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Cefiderocol therapy among immunocompromised adult patients: a descriptive analysis from a prospective, multicentre cohort study

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Abstract

Purpose The global rise in infections due to multidrug-resistant Gram-negative bacteria (MDRGNB) infections has disproportionately impacted immunocompromised (IC) hosts. Cefiderocol, a novel siderophore cephalosporin, exhibits potent activity against MDRGNB, but limited data exist on its use in IC patients. This study aimed to describe cefiderocol use in IC patients.

Methods Patients and therapy characteristics were descriptively reported, and outcomes were compared between IC and non-IC patients. Cox regression models were used to identify factors associated with mortality.

Results Among 185 patients, 84 (45.4%) were IC. Similar descriptive rates were observed in IC and non-IC groups regarding indications for cefiderocol use, choice of monotherapy versus combination therapy, or empirical versus targeted treatment. The 28-day clinical cure rates were similar across patients receiving targeted cefiderocol therapy for infection due to *Pseudomonas aeruginosa* (81%, 17/21), Enterobacterales (77.3%, 17/22) and *Acinetobacter baumannii* (42%, 21/50). Thirty-day mortality was comparable between IC and non-IC patients (40.8%, 95%

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confidence interval [CI] 27.9–56.8 vs 33.3%, 95% CI 22.9–46.9; p = 0.5430). In multivariable analysis IC status was not associated with higher mortality.

Conclusion Cefiderocol use in IC patients resulted in clinical outcomes comparable to non-IC patients when treating MDRGNB infections. IC status was not associated with an increased mortality, emphasising the importance of effective antimicrobial therapy. Further investigation is needed to clarify the relative impact of the administered treatment vs. the patients' clinical condition in influencing the prognosis of *Acinetobacter baumannii* infections.

Keywords Cefiderocol, Antibiotic therapy, Antimicrobial resistance, SOT, Mortality

Introduction

Prevalence of infections due to multidrug-resistant Gram-negative bacteria (MDRGNB) is increasing worldwide and particularly among immunocompromised (IC) hosts such as solid-organ transplant recipients (SOT) and haematopoietic stem-cell transplant (HSCT) recipients. Among the first group, in the first year after transplantation, the infection prevalence ranges between 30–65% and MDRGNB have been identified in 14–20% of these events [1]

Having an MDRGNB as the pathogen responsible for bloodstream infections (BSI) has been identified as a factor leading to increased mortality, with attributable mortality rates of 5% for *Klebsiella pneumoniae* carbapenemase (KPC)-producing Enterobacterales, 35% for metallo-β-lactamases (MBL)-producing Enterobacterales, 19% for carbapenem-resistant-*Pseudomonas aeruginosa* (CRPA), and 16% for carbapenem-resistant-*Acinetobacter baumannii* (CRAB) [2] This has also been confirmed among IC patients, with BSI due to MDRGNB being consistently associated with higher mortality compared to BSI due to drug-susceptible pathogens and reaching crude mortality rates of 65.5% among liver transplant recipients with CRAB infections [3, 4] Cefiderocol is a novel siderophore cephalosporin with a broad activity spectrum against MDRGNB, including carbapenem-resistant Enterobacterales, *P. aeruginosa*, and *A. baumannii*. This potent activity derives from its high stability against various extended-spectrum beta-lactamases and carbapenemases and the ability to form a chelating complex with iron, which is actively transported inside target pathogens [5].

In vitro data showed how clinical isolates of Enterobacterales (99.8%), *P. aeruginosa* (99.9%), *A. baumannii* (96.0%), and *S. maltophilia* (98.6%) collected in North America and Europe from 2014 to 2019 were highly susceptible to cefiderocol [6] However, recent data suggest a less benign scenario with high cefiderocol-resistance rates among New Delhi (NDM) MBL-producing Enterobacterales (38.8%), NDM-producing *A. baumannii* (44.7%) and ceftazidime/avibactam-resistant Enterobacterales (36.6%) [7].

Current IDSA and ESCMID guidelines agree in suggesting cefiderocol use in infections due to carbapenem-resistant Enterobacterales, especially MBL-producing; however, indications for CRPA and CRAB are divergent due to the limited amount of evidence available [8–10] Among IC patients, cefiderocol use has been advocated in selected conditions [11] but the evidence currently available is limited [12, 13] In the largest experience, 114 IC patients treated with regimens containing cefiderocol displayed at 28 days an infection cure rate of 53.3% and an overall mortality of 37.7% [14].

In this study, we performed a post-hoc analysis of the first collected data from the CEFI-SITA study [15], aiming to describe the use of cefiderocol among IC patients in the Italian setting regarding indications, patients' characteristics, 28-day clinical cure and 30-day mortality rate.

Methods

Setting and Objectives

The MULTI-SITA project has been developed by the Italian Society of Anti-Infective Therapy (SITA) as a platform for conducting observational studies in the field of on invasive bacterial and fungal diseases. One of the studies conducted within the MULTI-SITA project is CEFI-SITA, a prospective, observational, multicentre study describing cefiderocol use in adult patients in Italian hospitals. The CEFI-SITA study is ongoing, with a prospective period of enrollment from 1 August 2022 to 31 December 2025. The descriptive results of the first 200 patients enrolled in the CEFI-SITA study across 17 Italian hospitals from August 2022 to September 2023 have been recently published [15].

In the present post-hoc analysis, the primary objective was to describe cefiderocol use according to the IC host status in the first patients included in the CEFI-SITA study.

The secondary objectives of the present post-hoc analyses were: (1) to describe the factors associated with cefiderocol use as monotherapy versus a combined regimen in IC patients versus non-IC patients, and (2) to describe 30-day mortality and 28-day clinical cure rates in IC patients versus non-IC patients treated with cefiderocol.

Patients treated with at least one dose of cefiderocol as per local clinical practice were included in the CEFI-SITA study. Exclusion criteria were (1) patients aged less than

18 years, (2) patients previously included in the study for a previous treatment with cefiderocol, and (3) missing key data for defining the IC category.

IC status was defined as being a SOT recipient (SOT group), having any acute or chronic haematological malignancy (Haematology group) or solid neoplasm, people with human immunodeficiency virus (HIV), autoimmune disease or previous immunosuppressant therapy (other than steroids) for other reasons (Other IC group) [16].

Statistical analysis

Characteristics of adult patients treated with cefiderocol in terms of baseline conditions, infections, therapy, and clinical cure (at 28 days after cefiderocol initiation) were reported according to categories of IC patients (SOT, Haematology, Other IC) and non-immunocompromised patients (non-IC), for descriptive purposes. To this aim, continuous variables were summarised through median and interquartile range (IQR), while categorical variables were expressed as frequencies (%).

The crude 30-day mortality from initiation of cefiderocol therapy was summarised graphically using the Kaplan–Meier method in patients receiving targeted cefiderocol for Enterobacterales, *P. aeruginosa*, *A. baumannii*, or MBL-producing Gram-negative bacteria infections (this latter group including infections from MBL-producing organisms of the former three groups), and descriptively compared between IC and non-IC patients by means of the log-rank test. All Kaplan–Meier curves included patients with infection by only one Gram-negative genus (except for Enterobacterales infection, for which concomitant infection by more than one member of the Enterobacterales order was also considered).

