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Efficacy of cefiderocol- vs colistin-containing regimen for treatment of bacteraemic ventilator-associated pneumonia caused by carbapenem-resistant *Acinetobacter baumannii* in patients with COVID-19

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ABSTRACT

Introduction: Ventilator-associated pneumonia (VAP) caused by carbapenem-resistant *Acinetobacter baumannii* (CRAB) in patients hospitalized in intensive care units (ICUs) is an important and challenging complication, including in patients with coronavirus disease 2019 (COVID-19). Considering the poor lung penetration of most antibiotics, including intravenous colistin due to the poor pharmacokinetics/pharmacodynamics at the infection site, the choice of the best antibiotic regimen is still being debated.

Methods: This single-centre, observational study was conducted from March 2020 to August 2022, and included all patients hospitalized consecutively with VAP and concomitant bloodstream infection due to CRAB in the COVID-ICU. The main goal of the study was to evaluate risk factors associated with survival or death at 30 days from VAP onset. A propensity score for receiving therapy was added to the model.

Results: During the study period, 73 patients who developed VAP and concomitant positive blood cultures caused by CRAB were enrolled in the COVID-ICU. Of these patients, 67 (91.7%) developed septic shock, 42 (57.5%) had died at 14 days and 59 (80.8%) had died at 30 days. Overall, 54 (74%) patients were treated with a colistin-containing regimen and 19 (26%) were treated with a cefiderocol-containing regimen. Cox regression analysis showed that chronic obstructive pulmonary disease and age were independently associated with 30-day mortality. Conversely, cefiderocol-containing regimens and cefiderocol + fosfomycin in combination were independently associated with 30-day survival, as confirmed by propensity score analysis.

Conclusions: This real-life study in patients with bacteraemic VAP caused by CRAB provides useful suggestions for clinicians, showing a possible benefit of cefiderocol and its association with fosfomycin.

1. Introduction

In recent years, ventilator-associated pneumonia (VAP) due to carbapenem-resistant Gram-negative bacteria such as *Acinetobacter baumannii* (CRAB) has been observed increasingly among hospitalized patients admitted to the intensive care unit (ICU) [1,2]. Moreover, the pandemic caused by severe acute respiratory syndrome coronavirus-2 increased the role of Gram-negative pathogens as superinfections in critically ill patients, including CRAB. CRAB has been defined one of the top-priority pathogens by the World

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Health Organization. Specifically in Italy, increased incidence of multi-drug-resistant (MDR) *A. baumannii* has been observed in recent years [3].

A. baumannii are usually resistant to carbapenems and other classes of antibiotics. In cases of resistance, there are limited therapeutic options, and these often result in inappropriate therapy and a subsequent negative impact on outcome [4]. Of note, data about the pharmacokinetics/pharmacodynamics (PK/PD) of intravenous colistin showed poor epithelial lung fluid penetration, suggesting a possible role of aerosolized administration of colistin as adjunctive therapy for the treatment of MDR Gram-negative pneumonia [2]. A mortality rate of >60% has been reported, particularly in patients with septic shock [5].

New agents with microbiological activity against MDR *A. baumannii* strains have been developed recently [6–8]. Results from the CREDIBLE-CR study comparing cefiderocol with the best-available therapy in patients with carbapenem-resistant carbapenem-resistant Gram-negative status showed an unexpected increase in mortality in the subset of patients with CRAB [9]. However, real-life experiences from case series including patients with carbapenem-resistant Gram-negative bacteria were not focused solely on CRAB [10]. Thus, a gap between the results from the CREDIBLE-CR study and real-world observations continues to exist, and data on the efficacy of cefiderocol in patients with CRAB infections are still lacking, with there being few observations among patients with VAP [11]. Moreover, data about the efficacy of cefiderocol in patients with severe coronavirus disease 2019 (COVID-19) are not available.

The aim of this study was to evaluate the impact of cefiderocol-containing regimens compared with colistin-containing regimens on the outcome of patients with VAP and concomitant bloodstream infection (BSI) caused by CRAB infection in patients with COVID-19.

2. Methods

2.1. Study design and patient selection

This single-centre, retrospective, observational study included patients with CRAB infections admitted consecutively from March 2020 to August 2022 to the COVID-ICU of the tertiary care 'Mater Domini' Hospital of 'Magna Graecia' University of Catanzaro in Italy.

The inclusion criteria were: (1) age ≥18 years; (2) blood culture and respiratory tract culture positive for CRAB; and (3) clinical signs and symptoms consistent with VAP. Polymicrobial aetiology was excluded and only one episode of CRAB infection was reported for each patient in the study period. All patients were managed by the same team of physicians, and all antimicrobial therapies were selected according to clinical judgement by infectious disease specialists. However, all complete data were extracted retrospectively. The study was conducted according to the principles stated in the Declaration of Helsinki, and was approved by the local ethics committee. Collected data were anonymized and informed consent was waived.

