



Real-world use of cefiderocol as monotherapy or combination therapy for the treatment of Gram-negative bacterial infections: the multicentre retrospective CEFI-BAC study

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ABSTRACT

Objectives: This study aimed to characterise the real-world use of cefiderocol in treating Gram-negative bacterial infections (GNBIs) across Italian hospitals.

Methods: We conducted a multicentre retrospective study enrolling patients with GNBI treated with cefiderocol from January 2021 to February 2023. Statistical analyses included Kaplan–Meier survival estimates and multivariable Cox regression. A propensity score analysis with inverse probability of treatment weighting (IPTW) was also performed to compare the treatment effect of combination therapy versus monotherapy adjusting for imbalances between treatment groups.

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Results: A total of 239 patients were included. Bloodstream infections were the most common (49.8%), followed by ventilator-associated and hospital-acquired pneumonia. *Acinetobacter baumannii* was the most common isolate (64.8%), followed by *Klebsiella* spp. (23%), *Pseudomonas aeruginosa* (17.6%), and *Stenotrophomonas maltophilia* (8.8%). Overall 30-day survival was 71% (95% CI: 65–76), with no significant differences between monotherapy and combination therapy. Independent predictors of higher 30-day mortality were: having received 2 or 3 previous lines of antibiotic therapy (aHR: 4.26, 95% CI: 1.00–18.20; aHR: 7.33, 95% CI: 1.53–35.05), SARS-CoV-2 coinfection (aHR: 4.19, 95% CI: 2.04–8.59), and isolation of NDM-producing *Klebsiella* spp. (aHR: 6.22, 95% CI: 2.09–18.50).

Conclusions: Real-world experience supports the role of cefiderocol as a valuable option for GNBIs, with no clinical advantage of combination therapy over monotherapy. Notably, NDM-producing infections and use of cefiderocol as salvage therapy are associated with poor outcomes, highlighting the need for optimised treatment strategies.

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Introduction

Cefiderocol is a novel siderophore cephalosporin approved in 2019 by the US Food and Drug Administration (FDA) for the treatment of hospital-acquired pneumonia, ventilator-associated pneumonia, and complicated urinary tract infections, and in 2020 by the European Medicines Agency (EMA) for treating Gram-negative bacterial infections with limited therapeutic options. It exploits bacterial iron transport systems to penetrate the outer membrane of Gram-negative bacteria and inhibit cell wall synthesis, thereby overcoming resistance mechanisms like porin mutations and β -lactamase degradation [1–3].

Phase 3 randomised clinical trials (RCTs) demonstrated cefiderocol safety and efficacy, including against multidrug-resistant (MDR) pathogens [4–7]. Specifically, the APEKS-NP trial confirmed its non-inferiority to high-dose extended-infusion meropenem in treating nosocomial pneumonia [4], while the CREDIBLE-CR trial showed comparable efficacy to the best available therapy for a broad range of carbapenem-resistant GNBIs, despite higher all-cause mortality in patients infected with *Acinetobacter baumannii* [5]. The recent GAME CHANGER trial also demonstrated non-inferiority of cefiderocol compared to standard of care in treating healthcare-associated bloodstream infections (BSIs) [7].

Real-world evidence, though limited and sometimes conflicting [8,9], suggests cefiderocol may improve outcomes in critically ill patients with bloodstream infections and ventilator-associated pneumonia (VAP), especially those in intensive care units [9–13]. Nevertheless, therapeutic effectiveness appears to be influenced by both infection type and causative pathogen, with lower efficacy observed in VAP cases attributed to *A. baumannii* [14].

Despite limited data from phase 3 RCTs (with cefiderocol administered exclusively as monotherapy in APEKS-NP and primarily as monotherapy in CREDIBLE-CR), real-world evidence supports its use both as monotherapy and in combination regimens, with no clear advantage of one approach over the other [8,9].

Therefore, the place-in-therapy of this drug is yet to be determined, and robust data are still needed to clarify areas where results have been conflicting or not fully addressed by RCTs.

In such a context, the multicentre, observational, retrospective CEFI-BAC study was designed to better define real-world use of cefiderocol across several Italian hospitals. The study specifically aimed to: (i) describe the demographic/clinical characteristics of patients treated with cefiderocol either as monotherapy or combination therapy, as well as the type of infections and the causative pathogens; (ii) assess 30-day survival overall and by therapy type (monotherapy *versus* combination); and (iii) identify predictors of all-cause 30-day mortality. This study ultimately intends to inform the evolving therapeutic positioning of cefiderocol and support antimicrobial stewardship strategies against MDR GNBIs.

Methods

Study design and population

CEFI-BAC is a multicentre, observational, retrospective study conducted in medical, surgical, and intensive care units across 17 Italian hospitals from January 1, 2021 to February 28, 2023. It included all hospitalised patients aged ≥ 18 years who received cefiderocol treatment for suspected or culture-documented GNBIs of any anatomical site during the study period.

Variables and definitions

Demographic and clinical characteristics of patients were retrospectively retrieved from electronic or paper medical records.

Collected data included baseline demographic information, with the comorbidity burden assessed by the Charlson Comorbidity Index (CCI) [15]. Immunosuppression was defined as: (i) the use of prednisone at a dose greater than 10 milligrams per day for more than three weeks; (ii) the presence of active solid or haematologic malignancies requiring chemotherapy; (iii) the use of immunosuppressive therapy following solid organ or allogeneic stem cell transplantation; (iv) autoimmune diseases requiring immunosuppressive therapy. Dates of hospital admission and discharge were recorded, along with information about the hospital ward at the time of admission. The status of colonisation by MDR Gram-negative bacteria and any stays in the intensive care unit (ICU) prior to cefiderocol administration were documented. The presence of septic shock (as per the Sepsis-3 criteria [16]), moderate-to-severe kidney injury (defined as an estimated glomerular filtration rate [eGFR] below 60 ml/minute), and SARS-CoV-2 coinfection at the infection onset were also registered.