The analysis of factors associated with 30-day mortality from cefiderocol initiation was performed in the subgroup of patients receiving targeted cefiderocol therapy for Enterobacterales, *P. aeruginosa*, or *A. baumannii* infections (defined, as above, as infection by only one Gram-negative genus, except for Enterobacterales infection, for which concomitant infection by more than one member of the Enterobacterales order was also considered). Rubin's multiple imputation was performed as a preliminary step [17], and categorical variables with one or fewer deaths in any single category were excluded from the analyses. Then, the potential association of demographics and clinical factors (including IC vs. non-IC) with 30-day mortality as a time-to-event endpoint was initially tested by means of univariable Cox regression models.

Subsequently, a multivariable Cox regression model (model A) was built by means of a stepwise backward selection procedure, initially considering variables showing a p-value < 0.10 in univariable analyses for their potential association with 30-day mortality. Of note, in line with the purpose of the present study, the independent variable IC vs. non-IC variable was forced into model A independent of backward selection. Variables included in model A were also included in a second multivariable Cox regression model (model B), which also included the centre as a shared frailty.

In a sensitivity analysis, clinical and demographic variables were tested for their association with 30-day mortality in univariable and multivariable Cox regression models as above, but with the independent variable IC vs. non-IC being substituted by a categorical variable composed of four categories (SOT, haematology, other IC, and non-IC, with the latter as reference). These led to multivariable models C and D, which included the centre as a shared frailty. The proportional hazards assumption was verified for all fixed-effect Cox regression models in the present study by means of cumulative sums of Martingale residuals and a Kolmogorov-type supremum test based on 1000 simulated patterns to evaluate deviations from the expected proportionality [18]. Where the assumption was not met, 7-day mortality and 8–30-day mortality were analysed separately, and the corresponding variable was eventually included in the multivariable Cox regression models as a time-dependent covariate.

Statistical analyses were performed with SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA), and a p-value less than 0.05 was considered statistically significant.

Results

Of the first 200 patients enrolled in the CEFI-SITA study, 185 were included in this post-hoc analysis, and 84 of them (45.4%) were considered IC (Supplementary Fig. 1).

The median age of the included patients was 65 years, and most of them were male (138/185, 74.6%). In terms of clinical characteristics, as preliminary descriptive findings, the IC patients had more previous hospitalisations, comorbidities, a history of steroid use and CRPA infection compared to non-IC patients Additionaly, neutropenia was present in more than one-third of patients in the haematology group. However, at cefiderocol initiation, it was less frequent that IC patients were in the ICU or were receiving total parenteral nutrition (Table 1).

The indications for cefiderocol administration are reported in Table 2. Sepsis was the most common indication (36/54, 66.7%) for empirical therapy, whereas lower respiratory tract infection predominated as a targeted therapy indication (56/131, 42.8%). The characteristics of cefiderocol therapy, overall and stratified according to pathogen, are reported in Table 3. Cefiderocol was employed equally between monotherapy and combination therapy (93/185 [50.3%] vs 92/185 [49.7%]), and most of the treatments were started with the availability of microbiological data (131/185, 70.8%). Monotherapy was the preferred choice for targeted treatment

Table 1 Demographic and clinical characteristics of adult patients treated with cefiderocol

Variables*	Total N = 185 (100)	SOT[b] n = 12 (6.5)	Haematology[a] n = 29 (15.7)	Other IC[c] n = 43 (23.2)	Non-IC n = 101 (54.6)
Demographics					
Age in years, median (IQR)	65.0 (52.0–76.0)	63.5 (56.5–69.0)	63.0 (46.0–72.0)	70.0 (62.0–77.0)	65.0 (51.0–77.0)
Female sex	47 (25.4)	2 (16.7)	9 (31.0)	16 (37.2)	20 (19.8)
Comorbidities and medical history					
Previous hospitalisation, missing = 7	88 (49.4)	7 (58.3)	19 (70.4)	23 (57.5)	39 (39.4)
Admission from LTCF, missing = 2	13 (7.1)	1 (8.3)	1 (3.7)	2 (4.7)	9 (8.9)
Diabetes mellitus	32 (17.3)	3 (25.0)	8 (27.6)	5 (11.6)	16 (15.8)
COPD	20 (10.8)	1 (8.3)	3 (10.3)	7 (16.3)	9 (8.9)
Previous myocardial injury, missing = 6	23 (12.9)	2 (18.2)	1 (3.7)	4 (9.5)	16 (16.2)
NYHA score, median (IQR)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)
Chronic liver disease	12 (6.5)	4 (33.3)	0 (0.0)	2 (4.7)	6 (5.9)
Chronic kidney disease, missing = 1	32 (17.4)	2 (16.7)	6 (20.7)	4 (9.3)	20 (20.0)
Chronic intermittent haemodialysis, missing = 2	7 (3.8)	0 (0.0)	1 (3.6)	2 (4.7)	4 (4.0)
Age-adjusted Charlson comorbidity index, median (IQR)	4.0 (2.0–6.0)	4.0 (3.0–6.0)	4.0 (3.0–6.0)	6.0 (3.0–9.0)	3.0 (2.0–6.0)
Previous cefiderocol, missing = 6	4 (2.2)	1 (10.0)	0 (0.0)	1 (2.3)	2 (2.0)
Previous antibiotic therapy other than cefiderocol, missing = 12	122 (70.5)	8 (72.7)	23 (82.1)	29 (70.7)	62 (66.7)
Previous piperacillin/tazobactam, missing = 12	81 (46.8)	5 (45.5)	18 (64.3)	18 (43.9)	40 (43.0)
Previous ceftazidime/cefepime, missing = 12	9 (5.2)	1 (9.1)	2 (7.1)	3 (7.3)	3 (3.2)
Previous ceftolozane/tazobactam, missing = 12	15 (8.7)	2 (18.2)	2 (7.1)	2 (4.9)	9 (9.7)
Previous carbapenems, missing = 12	54 (31.2)	2 (18.2)	12 (42.9)	14 (34.2)	26 (28.0)
Previous ceftazidime/avibactam, missing = 12	14 (8.2)	0 (0.0)	2 (7.1)	1 (2.4)	11 (11.8)
Previous meropenem/vaborbactam, missing = 12	1 (0.6)	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)
Previous imipenem/relebactam, missing = 12	0 (0.0)	-	-	-	-
Previous polymyxins, missing = 12	4 (2.3)	1 (9.1)	0 (0.0)	1 (2.4)	2 (2.2)
Previous steroid therapy, missing = 10	63 (36.0)	6 (50.0)	19 (76.0)	23 (54.8)	15 (15.6)
Previous major surgery	70 (37.8)	7 (58.3)	10 (34.5)	13 (30.2)	40 (39.6)
Previous isolation of CR-GNB, missing = 12	65 (37.6)	5 (45.5)	12 (48.0)	14 (34.2)	34 (35.4)
Previous CRE, missing = 12	36 (20.8)	2 (18.2)	7 (28.0)	9 (22.0)	18 (18.8)
Previous CRPA, missing = 12	8 (4.6)	2 (18.2)	2 (8.0)	2 (4.9)	2 (2.1)
Previous CRAB, missing = 12	26 (15.0)	1 (9.1)	4 (16.0)	4 (9.8)	17 (17.7)
Previous MBL-producing CR-GNB, missing = 12	16 (9.3)	1 (9.1)	1 (4.0)	5 (12.2)	9 (9.4)
Variables at cefiderocol introduction					
Days from admission to cefiderocol introduction, median (IQR)	22.0 (10.0–41.0)	27.5 (9.0–52.5)	24.0 (9.0–43.0)	21.0 (8.0–35.0)	23.0 (11.0–40.0)
ICU stay	91 (49.2)	4 (33.3)	10 (34.5)	18 (41.9)	59 (58.4)
SOFA score, median (IQR)	4.0 (3.0–7.0)	5.0 (2.0–6.5)	6.0 (3.0–9.0)	4.0 (2.0–7.0)	4.0 (3.0–7.0)
Presence of CVC, missing = 5	130 (72.2)	7 (58.3)	23 (82.1)	29 (69.1)	71 (72.5)
Presence of urinary catheter, missing = 4	143 (79.0)	10 (83.3)	17 (63.0)	33 (78.6)	83 (83.0)
Presence of septic shock, missing = 2	49 (26.8)	4 (33.3)	8 (27.6)	10 (24.4)	27 (26.7)
Presence of ARDS, missing = 6	19 (10.6)	1 (8.3)	3 (11.5)	4 (9.8)	11 (11.0)
Presence of AKI, missing = 1	66 (35.9)	2 (16.7)	10 (34.5)	18 (41.9)	36 (36.0)
Concomitant COVID-19, missing = 3	15 (8.2)	0 (0.0)	4 (14.3)	6 (14.3)	5 (5.0)
Total parenteral nutrition, missing = 9	48 (27.3)	0 (0.0)	6 (21.4)	7 (16.7)	35 (37.2)
Neutropenia	10 (5.4)	0 (0.0)	9 (31.0)	0 (0.0)	1 (1.0)
CRRT, missing = 2	25 (13.7)	3 (25.0)	3 (10.3)	5 (11.6)	14 (14.1)
ECMO, missing = 2	4 (2.2)	2 (16.7)	0 (0.0)	0 (0.0)	2 (2.0)
White blood cell × 10^{-3}/mm^3, median (IQR)	10.2 (5.5–15.4)	7.8 (5.2–12.6)	3.1 (0.5–7.4)	12.2 (4.9–17.0)	11.3 (8.1–16.6)