Patient data were collected from medical charts and from computerized hospital databases or clinical charts using a pre-established questionnaire. The following data were reviewed: demographics; clinical and laboratory findings; comorbid conditions; microbiological data; duration of ICU and hospital stay; any MDR infection during hospitalization; treatment and procedures [e.g. non-invasive ventilation (NIV), mechanical ventilation, continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation (ECMO)] carried out during hospitalization and/or in the 30 days prior to infection; class of antibiotics received at admission and/or during admission before a positive culture of a biological sample was obtained; sequential organ failure assessment (SOFA) score at time of infection; CRAB colonization or colonization during hospitalization; source of infection and its adequate control; antibiotic regimens used for CRAB infection; specific therapies for treatment of COVID-19; development of septic shock; and 14- and 30-day mortality.

2.2. Definitions

Infections were defined according to the standard definitions of the European Centre for Disease Prevention and Control [12].

Infection was defined as the presence of at least one positive culture from the lung for CRAB in individuals with signs and symptoms consistent with pneumonia [13], and concomitant isolation of CRAB from blood was mandatory. Colonization was considered as positive culture without concomitant signs and symptoms of infection. Moreover, isolation from urine, skin swabs or biopsies, or abdomen was also recorded. Infection onset was defined as the date of development of signs and symptoms of VAP.

VAP was considered as hospital-aquired pneumonia that developed >48 h after endotracheal intubation. The diagnosis of severe pneumonia was based on the Infectious Diseases Society of America/American Thoracic Society consensus guidelines, namely one major criterion (invasive mechanical ventilation or septic shock with the need for vasopressors) or three minor criteria [respiratory rate >30 breaths/min, partial pressure of arterial oxygen/fraction of inspired oxygen ratio <250, multilobar infiltrates, confusion/disorientation, uraemia (blood urea nitrogen >20 mg/dL), leukopenia (white blood cell count <4000 cells/mm^3), thrombocytopenia (platelet count <100,000 cells/mm^3), hypothermia (core temperature <36°C) or hypotension requiring aggressive fluid resuscitation] [14].

Septic shock was defined according to international definitions [15]. The severity of clinical conditions was determined using the SOFA score calculated at the time of infection onset. The length of hospital and ICU stay was calculated as the number of days from the date of admission to the date of discharge or death. The Charlson Comorbidity Index was calculated based on previous definitions [16].

A. baumannii colonization was evaluated weekly through active surveillance in hospitalized patients. Time to negativization of blood cultures was considered to be the number of days from the start of targeted therapy to the first negative follow-up blood culture, and was considered as microbiological failure if there was persistence of positive blood culture >5 days after the beginning of targeted therapy.

2.3. Microbiological identification

The identification of MDR *A. baumannii* strains was based on local laboratory techniques. From positive cultures, Gram staining and a rapid identification protocol were adopted. The bacterial pellet obtained directly from positive cultures was used for MALDI-TOF MS (Bruker Daltonics, Billerica, MA, USA) identification and for molecular analysis. The Vitek 2 automated system (bioMérieux, Marcy l'Etoile, France) was used for isolate identification and antimicrobial susceptibility testing. Antibiotic susceptibility tests for meropenem, amikacin, fosfomycin and trimethoprim/sulfamethoxazole were performed with the Vitek 2 automated system, whereas the determination of colistin resistance was obtained by dilution in broth. Minimum inhibitory concentrations (MICs) were established according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints, including cefiderocol MIC values that were determined using Kirby–Bauer disc diffusion test on regular unsupplemented Mueller-Hinton agar (Liofilchem, Roseto degli Abruzzi, Italy), and

discs impregnated with 30 µg of drug (Liofilchem) were used to assess sensitivity to cefiderocol [17]. A multiplex polymerase chain reaction combined with array detection, using an automated closed system that isolates, amplifies and detects nucleic acid for multiple causative pathogens within a single specimen in one step (FilmArray, BioFire Diagnostics, BioMérieux, Salt Lake City, UT, USA), was used to identify the possible organisms in respiratory samples and blood cultures, when appropriate, with detection of the corresponding bacterial resistance genes within 60–90 min.

2.4. Antimicrobial treatment evaluation

Empirical antibiotic regimens were selected according to clinical judgement by infectious disease specialists, and were subsequently modified according to the microbiological reports. During the study period, the usual antimicrobial dosages were as follows: for colistin, a loading dose of 9 million IU followed by 4.5 million IU every 12 h; for cefiderocol, a dosage of 2 g every 8 h (or every 6 h if creatinine clearance >120 mL/min); for tigecycline, a loading dose of 100 mg followed by 50 mg every 12 h; for gentamicin, a dosage of 5 mg/kg every 24 h; for rifampin, a dosage of 10 mg/kg/day; for meropenem, a dosage of 2 g every 8 h or 1.5 g every 6 h; for fosfomycin, a loading dose of 8 g followed by 12–24 g/day divided into doses every 6–8 h; for ampicillin/sulbactam, 3 g every 6 h; for trimethoprim/sulfamethoxazole, 15–20 mg/kg/day divided into doses every 6 h; and for colistin aerosol, 2 million IU every 8 h. When appropriate, the antimicrobial dosage was modified according to creatinine clearance and the use of CRRT and/or ECMO.

