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Cefiderocol-containing regimens for the treatment of carbapenem-resistant *A. baumannii* ventilator-associated pneumonia: a propensity-weighted cohort study

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Background: Cefiderocol is a novel β-lactam with activity against carbapenem-resistant *Acinetobacter baumannii* (CRAB), but its role in CRAB pulmonary infections is controversial due to limited evidence.

Objectives: To assess the association between cefiderocol-containing regimens treatment and 28-day mortality in carbapenem-resistant *A. baumannii* ventilator-associated pneumonia (VAP).

Methods: An observational cohort study including critically ill COVID-19 patients with CRAB-VAP admitted to two ICUs of a large academic hospital in Rome between September 2020 and December 2022. The primary outcome was 28-day all-cause mortality. A propensity score was created to balance the cefiderocol- and non-cefiderocol-containing groups. A propensity-weighted multiple logistic regression model was calculated to evaluate risk factors for 28-day mortality. Survival curves were calculated using the Kaplan–Meier method.

Results: 121 patients were enrolled, 55 were treated with cefiderocol- and 66 with non-cefiderocol-containing regimens. The 28-day all-cause mortality was 56% (68/121). A statistically significant difference in 28-day mortality was found between cefiderocol- and non-cefiderocol- containing regimens groups (44% versus 67%, $P=0.011$). In the propensity-adjusted multiple logistic regression, cefiderocol (OR 0.35 95% CI 0.14, 0.83) was a predictor of 28-day survival, Charlson comorbidity index (OR 1.36 95% CI 1.16, 1.78), SOFA score (OR 1.24 95% CI 1.09, 1.57) and septic shock (OR 3.71 95% CI 1.44, 12.73) were all associated with increased 28-day mortality.

Conclusion: Cefiderocol-containing regimens were associated with reduced 28-day mortality in CRAB-VAP. The sample size and the observational design limit the study's conclusions. Future RCTs are needed to establish cefiderocol's definite role in these infections.

Background

Antimicrobial-resistant pathogens represent a considerable menace to human health and are increasingly recognized as a significant cause of mortality and disability.[1] Among them, carbapenem-resistant *Acinetobacter baumannii* (CRAB) is considered an 'urgent threat' by the Centers for Disease Control and Prevention[2] due to the lack of new active antibiotics.[3] This pathogen is capable of life-threatening infections in hospitalized patients, including bloodstream infections and pneumonia, accounting for a high burden in terms of morbidity and mortality.[4,5] Additionally, it displays a critical resistance profile making available therapeutic options particularly scarce.[2] The COVID-19 pandemic further complicated the fight against this organism due to the increasing incidence of healthcare-associated infections[6] and ventilator-associated pneumonia (VAP).[7]

Cefiderocol, a novel siderophore cephalosporin, displays *in vivo* activity against *A. baumannii*.[8] However, the CREDIBLE-CR trial

has questioned the cefiderocol role for *A. baumannii* infections, including pneumonia, due to a higher mortality rate in the cefiderocol-treated *Acinetobacter* spp. subgroup.[9] Currently, few real-life data exist, mainly consisting of case series in heterogeneous sites of infection.[10–13] By contrast, a recent observational study found reduced 30-day mortality in severe CRAB infection treated with cefiderocol, except for the VAP subgroup.[14] Due to limited evidence, IDSA guidance recommends cefiderocol only for infections refractory to other antibiotics,[15] whereas ESCMID guidelines do not recommend cefiderocol use against CRAB infections.[16] Considering these controversial data for severe pulmonary infections, we sought to evaluate the association between cefiderocol use as monotherapy or as part of antibiotic combination regimens and 28-day all-cause mortality in a cohort of critically ill patients with VAP caused by CRAB.

Methods

Study design and setting

We performed an observational cohort study in a large academic hospital in Rome (Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Columbus COVID II Hospital), collecting demographic and clinical data of 121 patients with diagnosed CRAB-VAP admitted in ICUs between September 2020 and December 2022. A prospective registry collecting real-time data regarding infectious complications in ICU patients was used for the study question, formulated in April 2021 when cefiderocol became available in the study centre.

The study was performed following the Declaration of Helsinki and was approved by the Ethics Committee of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS (reference number ID3141). According to committee recommendations, written informed consent or proxy consent was waived due to the study's observational nature.

