Cefiderocol Versus Colistin for the Treatment of Carbapenem-Resistant *Acinetobacter baumannii* Complex Bloodstream Infections: A Retrospective, Propensity-Score Adjusted, Monocentric Cohort Study

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ABSTRACT

Introduction: Bloodstream infections (BSI) caused by carbapenem-resistant *Acinetobacter baumannii* (CRAB) are associated with high mortality with limited treatment. The aim of this study is to compare effectiveness and safety of colistin-based versus cefiderocol-based therapies for CRAB-BSI.

Methods: This is a retrospective observational study enrolling patients with monomicrobial CRAB-BSIs treated with colistin or cefiderocol from 1 January 2020, to 31 December 2022. The 30-day all-cause mortality rate was the primary outcome. A Cox regression analysis was performed to identify factors independently associated with mortality. A propensity score analysis using inverse probability of treatment weighting (IPTW) was also performed.

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Results: Overall 118 patients were enrolled, 75 (63%) and 43 (37%) treated with colistin- and cefiderocol-based regimens. The median (q1–q3) age was 70 (62–79) years; 70 (59%) patients were men.The 30-day all-cause mortality was 52%, significantly lower in the cefiderocol group (40% vs 59%, $p = 0.045$). By performing a Cox regression model, age (aHR = 1.03, 95% CI 1.00–1.05), septic shock (aHR = 1.93, 95% CI 1.05–3.53), and delayed targeted therapy (aHR = 2.42, 95% CI 1.11–5.25) were independent predictors of mortality, while cefiderocol-based therapy was protective (aHR = 0.49, 95% CI 0.25–0.93). The IPTW-adjusted Cox analysis confirmed the protective effect of cefiderocol (aHR = 0.53, 95% CI 0.27–0.98).
Conclusions: Cefiderocol may be a valuable treatment option for CRAB-BSI, especially in the current context of limited treatment options.

Keywords: Antimicrobial resistance; Bloodstream infections; Carbapenem-resistant *Acinetobacter baumannii*; Cefiderocol; Colistin

Key Summary Points

Why carry out the study?

Carbapenem-resistant *Acinetobacter baumannii* bloodstream infections (CRAB-BSI) are serious nosocomial infections associated with high mortality and healthcare costs.

Currently, treatment options available for CRAB-BSI are limited to a few antibiotics including high-dose sulbactam, colistin, and cefiderocol.

Cefiderocol may represent a valid alternative to colistin for the treatment of CRAB-BSI, but data are still limited.

What was learned from the study?

In this retrospective series of 118 patients with CRAB-BSI, cefiderocol was associated with a lower rate of mortality and adverse events than colistin.

Although the limited sample size did not allow a deeper analysis, combination therapy did not reduce mortality compared with monotherapy.

Emergence of in vivo cefiderocol resistance was rarely detected it this cohort: however, given its importance, future studies should investigate this issue.

INTRODUCTION

Infections caused by carbapenem-resistant *Acinetobacter baumannii* (CRAB) are increasing worldwide [1]; in particular, according to data released in the last European Center for Disease Control (ECDC) report on antimicrobial resistance surveillance, the annual number of invasive isolates of *Acinetobacter baumannii* has tripled in the last 4 years in several countries (including Italy), and the proportion of carbapenem-resistant isolates to total isolates of *Acinetobacter* spp. surpassed 85% [1].

Importantly, CRAB infections are burdened by a significant risk of poor outcome: focusing on CRAB bloodstream infections, the 30-days infection-related mortality could reach the 30–50% of all cases, higher than that caused by carbapenem-susceptible strains [2, 3]. This can be partially explained by the underlying frailty of the patients infected by multidrug-resistant bacterial infections, often affected by multiple comorbidities, being immunocompromised, or having been exposed to prolonged antibiotic therapies; on the other hand, also the small antibiotic armamentarium available against these pathogens poses an increased risk of poor outcome [4].

In fact, despite its inclusion in 2017 WHO priority list as a "critical pathogen" for which new antibiotics are urgently needed [5], treatment options for severe CRAB infections remain limited.

To date, the available therapeutic options for severe CRAB infections are represented by ampicillin/sulbactam or colistin in monotherapy or in combo-therapy with other molecules (high-

dose tigecycline, aminoglycosides, minocycline, high-dose meropenem) [6, 7]. However, as underlined in the current published guidelines [6, 7], evidence supporting the choice of the best therapeutic approach is not available.

In this context, cefiderocol, a new siderophore cephalosporin, showed remarkable in vitro activity against CRAB [8], representing a potential valid option against this pathogen.

Nevertheless, although early data emerging from "real-life" use are promising [9–11], current international guidelines [6, 7] suggest a "second-line" place in therapy of this new molecule for severe CRAB infections, since data of effectiveness deriving from current clinical trials are conflicting [12, 13].

Hence, the aim of this study was to compare the effectiveness and safety of cefiderocol-based regimens versus colistin-based ones in patients with CRAB bloodstream infection.

In particular, the primary objective of the study was to evaluate the 30-day all-cause mortality of the study population and compare this outcome between the two groups of patients. Secondary objectives included the evaluation of 30-day infection-related mortality, incidence of severe adverse events to antibiotic therapy, 90-day all-cause mortality, 90-day recurrence of CRAB-BSI, and emergence of cefiderocol or colistin resistance after or during therapy.

METHODS

Study Design and Inclusion Criteria

This was a comparative retrospective monocentric cohort study conducted at the University Hospital of the Polyclinic of Bari over 36 months, from 1 January 2020 to 31 December 2022.