Depending on the number of drugs used (one or more than one), treatment regimens were classified as either monotherapy or combination therapy. Empirical antibiotic therapy, defined as antimicrobial chemotherapy implemented within 24 h of the onset of infection, was assessed along with targeted antibiotic therapy, defined as antimicrobial treatment based on in-vitro CRAB isolate susceptibility. Drugs in targeted therapy must have been administered for at least 50% of the total duration of therapy (except for patients who died, who were included if they received at least 1 complete day of therapy).

2.5. Primary endpoint and statistical analysis

The endpoint of this study was to evaluate the impact of cefiderocol-containing regimens compared with colistin-containing regimens on the outcome of patients with VAP and concurrent bacteraemia caused by CRAB infection in patients with COVID-19. Risk factors associated with 30-day survival or death after VAP onset were also examined.

Continuous variables were reported as median and interquartile range (IQR) or mean with standard deviation (±SD) according to normal distribution. The normality of distributions was evaluated using the Kolmogorov–Smirnov test. To detect significant differences between groups, Chi-squared test or Fisher's exact test was used for categorical variables, and the two-tailed Student's *t*-test or Mann–Whitney *U*-test was used for continuous variables, as appropriate. In a multi-variate analysis of survival, the Cox regression model, adjusted for confounding factors including sex and age, was tested using a proportional hazards model analysis with backward stepwise selection and $P<0.05$ for all variables to identify factors that were independently associated, and to determine the effects of all clinical and therapeutic variables on 30-day survival. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were reported.

To address the non-randomized treatment assignment, a propensity score (PS) for receiving therapy with fosfomycin was added to the model. The PS was calculated using a non-parsimonious multi-variate logistic regression model. Covariate parameters included to generate the PS were determined referring to all potential risk factors for death reported in previous studies [18] and included: age, sex, previous ICU admission, Charlson Comorbidity Index, type of infection, SOFA score, septic shock, ECMO and more than two comorbidities (Table S2, see online supplementary material).

Kaplan––Meier curves were used to determine survival at 30 days in patients treated with the antibiotic regimens. Survival curves for time-to-event variables, constructed using Kaplan–Meier estimates, were based on all available data and were compared using the log-rank test. Wald CIs and tests for HR were computed based on the estimated standard errors. Possible confounding factors and interactions were weighted during analysis. Statistical significance was established at $P\leq0.05$. All reported *p*-values are two-tailed. The results obtained were analysed using SPSS Version 20.0 (IBM Corp., Armonk, NY, USA).

3. Results

During the study period, 73 patients who developed VAP and concomitant positive blood cultures caused by CRAB were enrolled in the COVID-ICU. Of these patients, 67 (91.7%) developed septic shock, 42 (57.5%) had died at 14 days and 59 (80.8%) had died at 30 days. All *A. baumannii* strains were classified as extensively drug resistant (XDR) or pan-drug resistant (PDR).

Clinical characteristics and outcomes for all the study population are reported in the online supplementary material. Fifty-five (75.3%) patients were male, the median age was 60 (IQR 52–69) years, the median Charlson Comorbidity Index was 3 (IQR 1–4), nine (12.3%) patients exhibited a CRAB infection at ICU admission, and 47 (64.3%) patients showed CRAB colonization during hospitalization. The median duration of targeted therapy was 11.5 (IQR 7–15) days and the median length of ICU stay was 16 (IQR 11–28) days. In terms of specific therapy for COVID-19, all patients were treated with the standard dosage of dexamethasone (6 mg once daily); before ICU admission, only two patients (both died) underwent remdesivir therapy, while one patient (also died) underwent sotrovimab therapy. None of the patients enrolled in this study had received tocilizumab or other immunosuppressive therapies before CRAB infection.

Table 1 reports the antibiotic regimens used in targeted therapy for the cefiderocol-containing group and the colistin-containing group. Overall, 54 (74%) patients were treated using a colistin-containing regimen: 12 (22.2%) patients received colistin monotherapy, 12 (22.2%) patients received colistin plus meropenem plus tigecycline, and nine (16.6%) patients received colistin plus meropenem. Nineteen (26%) patients were treated with a cefiderocol-containing regimen: no patients were treated with cefiderocol as monotherapy, six (31.5%) patients received cefiderocol plus fosfomycin, three (15.8%) patients received cefiderocol plus fosfomycin plus tigecycline, and three (15.8%) patients received cefiderocol plus meropenem plus fosfomycin plus tigecycline. Finally, 33 (45.2%) patients were treated with colistin aerosol as adjunctive therapy.