Participants

ICU physicians daily screened eligible patients according to CRAB-VAP diagnosis. Inclusion criteria were: (i) age ≥18 years; (ii) documented VAP caused by CRAB isolated in bacterial cultures from bronchoalveolar lavage (BAL) or endotracheal aspirate (ETA) and (iii) received at least one dose of the selected anti-CRAB agent. Patients were excluded if: (i) any CRAB-targeted antimicrobials were started more than 24 hours after the diagnosis of the infection and (ii) ICU admission reason was not COVID-19 to apply a restriction to the sample. The exposure of groups was based on cefiderocol presence either as monotherapy or as a part of combination regimens. Therefore, participants were divided into cefiderocol (FDC)- and non-FDC-containing. Each infection recorded stands for one single patient.

Study variables

Cefiderocol exposure was considered by its prescription either as monotherapy or plus one or more other active agents against CRAB within 72 hours of the anti-CRAB therapy commencement. Potential confounders were identified according to the investigators' knowledge and literature revision[17] and subsequently verified during the analysis phase.

VAP was defined according to the IDSA/American Thoracic Surgery Society definitions when diagnostic criteria were met.[18] An infection was considered polymicrobial if at least another pathogen was identified in the respiratory sample. Gram-positive co-infections and pulmonary fungal co-infection were defined by diagnosing a Gram-positive infection or *Aspergillus* spp. pulmonary infection, which required specific treatment during the VAP course.

Immunocompromised patients were defined according to the NIH Coronavirus Disease 2019 guidelines.[19] Acute kidney injury was defined following the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[20] Patients' data were anonymously collected by trained investigators not involved in the study population care from the hospital's electronic medical records or patient contact until the study endpoint of 28 days to ascertain the outcome status.

Outcome

The primary outcome was all-cause 28-day mortality. Outcome status was assessed according to the patient's clinical records on day 28 from the VAP diagnosis or through patient telephone contact in case of discharge before 28 days. Other outcomes were 28-day invasive mechanical ventilation (IMV), cefiderocol resistance development, VAP relapse and microbiological failure. 28-day IMV was defined as the need for invasive mechanical ventilation after 28 days of the diagnosis of CRAB-VAP; it was assessed by clinical records. Cefiderocol resistance development was defined as the evidence in a single patient of a new antibiogram demonstrating *A. baumannii* cefiderocol resistance when previously susceptible after therapy with cefiderocol; it was assessed comparing antibiograms of patients when follow-up cultures were available during the hospitalization. VAP relapse was defined as a new diagnosis of CRAB-VAP during the hospitalization after a successful course of therapy for the prior VAP. Microbiological failure was defined as the isolation of CRAB from bacterial cultures of lower respiratory samples after appropriate treatment; it was assessed by comparing lower respiratory tract samples for patients with available follow-up respiratory cultures during hospitalization.

Antimicrobial therapy

ICU physicians prescribed antibiotic treatments according to the isolates in the respiratory samples and susceptibility testing.[21] Antibiotic treatment was initially started based on the multiplex molecular assays for pneumonia available for all patients, confirming the therapy only if *A. baumannii* grew in bacterial cultures. FDC was administered at a dosage of 2 g as an extended infusion of 3 hours every 8 hours adjusted for renal function, according to the manufacturer's indications. Other anti-CRAB antibiotics used in study regimens with or without cefiderocol were intravenous colistin 9 000 000 UI as a loading dose and then 4 500 000 UI every 12 hours in 2-hour infusions, fosfomycin 8 g every 8 hours in 2-hour infusions, tigecycline 200 mg as a loading dose, and then 100 mg every 12 hours in 1-hour infusions and ampicillin/sulbactam 9 g every 8 hours in 4-hour infusions. High-dose nebulized colistimethate (5 MIU in 6 mL of normal saline solution over 30 minutes every 8 hours) was used in all patients in adjunction with intravenous antibiotics.[22] All concomitant respiratory isolates were treated according to antibiogram results if considered clinically significant.

Microbiology

Lower respiratory tract samples were processed for standard of care (SoC), starting with conventional Gram stain to assess sample quality and semi-quantitative culture on both selective/differential (i.e. blood, chocolate, MacConkey and Columbia colistin-nalidixic acid, CNA) and screening [chromID *S. aureus* elite (SAIDE; bioMérieux, Marcy l'Étoile, France) and chromID extended-spectrum β-lactamase (ESBL) (bioMérieux)] agars. After 24–48 hours of incubation in 5% CO_2-enriched air, bacterial colonies grown at or above the threshold (1×10^4 cfu/mL for a BAL fluid sample or 1×10^5 cfu/mL for an ETA sample) were identified using MALDI-TOF mass spectrometry. In parallel to SoC and upon clinicians' request, the multiplexed and semiquantitative FilmArray pneumonia plus panel (BioFire, Salt Lake City, UT, USA) assay was performed on BAL/ETA according to the manufacturer's recommendations.