Data on the infection episode for which cefiderocol was prescribed included the causative bacteria with their resistance mechanisms and the infection type by anatomical site. Recorded GNBIs included bloodstream infections (BSIs), hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), complicated urinary tract infections (cUTIs), complicated intra-abdominal infections (cIAIs), bone and joint infections (BJIs), and others. For BSIs, the origin of the infection was determined according to the following criteria: concomitant isolation of the same bacteria from a biological sample other than blood (i.e., bronchoaspirate, bronchoalveolar lavage fluid, urines, abdominal drainage fluid), clinical suspicion based on compatible signs/symptoms, or known bacterial colonisation prior to the infection episode onset (when available). Details of previous antibiotic treatments for the same infection episode were recorded. Additionally, information was collected on whether cefiderocol was initiated as empiric therapy (before microorganism identification and susceptibility profiling) and

whether it was used alone (monotherapy) or combined for at least 48 hours with other antibiotics targeted to the same pathogen(s) based on the antibiogram (combination therapy).

In-hospital deaths as well as deaths at 30-day follow-up were also recorded.

Statistical analysis

Categorical variables are presented as counts and percentages, while continuous variables as medians with interquartile ranges (IQR). Comparisons of categorical variables were performed using Chi-square or Fisher exact tests, whilst continuous variables were compared using either the Student's t-test or the Mann-Whitney test, depending on the data distribution.

30-day survival overall and according to therapy type (monotherapy versus combination therapy) was computed by survivor function (Kaplan–Meier estimator) and compared with the log-rank test. Patients who were discharged alive before 30 days since cefiderocol start were considered alive at 30 days.

Predictors of 30-day mortality were identified using univariable and multivariable Cox regression analysis. Variables included in the multivariable model were those with a *P* value <0.2 in univariable analysis along with those deemed clinically relevant.

To account for imbalances in patients' characteristics according to treatment allocation (monotherapy versus combination therapy), the propensity score (PS) to receive a combination regimen was estimated for each patient. The variables included to generate the PS were chosen with two different approaches: (i) potential confounders associated with both the exposure (administration of a combination regimen) and the outcome (30-day mortality), i.e., age, Charlson Comorbidity Index (CCI), and septic shock (model I); (ii) variables included in the final multivariable Cox regression model, as reported above (model II). A PS weighting was then computed using inverse probability of treatment weighting (IPTW) to estimate the average treatment effect of combination therapy versus monotherapy. Cox regression analysis was performed on the weighted sample to compare the outcome between the two treatment groups.

P values <0.05 were considered statistically significant. All statistical analyses were performed using STATA v18. The UpSet plot was generated with Python using the "upsetplot" library [17].

Results

Study population

A total of 239 patients were included in the study. Demographic and clinical characteristics of the study population overall and according to cefiderocol mono- or combination therapy are detailed in Table 1.

The median age was 68 (IQR: 56–76) years, and the majority of them were males (155/239, 64.9%). The median Charlson Comorbidity Index was 5 (IQR: 3–7). A small proportion of the patients (35/239, 14.6%) were immunosuppressed. Before the onset of infection, 155/239 (64.9%) were colonised by MDR bacteria (Supplementary Table 1), and 77/239 (35.3%) had been admitted to ICU during the same hospitalisation. At the onset of infection, 53/239 (22.2%) presented with septic shock, 76/239 (31.8%) had chronic-to-severe kidney impairment, and 36/239 (15.1%) had a SARS-CoV-2 coinfection.

Gram-negative bacterial infections

The most frequent GNBI type was BSI (119/239, 49.8%), followed by VAP (48/239, 20.1%), HAP (48/239, 20.1%), and cUTI (29/239, 12.1%) (Figure 1a). Almost half of BSIs (53/119, 44.5%)

were of unknown origin; when known, the most common origin was catheter-related (31/119, 26.1%), followed by respiratory (21/119, 17.6%), and urinary tract (9/119, 7.6%) (Figure 1b). Thirty-two (13.4%) patients had an infection in more than one anatomical site concurrently (Figure 2).

Bacterial isolates were available in 209/239 (87.4%) patients. Of note, 64/239 (26.8%) infections were polybacterial (Figure 3a). Thus, a total of 284 bacterial isolates were recorded. *Acinetobacter baumannii* was the most prevalent one (155/239, 64.8%), followed by *Klebsiella* spp. (55/239, 23%), *Pseudomonas aeruginosa* (42/239, 17.6%), and *Stenotrophomonas maltophilia* (21/239, 8.8%) (Figure 3b).

The majority of bacterial isolates were carbapenem-resistant (Figure 3c–e). In detail, 153/155 (98.7%) of *A. baumannii* isolates and 38/42 (90.5%) of *P. aeruginosa* isolates were carbapenem-resistant. Regarding *Klebsiella* spp., all isolates were carbapenem-resistant, with resistance mechanisms including New Delhi metallo-beta-lactamase (NDM) [19/55 (34.5%)], *Klebsiella pneumoniae* carbapenemase (KPC) [33/55 (60%)], and oxacillinase-48 (OXA-48) [3/55 (5.5%)].

Use of cefiderocol

Most patients (210/239, 87.9%) received at least one prior line of antibiotic therapy for the same infection episode before cefiderocol initiation. Cefiderocol was prescribed empirically in 34/239 (14.2%) cases and used in combination therapy for 134/239 (56.1%) patients. Combination regimens included fosfomycin (39/134, 29.1%), colistin (23/134, 17.1%), tigecycline (13/134, 9.7%), aminoglycosides (10/134, 7.4%), ampicillin/sulbactam (10/134, 7.4%), and carbapenems (6/134, 4.4%). Cefiderocol was administered at standard dosage (2 g every 8 hours) in 179/239 (74.9%); in the remaining patients, cefiderocol dosage was adjusted according to renal function (Supplementary Table 2). The median duration of therapy was 10 (IQR: 7–15) days (Table 1). Adverse events attributable to cefiderocol occurred only in five cases (2.1%), including elevated transaminases in four patients and a skin rash in one patient.