Comparisons of clinical characteristics and outcomes for survivors and non-survivors at 30 days are reported in Table 2. Compared with survivors, non-survivors showed a higher median age (64 years vs 60 years; $P=0.031$), higher rates of chronic kidney disease (10.1% vs 0%; $P=0.013$) and chronic obstructive pulmonary disease (COPD) (25.4% s 7.1%; $P=0.026$), and longer time to negativization of blood cultures (4 days vs 2 days; $P=0.002$).

Table 3 shows Cox regression analysis of risk factors associated with death at 30 days. COPD (HR 1.4, 95% CI 1.3–12.2; $P=0.022$) and age (HR 1.12, 95% CI 1.01–1.1; $P=0.001$) were independently as-

Table 1
Antibiotic regimens used in targeted therapy.

Treatment regimens	*n*=73 patients (%)
Colistin-containing regimens	**54 (74)**
Colistin monotherapy	12 (22.2)
Colistin + meropenem + tigecycline	12 (22.2)
Colistin + meropenem	9 (16.6)
Colistin + tigecycline	6 (11.1)
Colistin + fosfomycin	3 (5.5)
Colistin + trimethoprim/sulfamethoxazole	3 (5.5)
Colistin + trimethoprim/sulfamethoxazole + meropenem + tigecycline	3 (6)
Colistin + meropenem + fosfomycin	2 (4)
Colistin + meropenem + tigecycline + ampicillin/sulbactam	2 (4)
Colistin + trimethoprim/sulfamethoxazole + tigecycline	2 (4)
Cefiderocol-containing regimens	**19 (26)**
Cefiderocol + fosfomycin	6 (31.5)
Cefiderocol + fosfomycin + tigecycline	3 (15.8)
Cefiderocol + meropenem + fosfomycin + tigecycline	3 (15.8)
Cefiderocol + trimethoprim/sulfamethoxazole	2 (10.5)
Cefiderocol + tigecycline	1 (5.2)
Cefiderocol + trimethoprim/sulfamethoxazole	1 (5.2)
Cefiderocol + ampicillin/sulbactam	1 (5.2)
Cefiderocol + fosfomycin + ampicillin/sulbactam	1 (5.2)
Cefiderocol + meropenem + fosfomycin + tigecycline + trimethoprim/sulfamethoxazole	1 (5.2)
Cefiderocol monotherapy	0
Colistin aerosol	**33 (45.2)**

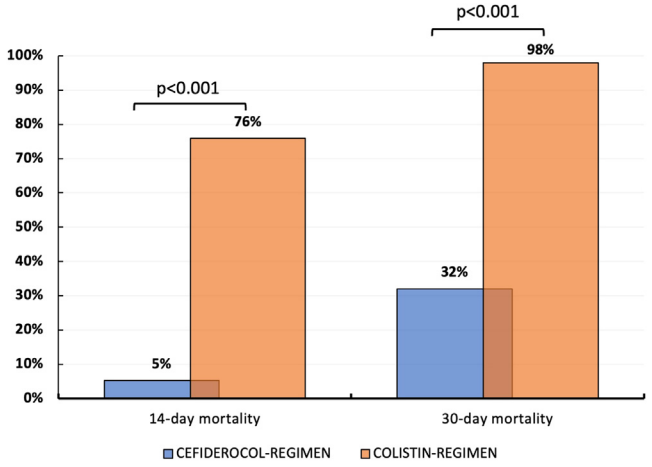

Fig. 1. Rates of 14- and 30-day mortality in patients treated with cefiderocol- or colistin-containing regimens.

sociated with 30-day mortality. Conversely, cefiderocol-containing regimens (HR 0.34, 95% CI 0.18–0.56; $P<0.001$) and cefiderocol plus fosfomycin combination therapy (HR 0.22, 95% CI 0.1–0.55; $P<0.001$) were independently associated with 30-day survival, as also confirmed by PS analysis (see online supplementary material).

Comparison between patients treated with cefiderocol- and colistin-containing regimens in targeted therapy is reported in Table 4. No differences were observed in relation to sex, age, comorbidities, septic shock or length of ICU stay. Patients treated with colistin-containing regimens showed higher rates of 14-day (75.9% vs 5.2%; $P<0.001$) and 30-day mortality (98.1% vs 31.5%; $P<0.001$) compared with patients treated with cefiderocol-containing regimens (Fig. 1).

Finally, Kaplan–Meier curves on 14-day ($P<0.001$) and 30-day ($P<0.001$) survival in patients treated with cefiderocol- or colistin-containing regimens are shown in Fig. 2.

4. Discussion

To the authors' knowledge, this is the largest study evaluating clinical outcome for patients with bacteraemic VAP caused by CRAB treated with cefiderocol- or colistin-based regimens in patients with COVID-19 in the ICU. This experience confirms the importance of superinfections caused by Gram-negative strains in the ICU, including those in patients with COVID-19 [19,20], but it is important to underline that these data also confirm the high rate of unfavourable outcomes in patients with CRAB BSI, especially in those developing a concomitant VAP [21]. Data from this study showed a possible benefit deriving from the use of a cefiderocol-based regimen for bacteraemic VAP caused by XDR or PDR *A. baumannii* strains.