AST of *A. baumannii* was performed using the Micronaut broth microdilution panel (Merlin Diagnostika GmbH, Bornheim, Germany). The susceptibility to cefiderocol was assessed by disc-diffusion method following the European Committee of Antimicrobial Susceptibility Testing (EUCAST) recommendations.[23] MIC and zone diameters were interpreted according to the EUCAST clinical breakpoints (https://www.eucast.org/clinical_breakpoints).

Statistical analysis

Continuous variables were described using median and interquartile ranges, and categorical variables using frequencies and percentages. Wilcoxon rank-sum test was used to compare continuous variables and Pearson's χ^2 test for categorical variables. A P value of <0.05 was used to consider differences statistically significant. Since the these comparisons were potentially affected by small sample sizes, standardized differences were calculated by dividing the difference between the groups by the pooled standard deviation of the two groups. A standardized difference >0.1 was interpreted as a meaningful difference.

A propensity score (PS) of receiving cefiderocol was estimated using a generalized boosted model due to the variety of response variables and the absence of formal distributional assumptions. Covariates to include in the PS were identified by selecting variables with a standardized difference >0.1 both in the comparison between FDC- versus non-FDC-containing and survivors versus non-survivors. Thereafter, a patient who was treated with FDC was weighted by the inverse of the probability that they would be treated with FDC, and a patient who did not receive FDC was weighted by the inverse of the probability that they would not receive FDC, equivalent to 1 minus their PS. The balance of the propensity model was evaluated by verifying the obtained balance of PS covariates and comparing the baseline characteristics of the two exposure groups after applying the IPTW. After that, crude and propensity-weighted single and multiple logistic regression models were performed to ascertain risk factors independently associated with 28-day mortality. A logistic regression strategy was preferred due to the complete follow-up available regarding the outcome status and the absence of missing data. Variables in the model were included if they had an influence on the 28-day mortality outcome based on clinical meaningfulness by investigators' consensus, had a standardized difference >0.25 in the weighted comparison between the exposure groups and if PS covariates were not balanced after the PS estimation.[24] OR and 95% CI were calculated. Given the pseudo-population created by the PS weighting, the standard errors (SE) of the logistic regression coefficients might be underestimated. Therefore, we used a bootstrap approach to estimate robust SE and CI for the simple and multiple PS-adjusted logistic regression coefficients. Specifically, we performed 1000 bootstrap resamples of the data, recalculating the PS and refitting the logistic regression model for each resample. From each fitted model, we extracted and stored the regression coefficients. When all resamples were performed, the distribution of these bootstrap estimates was used to calculate the 95% CI for each regression coefficient.

Multicollinearity was assessed by computing the variance inflation factor. Model overfitting was not verified due to the limited number of observations. Although the models were explanatory in purpose, measures of predictive performance were assessed by calculating the receiver operator characteristic curves and McFadden's R^2.

Sensitivity analyses were carried out to compare monomicrobial versus polymicrobial infections, cefiderocol monotherapy versus cefiderocol combination therapies and, finally, for the intention-to-treat- (ITT) population, only patients who were immediately started on FDC.

Survival analysis was performed using both the crude and propensity-adjusted Kaplan–Meier curves. A non-parametric (log-rank) test was used to define their statistical significance.

Statistical analyses were retrospectively performed with R software v.4.2.2 and RStudio 2022.12.0+353 (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available online: https://www.R-project.org/ (accessed on 7 February 2023)).

Results

Demographic and clinical characteristics of the two groups

Overall, 134 patients were assessed for eligibility, and 13 were excluded due to reasons reported in Figure 1. Finally, 121 were included according to the inclusion criteria and subsequently analysed.

