reports the results of univariable analyses of factors associated with administration of cefiderocol as a combined therapy for CR-GNB infections, whereas factors retaining an independent association with combined therapy for CR-GNB infections in the final multivariable models are presented in Table 3. In model A, previous isolation of carbapenem-resistant *Acinetobacter baumannii* [odds ratio (OR) 2.56, 95% CI 1.01–6.46, $p = 0.047$) and previous hematopoietic stem cell transplantation (OR 8.73, 95% CI 1.05–72.54, $p = 0.045$) were associated with administration of cefiderocol within a combined regimen, whereas chronic kidney disease was associated with cefiderocol monotherapy (OR 0.38 for combined regimen, 95% CI 0.16–0.91, $p = 0.029$). In model B, including the same variables of model A plus center as a random effect, the direction of fixed effects was the same registered in model A.

Cure Rates and Tolerability

Cure rates at days 14, 21, and 28 are descriptively summarized in supplementary Table S4, divided by pathogen and combination or monotherapy. As shown in Fig. 1, the cumulative 30-day mortality was 19.8% (95% CI 7.0–37.4) in patients receiving targeted cefiderocol therapy for Enterobacterales infection (panel A), 45.0% (95% CI 32.4–56.8) in those receiving targeted cefiderocol therapy for *A. baumannii* infection (panel B), 20.7% (95% CI 7.3–38.7) in patients receiving targeted cefiderocol therapy for *P. aeruginosa* infection (panel C), and 22.7% (95% CI 8.0–41.9) in patients receiving targeted cefiderocol therapy for MBL-producing GNB (panel D). Overall, 4/200 patients (2.0%) experienced a suspected drug-related AE during cefiderocol administration. Two patients developed mild skin rash, one patient experienced hyperchromic urine and moderate increase in liver enzymes values, and one patient developed status epilepticus categorized as SAE. Cefiderocol was discontinued in 2/4 patients (50.0%) experiencing AE.

Table 3 Multivariable analysis of factors associated with use of cefiderocol in combination with other anti-CR-GNB agents [a]

Model A (AIC 265.28)	OR (95% CI)	*P*
Chronic kidney disease	0.38 (0.16–0.91)	**0.029**
Previous HSCT	8.73 (1.05–72.54)	**0.045**
Previous CRAB	2.56 (1.01–6.46)	**0.047**
ICU stay	1.57 (0.83–2.98)	0.168
Presence of septic shock	1.77 (0.86–3.62)	0.120
Urinary tract infection	0.21 (0.02–1.99)	0.174
Model B [b] (AIC 289.36)	**OR (95% CI)**	***P***
Chronic kidney disease	0.81 (0.68–0.97)	**0.024**
Previous HSCT	1.50 (1.09–2.07)	**0.013**
Previous CRAB	1.21 (0.99–1.48)	0.062
ICU stay	1.12 (0.97–1.30)	0.124
Presence of septic shock	1.13 (0.96–1.33)	0.137
Urinary tract infection	0.77 (0.53–1.11)	0.156

Analyses conducted after multiple imputation (see study methods). Values in bold are significant, $p < 0.05$

AIC Akaike information criterion, *CI* confidence interval, *CR-GNB* carbapenem-resistant Gram-negative bacteria, *OR* odds ratio, *HSCT* hematopoietic stem cell transplantation, *CRAB* carbapenem-resistant *Acinetobacter baumannii*, *COVID-19* coronavirus disease 2019

[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]Model B also included center as a random effect. For complete details, see Methods