Firstly, it is crucial to underline that COVID-19 represents an independent predictor of unfavourable outcome in ICU patients [21]. Age, Charlson Comorbidity Index, SOFA score, septic shock and the use of ECMO were evaluated carefully at PS analysis as potential independent risk factors for death. Moreover, in the multi-variate analysis of survival, the Cox regression model was adjusted for confounding factors including age that were recognized as important risk factors for mortality in patients with COVID-19, especially in ICU patients [22,23].

It is important to note that patients with CRAB bacteraemic VAP who received cefiderocol, including the subpopulation of patients treated with cefiderocol and fosfomycin combination therapy, showed lower 14- and 30-day mortality compared with patients who received a colistin-containing regimen. An increased rate of microbiological clearance was found in survivors compared with non-survivors (as demonstrated by time to negativization of blood cultures). In the study by Falcone et al. [11], microbiological failure occurred more frequently in patients who received cefiderocol monotherapy compared with combination therapy, with the development of resistance to cefiderocol in 8.5% of patients treated with this drug [24]. Conversely, no patients in the study population were treated with cefiderocol as monotherapy, and the development of resistance to cefiderocol was only identified in two patients treated with this drug. However, further studies are needed to assess risk factors associated with microbiological failure and in-vivo development of resistance in patients administered cefiderocol.

Another important strength of this study is that it only included patients who developed VAP with concomitant isolation of CRAB from blood cultures. This is a very important point because the diagnosis of VAP in patients with COVID-19 can be challenging, considering clinical and radiological findings in severe COVID-19 with or without superinfection (including VAP) [25]. Moreover, the exact role of colonization of the lower respiratory tract by CRAB is not well defined [21]. The analysis of bacteraemic VAP alone may therefore reduce this bias and make this population more homogenous, especially in patients affected by COVID-19. Moreover, polymicrobial aetiology was excluded.

This study represents a real-life analysis of patients with bacteraemic VAP caused by CRAB, and advocates some important considerations.

CRAB BSI remains a peculiar ICU-acquired infection, and VAP is recognized as the primary source of infection caused by CRAB in many studies, considering pneumonia as independently associated with higher risk of septic shock and unfavourable outcome. Indeed, in this analysis, all strains of *A. baumannii* were classified as XDR or PDR, reducing therapeutic options for treatment of this severe infection, in line with previous reports in Italy [3,5].

VAP remains a difficult-to-treat infection and, considering the poor lung penetration of most antibiotics, the choice of the best antibiotic regimen is still debated. Indeed, some antibiotics such as

Table 2
Comparison between survivors and non-survivors at 30 days.

Variables	Survivors n=14 (%)	Non-survivors n=59 (%)	P-value
Patient history factors and comorbidities			
Male, sex	11 (78.5)	44 (74.5)	0.124
Age, median, IQR (years)	60 (56.75–63.75)	64 (49–69)	**0.031**
Previous hospitalization (90 days)	0	3 (5)	0.083
Previous ICU admission (90 days)	0	1 (1.7)	0.322
More than two comorbidities	6 (42.8)	35 (59.3)	0.090
Cardiovascular disease	7 (50)	36 (61)	0.166
Heart failure	1 (7.1)	8 (13.5)	0.283
Charlson Comorbidity Index, median, IQR (points)	2.5 (1.25–3.75)	3 (1–4)	0.937
Diabetes	5 (35.7)	16 (27.1)	0.773
Chronic kidney disease	0	6 (10.1)	**0.013**
Dialysis	0	1 (1.7)	0.322
Neurological disease	1 (7.1)	12 (20.3)	0.088
Vasculitis	0	4 (6.7)	**0.044**
COPD	1 (7.1)	15 (25.4)	**0.026**
Solid tumour	0	3 (5)	0.083
Haematological malignancies	0	4 (6.7)	**0.044**
Chronic corticosteroid therapy	0	8 (13.5)	**0.003**
Previous *A. baumannii* colonization or infection	0	1 (1.7)	0.322
Intravascular device	0	5 (8.4)	**0.024**
Previous antibiotic therapy before hospitalization (30 days)	0	5 (8.4)	**0.023**
Characteristics at time of infection			
Fever	1 (7.1)	6 (10.1)	0.143
PaO_2/FiO_2, median, IQR	114.5 (87.675–129.75)	135.05 (103.25–204.25)	0.148
WBC, median, IQR ($x10^3/\mu L$)	13.29 (10.4925–17.455)	14.965 (10.14–21.485)	0.120
Creatinine, median, IQR (mg/dL)	0.84 (0.6475–1.0675)	0.91 (0.515–1.275)	0.597
PTL, median, IQR ($x10^3/\mu L$)	163 (136–270)	228 (172.5–336.5)	0.072
CRRT	2 (14.2)	11 (18.6)	0.695
ECMO	6 (42.8)	15 (25.4)	0.256
SOFA score at admission, median, IQR (points)	10.5 (10–11.75)	9 (8.25–11)	0.071
PCT, median, IQR (ng/mL)	0.375 (0.2275–2.33)	0.37 (0.195–1.215)	0.931
Serum lactate level, median, IQR (mmol/L)	2.29 (1.48–3.42)	2.92 (1.51–3.745)	0.600
CRP, median, IQR (mg/dL)	150 (70–234.5)	95.4 (34.975–150.25)	0.111
Colonization and/or infection at admission and during hospitalization			
A. baumannii colonization at admission	3 (21.4)	11 (18.6)	0.911
Colonization by other pathogens at admission	6 (42.8)	16 (27.1)	0.372
A. baumannii infection at admission	1 (7.1)	8 (13.5)	0.454
Time to negativization of blood cultures, median, IQR (days)	2 (1–4.75)	4 (3–7)	**0.002**
A. baumanii colonization during hospitalization	13 (92.8)	34 (57.6)	**0.042**
Previous and targeted antibiotic therapy during hospitalization			
Duration of previous therapy, median, IQR (days)	10.5 (6.5–12)	9 (5–13)	0.664
Duration of targeted therapy, median, IQR (days)	13 (10–14)	11 (6–15)	0.450
Outcomes			
Septic shock	14 (100)	53 (89.8)	**0.013**
Length of ICU stay, median, IQR (days)	22.5 (15–28.75)	15 (7.5–27)	0.977
Length of hospitalization, median, IQR (days)	26.5 (20.75–33.75)	27 (15.5–37.5)	0.182