All available information, including demographics and clinical, microbiological, and instrumental data, were anonymized and collected on an electronic database.

All consecutive adult (aged $\geq$ 18 years) patients who developed a BSI caused by carbapenem-resistant *Acinetobacter baumannii* complex were screened.

The criteria for inclusion of the study were: (1) CRAB monomicrobial bacteremia (CRAB-BSI); (2) therapy based on cefiderocol or colistin; (3) acquisition of informed consent.

Exclusion criteria were: (1) patients died within 48 h from targeted treatment initiation or before receiving any effective therapy; (2) patients treated for < 48 h with cefiderocol or colistin; (3) patients with incomplete data; (4) concurrent infections in blood or in any other body site; (5) concurrent COVID-19; (6) patients treated with regimens not containing cefiderocol or colistin; (7) patients treated with both cefiderocol and colistin (in serial or in parallel).

Figure 1 describes the flowchart of inclusion and exclusion of patients.

## Study Endpoints

The primary endpoint of the study was evaluating the 30-day all-cause mortality.

Secondary outcomes of the study were:

- Evaluating incidence of 30-day infection-related mortality.
- Evaluating incidence of severe (grade 3–5) adverse events to antibiotic therapy (evaluated within 14 days of discontinuation).
- Ninety-day all-cause mortality and 90-day CRAB-BSI recurrence.
- Emergence of cefiderocol or colistin resistance after of during therapy.

Infection-related mortality was determined by an adjudication committee of at least two independent infectious disease specialists (DFB, AB, LD, RP, FDG, NDG) and was considered infection related if the death was caused by the direct complications of infection (e.g., septic shock, acute respiratory failure, or following infection control surgery) or in case of persistent signs of infection (ongoing fever, persistent positive blood cultures, leukocytosis, elevated CRP) at the time of death. Contrarily, a non-infection-related mortality was adjudicated if patients had died from a definite other cause that was independent from the CRAB-BSI. Mortality events that did not clearly fit the definitions of infection related or non-infection related were discussed within the committee
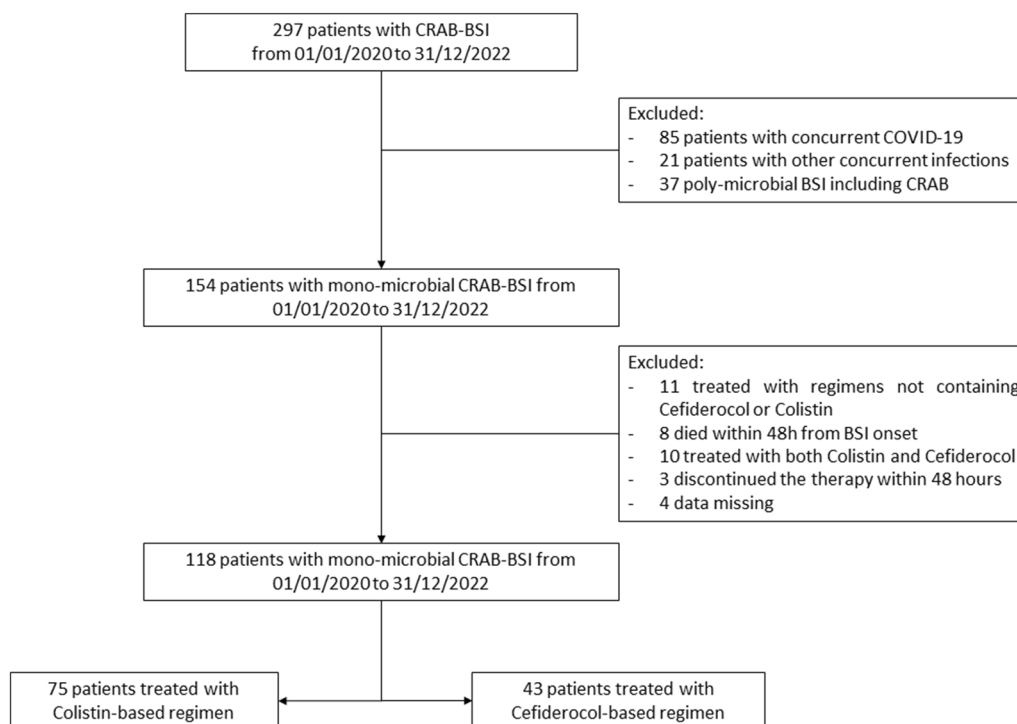
Fig. 1 Flowchart of inclusion and exclusion of patients

and with the study research supervisors (AS, SG, LD) and attributed according to the most probable cause.

Patients were followed until discharge or until the day of death. In case of discharge before day 30 after infection onset, mortality was evaluated using information from hospital records which were linked with a municipal records database. Our hospital information system allows us access to patient personal data (living or deceased status, date of death). Therefore, we have no patients lost to follow-up in mortality analyses.

Sampling Process and Antimicrobial Susceptibility Testing

According to current guidelines and hospital protocols, blood cultures were performed for all patients by collecting 20–30 ml blood per culture set before starting an empirical antimicrobial therapy. Two bottles (for aerobic and anaerobic bacteria culture, respectively) were collected for each set and immediately placed into a BACT/ALERT® 3D instrument (Biomerieux Inc., France). Positive aerobic blood cultures were subcultured on MacConkey agar, CNA blood agar, Sabouraud dextrose agar, mannitol-salt agar, and chocolate agar and incubated aerobically at 37 °C for 24 h.

Identification and antibacterial phenotypic susceptibility were tested on either the automated VITEK 2 system or VITEK MS (Biomerieux) according to the manufacturer's instructions. The interpretative breakpoints of MIC values were based on the criteria of the European committee on antimicrobial susceptibility testing (EUCAST).