Compared to patients treated with combination regimens, patients receiving cefiderocol as monotherapy were older (70 [IQR: 60–77] years versus 66 [IQR: 52–73] years, *P* = 0.013), less frequently males (61/105 [58.1%] versus 94/134 [70.1%], *P* = 0.053), and had a higher CCI (6 [IQR: 4–7] versus 4 [IQR: 2–6], *P* = 0.002). Combination therapy was more frequently administered in patients with septic shock (37/134 [27.6%] versus 16/105 [15.2%], *P* = 0.022), in those who were colonised by MDR bacteria (95/134 [70.9%] versus 60/105 [57.1%], *P* = 0.027) or previously stayed in ICU during the same hospitalisation (53/134 [40.8%] versus 24/105 [27.3%], *P* = 0.027) (Table 1). As compared to cefiderocol monotherapy, combination regimens were more frequently administered for the treatment of VAP (33/134 [24.6%] versus 15/105 [14.3%], *P* = 0.048), with no other differences according to type of infection (Figure 1a). Monotherapy was preferred in *A. baumannii* infections (76/105 [72.4%] versus 79/134 [59%], *P* = 0.031); on the contrary, combination therapy was more often used to treat *P. aeruginosa* (30/134 [22.4%] versus 12/105 [11.4%], *P* = 0.027), and *S. maltophilia* infections (16/134 [11.9%] versus 5/105 [4.8%], *P* = 0.052) (Figure 3b).

Survival and mortality predictors

Overall, in-hospital death was registered in 92/239 (38.5%) cases, whilst 30-day death in 70/239 (29.3%), with no significant differences between monotherapy and combination therapy (in-hospital deaths: 34/105 [32.4%] versus 58/134 [43.3%], *P* = 0.217; 30-day deaths: 27/105 [25.7%] versus 43/134 [32.1%], *P* = 0.282) (Table 1).

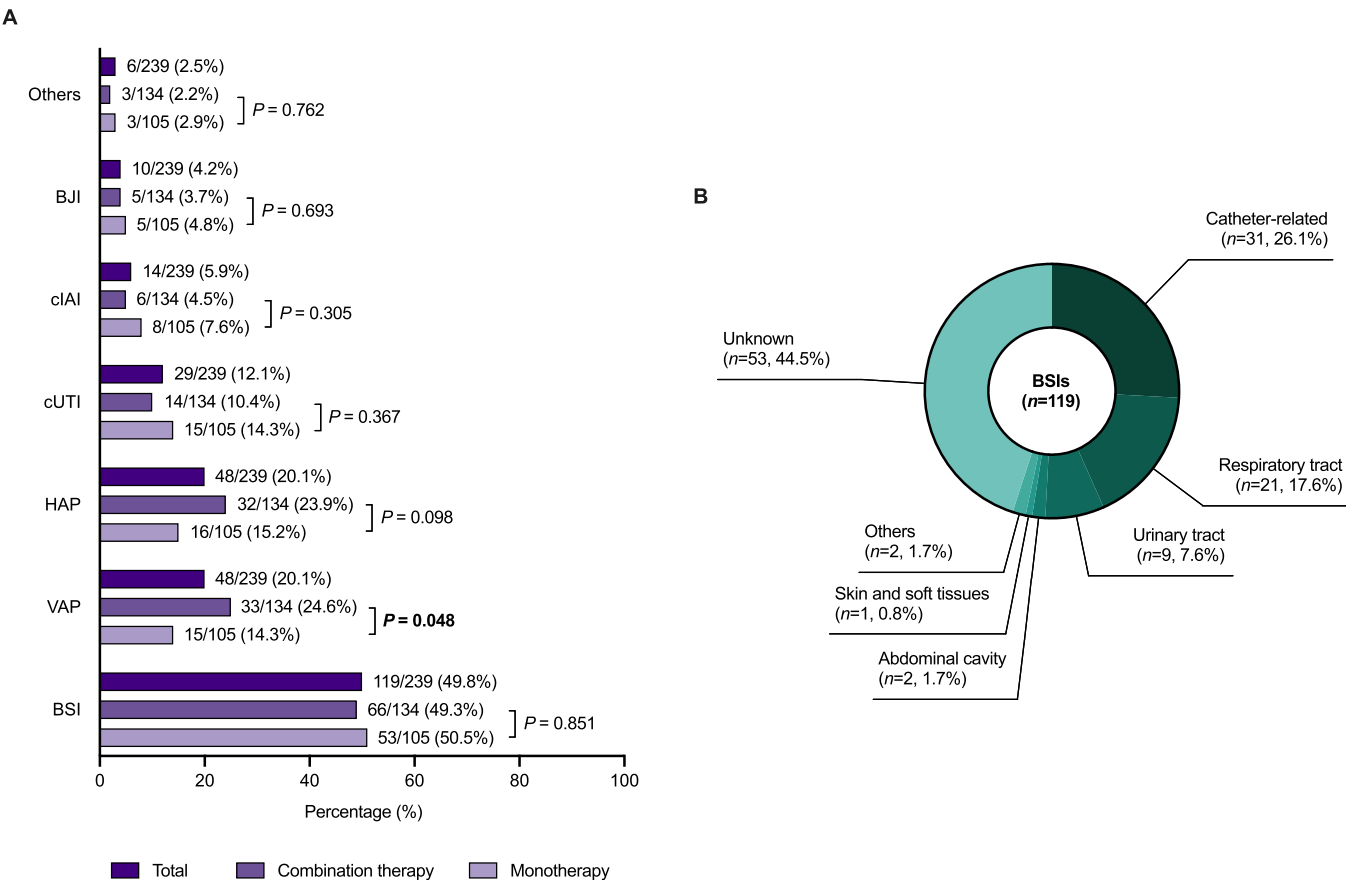


Figure 1. (a) Distribution of anatomical sites of infection in patients treated with cefiderocol ($n = 239$); the P values indicate statistical comparisons (Chi-square test or Fisher exact test, as appropriate) between monotherapy and combination therapy groups. *BJI*, bone and joint infection; *BSI*, bloodstream infection; *cIAI*, complicated intra-abdominal infection; *cUTI*, complicated urinary tract infection; *HAP*, hospital-acquired pneumonia; *VAP*, ventilator-associated pneumonia. (b) Patients with infection in more than one anatomical site concurrently (c) Distribution of origins of bloodstream infections.