A. baumannii, Acinetobacter baumannii; IQR, interquartile range; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; WBC, white blood cells; PTL, platelets; PICC, peripherally inserted central catheter; CVC, central venous catheter; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; SOFA, sequential organ failure assessment; PCT, procalcitonin; CRP, C-reactive protein.

Table 3
Cox regression analysis on risk factors associated with death at 30 days and propensity score analysis.

Variables	Adjusted HR (95% CI)	P-value
COPD	1.4 (1.3–12.2)	0.022
Age	1.12 (1.01–1.1)	0.001
Cefiderocol-containing regimens (colistin-containing regimens as reference variable)	0.34 (0.18–0.56)	<0.001
Cefiderocol – fosfomycin	0.22 (0.1–0.55)	<0.001
Propensity score analysis		
Cefiderocol-containing regimens (IPTW-adjusted)	0.44 (0.22–0.66)	<0.001
Cefiderocol plus fosfomycin (IPTW-adjusted)	0.33 (0.12-0.54)	<0.001

COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval; IPTW, inverse probability of treatment weighting.

colistin and aminoglycosides should probably be avoided in cases of CRAB-induced pneumonia, considering the poor lung penetration of these drugs [26,27]. Moreover, EUCAST recommendations based on recent observations [28] warned of potential false susceptibility to colistin in approximately 50% of *A. baumannii* strains using automated systems or E-tests. Therefore, the very high rates of mortality observed in the study population and in published studies [3,5,21,29] may also be attributed to a reported false susceptibility to colistin in patients for whom physicians were confident in prescribing a colistin-based regimen.

Different antibiotic combinations have been studied for the treatment of severe infections caused by CRAB, suggesting the advantage of various combinations based on high in-vitro synergy rates. A combination of carbapenem plus colistin was one of the

Table 4
Comparison between cefiderocol regimen and colistin regimen in targeted therapy.