Colistin susceptibility testing was made by broth microdilution. Minimum inhibitory concentration (MIC) values were interpreted according to clinical breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Cefiderocol susceptibility testing was made by disk diffusion method using 30-μg cefiderocol discs (Liofilchem®, Italy) in standard Mueller-Hinton agar plates. Inhibition zone diameters > 17 mm for cefiderocol corresponded to MIC values

below the PK/PD breakpoint of sensitivity < 2 mg/l.

Statistical Analysis

All data were anonymized and collected on an electronic database.

Descriptive statistics were produced for demographic, clinical, and laboratory characteristics of patients. Medians and interquartile ranges (q1–q3) were produced for continuous variables, and numbers and percentages were produced for categorical variables.

For analysis purposes, patients were divided into two groups according to backbone antibiotic therapy (colistin or cefiderocol) or outcome (survived and non-survived to infection).

Since this was not a randomized controlled trial, the sample size was not pre-determined. However, after data retrieving and initial descriptive statistics needed for data cleaning, a full assessment of statistical power and sample size was performed to evaluate whether the study reached adequate statistical soundness.

The sample size analysis was as follows.

Considering a potential mortality rate associated with CRAB-BSI of 40–50%, we determined that a sample size of at least 40 patients per arm reached $\geq$ 80% power in case of a mortality rate difference of at least 20% (considered clinically significant) with an alpha (type I error) of 0.05.

The distribution of outcomes, clinical findings, and laboratory findings between groups was analyzed with univariate parametric and nonparametric tests, with Kruskal-Wallis and Mann-Whitney U tests (where appropriate) for continuous variables and with Pearson's χ^2 test (Fisher's exact test where appropriate) for categorical variables, according to data distribution.

To assess predictors of 30-day all-cause mortality, a univariate Cox regression model was produced for variables of interest. Then, a stepwise multivariable Cox regression was applied to control for potential confounders and was adjusted for associated variables ($p < 0.1$) with endpoints on univariate analysis or considered significant according to the current literature.

Additionally, Kaplan-Meier curve estimates were also performed for variables of interest.

Finally, an inverse-probability treatment-weighted (IPTW) adjusted analysis was applied to compare the impact of colistin and cefiderocol on risk of 30-day all-cause mortality after balancing the cohort for variables influencing treatment assignment. The analysis was performed using the treatment effects module implemented in Stata 16.1 Special Edition.

Hence, the final analysis was balanced in terms of variables influencing assignment to treatment as follows: each patient's probability of receiving cefiderocol or colistin was determined through a non-parsimonious multivariable logistic regression model (Supplementary Table 1) constructed to estimate each patient's probability of receiving the drug (i.e., the propensity score) [14].

Stabilized weights (Supplementary Table 2), based on the inverse of the propensity score, were then applied to generate a weighted cohort in which covariate distributions were independent of treatment assignment [15]

Standardized differences were examined to assess balance using a threshold of 10% to indicate clinically meaningful imbalance requiring further adjustment in outcome analyses [15].

The weighted propensity score distributions were visually inspected, and an overidentification test for covariate balance was performed to ensure that the final model and all covariates were balanced between groups, to allow valid comparisons. Similarly, treatment group was conditioned on covariates that were not optimally balanced after IPTW (standardized difference $\geq$ 10%).

Finally, the IPTW-adjusted Cox regression was computed by taking the average of the difference between the observed and potential outcomes for each patient.

In all cases, $p < 0.05$ was considered statistically significant. Statistical analysis was performed using STATA "Special Edition," version 16.1 (StataCorp, College Station, TX, USA).

Ethics

This study was performed with the formal approval of the Ethics Committee of University Hospital-Polyclinic of Bari (study number: 6527) and in accordance with the Declaration of Helsinki and national and institutional standards. Data were previously pseudo-anonymized, according to the requirements set by Italian data protection code (leg. decree 196/2003) and European general data protection regulation (GDPR 2016/679). The patients provided written informed consent (available from the corresponding author) for use of their data for research purposes.

RESULTS

General Characteristics of the Study Population and CRAB-BSI

A total of 297 patients with CRAB-BSI were screened in the study period, as described in Fig. 1.

One hundred seventy-nine patients were excluded, and 118 were included in the final analysis: of them, 75 and 43 were treated with colistin- and cefiderocol-based regimens, respectively.

The median (q1–q3) age was 70 (62–79) years, with 70 (59%) patients being men, with a median Charlson comorbidity index of 6 (4–8). The most frequent comorbidity was chronic kidney failure (42%), followed by type II diabetes (36%) and chronic heart diseases (25%).

Overall, 67 (57%) patients were hospitalized in a medical ward, 31 (26%) in ICU, and 20 (17%) in a surgical unit. CRAB-BSI occurred with septic shock, acute lung failure, and acute kidney failure in 36%, 42%, and 31% of patients, respectively. At presentation, the median SOFA score was 5 (2–6), and 30 (25%) patients had a PITT bacteriemia score > 4.

All CRAB isolates were sensitive to colistin [median (q1–q3) MIC = 0.5 (0.5–1) mg/l] and to cefiderocol [median (q1–q3) disk diffusion diameter 20 (18–22) mm], except two strains which were resistant to cefiderocol at baseline. Of note, all the strains were resistant to aminoglycosides, carbapenems, fluoroquinolones, and ampicillin/sulbactam; finally, tigecycline sensitivity (MIC ≤ 2 mg/l) was documented in 11 (9%) cases.