Table 1 (continued)

Variables*	Total N = 185 (100)	SOT[b] n = 12 (6.5)	Haematology[a] n = 29 (15.7)	Other IC[c] n = 43 (23.2)	Non-IC n = 101 (54.6)
Serum C reactive protein in mg/L, median (IQR), missing = 10	84.5 (22.8–153.7)	25.8 (9.0–152.6)	86.8 (20.5–127.2)	105.0 (22.8–168.0)	88.4 (35.0–145.0)
Serum procalcitonin in ng/mL, median (IQR), missing = 39	1.4 (0.3–5.2)	2.3 (1.6–8.2)	1.1 (0.2–6.7)	1.4 (0.5–3.9)	1.5 (0.3–5.6)

Where not otherwise indicated, results are presented as number of patients (percentage). AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRAB, carbapenem-resistant A. baumannii; CRE, carbapenem-resistant Enterobacterales; CR-GNB, carbapenem-resistant Gram-negative bacteria; CRPA, carbapenem-resistant P. aeruginosa; CRRT, continuous renal replacement therapy; CVC, central venous catheter; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; IC, immunocompromised; ICU, intensive care unit; IQR, interquartile range; LTCF, long-term care facility; MBL, metallo-β-lactamases; NYHA, New York Heart Association; SOFA, sequential organ failure assessment

*Number of missing values, impacting frequency and percentage calculation, are reported

[a]Acute myeloid leukemia (n = 10), non-Hodgkin lymphoma (n = 7), Hodgkin lymphoma (n = 3), acute lymphoblastic leukemia (n = 2), chronic myeloid leukemia (n = 2), hairy cell leukemia (n = 1), lymphoproliferative diseases (not further specified, n = 1), multiple myeloma (n = 1), peripheral B-cell lymphoma (n = 1), Sézary syndrome (n = 1)

[b]Liver (n = 7), heart (n = 2), lung (n = 2), kidney (n = 1)

[c]Solid neoplasm (n = 20), people with HIV (n = 3), autoimmune disease (n = 15), previous immunosuppressant therapy for other reasons (n = 3), not specified (n = 1), solid neoplasm and autoimmune disease (n = 1)

of infections due to Enterobacterales (13/25, 52%), *P. aeruginosa* (13/23, 56.5%), *S. maltophilia* (2/3, 66.7%) and MBL-producing Gram-negative infections (12/21, 57.1%). Instead, combination therapy was the preferred choice for targeted treatment of *A. baumannii* infections (34/61, 55.7%). Overall, similar descriptive rates were observed in IC and non-IC groups regarding indications for cefiderocol use, choice of monotherapy versus combination therapy, or empirical versus targeted treatment (Tables 2 and 3).

Regarding the 28-day clinical cure rates, they are reported in Supplementary Table 1. Higher rates were descriptively observed among *P. aeruginosa* infections (81%), followed by Enterobacterales infections (77.3%), MBL-producing Gram-negative infections (76.2%) and *A. baumannii* infections (42%). Similar cure rates were also descriptively observed after adjustment with the inclusion of discharged patients in the denominator (Supplementary Table 2).

The 30-day mortality rate was 40.8% (95% CI: 27.9–56.8) in IC hosts and 33.3% (95% CI: 22.9–46.9) in non-IC hosts. With the limitation of subgroup analyses and the consequently reduced samples, no significant difference in 30-day mortality was observed between IC and non-IC patients receiving cefiderocol-targeted treatment for infections caused by Enterobacterales, *P. aeruginosa* or *A. baumannii* ($p = 0.5430$, Fig. 1). Similar results were descriptively registered after stratification for specific IC conditions (p for four groups comparison = 0.4208, Supplementary Fig. 2).

Finally, we examined the factors associated with 30-day mortality in patients receiving cefiderocol targeted therapy for infections caused by Enterobacterales, *P. aeruginosa*, or *A. baumannii*. As shown in Table 4 and Supplementary Table 3, across all multivariable models and shared frailty models, previous myocardial injury, presence of ARDS, and *A. baumannii* infection were consistently associated with this outcome. Age was linked to increased mortality in primary models A and B and in model C of sensitivity analysis (with the direction of the effect being consistent with increased mortality also in model D). Admission from a long-term care facility was also linked to increased mortality in primary models A and B (Table 4). Conversely, prior steroid therapy showed a significant association with mortality only in sensitivity analysis (models C and D, Supplementary Table 3). IC status was not associated with mortality in either univariable or multivariable analyses (Table 4), nor was any specific type of IC condition identified as a significant prognostic factor (Supplementary Table 3).

Discussion

In this study, we present the results of a post-hoc analysis of the first results of the CEFI-SITA study, focusing on the use of cefiderocol in 84 IC patients, one of the largest cohorts of such patients reported in the literature to date. Compared to non-IC patients, IC patients were more complex, with more frequent prior hospitalisations, a higher burden of comorbidities, a history of steroid use, and a history of CRPA infection. Notably, neutropenia was observed in more than one-third of patients in the haematology group.