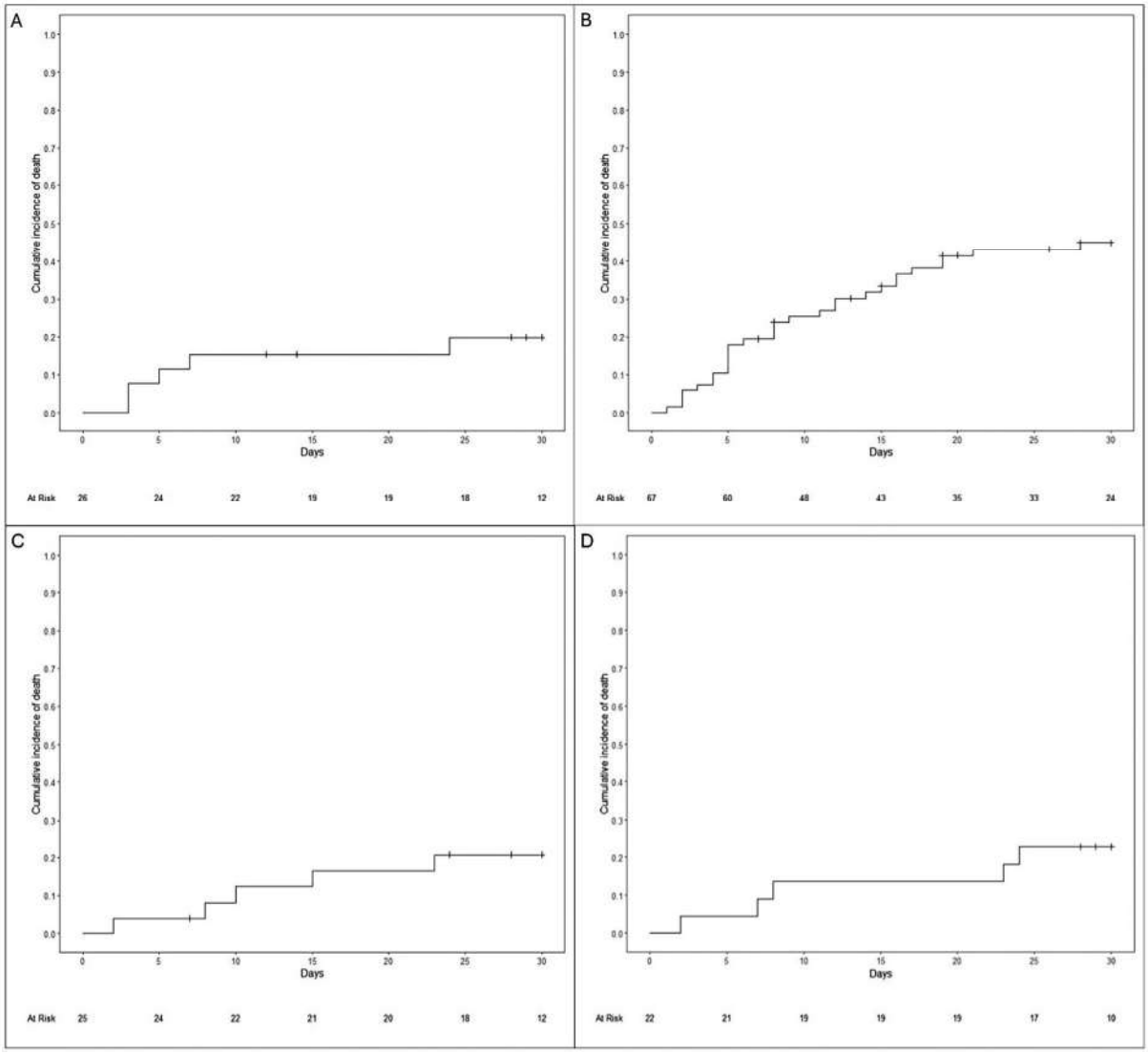
DISCUSSION

In this multicenter study, cefiderocol was mostly administered as targeted therapy (72.5% vs. 27.5% as empirical therapy), mainly for lower respiratory tract infections and bloodstream infections caused by *A. baumannii*, followed by

P. aeruginosa. Cefiderocol was almost equally administered as monotherapy or as combination therapy (50.5% vs. 49.5%).

Most available studies on the use of cefiderocol in real life are focused on the targeted treatment of infections caused by various or specific CR-GNB [7, 10–15, 17, 18, 21–24, 26–35]. While useful for reporting cure rates in specific infections, these studies were unable to generally depict how cefiderocol is currently used by physicians, having been designed for other purposes. In our opinion, this topic is of interest considering the following: (1) current international and national guidelines/guidance documents provide recommendations on the use of cefiderocol for targeted treatment, while there is still no clear guidance regarding its empirical use [47–51]; and (2) various studies have reported use of cefiderocol either in combination or as monotherapy, thus we deemed it of interest to descriptively explore their relative frequency [30, 52]. Regarding the first point, in our study, cefiderocol was mainly administered as targeted therapy. However, the proportion of empirical therapies was not negligible, representing more than one-quarter of all cefiderocol prescriptions. This could reflect the physicians' willingness to prescribe an active therapy without delay in patients with severe infections and risk factors for CR-GNB, in areas where the prevalence rate of CR-GNB, especially MBL producers, is high. Overall, these results suggest the need for standardized consensus regarding the use of cefiderocol within empirical therapeutic algorithms, in order to maximize proper indications in line with antimicrobial stewardship principles, but also to not perilously delay treatment in patients with infections caused by cefiderocol-susceptible CR-GNB.