Description of Antibiotic Therapies and Comparison of Patients Treated with Colistin and Cefiderocol

Demographic and clinical characteristics of patients treated with a colistin- or cefiderocol-based regimen were compared and are shown in Table 1.

The two groups were comparable in terms of age, sex, Charlson comorbidity index, hospitalization ward, and characteristics of the bloodstream infection at the onset, including presentation with septic shock, acute respiratory or kidney failure, and median SOFA score (5 versus 4, respectively, $p = 0.245$).

Nevertheless, some important differences emerged. At first, compared with cefiderocol, colistin was used less frequently in monotherapy (37% versus 4% respectively, $p < 0.001$); in particular, colistin was associated with > 2 drugs in 48 patients (66%), especially tigecycline (51%) or ampicillin/sulbactam (35%). On the other hand, for combination therapy, the preferred companion drug to cefiderocol was fosfomycin (74%), followed by ampicillin/sulbactam (37%); in addition, three cases of cefiderocol plus fosfomycin plus ampicillin/sulbactam were recorded. None of the patients in the cefiderocol group was treated with tigecycline or with > 2 companion antibiotics. Another difference was the higher incidence of BSI in patients, which required surgical source control in the colistin group (31% versus 7%, $p = 0.003$).

Importantly, time to targeted antimicrobial therapy administration was dissimilar between the two groups ($p = 0.036$). In detail, in the colistin group, only 21% of patients received targeted therapy within 24 h of infection onset and 30% received it after > 72 h. In the cefiderocol group, 37% received targeted antibiotic therapy within 24 h of onset of infection and 19% after 72 h.

Table 1 Clinical features of patients treated with colistin- and cefiderocol-based regimens

	Overall (*n.* 118)	Colistin-based regimens (*n.* 75)	Cefiderocol-based regimens (*n.* 43)	*p* value
Median (q1–q3) age, years	70 (62–79)	71 (62–78)	69 (60–81)	0.917
Male sex, *n* (%)	70 (59)	44 (59)	26 (60)	0.848
Previous COVID-19 infection, *n* (%)	30 (25)	18 (24)	12 (28)	0.639
Median (q1–q3) Charlson comorbidity index	6 (4–8)	6 (4–7)	6 (4–8)	0.712
Severe immunocompromised state, *n* (%)	21 (18)	14 (19)	7 (16)	0.744
Characteristics of infection, *n* (%)				
Fever (TC > 38 °C)	76 (64)	43 (57)	33 (77)	**0.034**
Septic shock	42 (36)	27 (36)	15 (35)	0.903
Acute lung failure	49 (42)	35 (47)	14 (33)	0.134
Acute kidney failure	36 (31)	24 (32)	12 (28)	0.642
Ward of evaluation, *n* (%)				
Medical ward	67 (57)	46 (61)	21 (49)	0.391
Surgical ward	20 (17)	12 (16)	8 (19)	
Intensive care unit	31 (26)	17 (23)	14 (33)	
Median (q1–q3) SOFA score at onset	5 (2–6)	5 (2–7)	4 (2–6)	0.245
PITT bacteriemia score > 4, *n* (%)	30 (25)	20 (27)	10 (23)	0.682
Site of infection treated with surgical source control, *n* (%)	26 (22)	23 (31)	3 (7)	**0.003**
Site of infection, *n* (%)				
Primary BSI or urinary tract	37 (31)	21 (28)	16 (37)	0.154
CVC-related	36 (31)	25 (33)	11 (26)	
Intra-abdominal	19 (16)	16 (21)	3 (7)	
Lung	12 (10)	5 (7)	7 (16)	
Skin and soft tissue	12 (10)	6 (8)	6 (14)	
Endovascular	1 (1)	1 (1)	0	
Osteoarticular	1 (1)	1 (1)	0	
Monotherapy, *n* (%)	19 (16)	3 (4)	16 (37)	**< 0.001**
Combination with other antibiotics, *n* (%)	99 (84)	72 (96)	27 (63)	
Ampicillin/sulbactam	35 (30)	25 (33)	10 (23)	0.249
Fosfomycin	42 (36)	22 (29)	20 (47)	0.061
Tigecycline	37 (31)	37 (49)	0	**< 0.001**

Table 1 continued

	Overall (*n.* 118)	Colistin-based regimens (*n.* 75)	Cefiderocol-based regimens (*n.* 43)	*p* value
Combinations of more than 2 drugs	48 (41)	48 (64)	0	**< 0.001**
Time to targeted antibiotic therapy, *n* (%)				
Within 24 h from infection onset	32 (27)	16 (21)	16 (37)	**0.036**
From 24 to 72 h from infection onset	48 (41)	29 (39)	19 (44)	
After 72 h from infection onset	38 (32)	30 (30)	8 (19)	
Adverse events to antimicrobial therapy, *n* (%)	13 (11)	12 (16)	1 (2)	**0.022**
Median (q1–q3) duration of antibiotic therapy	11 (8–16)	13 (8–18)	10 (9–13)	**0.017**
30-day all-cause mortality, *n* (%)	61 (52)	44 (59)	17 (40)	**0.045**
30-day infection related mortality, *n* (%)	55 (47)	42 (56)	13 (30)	**0.007**
90-day infection recurrence/relapse, *n* (%)	8 (7)	4 (5)	4 (9)	0.409
90-day all-cause mortality, *n* (%)	67 (58)	48 (64)	19 (42)	**0.032**

q1–q3 first–third quartile, *BSI* bloodstream infection, *CVC* central venous catheter
Boldface means statistically significant ($p < 0.05$)

Interestingly, the incidence of adverse events because of antibiotic therapy was higher for colistin ($p = 0.022$): 1 (2%) patient treated with cefiderocol developed an allergic skin rash, while 12 (16%) patients treated with colistin developed a grade 3–4 adverse event, including 10 cases of acute kidney injury and 2 cases of peripheral neuropathy. In addition, two patients (5%) developed resistance to cefiderocol (both in the monotherapy group) after treatment, while no resistance to colistin was detected.