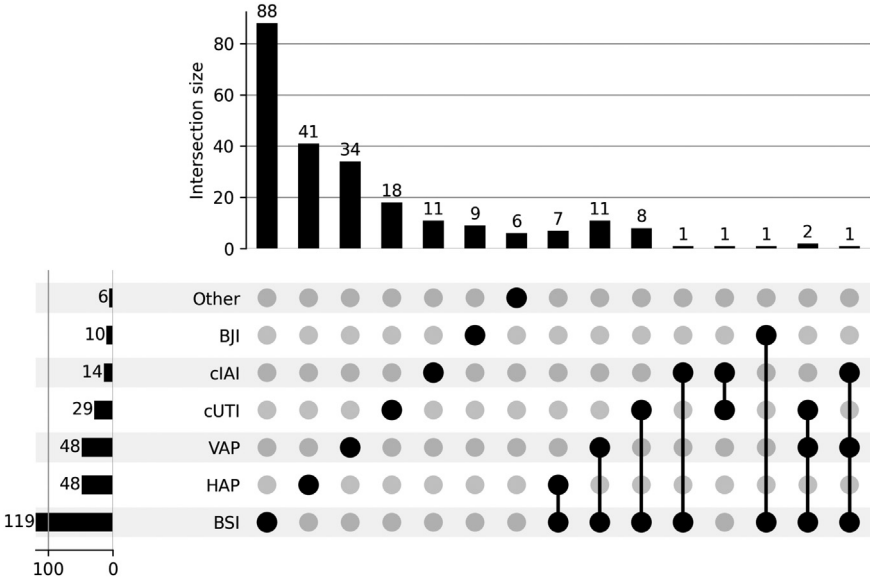


Figure 2. UpSet plot displaying the intersections among anatomical sites of infection in patients treated with cefiderocol ($n = 239$). Each horizontal bar on the left indicates the total number of infections according to the anatomical site. The vertical bars on the top quantify the size of each intersection between infections as defined by the connected dots below. Thirty-two (13.4%) patients had an infection in more than one anatomical site concurrently: 7 BSI/HAP, 11 BSI/VAP, 8 BSI/cUTI, 1 BSI/cIAI, 1 cUTI/cIAI, 1 BSI/BJI, 2 BSI/VAP/cUTI, 1 BSI/VAP/cIAI. *BSI*, bloodstream infection; *HAP*, hospital-acquired pneumonia; *VAP*, ventilator-associated pneumonia; *cUTI*, complicated urinary tract infection; *cIAI*, complicated intra-abdominal infection; *BJI*, bone and joint infection.

Table 1

Demographic and clinical characteristics of patients treated with cefiderocol as monotherapy or combination therapy.

	Overall (n = 239)	Monotherapy (n = 105)	Combination therapy ^a (n = 134)	P value (monotherapy versus combination therapy) ^b
Demographics				
Age, years [median (IQR)]	68 (56–76)	70 (60–77)	66 (52–73)	0.016
Male sex [n (%)]	155 (64.9)	61 (58.1)	94 (70.1)	0.053
Comorbidities				
At least one comorbidity [n (%)]	212 (88.7)	102 (97.1)	110 (82.1)	<0.001
CCI [median (IQR)]	5 (3–7)	6 (4–7)	4 (2–6)	0.002
Immunosuppression ^c [n (%)]	34 (14.2)	12 (11.4)	22 (16.4)	0.273
Before infection onset				
ICU stay during the same hospitalisation [n (%)]	77 (35.3)	24 (27.3)	53 (40.8)	0.041
MDR bacteria colonisation [n (%)]	155 (64.9)	60 (57.1)	95 (70.9)	0.027
At infection onset				
Septic shock ^d [n (%)]	53 (22.2)	16 (15.2)	37 (27.6)	0.022
eGFR <60 ml/min [n (%)]	76 (31.8)	28 (26.7)	48 (35.8)	0.001
SARS-CoV-2 coinfection [n (%)]	36 (15.1)	15 (14.3)	21 (15.7)	0.641
Cefiderocol use				
Previous antibiotic therapy [n (%)]	210 (87.9)	89 (84.7)	121 (90.3)	0.193
One previous antibiotic line [n (%)]	79 (33.1)	40 (38.1)	39 (29.1)	0.155
Two previous antibiotic lines [n (%)]	76 (31.8)	29 (27.6)	47 (35.1)	
Three previous antibiotic lines [n (%)]	55 (23.1)	20 (19.1)	35 (26.1)	
Empiric therapy [n (%)]	34 (14.2)	16 (15.2)	18 (13.4)	0.692
Duration of therapy, days [median (IQR)]	10 (7–15)	10 (7–14)	11 (6–15)	0.444
Adverse events [n (%)]	5 (2.1)	2 (1.9)	3 (2.2)	0.657
Outcome				
Hospitalisation length, days [median (IQR)]	44 (25–73)	40 (24–72)	46 (25–77)	0.353
30-day death [n (%)]	70 (29.3)	27 (25.7)	43 (32.1)	0.282
In-hospital death [n (%)]	92 (38.5)	34 (32.4)	58 (43.3)	0.086

CCI, Charlson Comorbidity Index; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IQR, interquartile range; MDR, multidrug-resistant.