Variables	Cefiderocol regimen, *n*=19 (%)	Colistin regimen, *n*=54 (%)	*P*-value
Patient history factors and comorbidities			
Male sex	5 (26.3)	13 (24)	0.879
Age, median, IQR (years)	61 (52.5–70.5)	60 (52.5–65)	0.755
Previous hospitalization (90 days)	0	3 (5.5)	0.083
Previous ICU (90 days)	0	1 (1.8)	0.322
Moe than two comorbidities	13 (68.4)	28 (51.8)	0.391
Cardiovascular disease	15 (78.9)	28 (51.8)	0.060
Heart failure	2 (10.5)	7 (12.9)	0.765
Charlson Comorbidity Index, median, IQR (points)	2.6 (1.25–3.75)	2.9 (1–4)	0.216
Diabetes	6 (31.5)	15 (27.7)	0.771
Chronic kidney disease	2 (10.5)	4 (7.4)	0.760
Dialysis	0	1 (1.8)	0.323
Neurological disease	2 (10.5)	11 (20.3)	0.219
Vasculitis	1 (5.2)	3 (5.5)	0.901
COPD	6 (31.5)	10 (18.5)	0.359
Solid tumour	1 (5.2)	2 (3.7)	0.838
Haematological malignancies	2 (10.5)	2 (3.7)	0.411
Chronic corticosteroid therapy	1 (5.2)	7 (12.9)	0.420
Previous *A. baumannii* colonization or infection	0	1 (1.8)	0.323
Intravascular devices	1 (5.2)	4 (7.4)	0.736
Previous antibiotic therapy before hospitalization (30 days)	0	5 (9.2)	**0.024**
Characteristics at time of infection			
Fever	1 (5.2)	6 (11.1)	0.916
PaO_2/FiO_2, median, IQR	194 (59–244.4)	119 (101–145)	0.566
WBC, median, IQR ($x10^3/\mu L$)	14.07 (10.575–17.815)	15.13 (9.9–21.23)	0.977
Creatinine, median, IQR (mg/dL)	0.92 (0.5–1.445)	0.88 (0.555–1.0975)	0.976
PTL, median, IQR ($x10^3/\mu L$)	205 (162–264)	217.5 (163–322.75)	0.380
CRRT	3 (15.7)	10 (18.5)	0.789
ECMO	4 (21)	17 (31.4)	0.372
SOFA score at admission, median, IQR (points)	9 (9–10)	10 (9–11)	0.733
PCT, median, IQR (ng/mL)	0.33 (0.18–1.21)	0.425 (0.21–1.2575)	**0.031**
Serum lactate, median, IQR (mmol/L)	3.59 (3.435–3.745)	2.29 (1.43–3.42)	**0.041**
CRP, median, IQR (mg/dL)	66.2 (35.15–147.5)	98 (54–169)	0.622
Colonization and/or infection at admission and during hospitalization			
A. baumannii colonization at admission	3 (15.7)	11 (20.3)	0.651
Colonization by other pathogens at admission	6 (31.5)	16 (29.6)	0.883
A. baumannii infection at admission	2 (10.5)	7 (12.9)	0.778
Time to negativization of blood cultures, median, IQR (days)	5 (4–7.5)	4 (2–6)	0.093
A. baumanii colonization during hospitalization	11 (57.8)	36 (66.6)	0.880
Previous and targeted antibiotic therapy during hospitalization			
Duration of previous therapy, median, IQR (days)	9 (5.5–12)	9 (5–13)	0.912
Duration of targeted therapy, median, IQR (days)	12 (9–14)	11 (6–15)	0.566
Outcomes			
Length of ICU stay, median, IQR (days)	19 (10–29.5)	15 (11–28)	0.609
Length of hospitalization, median, IQR (days)	31 (23–38.75)	25 (18–35)	0.671
Septic shock	18 (94.7)	49 (90.7)	0.548
Mortality at 14 days	1 (5.2)	41 (75.9)	**<0.001**
Mortality at 30 days	6 (31.5)	53 (98.1)	**<0.001**

A. baumannii, Acinetobacter baumannii; IQR, interquartile range; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; WBC, white blood cells; PTL, platelets; PICC, peripherally inserted central catheter; CVC, central venous catheter; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; SOFA, sequential organ failure assessment; PCT, procalcitonin; CRP, C-reactive protein.

most important options for treatment of CRAB infections [30]. A subgroup analysis on patients with *Acinetobacter* spp. infections reported that colistin monotherapy was associated with a better outcome compared with colistin and meropenem combination therapy [31]. It is important to underline that these studies comparing the efficacy of monotherapy (mainly colistin) with combination regimens for *A. baumannii* infections included a spectrum of different severe infections, such as VAP, but these were not always associated with bacteraemia.

The role of cefiderocol for the treatment of CRAB is actually limited by data from CREDIBLE-CR that showed more deaths occurring in the subgroup of patients with CRAB infections [9]. However, it is important to emphasize that, in the present study, patients with CRAB infections had a higher frequency of septic shock and were more frequently hospitalized in the ICU, suggesting a higher baseline mortality risk. In this analysis, the comparison between patients treated with cefiderocol- or colistin-containing regimens showed a very homogenous population (as demonstrated by SOFA score, lactate level and other parameters). However, new data showed that combination therapy with colistin and meropenem was not superior to colistin monotherapy for the treatment of pneumonia or BSI caused by MDR pathogens, including XDR *A. baumannii* [32].

Thus, the role of antibiotic therapy in influencing the risk of mortality in patients with bacteraemic VAP is very difficult, and it is possible that penetration of cefiderocol into the epithelial lining fluid (ELF) is suboptimal at current dosages [33]. In a recent study on critically ill patients with pneumonia, cefiderocol reached ELF concentrations that were sufficient to treat Gram-negative bacteria with an MIC of 4 mg/L [34]. However, the ELF penetration of antibiotics is variable after systemic administration, and PK data are necessary to evaluate the usefulness of therapeutic drug monitoring in this specific category of patients. It is interesting to note that the study by Gatti et al. [35] showed that the suboptimal attainment of PK/PD targets for cefiderocol could lead to microbiological failure of cefiderocol treatment of critically ill patients affected by XDR *A. baumannii* VAP. Further data are necessary to assess the correct dosage of cefiderocol in critically ill patients with altered