Finally, a shorter median duration of therapy was noticed in the cefiderocol versus colistin group (10 versus 13 days respectively, $p = 0.017$).

Of note, 7% (8 cases) of patients experienced a CRAB-BSI relapse/recurrence within 90 days, without significant difference in incidence between the two groups (5% versus 9% for colistin- versus cefiderocol-based regimens, respectively, $p = 0.409$).

Analysis of 30-Day Mortality

Fifty-two percent (61 of 118) and 47% (55 of 118) of 30-day all-cause and infection-related mortality were registered in the whole population, respectively.

The clinical and demographic characteristics of patients who survived and experienced 30-day all-cause mortality are summarized in Table 2 (in Supplementary Table 3 the analysis of 30-day infection-related mortality is given).

By considering the analysis of 30-day all-cause mortality and comparing the two groups, a higher median age (74 versus 69, $p = 0.008$), Charlson comorbidity index (6 versus 5, $p = 0.004$), SOFA score (5 versus 4, $p = 0.030$), incidence of septic shock (46% versus 25%, $p = 0.016$), and incidence of chronic renal failure (52% versus 32%, $p = 0.022$) were observed in patients who did not survive at day 30.

The 30-day all-cause mortality rate was different in the two groups: 59% (44/75) for the

Table 2 Comparison of clinical characteristics of patients who survived or died after CRAB BSI

	Overall (*n.* 118)	Clinical cure (*n.* 57)	30-day all-cause mortality (*n.* 61)	*p* value
Median (q1–q3) age, years	70 (62–79)	69 (58–75)	74 (66–82)	**0.008**
Male sex, *n* (%)	70 (59)	36 (63)	34 (56)	0.412
Previous COVID-19 infection, *n* (%)	30 (25)	15 (26)	15 (25)	0.830
Median (q1–q3) Charlson comorbidity index	6 (4–8)	5 (3–7)	6 (5–8)	**0.004**
Comorbidities, *n* (%)				
Cardiovascular diseases	29 (25)	12 (21)	17 (28)	0.390
Type II diabetes	42 (36)	20 (35)	22 (36)	0.912
Chronic kidney failure (eGFR < 60 ml/min)	50 (42)	18 (32)	32 (52)	**0.022**
Chronic obstructive pulmonary disease	25 (21)	9 (16)	16 (26)	0.165
Obesity (BMI > 30 kg/m^2)	24 (20)	9 (16)	15 (25)	0.235
Solid neoplasia	17 (14)	8 (14)	9 (15)	0.912
Hematologic neoplasia	6 (5)	0 (0)	6 (10)	**0.015**
Severe immunocompromised state, *n* (%)	21 (18)	6 (11)	15 (25)	**0.046**
Ward of evaluation, *n* (%)				
Medical ward	67 (57)	27 (47)	40 (66)	0.106
Surgical ward	20 (17)	13 (23)	7 (11)	
Intensive care unit	31 (26)	17 (30)	14 (23)	
Characteristics of infection, *n* (%)				
Fever (TC > 38 °C)	76 (64)	37 (65)	39 (64)	0.912
Septic shock	42 (36)	14 (25)	28 (46)	**0.016**
Acute lung failure	49 (42)	20 (35)	29 (48)	0.170
Acute kidney failure	36 (31)	14 (25)	22 (36)	0.175
Median (q1–q3) SOFA score at onset	5 (2–6)	4 (2–6)	5 (4–7)	**0.030**
PITT bacteriemia score > 4, *n* (%)	30 (25)	12 (21)	18 (30)	0.292
Site of infection treated with surgical source control, *n* (%)	26 (22)	11 (19)	15 (25)	0.488

Table 2 continued

	Overall (*n*. 118)	Clinical cure (*n*. 57)	30-day all-cause mortality (*n*. 61)	*p* value
Site of infection, *n* (%)				
Primary BSI or urinary tract	37 (31)	18 (32)	19 (31)	0.880
CVC-related	36 (31)	17 (30)	19 (31)	
Intra-abdominal	19 (16)	9 (16)	10 (16)	
Lung	12 (10)	7 (13)	5 (8)	
Skin and soft tissue	12 (10)	6 (11)	6 (10)	
Endovascular	1 (1)	0	1 (2)	
Osteoarticular	1 (1)	0	1 (2)	
Time to targeted antibiotic therapy, *n* (%)				
Within 24 h from infection onset	32 (27)	21 (37)	11 (18)	**0.032**
From 24 to 72 h from infection onset	48 (41)	23 (40)	25 (40)	
After 72 h from infection onset	38 (32)	13 (23)	25 (41)	
Definitive antibiotic therapy for BSI, *n* (%)				
Colistin-based	75 (64)	31 (54)	44 (72)	**0.045**
Cefiderocol-based	43 (36)	26 (46)	17 (28)	
Severe adverse events to antibiotic therapy, *n* (%)	13 (11)	7 (12)	6 (10)	0.672
Median (q1–q3) duration of antibiotic therapy	11 (8–16)	12 (10–17)	9 (6–14)	**0.005**
Median (q1–q3) days from symptom onset to discharge or death for infection	17 (8–28)	23 (16–45)	9 (6–20)	**< 0.001**

q1–q3 first–third quartile, *BSI* bloodstream infection
Boldface means statistically significant (*p* < 0.05)

colistin group and 40% (17/43) for the cefiderocol one (*p* = 0.045); similarly, also 30-day infection-related mortality was lower in the cefiderocol group (30% versus 56%, *p* = 0.007, see Supplementary Table 2).