^a Combination regimens included fosfomycin (39/134, 29.1%), colistin (23/134, 17.1%), tigecycline (13/134, 9.7%), aminoglycosides (10/134, 7.4%), ampicillin/sulbactam (10/134, 7.4%), and carbapenems (6/134, 4.4%).^b Statistical analysis: Chi-square test or Fisher exact test as appropriate.^c Immunosuppression defined as: (i) the use of prednisone at a dose greater than 10 milligrams per day for more than three weeks; (ii) the presence of active solid or haematologic malignancies requiring chemotherapy; (iii) the use of immunosuppressive therapy following solid organ or allogeneic stem cell transplantation; (iv) autoimmune diseases requiring immunosuppressive therapy.^d Septic shock defined as per Sepsis-3 criteria.

The overall 30-day cumulative probability of survival was 71% (95% CI: 65–76) (Figure 4a), with no significant differences according to mono- versus combination therapy (Figure 4b).

At univariable Cox regression analysis, 30-day mortality was associated with age, CCI, eGFR <60 ml/min, SARS-CoV-2 coinfection, having received 2 or 3 previous lines of antibiotic therapy, and an infection sustained by NDM-producing *Klebsiella* spp. (Table 2). The multivariable Cox regression model revealed an independent association with the following: having received 2 or 3 previous lines of antibiotic therapy before cefiderocol (aHR: 4.26, 95% CI: 1.00–18.20, $P = 0.051$; aHR: 7.33, 95% CI: 1.53–35.05, $P = 0.013$, respectively), a SARS-CoV-2 coinfection (aHR: 4.19, 95% CI: 2.04–8.59, $P < 0.001$), and an infection sustained by NDM-producing *Klebsiella* spp. (aHR: 6.22, 95% CI: 2.09–18.50, $P = 0.001$). Interestingly, combination therapy was not associated with 30-day mortality, even when performing the IPTW-adjusted Cox regression analysis (Table 3).

Discussion

In this multicentre retrospective study, we described the real-world use of cefiderocol for the treatment of GNBIs across 17 different Italian hospitals, with a focus on the therapeutic indications and the clinical outcomes according to the therapy type, i.e., monotherapy versus combination therapy.

This is one of the largest collection of real-world evidence on cefiderocol use. While the majority of previous observational studies focused on infections sustained by specific pathogens and/or involving specific anatomical sites [9,10,14,18–23], we herein included infections from different sites caused by diverse Gram-negative bacteria, thus providing a comprehensive description of how cefiderocol is currently used in the clinical practice.

The most common infections in our cohort were BSIs, followed by VAP, HAP, and cUTIs. As for isolated pathogens, *A. baumannii* was the most frequent one, exhibiting high levels of carbapenem resistance, followed by *Klebsiella* spp., which harboured resistance mechanisms such as NDM, KPC, and OXA-48, and *P. aeruginosa*, predominantly carbapenem-resistant. The prevalence of these pathogens and their resistance profiles aligns with data from previous observational studies describing infections treated with cefiderocol [24–27] as well as with surveillance reports in Europe [28].

In keeping with previous reports [24–27,29], most patients in our cohort received at least one previous antibiotic line prior to cefiderocol prescription. These data indicate that cefiderocol is currently used mainly as a rescue therapy in patients with limited therapeutic options, and only in a minority of cases as a first-line regimen.

Although current national and international guidelines offer recommendations on the use of cefiderocol for targeted treatment, clear guidance regarding its empirical use remains lacking [30–32]. In our study, cefiderocol was prescribed as empiric therapy in 14% of cases, a percentage slightly lower to those reported in other cohorts [25]. The propensity of clinicians to prescribe empirically cefiderocol in some cases may reflect their confidence in this therapeutic option in patients with risk factors for Gram-negative bacterial infections, especially in areas with high prevalence rate of MDR pathogens. However, this observation also highlights the need for a consensus regarding the use of cefiderocol in empirical therapeutic strategies in order to avoid the selection of resistance in compliance with antimicrobial stewardship principles.

International guidelines issued by ESCMID and the IDSA recommend a combination therapy including two *in vitro* active