However, although with the limitation of the preliminary nature of our analysis, similar descriptive rates were observed in IC and non-IC patients regarding the indications for initiating cefiderocol therapy, whether for empirical or targeted treatment. Sepsis was the most common indication for empirical therapy, while lower respiratory tract infections were the primary reason for targeted therapy. Similarly, there were no apparent descriptive differences in the use of cefiderocol as monotherapy or combination therapy, nor in its use for empirical versus targeted treatment, even when stratified by

Table 2 Infections treated with empirical and targeted cefiderocol therapy

Variables*	Total N=185 (100)	SOT n=12 (6.5)	Haematology n=29 (15.7)	Other IC n=43 (23.2)	Non-IC n=101 (54.6)
Reported indication for empirical therapy	**n=54 (100)**	**n=3 (100)**	**n=11 (100)**	**n=13 (100)**	**n=27 (100)**
Sepsis	36 (66.7)	0 (0.0)	8 (72.7)	9 (69.2)	19 (70.4)
Lower respiratory tract infection	10 (18.5)	2 (66.7)	2 (18.2)	3 (23.1)	3 (11.1)
Intra-abdominal infection	6 (11.1)	1 (33.3)	0 (0.0)	1 (7.7)	4 (14.8)
Surgical site infection	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)
Other indications	1 (1.9)	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)
Infections treated with targeted cefiderocol[a]	**n=131 (100)**	**n=9 (100)**	**n=18 (100)**	**n=30 (100)**	**n=74 (100)**
Lower respiratory tract infection	56 (42.8)	2 (22.2)	7 (38.9)	9 (30.0)	38 (51.4)
Bloodstream infection	50 (38.2)	4 (44.4)	8 (44.4)	14 (46.7)	24 (32.4)
Urinary tract infection	7 (5.3)	0 (0.0)	1 (5.6)	4 (13.3)	2 (2.7)
Intra-abdominal infection	3 (2.3)	1 (11.1)	0 (0.0)	2 (6.7)	0 (0.0)
Other indications	8 (6.1)	0 (0.0)	1 (5.6)	1 (3.3)	6 (8.1)
More than one indication	7 (5.3)	2 (22.2)	1 (5.6)	0 (0.0)	4 (5.4)

Results are presented as number of patients (percentage). No missing values were detected

[a]Cefiderocol therapy started after identification of the causative agent. Causative agents: *Acinetobacter baumannii* (*n*=61); *Pseudomonas aeruginosa* (*n*=23); *Klebsiella* spp. (*n*=18); *Enterobacter* spp. (*n*=6); *A. baumannii* plus *Klebsiella* spp. (*n*=3); *A. baumannii* plus *P. aeruginosa* (*n*=3); *Stenotrophomonas maltophilia* (*n*=3); *Klebsiella* spp. plus *P. aeruginosa* (*n*=2); *A. baumannii* plus *Enterobacter* spp. (*n*=1); *A. baumannii* plus *Enterobacter* spp. plus *S. maltophilia* (*n*=1); *A. baumannii* plus *Klebsiella* spp. plus *P. aeruginosa* (*n*=1); *A. baumannii* plus *S. maltophilia* (*n*=1); *Achromobacter xylosoxidans* (*n*=1); *A. xylosoxidans* plus *Escherichia coli* plus *P. aeruginosa* (n=1); *A. xylosoxidans* plus *P. aeruginosa* (*n*=1); *A. xylosoxidans* plus *Elizabethkingia miricola* plus *S. maltophilia* (*n*=1); *Elizabethkingia miricola* plus *S. maltophilia* (*n*=1); *Enterobacter* spp. plus *P. aeruginosa* (n=1); *Enterobacter* spp. plus *Klebsiella* spp. (*n*=1); *P. aeruginosa* plus *S. maltophilia* (*n*=1)

pathogen. Of note, combination therapy was preferred for the targeted treatment of *Acinetobacter baumannii* infections in both IC and non-IC groups.

The most relevant finding is how, across all multivariable and shared frailty models, prior myocardial injury, presence of ARDS, and *Acinetobacter baumannii* infection were consistently and significantly associated with 30-day mortality, while IC status and specific IC-defining conditions were not. Moreover, an interesting signal was observed, indicating that 28-day clinical cure rates, stratified by the pathogen and 30-day mortality, were descriptively comparable between IC and non-IC patients. Interestingly, 30-day mortality remained similar even when further stratified by specific IC conditions, but the limited sample size of the different groups should be considered when interpreting this result.

In the studies that led to the drug approval by regulatory agencies, IC hosts were scarcely represented, and details regarding the IC-defining condition were not provided [19–21]

The APEKS-cUTI trial was designed to include patients immunocompromised with comorbid conditions, including renal transplantation, but also in this study, no further details were provided [19].

The APEKS-NP trial reported that a substantial proportion of patients treated with cefiderocol (42%, 61/145) received systemic corticosteroids at randomisation. However, further details on IC condition were not reported. Notably, the study's exclusion criteria included conditions such as neutropenia, cystic fibrosis, bronchiectasis, peritoneal dialysis, and ongoing methotrexate therapy. factors likely contributing to the underrepresentation of IC hosts in the study population [20].

Finally, in the CREDIBLE-CR trial, 27% (27/101) of patients receiving cefiderocol were classified as IC, with systemic corticosteroid use reported in 44% (44/101) cases. However, as with other studies, further details were lacking. Additionally, exclusion criteria such as severe neutropenia, cystic fibrosis, and bronchiectasis likely contributed to the study population's limited representation of IC hosts [21]. Regarding real-world data, the CEFI-ID study, a retrospective study from France, showed 28-day mortality rates similar to those of our study (37.7%), but lower cure rates (53.3%). It should be noted that the two cohorts have some differences: our is prospectively collected, has a lower prevalence of SOT and infection due to *S. maltophilia* and *P. aeruginosa* and a higher prevalence of infection due to *A. baumannii* [14].

Other evidence suggesting that IC status does not necessarily lead to worse outcomes was provided by the Perseus study, which described the Spanish cefiderocol early access program, which included a substantial proportion of IC patients (79/261, 30.3%). In the study, IC status was not associated with a lower clinical cure rate (p=0.3847, OR 0.75, 95% CI 0.40–1.45). Conversely, factors such as septic shock, a higher Charlson comorbidity index, and mechanical ventilation at enrolment were linked to poorer outcomes [22].

Moreover, Persaud et al. explored the use of cefiderocol among lung transplant recipients in an insightful case series. The study described 15 cases in which cefiderocol was administered for various indications, including prophylaxis, empirical, and targeted treatment, primarily against multidrug-resistant *P. aeruginosa*. Treatment durations ranged from 1 to 93 days, with a 30-day mortality rate of 26% and microbiological clearance achieved in 9 out of 13 cases [13].