Regarding the use of cefiderocol as monotherapy or within combined regimens, our results could reflect the current lack of solid evidence on this aspect. Against this background, the possible perception of some clinicians of potential reduced activity of cefiderocol in patients with severe *A. baumannii* infections could have prompted to consider combination therapy in some cases. This is in line with the independent association we found in multivariable models between previous isolation of carbapenem-resistant *A. baumannii* and use of cefiderocol in combined regimens, although it is also of note that no association was found between targeted treatment of *A. baumannii* infections and use of cefiderocol within combined regimens. Furthermore, in our opinion, this controversial point merits some additional considerations. First, it should be considered that the apparently higher mortality rates (50% [21/42] vs. 18% [3/17] for best available therapy, as 49-day mortality) in patients with *A. baumannii* infections treated with cefiderocol in the CREDIBLE-CR RCT were possibly confounded by factors such as severity of presentation and baseline diseases (e.g., severe renal dysfunction, ongoing shock, shock 31 days before randomization, and ICU stay at randomization were more frequent in patients treated with cefiderocol than in those receiving best available therapy) [5]. A similar situation was present in our study, in which mortality of *A. baumannii* infection was higher than mortality of infections caused by other organisms. Indeed, severe clinical presentation was more frequent in patients with *A. baumannii* infections than in those with infections caused by other organisms (e.g., septic shock was present in 29% of patients receiving cefiderocol for the targeted treatment of *A. baumannii* infections vs. 15.4% and 16.0% in patients receiving cefiderocol for the targeted treatment of Enterobacterales infections and *P. aeruginosa* infections, respectively, as shown in supplementary Table S2). Second, it should also be noted that, although mortality rates of cefiderocol-treated *A. baumannii* infections in some other studies were in line with our results [13, 15, 18, 23, 24, 33], in many other studies, including the APEKS-NP randomized controlled trial, they were far lower, ranging from 18 to 37% [3, 7, 12, 14, 16, 27, 29, 32, 53]. Third, lower mortality of cefiderocol-treated *A. baumannii* infections in comparison with non-cefiderocol-based regimens was suggested by recent meta-analyses including data from both CREDIBLE-CR and observational studies [54–56]. Lastly, among isolates subjected to cefiderocol AST, non-susceptibility (i.e., non-wild-type) was exclusively detected in *A. baumannii*, a finding consistent with that of a recent meta-analysis reporting the highest prevalence of cefiderocol non-susceptibility for



A. baumannii, compared to other major Gram-negative pathogens [57]. Overall, considering all the above, in our opinion, the relevant research question for future studies should regard which subgroups of patients with *A. baumannii* infections could benefit the most from cefiderocol monotherapy versus combination therapy (in turn possibly influencing the choice of combined regimens). Regarding other results, the significant association between previous HSCT and administration of cefiderocol within a combined regimen deserves further investigations. Indeed, while the perception of severe baseline conditions and increased mortality due to immunosuppression connected to baseline disease and/or its treatment could have played a role in influencing the choice of combination, also for targeted treatment, the subgroup of patients who underwent HSCT was small in this preliminary analysis ($n = 9$), thus a spurious association due to chance alone cannot be definitely ruled out pending further dedicated data. By contrast, the association between chronic kidney disease and cefiderocol monotherapy could reflect the physicians' decision, at least in some cases, not to administer cefiderocol together with potentially nephrotoxic agents (e.g., polymyxins, aminoglycosides) in patients with already impaired renal function, or the fact that these patients are at increased risk of urinary tract infections

◂**Fig. 1** Cumulative mortality up to day 30 in patients receiving targeted cefiderocol therapy for Enterobacterales infection (panel **A**), *Acinetobacter baumannii* infection (panel **B**), *Pseudomonas aeruginosa* infection (panel **C**), and MBL-producing Gram-negative bacteria (panel **D**). *MBL* metallo-β-lactamases. 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 the Enterobacterales order was also considered). The time of origin was set at 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 = 12); lower respiratory tract infection (n = 7); urinary tract infection (n = 2); skin and soft tissue infection (n = 1); intra-abdominal infection (n = 1); intra-abdominal infection plus bloodstream infection (n = 1); lower respiratory tract infection plus bloodstream infection (n = 1); urinary tract infection plus bloodstream infection (n = 1). Site/s of *P. aeruginosa* infection (n = 25): lower respiratory tract infection (n = 12); bloodstream infection (n = 6); urinary tract infection (n = 2); bone and joint infection plus bloodstream infection (n = 1); intra-abdominal infection (n = 1); lower respiratory tract infection plus bloodstream infection (n = 1); skin and soft tissue infection (n = 1); skin and soft tissue infection plus bloodstream infection (n = 1). Site/s of *A. baumannii* infection (n = 67): lower respiratory tract infection (n = 30); bloodstream infection (n = 29); bone and joint infection (n = 2); urinary tract infection (n = 2); intra-abdominal infection (n = 1); lower respiratory tract infection plus bloodstream infection (n = 1); skin and soft tissue infection (n = 1); site/s not reported (n = 1). Site/s of MBL-producing Gram-negative infection (n = 22): lower respiratory tract infection (n = 8); bloodstream infection (n = 5); urinary tract infection (n = 3); intra-abdominal infection (n = 2); skin and soft tissue infection (n = 2): lower respiratory tract infection plus bloodstream infection (n = 1); skin and soft tissue infection plus bloodstream infection (n = 1). Type of MBL enzyme (n = 20): NDM (n = 12); VIM (n = 19); NDM (n = 3). Type of MBL-producing causative agent: *P. aeruginosa* (n = 12); Enterobacterales (n = 10)