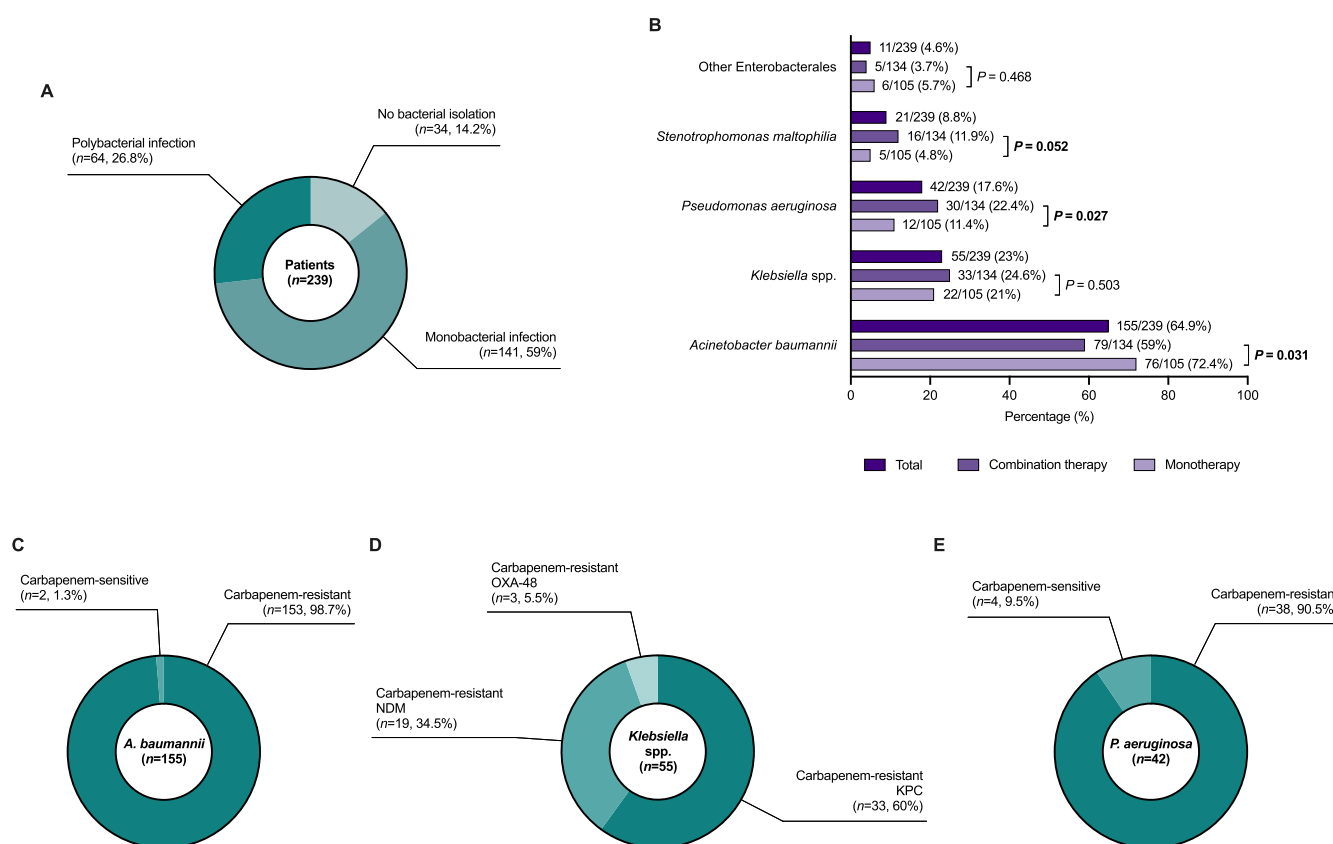


Figure 3. (a) Distribution of monobacterial and polybacterial infections. (b) Distribution of the different bacterial isolates; the *P* values indicate statistical comparisons (Chi-square test or Fisher exact test, as appropriate) between monotherapy and combination therapy groups. (c) Resistance profiles and mechanisms of bacterial isolates. KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo- β -lactamase; OXA-48, oxacillinase-48.

antibiotics for patients with moderate to severe and high-risk carbapenem-resistant *A. baumannii* infections [30,31]. Nevertheless, although *in vitro* studies suggest synergistic effects of cefiderocol-based combinations [33], the clinical value of combination therapy remains controversial due to the limited availability of robust evidence [8,9]. More than half of the patients in our study received cefiderocol in combination with other antibiotics. Combination regimens were more commonly administered in patients with septic shock and in those colonised with MDR bacteria or who previously stayed in ICU, pointing to a preference of clinicians for combination therapy in patients with more severe infections and in those with risk factors for MDR bacteria. Conversely, patients receiving monotherapy were generally older and had a higher comorbidity burden, likely reflecting an effort to minimise the risk of drug-drug interactions and toxicity in fragile populations. With regards to bacterial isolates, cefiderocol monotherapy was more often used in *A. baumannii* infections, whereas combination therapy appeared preferred in those sustained by *P. aeruginosa*. This is consistent with a previous study by Palermo et al. [27], yet in discordance with the study by Giacobbe et al., that reported combination regimens to be more commonly administered in patients with *A. baumannii* infections [25]. The preference for monotherapy in *A. baumannii* infections in our cohort may reflect the growing confidence in cefiderocol *in vitro* activity as well as concerns about added toxicity from combination treatments, such as colistin-related nephrotoxicity. Conversely, the greater use of combination regimens in *P. aeruginosa* infections may be explained by its complex and variable resistance mechanisms—including AmpC overexpression, porin loss, and efflux pump activation—which may contribute to monotherapy suboptimal outcomes.

The 30-day mortality in our cohort was 29.3%. Notably, this was slightly lower than that reported in previous real-world studies in Europe [14,19,21,22,24,27,34], in which 30-day mortality among patients treated with cefiderocol ranged between 34% and 40%. Contrarily, another study conducted in the United States found a 30-day mortality of 18.8%, significantly lower than in our study [26]. Differences in age, comorbidity burden, infection site and severity, causative pathogens, and clinical management strategies may explain variance in mortality across studies.

When exploring potential mortality predictors in patients treated with cefiderocol, we found that SARS-CoV-2 coinfection, having received 2 or 3 previous lines of antibiotic therapy, and the isolation of NDM-producing *Klebsiella* spp. were independently associated with higher 30-day mortality.

The association of SARS-CoV-2 coinfection with increased mortality is consistent with prior studies reporting that COVID-19 can complicate the clinical course of bacterial infections [14,19]. The viral infection may impair host immune responses, exacerbate inflammation, and contribute to multi-organ dysfunction, all of which can negatively impact outcomes, even in the context of appropriate antibiotic therapy.

Interestingly, our finding of a 4- to 7-fold increased risk of mortality in patients receiving cefiderocol as second- or third-line therapy aligns with data from other cohorts, collectively indicating a cumulative failure of previous antibiotic treatments rather than an intrinsic inefficacy of the drug, and thus a significant clinical disadvantage associated with the use of cefiderocol as salvage therapy [23,29], albeit this aspect should be specifically addressed by larger studies.