Table 3 Characteristics of cefiderocol therapy

Variables	Total *N* = 185 (100)	SOT *n* = 12 (6.5)	Haematology *n* = 29 (15.7)	Other IC *n* = 43 (23.2)	Non-IC *n* = 101 (54.6)
Type of anti-CR-GNB therapy					
Monotherapy	93 (50.3)	7 (58.3)	13 (44.8)	24 (55.8)	49 (48.5)
Combination therapy[a]	92 (49.7)	5 (41.7)	16 (55.2)	19 (44.2)	52 (51.5)
Timing of cefiderocol therapy					
Empirical therapy[b,g]	54 (29.2)	3 (25.0)	11 (37.9)	13 (30.2)	27 (26.7)
Targeted therapy[h]	131 (70.8)	9 (75.0)	18 (62.1)	30 (69.8)	74 (73.3)
Targeted therapy for Enterobacterales infection[c,i]					
Monotherapy	13/25 (52.0)	-	2/5 (40.0)	4/7 (57.1)	7/13 (53.8)
Combination therapy[a]	12/25 (48.0)	-	3/5 (60.0)	3/7 (42.9)	6/13 (46.2)
Targeted therapy for *Pseudomonas aeruginosa* infection[d,i]					
Monotherapy	13/23 (56.5)	2/3 (66.7)	2/3 (66.7)	4/4 (100.0)	5/13 (38.5)
Combination therapy[a]	10/23 (43.5)	1/3 (33.3)	1/3 (33.3)	0/4 (0.0)	8/13 (61.5)
Targeted therapy for *Acinetobacter baumannii* infection[e,i]					
Monotherapy	27/61 (44.3)	4/5 (80.0)	1/6 (16.7)	5/13 (38.5)	17/37 (45.9)
Combination therapy[a]	34/61 (55.7)	1/5 (20.0)	5/6 (83.3)	8/13 (61.5)	20/37 (54.1)
Targeted therapy for *Stenotrophomonas maltophilia* infection[f,i]					
Monotherapy	2/3 (66.7)	-	2/2 (100.0)	-	0/1 (0.0)
Combination therapy[a]	1/3 (33.3)	-	0/2 (0.0)	-	1/1 (100.0)
Targeted therapy for MBL-producing Gram-negative infection[i,m,n]					
Monotherapy	12/21 (57.1)	1/1 (100.0)	4/6 (66.7)	3/5 (60.0)	4/9 (44.4)
Combination therapy[a]	9/21 (42.9)	0/1 (0.0)	2/6 (33.3)	2/5 (40.0)	5/9 (55.6)
Initial cefiderocol dosage according to estimated CLCr or haemodialytic treatment					
CLCr > = 120 mL/min	32 (17.3)	0 (0.0)	4 (13.8)	5 (11.6)	23 (22.8)
CLCr 60 to 119 mL/min	87 (47.0)	9 (75.0)	16 (55.2)	20 (46.5)	42 (41.6)
CLCr 30 to 59 mL/min	34 (18.4)	1 (8.3)	4 (13.8)	9 (20.9)	20 (19.8)
CLCr 15 to 29 mL/min	18 (9.7)	1 (8.3)	3 (10.3)	6 (14.0)	8 (7.9)
CLCr < 15 mL/min	6 (3.2)	0 (0.0)	1 (3.5)	2 (4.7)	3 (3.0)
IHD	3 (1.6)	0 (0.0)	0 (0.0)	1 (2.3)	2 (2.0)
CRRT	5 (2.7)	1 (8.3)	1 (3.5)	0 (0.0)	3 (3.0)

Results are presented as number of patients (percentage). No missing values were detected. CLCr, creatinine clearance; CR-GNB, carbapenem-resistant Gram-negative bacteria; CRRT, continuous renal replacement therapy; IC, immunocompromised; IHD, intermittent haemodialysis; MBL, metallo-β-lactamases; SOT, solid organ transplantation

[a]Anti-CR-GNB combination was defined as treatment with cefiderocol in combination with at least one of the following agents: aminoglycosides; fosfomycin; tigecycline (with the exception of targeted therapy of *P. aeruginosa* infections); polymyxins; sulbactam or ampicillin/sulbactam (as empirical treatment of as targeted therapy for *A. baumannii* infections)

[b]Agents combined with cefiderocol for empirical therapy: fosfomycin (*n* = 9); tigecycline (*n* = 6); colistin (*n* = 3); colistin plus tigecycline (*n* = 2); aminoglycoside (n = 1); aminoglycoside plus fosfomycin (n = 1); ampicillin/sulbactam plus tigecycline (n = 1)

[c]Agents combined with cefiderocol for targeted therapy of Enterobacterales infection: fosfomycin (n = 5); tigecycline (*n* = 4); aminoglycoside (n = 2); aminoglycoside plus tigecycline (*n* = 1)

[d]Agents combined with cefiderocol for targeted therapy of *Pseudomonas aeruginosa* infections: fosfomycin (n = 7); aminoglycosides (*n* = 2); colistin (*n* = 1)

[e]Agents combined with cefiderocol for targeted therapy of *Acinetobacter baumannii* infections: fosfomycin (*n* = 11); ampicillin/sulbactam (*n* = 8); colistin (*n* = 8); tigecycline (*n* = 4); aminoglycosides (*n* = 1); ampicillin/sulbactam plus tigecycline (n = 1); colistin plus tigecycline (*n* = 1)

[f]Agents combined with cefiderocol for targeted therapy of *Stenotrophomonas maltophilia* infections: colistin plus tigecycline (*n* = 1)

[g]In 27/54 cases of empirical therapy (50%), a Gram-negative etiological agent grew from cultures collected at the time of treatment initiation, of which 13/25 (52%, missing = 2/27) were carbapenem-resistant (of them 3/11, 27%, were MBL producers, missing = 2/13)

[h]Cefiderocol therapy started after identification of the causative agent

[i]Analyses limited to Infection by only one Gram-negative genus (with the exception of Enterobacterales infection, for which concomitant infection by more than one member of Enterobacterales was also considered)

[m]Type of MBL enzyme: VIM (n = 18); NDM (n = 3)

[n]Type of MBL-producing causative agent: *P. aeruginosa* (n = 11); Enterobacterales (*n* = 10)

The most controversial aspect of cefiderocol therapy is its efficacy against infection due to CRAB. The CREDIBLE-CR study provided preliminary negative signals, with subsequent studies and meta-analyses reporting conflicting results [21, 23–27]. In our study, *A. baumannii* infection was consistently associated with 30-day mortality across all four models developed, with hazard ratios ranging from 2.61 to 4.13. As we lacked a comparator