(for which a trend towards preference of monotherapy was observed in our study, albeit not statistically significant, as reported in Supplementary Table S3).

This present preliminary analysis of the CEFI-SITA study has some limitations to be acknowledged. The first is that, while we reported cumulative mortality in patients receiving cefiderocol in subgroups according to different causative organisms, the analysis was not primarily designed with this aim, thus the resulting unadjusted estimates (e.g., not adjusted for appropriateness of targeted therapy based on in vitro activity) should be interpreted with caution pending further data. However, the low cumulative mortality registered in infections by Enterobacterales, *P. aeruginosa*, and MBL producers is worth mentioning, and is in line with our previous findings of the possibly changing landscape in the treatment of CR-GNB registered in the past few years [58]. A second limitation is connected to the small sample size of patients treated with empirical cefiderocol. Indeed, although the registered 27.5% proportion of patients receiving empirical cefiderocol is solidly based on sample size estimates, subgroup proportions (within empirical therapy) have a larger degree of uncertainty and may require confirmation in further dedicated studies. Of note, this also includes the analysis of either crude or adjusted mortality in patients receiving empirical cefiderocol with subsequent isolation of CR-GNB as etiological agents, which has been deferred to a later phase of CEFI-SITA due to the limited sample size of this subgroup in this preliminary analysis. Third, no standardized microbiological approach was used for cefiderocol AST across participating centers, due to the observational, descriptive representation of daily routine practice. Fourth, owing to the expression of genes not commonly included among targets of rapid molecular tests, production of carbapenemases might have not been thoroughly evaluated in some cases (e.g., OXA-23 in *A. baumannii*). Additional studies employing WGS are therefore needed to decipher the molecular bases of carbapenem resistance in study isolates.

CONCLUSIONS

Cefiderocol is mainly used for targeted treatment in Italian hospitals, although empirical therapies account for more than 25% of prescriptions and should require dedicated standardization and guidance. The almost equal distribution of

cefiderocol monotherapy and cefiderocol-based combination therapies underlines the need for further study to ascertain possible differences in efficacy between the two approaches.

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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

Conflict of Interest. Outside the submitted work, Daniele Roberto Giacobbe reports investigator-initiated grants from Pfizer, BioMérieux, and Gilead Italia, and speaker/advisory board 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 Angelini, Astellas, Bayer, bioMérieux, Cidara, Cipla, Gilead, Menarini, MSD, Pfizer, Shionogi, Tetraphase, and Nabriva. Outside the submitted work, Vincenzo di Pilato reports travel grants from Arrow Diagnostic, and speaker honoraria from A.D.A. Outside the submitted work, Emanuele Pontali has received funding for scientific advisory boards, travel, and/or speaker honoraria from Abbvie, Angelini, Gilead, Janssen, MSD, and Viiv. Outside the submitted work, Andrea Lombardi reports travel grants from Shionogi. Outside the submitted work, Rosario Cultrera has received funding for scientific advisory boards, travel, and speaker honoraria from Angelini, Menarini, MSD, Pfizer, Shionogi, and TRX Italy. Outside the submitted work, Andrea Cortegiani reports fees for lectures/ advisory board membership from Gilead, MSD, Mundipharma, Pfizer, Shionogi. The other authors have no conflicts of interests to disclose.

Ethical Approval. The MULTI-SITA project was approved by the ethics committee of the coordinating center (Liguria Region Ethics Committee, registry number 390/2020). The amendment authorizing 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 centers followed the local ethical committees requirements and started to enroll patients prospectively once activated. All conscious patients at time of enrollment signed an informed consent to participate in the study. A waiver of informed consent for data collection from unconscious patients at the time of enrollment due to severe clinical conditions was obtained within the 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.

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