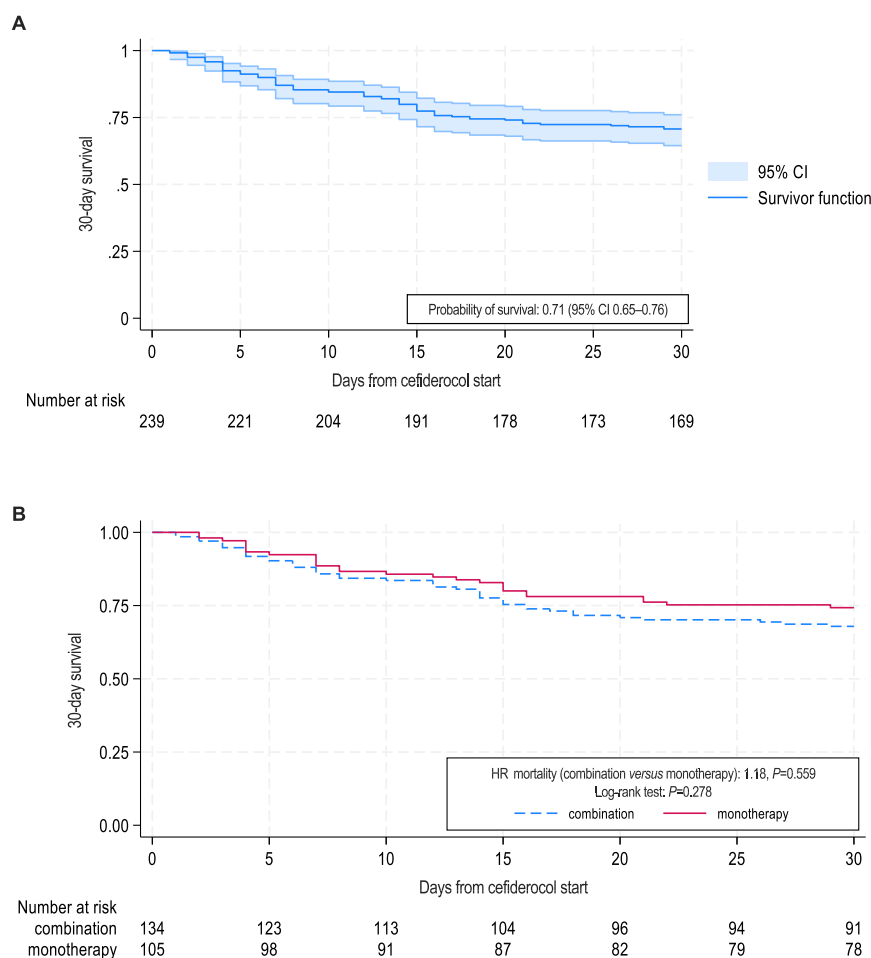


Figure 4. 30-day survival overall (a) and stratified by therapy type (combination therapy versus monotherapy) (b).

In a *post-hoc* analysis of the CREDIBLE-CR and APEKS-NP trials, cefiderocol has been shown to lead to numerically higher clinical cure and microbiological eradication rates than comparators against pathogens producing metallo- β -lactamases (MBLs), including NDM [6]. Conversely, the GAME CHANGER trial reported that in infections caused by MBL-producing Enterobacterales—most of which being NDM-producers—patients treated with cefiderocol experienced numerically higher mortality, thereby failing to achieve the 14-day mortality superiority target [7]. Notwithstanding, our data suggest that, despite treatment with cefiderocol, infections sustained by NDM-producing *Klebsiella* spp. are still associated with a high mortality rate. This observation is consistent with emerging evidence reporting clinical failures of cefiderocol in the context of NDM-producing infections [1]. Notably, a recent study showed that, among MBLs, the NDM-1 and NDM-5 enzymes are able to hydrolyse cefiderocol at levels sufficient to drive clinically meaningful resistance [35]. In this context, combination strategies pairing cefiderocol with β -lactamase inhibitors (e.g., xeruborbatam) may represent a critical and necessary approach to preserve the clinical utility of this potent cephalosporin.

Previous evidence from both the CREDIBLE-CR trial [5] and observational studies [14] suggested that cefiderocol may be less effective in treating *A. baumannii* infections, especially pneumonia, likely due to a suboptimal penetration of the drug in the alveolar epithelial lining fluid [36]. However, neither the infection site nor the microbiological isolate appeared to influence the mortality in our analysis, supporting the effectiveness of cefiderocol for the

treatment of pulmonary infections sustained by this pathogen, as also evidenced by other real-world studies [11,12,24,26].

Remarkably, no significant differences in 30-day survival were observed between patients who received cefiderocol as monotherapy and those who received combination regimens. Accordingly, combination therapy did not emerge as a predictor of 30-day mortality at Cox regression analysis, even after adjusting the models for patients' probability of receiving combination therapy or monotherapy by propensity score. Although combination therapy was more commonly used in severe cases, i.e., those with septic shock, suggesting that it might be preferable for patients in critical conditions, no clear survival benefit was observed. Multiple observational studies found no differences in mortality between patients treated with cefiderocol in mono- or combination therapy [18,21,24,26,27]. A meta-analysis including both RCTs and observational studies found that mortality rate was lower among patients with carbapenem-resistant *A. baumannii* receiving cefiderocol in monotherapy as compared to those treated with combination regimens, without significant differences in clinical or microbiological failure. However, these findings were not confirmed in sub-analyses including only patients with BSIs or pneumonia, and are likely biased by the fact that in the real-world clinical practice cefiderocol in monotherapy is more often prescribed in patients with less severe infections [9].

This study has some limitations. Firstly, its retrospective design, which inherently introduces selection biases, potential data incom-

Table 2
Univariable Cox regression analysis exploring predictors of 30-day mortality.