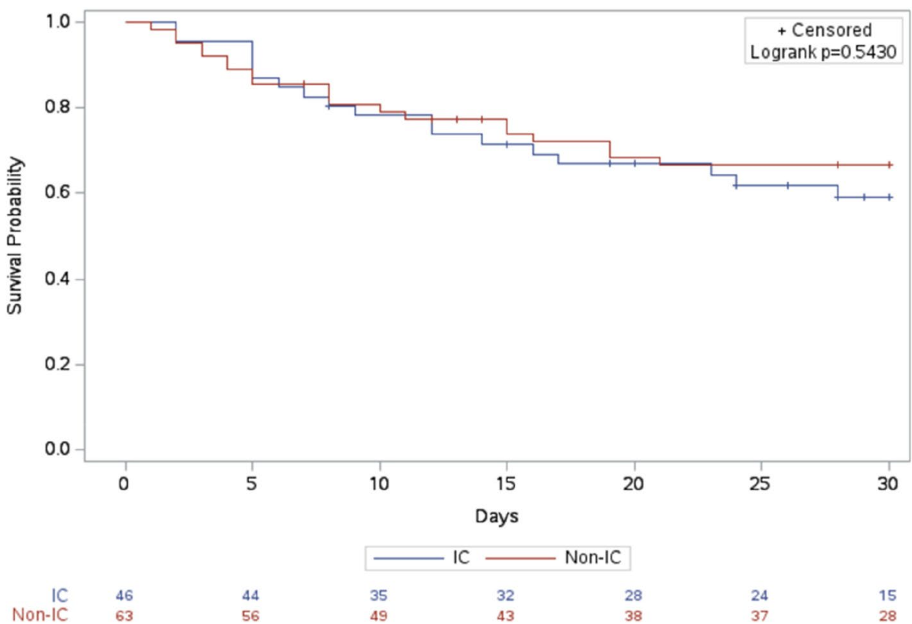

Fig. 1 Kaplan_Meier curves in patients with cefiderocol targeted treatment for Enterobacterales, *P. aeruginosa*, or *A. baumannii* infections (IC vs. non-IC). The time of origin was set on the day of cefiderocol initiation. Death was the event of interest, and right-censoring was applied at the end of follow-up (hospital discharge or day 30, whichever came first). Site/s of Enterobacterales infection: bloodstream infection ($n=11$); lower respiratory tract infection ($n=7$); urinary tract infection ($n=2$); skin and soft tissue infection ($n=1$); intra-abdominal infection ($n=1$); more than one indication ($n=3$). Site/s of *P. aeruginosa* infection: lower respiratory tract infection ($n=11$); bloodstream infection ($n=6$); urinary tract infection ($n=2$); intra-abdominal infection ($n=1$); skin and soft tissue infection ($n=1$); more than one indication ($n=2$). Site/s of *A. baumannii* infection: lower respiratory tract infection ($n=27$); bloodstream infection ($n=26$); bone and joint infection ($n=2$); urinary tract infection ($n=2$); intra-abdominal infection ($n=1$); more than one indication ($n=2$); site/s not reported (n = 1)

drug, no conclusions can be drawn regarding the efficacy of cefiderocol against this pathogen. However, our findings underscore that, even within the IC host population, *A. baumannii* infection remains a significant predictor of poor outcomes. Further investigation is needed to clarify the relative impact of the administered treatment versus the patients' clinical condition in determining these outcomes.

Another noteworthy finding from our results is the lack of association between infections caused by MBL-producing bacteria and 30-day mortality. Notably, in a *post-hoc* analysis of the CREDIBLE-CR and APEKS-NP trials, cefiderocol—used primarily as monotherapy, like our cohort—demonstrated numerically higher clinical cure and microbiological eradication rates vs. comparators when treating MBL-producing pathogens [28]. In our IC host population, it is reassuring that outcomes for infections caused by these pathogens were similar to those seen in non-IC hosts. Unfortunately, the limited number of different MBLs included prevents meaningful comparisons between them.

Regarding the strengths of our analysis, collecting data on cefiderocol use from multiple centres and prescribers across the Italian peninsula enables us to present a comprehensive, real-world perspective on its clinical applications. This is evidenced by mortality rates, which appear higher than those reported in registration studies, where marginal patients are usually excluded. However, this is an interim sub-analysis of a much larger prospective study, and definitive conclusions should be based on the final cohort. Furthermore, the subdivision of the IC population into smaller subgroups resulted in limited sample sizes in some secondary analyses, restricting the ability to compare outcomes between these groups effectively. Another limitation to be acknowledged is that we considered previous steroid therapy among potential prognostic predictors, rather than as a proxy of immunosuppression for categorising patients as IC or non-IC, due to the lack of precise information about the length and dosage of previous steroid therapy. This reflected the post-hoc nature of the analysis, as the original study was not explicitly focused on the IC population.

In conclusion, our study suggests that, despite being a clinically more complex population, IC patients with infections caused by MDRGNB may not experience worse outcomes than non-IC patients; IC status and underlying conditions were not associated with mortality.

We can speculate that even IC hosts, as observed in other studies on BSI caused by carbapenem-resistant *K. pneumoniae* [2, 29], the use of an effective antibiotic regimen may mitigate the excess mortality associated with carbapenemase-producing Enterobacterales. This

Table 4 Results of univariable models, multivariable analysis after backward selection (model A), and shared frailty analysis (model B) of factors associated with 30-day mortality in the study population receiving cefiderocol targeted therapy for Enterobacterales, *Pseudomonas aeruginosa* or *Acinetobacter baumannii* infection ($n = 109$)

	Univariable models		Backward multivariable model (Model A)[a]		Shared frailty model (Model B)[b]	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Demographic and clinical characteristics						
Age in years	1.02 (1.00–1.04)	0.0574	1.02 (1.00–1.05)	**0.0470**	1.02 (1.00–1.05)	**0.0371**
Female sex	1.11 (0.52–2.34)	0.7932				
Previous hospitalisation	1.72 (0.89–3.32)	0.1053				
Admission from LTCF	2.61 (1.01–6.71)	**0.0471**	3.28 (1.20–8.99)	**0.0209**	3.07 (1.07–8.82)	**0.0376**
Diabetes mellitus	2.02 (1.02–4.02)	**0.0439**				
COPD	1.14 (0.40–3.20)	0.8101				
Previous myocardial Injury	3.55 (1.74–7.25)	**0.0005**	4.87 (2.25–10.54)	**< 0.0001**	3.99 (1.77–9.00)	**0.0008**
NYHA score	1.49 (1.07–2.06)	**0.0172**				
Chronic liver disease*						
Chronic kidney disease	0.90 (0.37–2.15)	0.8073				
Chronic intermittent haemodialysis*						
Age-adjusted Charlson comorbidity Index	1.04 (0.93–1.16)	0.4611				
Previous cefiderocol*						
Previous piperacillin/tazobactam	1.24 (0.64–2.41)	0.5305				
Previous ceftazidime/cefepime*						
Previous ceftolozane/tazobactam	0.55 (0.09–3.24)	0.5069				
Previous carbapenems	1.01 (0.46–2.18)	0.9872				
Previous ceftazidime/avibactam	1.24 (0.49–3.18)	0.6511				
Previous meropenem/vaborbactam*						
Previous imipenem/relebactam*						
Previous polymyxins*						
Previous steroid therapy	2.53 (1.32–4.84)	**0.0050**				
Previous major surgery**						
0–7 days	1.39 (0.53–3.64)	0.5081				
8–30 days	0.30 (0.09–1.01)	0.0515				
Previous isolation of CR-GNB	1.03 (0.52–2.04)	0.9314				
Previous CRE	1.03 (0.46–2.28)	0.9448				
Previous CRPA*						
Previous CRAB	1.83 (0.77–4.34)	0.1727				
Previous MBL	0.84 (0.26–2.74)	0.7683				
Days from admission to cefiderocol initiation	0.99 (0.98–1.01)	0.2160				
ICU stay	0.98 (0.52–1.85)	0.9389				
SOFA score	1.03 (1.00–1.07)	0.0816				
Presence of CVC	1.42 (0.69–2.93)	0.3425				
Presence of urinary catheter	0.96 (0.44–2.09)	0.9120				
Presence of septic shock	1.84 (0.94–3.59)	0.0760				
Presence of ARDS	2.24 (0.93–5.37)	0.0712	3.97 (1.58–10.00)	**0.0034**	4.47 (1.61–12.39)	**0.0040**
Presence of AKI	1.63 (0.86–3.08)	0.1333				
Concomitant COVID-19	2.14 (0.76–6.05)	0.1500				
Total parenteral nutrition	1.12 (0.54–2.31)	0.7596				
Neutropenia	1.46 (0.35–6.05)	0.6053				
CRRT	0.98 (0.38–2.51)	0.9673				
ECMO*						
White blood cell $\times 10^{-3}$/mm^3	1.00 (0.96–1.05)	0.9762				
Serum C reactive protein in mg/L	1.01 (0.98–1.04)***	0.5224				
Serum procalcitonin in ng/mL	1.00 (0.98–1.02)	0.9361				
Infections treated with targeted cefiderocol						
Lower respiratory tract infection	1.28 (0.68–2.42)	0.4505				
Bloodstream infection	1.05 (0.55–2.02)	0.8782				

