figure 1**).

Figure 1 Distribution of CRE species and MBL enzymes in CRE infections[a] with S or R isolates



CRE, carbapenem-resistant Enterobacterales; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-beta-lactamase; NDM, New Delhi MBL; OXA, oxacillinase; R, resistant; S, susceptible; UTI, urinary tract infection; VIM, Verona integron-encoded MBL.
[a]Non-UTI infections: S: 67.6% (48/71) vs R: 74.2% (46/62); UTI: S: 32.4% (23/71) vs R: 25.8% (16/62).

- Clinical cure and clinical response rates at Day 14, and survival rates at Day 14 and Day 28 were similar among patients with S and R isolates and were consistent with the results seen in the wider CIRCE study [6] (**Figure 2**). The analysis of clinical cure and clinical response by zone inhibition diameter showed that patients with R isolates were just as likely to achieve clinical cure or clinical response as those categorised as S (**Figure 3**). Most patients had CRE isolates with cefiderocol susceptibility zone inhibition within the ATU range. The distribution of non-response and non-cure remained similar within R, ATU and S categories when patients with urinary tract infections (UTIs) were excluded from the analysis (**Figure 3**).
- ***Limitation:*** *susceptibility testing was performed locally using routine disk diffusion methods in real-world settings without confirmation by reference broth microdilution method. Additional susceptibility tests in a central laboratory will be performed, and results will be published later.*

CONCLUSIONS

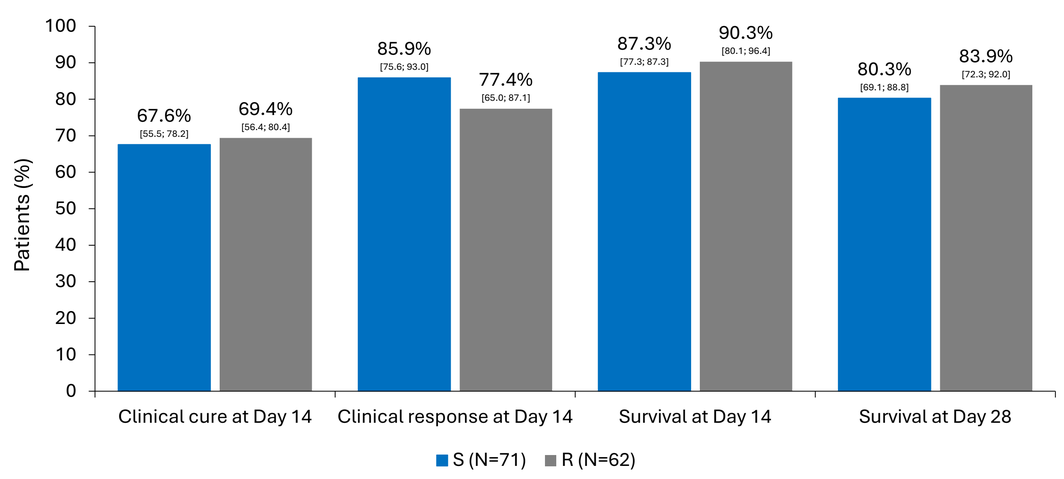
- Clinical outcomes in patients treated with cefiderocol for MBL-CRE infections were independent of the susceptibility of causative isolates (S or R) according to current EUCAST interpretive criteria for disk diffusion testing.
- Similar results were found when patients with UTI were excluded from the overall data set, indicating that high rates of clinical response against isolates regarded as R in the overall population was not a result of bias from patients with UTI, where cefiderocol concentrations in the urine would greatly exceed the minimum inhibitory concentration.
- The results highlight that current EUCAST disk diffusion breakpoints cannot reliably predict clinically relevant resistance leading to clinical failure for cefiderocol in MBL-producing CRE infections and risk over-reporting S isolates as R. Where disk diffusion testing is used, laboratories should consider re-testing isolates with zone diameters <23 mm by a broth microdilution method.

Table 1 Demographics, clinical characteristics, disease severity and cefiderocol use in patients with MBL-CRE infections with S or R isolates.