	HR	95% CI	P value
Age (10-year increase)	1.38	1.14-1.67	0.001
Female sex	0.82	0.48-1.40	0.469
CCI (each unit more)	1.15	1.03-1.28	0.014
Immunosuppression	1.18	0.70-1.99	0.545
eGFR <60 ml/min	1.84	1.06-3.20	0.031
Septic shock	1.72	0.97-3.07	0.065
SARS-CoV-2 coinfection	2.70	1.49-4.92	0.001
Previous antibiotic therapy	3.48	1.02-11.85	0.046
1 previous line	2.39	0.66-8.68	0.184
2 previous lines	3.72	1.02-13.56	0.046
3 previous lines	5.05	1.30-19.67	0.020
Infection type			
BSI	0.85	0.46-1.57	0.606
HAP	1.99	0.97-4.08	0.059
VAP	0.89	0.29-2.71	0.833
cUTI	1.28	0.47-3.49	0.636
cIAI	0.37	0.05-3.03	0.355
Others	0.39	0.05-2.91	0.356
BSI origin			
Abdominal	0.68	0.22-2.18	0.522
Catheter-related	0.56	0.21-1.48	0.243
Respiratory	1.13	0.54-2.34	0.744
Urinary	0.50	0.12-2.16	0.354
Others	1.27	0.49-3.26	0.624
Unknown	1.59	0.68-3.69	0.285
Microbiological isolate			
<i>A. baumannii</i>	0.83	0.50-1.40	0.494
<i>Klebsiella</i> spp.	1.21	0.65-2.23	0.545
<i>P. aeruginosa</i>	0.57	0.27-1.21	0.142
Others	1.00	0.46-2.15	0.990
Resistance mechanisms			
Carbapenem-resistant <i>A. baumannii</i>	0.84	0.50-1.41	0.501
Carbapenem-resistant <i>P. aeruginosa</i>	0.69	0.29-1.62	0.391
KPC-producing <i>Klebsiella</i> spp.	1.19	0.47-3.01	0.712
NDM-producing <i>Klebsiella</i> spp.	2.52	1.06-6.02	0.037
Others	2.88	0.35-23.52	0.325
Cefiderocol in combination therapy	1.18	0.67-2.09	0.559

BSI, bloodstream infection; CCI, Charlson Comorbidity Index; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; eGFR, estimated glomerular filtration rate; HAP, hospital-acquired pneumonia; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo- β -lactamase; VAP, ventilator-associated pneumonia.

Table 3
Multivariable Cox regression analysis exploring predictors of 30-day mortality.

	aHR	95% CI	P value
Multivariable Cox regression analysis^a			
Age (10-year increase)	1.21	0.97-1.50	0.087
CCI	1.08	0.95-1.23	0.244
eGFR <60 ml/min	1.79	0.95-3.38	0.072
Septic shock	1.18	0.62-2.24	0.619
SARS-CoV-2 coinfection	4.19	2.04-8.59	<0.001
Previous antibiotic therapy (1 previous line)	3.03	0.69-13.27	0.141
Previous antibiotic therapy (2 previous lines)	4.26	1.00-18.20	0.051
Previous antibiotic therapy (3 previous lines)	7.33	1.53-35.05	0.013
Infection type (HAP)	1.67	0.73-3.86	0.227
Microbiological isolate (<i>P. aeruginosa</i>)	0.58	0.25-1.31	0.187
Resistance mechanisms (NDM)	6.22	2.09-18.50	0.001
Cefiderocol in combination therapy	1.54	0.74-3.20	0.247
Propensity score analysis			
Cefiderocol in combination therapy (IPTW-adjusted, model I) ^b	0.94	0.50-1.75	0.844
Cefiderocol in combination therapy (IPTW-adjusted, model II) ^c	0.93	0.46-1.85	0.829

CCI, Charlson Comorbidity Index; HAP, hospital-acquired pneumonia; IPTW, inverse probability of treatment weighting.

^a Variables included in the multivariable model those with a *P* value <0.2 in univariable analysis along with those deemed clinically relevant.

^b Model I: variables included to generate the propensity score were age, CCI, septic shock.

^c Model II: variables included to generate the propensity score were those included in the multivariable model (age, CCI, eGFR <60 ml/min, septic shock, SARS-CoV-2 coinfection, HAP, *P. aeruginosa*, NDM).

pleteness, and difficulty in controlling for confounders. Another limitation is the lack of a comparison group of patients treated with agents other than cefiderocol; however, the evaluation of the effectiveness of cefiderocol compared to other antibiotic regimens was beyond the scope of this study. Lastly, the relatively limited sample size for individual pathogens precluded the assessment of

mortality differences between monotherapy and combination therapy stratified by bacterial isolate.

In conclusion, this large, multicentre retrospective study provides a comprehensive overview of cefiderocol use in a real-world setting across Italy. These data highlight that cefiderocol is widely employed for the treatment of diverse MDR GNIs, predominantly

in patients with complex clinical profiles and previously exposed to multiple antibiotics. Notably, while combination therapy is often preferred in patients with more severe infections and in those with risk factors for MDR bacteria, there is no significant difference in 30-day survival compared to monotherapy. Multiple previous antibiotic lines, SARS-CoV-2 coinfection, and isolation of NDM-producing *Klebsiella* spp. are critical predictors of increased mortality in patients with GNBs treated with cefiderocol, suggesting that the management of such conditions should account for those factors in order to optimise treatment strategies. Future prospective studies are warranted to better delineate the optimal place-in-therapy of cefiderocol in line with the antimicrobial stewardship principles and to improve outcomes of these difficult-to-treat infections.

Declaration of competing interest

The authors have no conflicts of interest related to this work to disclose.

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Ethical approval

The study was approved by the Ethics Committee of Milan Area 1 (trial register no. 2023/ST/084).

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Author contributions

M.A. participated in study and statistical analysis design, interpreted the data, created the figures, and wrote the final version of the manuscript. F.B.D. participated in study design, enrolled participants, contributed to data entry, and contributed to the manuscript writing. B.V. participated in study design, enrolled participants and contributed to data entry. L.T. performed statistical analyses. M.B., P.B., F.B., R.B., L.B., S.C., A.M.C., R.C., M.C., A.C., N.C., L.F., M.F., P.F., S.G., G.G., C.I., M.M., C.M., A.M., C.M., S.P., G.P., M.R., N.R., S.R., M.S., A.S., V.S., G.T., C.T., and M.V. enrolled participants, contributed to data entry, and critically revised the manuscript. G.M. designed and supervised the study, interpreted the data, and wrote the manuscript. All authors contributed to the article and approved the submitted version.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.108305.

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