Moreover, a Cox regression univariate and multivariate analysis (Table 3) for predictors of 30-day infection-related mortality was conducted.

At univariable model, age (HR = 1.03, 95% CI 1.00–1.05), Charlson comorbidity index (HR = 1.17, 95% CI 1.05–1.31), septic shock (HR = 1.82, 95% CI 1.06–3.11), and delayed appropriate antimicrobial therapy (> 72 h from BSI onset) (HR = 2.43, 95% CI 1.16–5.12) were

associated with increased mortality, while the use of a cefiderocol-based regimen (HR = 0.51, 95% CI 0.28–0.94) was protective.

Interestingly, the use of combination therapy was not associated with a significant reduction in 30-day infection-related mortality (HR = 0.81, 95% CI 0.39–1.66) compared to monotherapy; however, the presence of fosfomycin in case of combination regimens was associated with a reduced mortality (HR = 0.43, 95% CI 0.22–0.81).

The multivariate analysis confirmed that the independent risk factors for 30-day infection-related mortality were age increase (aHR = 1.03, 95% CI 1.00–1.05), septic shock (aHR = 1.93,

Table 3 Univariable, multivariable, and IPTW-adjusted multivariable Cox model for 30-day all-cause mortality

	Univariable analysis			Multivariable analysis			IPTW-adjusted multivariable analysis		
	HR	95% CI	*p* value	aHR	95% CI	*p* value	aHR	95% CI	*p* value
Age per 1 year increase	1.03	1.00–1.05	**0.005**	1.03	1.00–1.05	**0.035**	1.03	0.99–1.06	0.097
Male sex	0.79	0.46–1.36	0.414	–					
Previous COVID-19	1.04	0.77–1.41	0.773	–					
Charlson comorbidity per 1 point increase	1.17	1.05–1.31	**0.003**	1.09	0.96–1.24	0.161			
Severe immunocompromission	1.53	0.82–2.86	0.179	–					
Site of infection treated with surgical source control	0.91	0.48–1.74	0.792	–					
SOFA score per 1 point increase	1.07	0.98–1.16	0.095	–					
PITT bacteriemia score	1.20	0.67–2.15	0.534	–					
Septic shock at presentation	1.82	1.06–3.11	**0.028**	1.93	1.05–3.53	**0.033**	2.81	1.35–5.84	**0.005**
Acute kidney injury at presentation	1.30	0.74–2.27	0.358	–					
Acute respiratory failure at presentation	1.49	0.87–2.54	0.142	–					
Time to appropriate antimicrobial therapy									
Within 24 h from infection onset	1			1					
From 24 to 72 h from infection onset	1.61	0.75–3.42	0.216	1.64	0.75–3.59	0.210			
After 72 h from infection onset	2.43	1.16–5.12	**0.019**	2.42	1.11–5.25	**0.025**			
Cefiderocol-based antibiotic therapy	0.51	0.28–0.94	**0.031**	0.49	0.25–0.93	**0.029**	0.53	0.27–0.98	**0.047**
Antibiotic therapy including sulbactam	0.98	0.55–1.77	0.972	–					
Antibiotic therapy including fosfomycin	0.43	0.22–0.81	**0.010**	–					
Antibiotic therapy including tigecycline	1.65	0.95–2.85	0.070	–					
Monotherapy vs combotherapy	0.81	0.39–1.66	0.570	–					

IPTW inverse probability treatment weighting

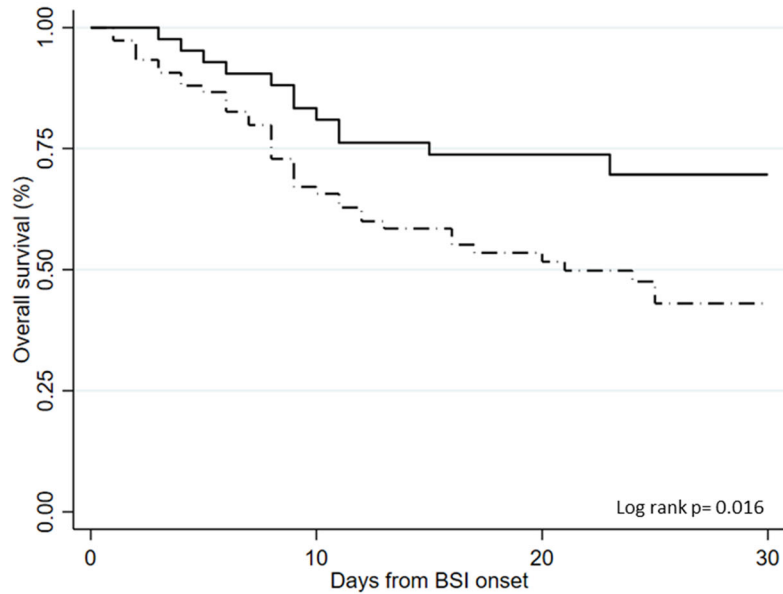Boldface means statistically significant ($p < 0.05$)
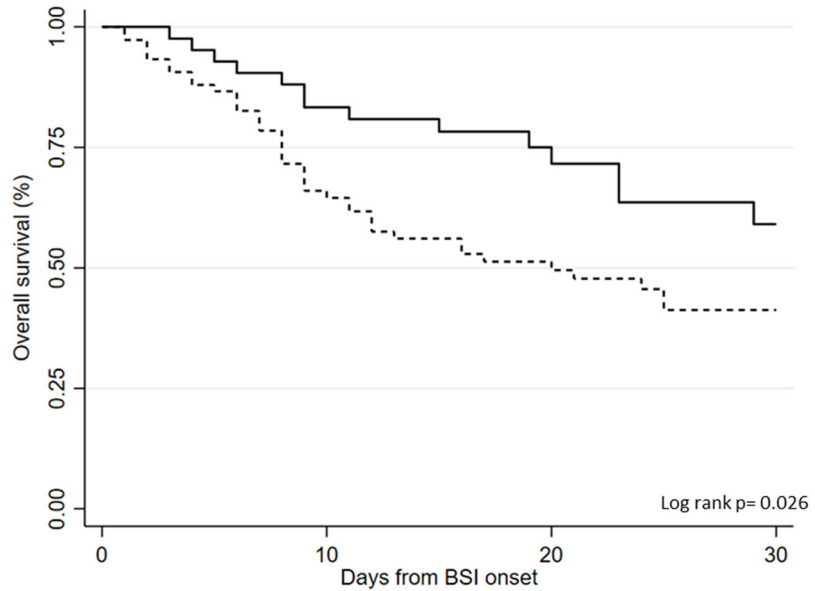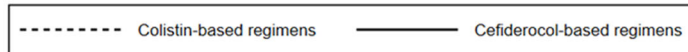
◄**Fig. 2** Kaplan-Meier survival curves of 30-day all-cause mortality (**a**) and infection-related mortality (**b**)