Table 4 (continued)

	Univariable models		Backward multivariable model (Model A)[a]		Shared frailty model (Model B)[b]	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Urinary tract infection*						
Intra-abdominal infection*						
Other indication	0.81 (0.20–3.38)	0.7756				
More than one indication*						
Type of anti-CR-GNB therapy						
Anti-CR-GNB combination therapy****	1.37 (0.71–2.60)	0.3444				
Type of infection						
Enterobacterales infection	0.34 (0.12–0.97)	**0.0426**				
Pseudomonas aeruginosa infection	0.49 (0.19–1.26)	0.1369				
Acinetobacter baumannii infection	3.14 (1.48–6.64)	**0.0028**	2.80 (1.28–6.13)	**0.0099**	4.13 (1.73–9.90)	**0.0015**
MBL-producing Gram-negative infection	0.53 (0.21–1.36)	0.1871				
Population category						
IC (vs. non-IC as ref.)	1.22 (0.64–2.30)	0.5440	1.52 (0.77–3.00)	0.2290	1.37 (0.69–2.72)	0.3723

Analyses conducted after multiple imputation. The reported p-values are from the Cox regression analysis. Bold values are significant at the selected level of significance ($\alpha = 0.05$). AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRAB, carbapenem-resistant *A. baumannii*; CRE, carbapenem-resistant Enterobacterales; CR-GNB, carbapenem-resistant Gram-negative bacteria; CRPA, carbapenem-resistant *P. aeruginosa*; CRRT, continuous renal replacement therapy; CVC, central venous catheter; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; IC, immunocompromised; ICU, intensive care unit; LTCF, long-term care facility; MBL, metallo-β-lactamases; NYHA, New York Heart Association; SOFA, sequential organ failure assessment

*Analysis not performed due to an insufficient number of events

**Variable with non-proportional hazards across the full 0–30 days span. It was included in the backward multivariable model (not selected by the procedure) as a time-dependent covariate, utilising an interaction term with time (significant: confirms that the association between the variable and the outcome varies over time, p = 0.0339)

***HR reflects the impact of a 10-unit increment in this variable

****Anti-CR-GNB combination was defined as treatment with cefiderocol in combination with at least one of the following agents: aminoglycosides; fosfomycin; tigecycline (with the exception of targeted therapy of *P. aeruginosa* infections); polymyxins; sulbactam or ampicillin/sulbactam (as empirical treatment of as targeted therapy for *A. baumannii* infections)

[a]Final multivariable model after backward selection. Type of immunosuppression was forced to remain among the variables selected by the backward selection procedure (for details, see methods)

[b]Centre included as shared frailty

suggests that other factors, but not the IC status per se, may play a more significant role in determining hard outcomes in these cases. Therefore, we suggest that cefiderocol can represent an effective therapeutic option among IC hosts with infections caused by Enterobacterales, including MBL-producing strains, and *P. aeruginosa*. Further investigation is needed to clarify the relative impact of the administered treatment vs. the patients' clinical condition in influencing the prognosis of CRAB infections.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-11573-3.

Supplementary Material 1.

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AL, DM, DRG, AB, MM, and MB conceived the study. AL wrote the first draft of the manuscript. AL, DRG, DM, BM, AMus, MMu, CA, FB, BC, ACal, FCM, ACar, ACat, LC, GC, SC, ACo, RC, FGDR, VDB, FDP, FC, FF, DF, NG, LG, ARL, IM, AM, MMa, MMe, RM, AMul, CO, CP, EP, FR, MRin, MRip, TAS, FSS, MS, CT, EMT, MT, MMi, AV, AB, and MB participated to data collection; AL, DRG, DM, BM, AMus, MMu, CA, FB, BC, ACal, FCM, ACar, ACat, LC, GC, SC, ACo, RC, FGDR, VDB, FDP, FC, FF, DF, NG, LG, ARL, IM, AM, MMa, MMe, RM, AMul, CO, CP, EP, FR, MRin, MRip, TAS, FSS, MS, CT, EMT, MT, MMi, AV, AB, and MB reviewed the final version of the manuscript.

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Data availability
The data presented in this study will be available from the corresponding author on reasonable request and provided all regulatory and privacy requirements are fulfilled.

Declarations

Ethics approval and consent to participate
The MULTI-SITA project was conducted according to the guidelines of the Declaration of Helsinki and approved by the ethics committee of the coordinating centre (Liguria Region Ethics Committee, registry number 390/2020). The amendment authorising the conduct of the CEFI-SITA study within the MULTI-SITA project was approved by the Liguria Region Ethics Committee on 12 April 2022. The other participating centres followed the local ethical committees' requirements and prospectively enrolled patients once activated. All conscious patients at enrolment signed an informed consent to participate in the study. A waiver of informed consent for data collection from unconscious patients at the time of enrolment due to severe clinical conditions was obtained within the Liguria Region Ethics Committee approval, in line with the observational nature of the analyses and in order not to bias research results towards high cure rates and low mortality prejudicing scientific validity.

Consent for publication
Not applicable.

Competing interests
Outside the submitted work, Andrea Lombardi has received travel grant from Gilead Sciences, Takeda and Shionogi Inc., research grant from Gilead Sciences. Outside the submitted work, Daniele Roberto Giacobbe reports investigator-initiated grants from Pfizer, BioMérieux, and Gilead Italia, and speaker/advisor fees from Pfizer, Menarini, and Tillotts Pharma. Outside the submitted work, Matteo Bassetti has received funding for scientific advisory boards, travel, and speaker honoraria from Cidara, Gilead, Menarini, MSD, Mundipharma, Pfizer, and Shionogi. Outside the submitted work, Andrea Cortegiani received fees for lectures/scientific advisory board from Gilead, Mundipharma, MSD, Pfizer. Outside the submitted work, Enrico Maria Trecarichi reports advisor fee from MSD Italia.