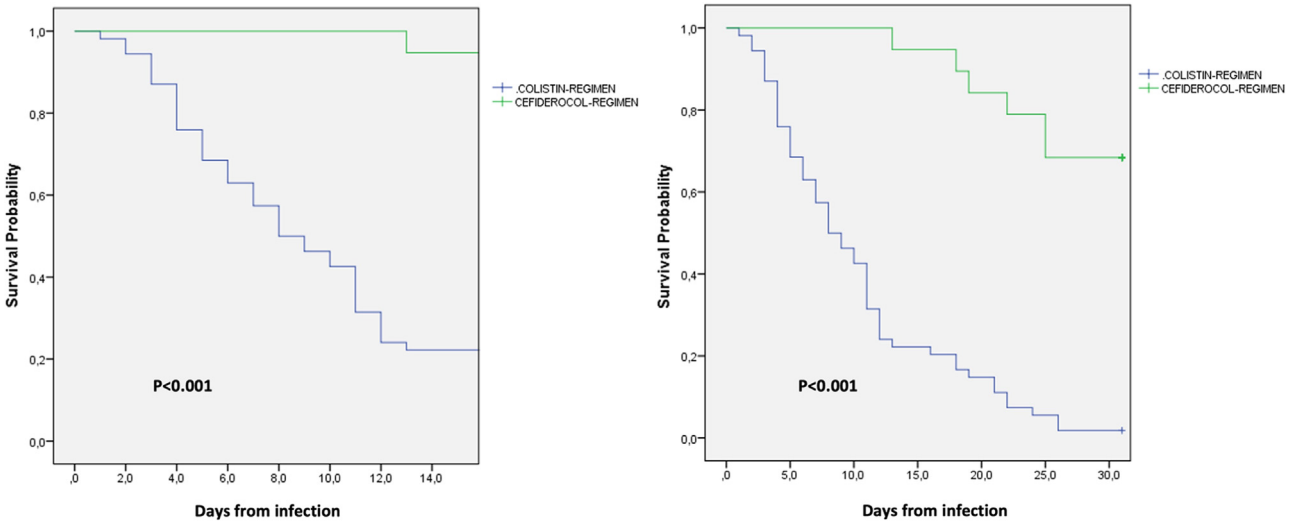

Fig. 2. Kaplan–Meier curves for 14- and 30-day survival in patients treated with cefiderocol- or colistin-containing regimens.

binding proteins, increased distribution volume and augmented renal clearance.

It should be noted that the study data showed the potential role of fosfomycin in association with cefiderocol. A previous study also showed the efficacy of a fosfomycin-containing regimen for treatment of severe pneumonia caused by CRAB [36]. Many in-vitro studies have also suggested a possible role for intravenous fosfomycin for the treatment of this infection [7,37]. Fosfomycin may be an effective adjunctive therapy for pneumonia caused by MDR/XDR *A. baumannii* strains, considering the synergistic effect reported in in-vitro studies. An important study has shown that fosfomycin achieved effective concentrations in infected lung tissue [38], and this drug has been introduced as a treatment option for the infection caused by CRAB [39,40]. However, fosfomycin concentrations in pneumonia should be correlated *in vivo* with MICs of fosfomycin for MDR *Acinetobacter* spp.

This study has some important limitations that should be acknowledged. Firstly, the observational nature of the study and the relatively small sample size mean that the analysis is intrinsically limited, including selection of antimicrobial therapies based on the clinical judgement of physicians. Secondly, the underlying mechanisms of resistance in these strains were not assessed routinely, and in-vitro synergistic combinations were not performed, except for a few cases. Third, this study was performed in a single geographical area of Europe (Italy) with a high incidence of MDR *A. baumannii* infections, and these results may not therefore be representative of other European or non-European centres. Therefore, all conclusions about the efficacy of the therapeutic regimen, outside of randomized trials, should be validated. Fourth, a direct relation between the MICs of antibiotics used in the different regimens and the outcome of the study population was not evaluated in the final analysis. Finally, only 20/54 (37.1%) patients who were treated with intravenous colistin received aerosolized colistin as adjunctive therapy; as the 2019 International Consensus Guidelines for the Optimal Use of the Polymyxins suggested the use of intravenous plus inhaled administration of colistin for the treatment of Gram-negative pneumonia (even with weak evidence but based on the recent PK/PD knowledge), this could represent a major limitation of the study conclusions [41].

In conclusion, this real-life clinical experience about the therapeutic approach in bacteraemic VAP caused by CRAB provides useful suggestions for clinicians about the management of this difficult-to-treat infection**.** VAP, especially in patients with COVID-19, represents a challenge for physicians, considering the high rates of septic shock and mortality associated with this infection. The study data reveal the clinical features and usage outcomes of different antibiotic regimens in this infection setting, assigning a predominant role for cefiderocol and its possible use in combination with fosfomycin. Further randomized clinical trials comparing different cefiderocol regimens with different dosages (i.e. patients with sepsis) are needed to confirm these observations.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2023.106825.

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