95% CI 1.05–3.53), and delayed targeted therapy (> 72 h from the BSI onset: aHR = 2.42, 95% CI 1.11–5.25); contrarily, the use of cefiderocol-based antibiotic therapy was protective (aHR = 0.49, 95% CI 0.25–0.93).

Similar results were also obtained by performing similar analysis exploring predictors of 30-day infection-related morality (Supplementary Table 4).

The 90-day all-cause mortality was also explored in our population: overall, 67 (58%) of patients died within 90 days of infection onset (64% vs 42% in the colistin versus cefiderocol group, respectively, p = 0.032).

Propensity Score Adjusted Analysis of 30-Day Mortality

To better evaluate the impact of treatment with cefiderocol or colistin on 30-day mortality risk, the whole cohort was balanced with a propensity score analysis by applying an IPTW-adjusted model (see Methods section: Supplementary Table 1 and Supplementary Table 2).

The multivariable Cox regression analysis was than newly performed on the pseudo-population (Table 3) balanced for age, sex, time to appropriate antimicrobial therapy, BSI treated with surgical source control, and use of mono- or combo-therapy. The analysis confirmed that septic shock (aHR = 2.81, 95% CI 1.35–5.84) was associated with mortality, while cefiderocol-based therapy was an independent predictor of a better outcome (aHR = 0.53, 95% CI 0.27–0.98).

Finally, to graphically explore the association between the two types of regimens and mortality, Kaplan-Meier curves were made for 30-day all-cause mortality (Fig. 2a) and 30-day infection-related mortality (Fig. 2b).

DISCUSSION

To the best of our knowledge, this is the largest observational study currently available designed to compare the all-cause and infection-related mortality of colistin- and cefiderocol-based regimens for monomicrobial CRAB-BSI.

Compared to colistin, an independent protective effect of cefiderocol on mortality risk was documented in this study, even after adjusting the survival model for patients' probability of receiving cefiderocol or colistin (the propensity score). In fact, given the observational nature of the study and the non-randomized prescription of therapies, which was solely based on clinical judgment, an IPTW regression analysis was also performed to balance the study cohort and improve the robustness of analysis.

Although the results of the CREDIBLE trial [12] evidenced higher mortality in the cefiderocol treatment group than in the "best-available therapy" arm, data deriving from observational studies are in line with our work, suggesting a valuable place for cefiderocol in therapy for CRAB infections. To date, only three studies have directly compared cefiderocol-based therapies with other current treatment options for severe CRAB infections [9–11] with a sample size comparable to this study but a different design.

In particular, the study of Pascale et al. [9] included a multicentric cohort of 107 patients admitted to the ICU for severe COVID-19 who developed a CRAB infection (pneumonia or bloodstream infection) during the ICU stay. The study explored the 28-day all-cause mortality of patients treated with cefiderocol (used in monotherapy in 100% of cases) versus other regimens composed of different drugs. The mortality rate reached 57% and was probably influenced by concurrent severe COVID-19, which was the primary cause of admission of patients to the ICU: indeed, although cefiderocol was apparently protective in this study (although this was not statistically significant), the only independent predictor of mortality was the SOFA score, which was significantly higher

in subjects who died at the end of follow-up (median SOFA: 10 versus 6 points).

Contrarily, the studies conducted by Falcone et al. [10] and Russo et al. [11] directly compared cefiderocol versus colistin and showed a significant beneficial effect of the new siderophore cephalosporin over the older drug. Of note, the study of Falcone et al. [10] is the largest work available and analyzed the outcome of 124 subjects (79 BSI and 35 VAP), identifying a mortality rate of 55.8% versus 35% in colistin versus cefiderocol group, respectively. However, in the subgroup analysis, the protective effect of cefiderocol was confirmed only in the BSI group. Importantly, in this study, cefiderocol and colistin were used in either mono- or combo-therapy, but the design and sample size were not suitable for exploring the impact of different combination therapies on mortality. In addition, despite the relevant sample size, some important limitations were noticed as stated by the authors, including several polymicrobial infections and cases of concurrent COVID-19 and CRAB infections.