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References

1. Pilmis B, Weiss E, Scemla A, Le Monnier A, Grossi PA, Slavin MA, et al. Multidrug-resistant Enterobacterales infections in abdominal solid organ transplantation. Clin Microbiol Infect. 2023;29:38–43. https://doi.org/10.1016/j.cmi.2022.06.005.
2. Falcone M, Tiseo G, Carbonara S, Marino A, Di Caprio G, Carretta A, et al. Mortality attributable to bloodstream infections caused by different carbapenem-resistant gram-negative bacilli: results from a nationwide study in Italy (ALARICO network). Clin Infect Dis. 2023;76:2059–69. https://doi.org/10.1093/cid/ciad100.
3. Liu AJ, Dennis ASM, Fariha Z, Pai Mangalore R, MacEsic N. Multidrug-resistant organism bloodstream infections in solid organ transplant recipients and impact on mortality: a systematic review. JAC-Antimicrobial Resistance. 2024. https://doi.org/10.1093/jacamr/dlae152.
4. Min EK, Yim SH, Choi MC, Lee JG, Joo DJ, Kim MS, et al. Incidence, mortality, and risk factors associated with carbapenem-resistant *Acinetobacter baumannii* bacteremia within 30 days after liver transplantation. Clin Transplant. 2023. https://doi.org/10.1111/ctr.14956.
5. Ito A, Nishikawa T, Matsumoto S, Yoshizawa H, Sato T, Nakamura R, et al. Siderophore cephalosporin cefiderocol utilizes ferric iron transporter systems for antibacterial activity against *Pseudomonas aeruginosa*. Antimicrob Agents Chemother. 2016;60:7396–401. https://doi.org/10.1128/AAC.01405-16.
6. Karlowsky JA, Hackel MA, Takemura M, Yamano Y, Echols R, Sahm DF. *In vitro* susceptibility of Gram-negative pathogens to cefiderocol in five consecutive annual multinational SIDERO-WT surveillance studies, 2014 to 2019. Antimicrob Agents Chemother. 2022. https://doi.org/10.1128/AAC.01990-21.
7. Karakonstantis S, Rousaki M, Vassilopoulou L, Kritsotakis EI. Global prevalence of cefiderocol non-susceptibility in Enterobacterales, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*: a systematic review and meta-analysis. Clin Microbiol Infect. 2024;30:178–88. https://doi.org/10.1016/j.cmi.2023.08.029.
8. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America guidance on the treatment of AmpC β-lactamase-producing Enterobacterales, carbapenem-resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* infections. Clin Infect Dis. 2021. https://doi.org/10.1093/cid/ciab1013.
9. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), andPseudomonas aeruginosawith Difficult-to-Treat Resistance (DTR-P. aeruginosa). Clin Infect Dis. 2021;72:1109–16. https://doi.org/10.1093/cid/ciab295.
10. Paul M, Carrara E, Retamar P, Tängdén T, Bitterman R, Bonomo RA, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). Clin Microbiol Infect. 2022;28:521–47. https://doi.org/10.1016/j.cmi.2021.11.025.
11. Lombardi A, Alagna L, Palomba E, Viero G, Tonizzo A, Mangioni D, et al. New antibiotics against multidrug-resistant Gram-negative bacteria in liver transplantation: clinical perspectives, toxicity, and PK/PD properties. Transplant Int. 2024. https://doi.org/10.3389/ti.2024.11692.
12. de la Fuente C, Rodríguez M, Merino N, Carmona P, Machuca I, Córdoba-Fernández M, et al. Real-life use of cefiderocol for salvage therapy of severe infections due to carbapenem-resistant gram-negative bacteria. Int J Antimicrob Agents. 2023. https://doi.org/10.1016/j.ijantimicag.2023.106818.
13. Persaud PN, Xhemali X, Neuhaus K, Budev M, Lum J. Cefiderocol utilization in lung transplant recipients at a single center. Transplant Infect Dis. 2024. https://doi.org/10.1111/tid.14319.
14. Soueges S, Faure E, Parize P, Lanternier-Dessap F, Lecuyer H, Huynh A, et al. Real-world multicentre study of cefiderocol treatment of immunocompromised patients with infections caused by multidrug-resistant Gram-negative bacteria: CEFI-ID. J Infect. 2025. https://doi.org/10.1016/j.jinf.2024.106376.
15. Giacobbe DR, Labate L, Russo Artimagnella C, Marelli C, Signori A, Di Pilato V, et al. Use of cefiderocol in adult patients: descriptive analysis from a prospective, multicenter, cohort study. Infect Dis Ther. 2024. https://doi.org/10.1007/s40121-024-01016-y.
16. Cheng G-S, Crothers K, Aliberti S, Bergeron A, Boeckh M, Chien JW, et al. Immunocompromised host pneumonia: definitions and diagnostic criteria: an official American thoracic society workshop report. Ann Am Thorac Soc. 2023;20:341–53. https://doi.org/10.1513/AnnalsATS.202212-1019ST.
17. Yuan YC. Multiple Imputation for Missing Data: Concepts and New Development. 2000 [last accessed 28 Nov 2024]. n.d.
18. Lin DY, Wei LJ, Ying Z. Checking the cox model with cumulative sums of martingale-based residuals. Biometrika. 1993;80:557–72. https://doi.org/10.1093/biomet/80.3.557.
19. Portsmouth S, van Veenhuyzen D, Echols R, Machida M, Ferreira JCA, Ariyasu M, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. Lancet Infect Dis. 2018;18:1319–28. https://doi.org/10.1016/S1473-3099(18)30554-1.
20. Wunderink RG, Matsunaga Y, Ariyasu M, Clevenbergh P, Echols R, Kaye KS, et al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis. 2021;21:213–25. https://doi.org/10.1016/S1473-3099(20)30731-3.
21. Bassetti M, Echols R, Matsunaga Y, Ariyasu M, Doi Y, Ferrer R, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. Lancet Infect Dis. 2021;21:226–40. https://doi.org/10.1016/S1473-3099(20)30796-9.
22. Torre-Cisneros J, Almirante B, Martos CDLF, Rascado P, Lletí MS, Sánchez-García M, et al. Effectiveness and safety of cefiderocol treatment in patients with Gram-negative bacterial infections in Spain in the early access programme: results of the PERSEUS study. Eur J Clin Microbiol Infect Dis. 2025. https://doi.org/10.1007/s10096-025-05108-6.
23. Gatti M, Cosentino F, Giannella M, Viale P, Pea F. Clinical efficacy of cefiderocol-based regimens in patients with carbapenem-resistant *Acinetobacter baumannii* infections: a systematic review with meta-analysis. Int J Antimicrob Agents. 2024. https://doi.org/10.1016/j.ijantimicag.2023.107047.
24. Onorato L, de Luca I, Monari C, Coppola N. Cefiderocol either in monotherapy or combination versus best available therapy in the treatment of carbapenem-resistant *Acinetobacter baumannii* infections: a systematic review and meta-analysis. J Infect. 2024. https://doi.org/10.1016/j.jinf.2024.01.012.
25. Gill K, Takamichi B, Cooper A. Clinical efficacy of cefiderocol-based regimens in patients with carbapenem-resistant *Acinetobacter baumannii* infections: new data from CREDIBLE-CR with an updated meta-analysis. Int J Antimicrob Agents. 2024. https://doi.org/10.1016/j.ijantimicag.2024.107167.
26. Russo A, Bruni A, Gullì S, Borrazzo C, Quirino A, Lionello R, et al. Efficacy of cefiderocol- vs colistin-containing regimen for treatment of bacteraemic ventilator-associated pneumonia caused by carbapenem-resistant *Acinetobacter baumannii* in patients with COVID-19. Int J Antimicrob Agents. 2023. https://doi.org/10.1016/j.ijantimicag.2023.106825.
27. Falcone M, Tiseo G, Leonildi A, Della Sala L, Vecchione A, Barnini S, et al. Cefiderocol- compared to colistin-based regimens for the treatment of severe infections caused by carbapenem-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother. 2022. https://doi.org/10.1128/aac.02142-21.
28. Timsit JF, Paul M, Shields RK, Echols R, Baba T, Yamano Y, et al. Cefiderocol for the treatment of infections due to Metallo-Β-lactamase-producing pathogens in the CREDIBLE-CR and APEKS-NP phase 3 randomized studies. Clin Infect Dis. 2022;75:1081–4. https://doi.org/10.1093/cid/ciac078.
29. Giacobbe DR, Marelli C, Cattardico G, Fanelli C, Signori A, Di Meco G, et al. Mortality in KPC-producing *Klebsiella pneumoniae* bloodstream infections: a changing landscape. J Antimicrob Chemother. 2023. https://doi.org/10.1093/jac/dkad262.

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