	Overall N=232	S N=71	R N=62	P value (S vs R)
Sex (male), n (%)	161 (69.4)	46 (64.8)	47 (75.8)	0.1669[b]
Age (years), median (min; max)	66.0 (19.0; 93.0)	63.00 (34.0; 91.0)	65.50 (20.0; 86.0)	0.6260[c]
Most frequent pre-existing medical condition, n/N' (%)	N'=200 (86.2)	N'=65 (91.6)	N'=48 (77.4)	
Tumour in the past 5 years[a]	70 (35.0)	17 (26.2)	22 (45.8)	0.0296[b]
Diabetes mellitus	56 (28.0)	19 (29.2)	16 (33.3)	0.6411[b]
Moderate or severe CKD	51 (25.5)	18 (27.7)	14 (29.2)	0.8635[b]
Severity of illness				
CCI, median (min; max)	5.0 (0; 13.0)	5.00 (0.0; 12.0)	5.00 (0.0; 13.0)	0.6040[c]
ICU, n (%)	62 (26.7)	16 (22.5)	16 (25.8)	0.6597[b]
Septic shock, n (%)	30 (12.9)	4 (5.6)	6 (9.7)	0.3777[b]
Immunosuppression, n (%)	67 (28.9)	19 (26.8)	21 (33.9)	0.3724[b]
Ventilation, n (%)	42 (18.1)	11 (15.5)	13 (21.0)	NA
Renal impairment, n/N' (%)	N'=154	N'=52	N'=50	
Mild	92 (59.7)	29 (55.8)	32 (64.0)	0.2376[d]
Moderate	34 (22.1)	11 (21.2)	11 (22.0)	
Severe	17 (11.0)	6 (11.5)	4 (8.0)	
End-stage renal disease	11 (7.1)	6 (11.5)	3 (6.0)	
Prior antibiotic treatment, n (%)	152 (65.5)	41 (57.8)	40 (64.5)	0.4248[b]
Duration of prior antibiotics (days), median (min; max)	3.0 (0; 111.0)	2.00 (0.0; 85.0)	3.00 (0.0; 111.0)	0.4260[c]
Use of cefiderocol, n (%)				
Targeted therapy	114 (49.1)	43 (60.6)	28 (45.2)	0.2045[e]
Empirical therapy	113 (48.7)	27 (38.0)	33 (53.2)	
Unsure if targeted or empirical	5 (2.2)	1 (1.4)	1 (1.6)	
Treatment duration (days), median (min; max)	8.0 (2.3; 91.2)	7.04 (3.0; 83.75)	8.49 (3.0; 91.2)	0.3800[c]
Monotherapy, n (%)	188 (81.0)	58 (81.7)	44 (71.0)	0.1446[b]
Combination therapy, n (%)[f,g]	44 (19.0)	13 (18.3)	18 (29.0)	

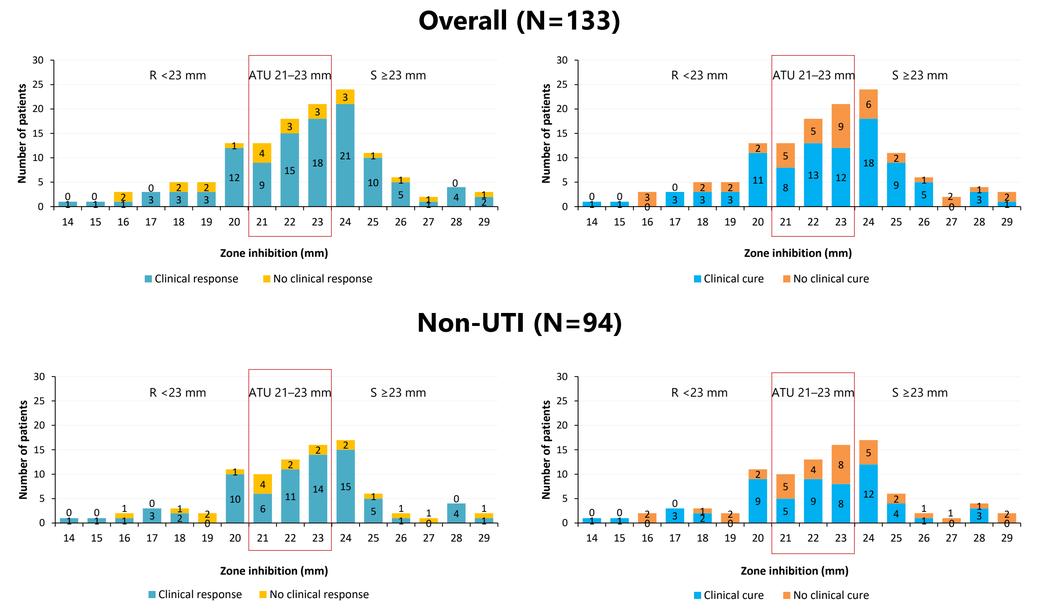
CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; CRE, carbapenem-resistant Enterobacterales; ICU, intensive care unit; MBL, metallo-beta-lactamase; NA, not available; R, resistant; S, susceptible.
[a]Solid or haematological. [b]Cochran–Armitage test. [c]Jonckheere–Terpstra test. [d]Linear by linear association test. [e]Chi-squared test. [f]Tigecycline (S n=5; R n=6); Amikacin (S n=1; R n=2); Colistin (S n=1; R n=4); Aztreonam (S n=2; R n=2); Ceftazidime/avibactam (S n=1; R n=0); Fosfomycin (S n=0; R n=1); Other (S n=4; R n=3). [g]Not mutually exclusive.

Figure 2 Clinical outcomes in MBL-producing CRE infections with S or R isolates.



CRE, carbapenem-resistant Enterobacterales; MBL, metallo-beta-lactamase; R, resistant; S, susceptible.
Data are % [95% confidence interval].

Figure 3 Distribution of clinical response and clinical cure at Day 14 by cefiderocol zone inhibition diameter.



ATU, area of technical uncertainty; CRE, carbapenem-resistant Enterobacterales; MBL, metallo-beta-lactamase; R, resistant; S, susceptible; UTI, urinary tract infection.

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