Finally, the study of Russo et al. [11] was conducted on a sample of 73 VAPs with associated BSI caused by CRAB (54 and 19 in the colistin and cefiderocol group, respectively). Herein, the mortality difference between the two arms was significantly higher (14-day mortality = 5% versus 76% and 30-day mortality = 32% versus 98% in the cefiderocol and colistin arm, respectively) than mortality difference emerging from previous studies analyzed. In addition, in this study, cefiderocol was used in combination in 100% of cases; however, only the association with fosfomycin was significantly associated with a better outcome in both the unadjusted and IPTW-adjusted populations. Finally, it should be noted that several COVID-19 and polymicrobial infections were also included in this study.

Compared with the aforementioned works, our study presents some noticeable aspects of novelty. First, in this work only monomicrobial infections were included, limiting the known biasing effect of polymicrobial infections [16]. Second, only patients with documented BSI were included to minimize the risk of overestimating CRAB infections by including patients with only a colonization (for instance, in case of CRAB isolation from non-sterile samples) and minimize the potential biasing effect of inadequate penetration of cefiderocol or colistin in deep sites, including the lower respiratory tract [17].

Third, to exclude patients with additional mortality risk related to other infectious diseases, subjects with concurrent COVID-19 or other serious concomitant infections were not analyzed. Fourth, only subjects treated with colistin or cefiderocol as first-line therapy were included, strengthening the validity of the comparison. Last, in this study both "all-cause" and "infection-related" mortalities are separately presented: given the complexity of the "real-world" population of patients affected by CRAB-BSI, evaluating the real impact of infection on mortality is clinically meaningful especially compared with all-cause mortality. In this case, the two endpoints were almost overlapping, demonstrating the clinical significance of monomicrobial CRAB-BSI on risk of poor outcome of patients.

Interestingly, in our work, the use of mono- or combo-therapy was not associated with a different outcome; however, a protective effect of fosfomycin was noticed with the univariable Cox model. Conversely, the addition of sulbactam did not modify the outcome, and the use of tigecycline increased the mortality risk. Nevertheless, the sample size limits the possibility to draw conclusions on this topic: further powered studies should explore these data. In fact, one of the major areas of concern regarding cefiderocol monotherapy is the potential emergence of in vivo resistance in the course of therapy, which may be reduced by using combination therapies [18].

Additional risk factors for mortality emerging from this study were older age, septic shock, and delayed appropriate antimicrobial therapy, as frequently reported by other studies conducted on gram-negative bacterial BSI [2, 9–11, 19, 20]. Importantly, to improve the outcome of BSIs, many additional factors are determinant: for instance, a multi-step bundle approach to manage gram-negative bacterial BSI may be beneficial, improving the identification of deep sites of infections and rate of early

targeted antimicrobial therapy and allowing rapid discontinuation of antibiotics in cases of uncomplicated BSIs, preventing adverse events [21].

Finally, by discussing secondary endpoints, it is interesting to notice the incidence of CRAB-BSI 90-day recurrence (7% of initial population) and 90-day all-cause mortality (58%) in our study. These results show the complexity of the "real-life" population experiencing BSI caused by multidrug-resistant organisms, often burdened by a high rate of mortality and infection relapse. Although this study was not primarily designed to evaluate these endpoints, their numerical relevance supports the need to further explore and investigate how to clarify the implications of BSI, from both a clinical and a methodological point of view [22].

Moreover, regarding secondary outcomes, it should be mentioned that the rate of adverse events to antibiotic therapy was significantly lower in the cefiderocol compared with colistin group: this reinforces the known safety profile of the drug [8], which is in line with other beta-lactams and cephalosporins.

To better read these data, some important limitations of the work should be acknowledged. First, the retrospective nature of the study and relatively small sample size may reduce the generalizability of results, although the sample size was sufficient to address the primary outcome of the study. Second, the decision to start cefiderocol or colistin-containing regimens was non-randomized but based on the physician's decision. This could generate a so-called "channeling bias," defined as the potential allocation of a certain drug in the groups of patients with possibly better prognoses. However, a propensity score analysis was performed to minimize this bias. Third, several patients received combination therapies with different antibiotics, including fosfomycin, ampicillin/sulbactam, and tigecycline; the impact of these therapies probably biased results, but the design of the study was not adequate to explore this point. Finally, all patients who received < 48 h of therapy or deceased within 48 h from treatment initiation were excluded from further analysis. Although this potentially introduces a selection bias, it also limits the risk of including patients who survived or died for causes different or independent from the BSI or the treatments administered, limiting in turn the risk of producing false statistical associations.

In conclusion, this work strengthens the hypothesis of a valuable role of cefiderocol for the therapy of CRAB-BSI, especially in the current context of limited treatment options. Further studies should confirm these findings and explore the other areas of uncertainties, including the role of mono- and combination therapies and the risk of in vivo emergence of resistance.

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study are available from the corresponding author on reasonable request.

Ethical Approval. This study was performed with the formal approval by the Ethical Committee of University Hospital-Polyclinic of Bari (study number: 6527) and in accordance with the Declaration of Helsinki and national and institutional standards. Data were previously pseudo-anonymized, according to the requirements set by the Italian data protection code (leg. decree 196/2003) and European general data protection regulation (GDPR 2016/679). The patients provided written informed consent (available from the corresponding author) for the use of their data for research purposes.

Conflict of Interest. The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained. The manuscript was written by the lead/corresponding author, and the authors have no financial conflicts of interest to declare related to this work.

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