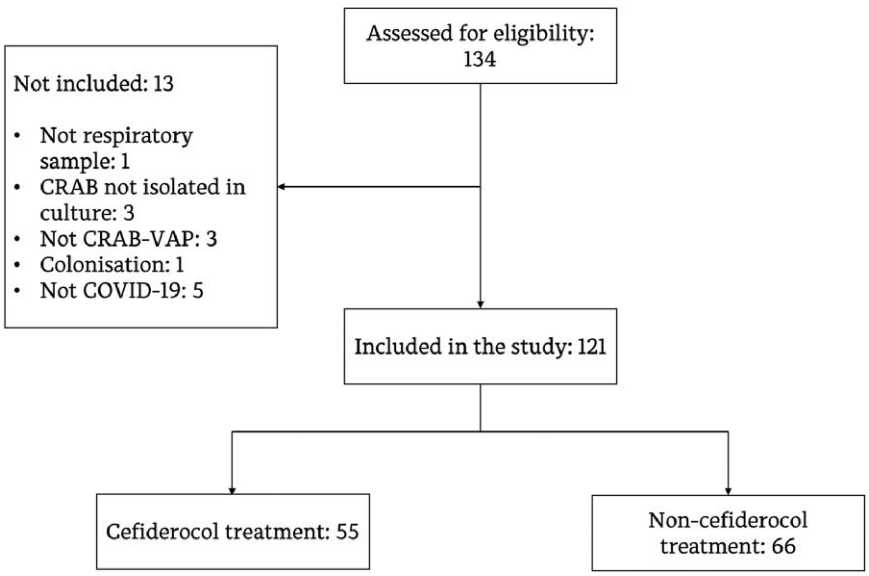

Figure 1. Study flow diagram.

Table 1. Non-cefiderocol-containing regimens versus cefiderocol-containing regimens

Characteristic	Overall, $N=121$[a]	Regimens		P value[b]
		Non-cefiderocol-containing, $N=66$[a]	Cefiderocol-containing, $N=55$[a]	
Age	66 (59, 72)	68 (61, 74)	64 (55, 70)	0.045
Female sex	28 (23)	15 (23)	13 (24)	0.91
BMI ≥ 30 kg/m^2	48 (40)	30 (45)	18 (33)	0.15
SARS-CoV-2 vaccination	15 (12)	2 (3)	13 (24)	<0.001
Dexamethasone therapy	103 (85)	57 (86)	46 (84)	0.67
CAD	22 (18)	9 (14)	13 (24)	0.16
HF	16 (13)	9 (14)	7 (13)	0.88
COPD	19 (16)	12 (18)	7 (13)	0.41
Peptic ulcer disease	0 (0)	0 (0)	0 (0)	
PAD	6 (5.0)	3 (4.5)	3 (5.5)	>0.99
CVD	5 (4.1)	2 (3.0)	3 (5.5)	0.66
Dementia	2 (1.7)	1 (1.5)	1 (1.8)	>0.99
Hemiplegia	5 (4.1)	2 (3.0)	3 (5.5)	0.66
Connective tissue disease	6 (5.0)	4 (6.1)	2 (3.6)	0.69
Diabetes mellitus	31 (26)	17 (26)	14 (25)	0.97
Liver disease	3 (2.5)	2 (3.0)	1 (1.8)	>0.99
Moderate to severe CKD	8 (6.6)	4 (6.1)	4 (7.3)	>0.99
Malignancy	5 (4.1)	4 (6.1)	1 (1.8)	0.38
Lymphoma/leukaemia	5 (4.1)	2 (3.0)	3 (5.5)	0.66
AIDS	2 (1.7)	0 (0)	2 (3.6)	0.20
CCI	4 (3, 6)	4 (3, 6)	4 (3, 6)	0.89
Immunocompromised	12 (9.9)	5 (7.6)	7 (13)	0.35
Days in hospital before VAP	16 (12, 27)	17 (12, 24)	16 (9, 29)	0.44
Days in ICU before VAP	11 (7, 20)	12 (8, 18)	10 (6, 21)	0.68
Days on IMV before VAP	10 (6, 19)	9 (7, 16)	10 (6, 20)	0.99
Tracheostomy before VAP	28 (23)	12 (18)	16 (29)	0.16
SOFA score	8 (5, 10)	8 (5, 10)	7 (5, 10)	0.58
Septic shock	36 (30)	21 (32)	15 (27)	0.59
CRRT	17 (14)	9 (14)	8 (15)	0.89
ECMO	4 (3.3)	2 (3.0)	2 (3.6)	>0.99
Polymicrobial infection	61 (50)	33 (50)	28 (51)	0.92
CRAB-BSI	20 (17)	12 (18)	8 (15)	0.59
Duration of targeted antibiotic therapy	10 (7, 13)	10 (6, 13)	10 (7, 13)	0.86
Aspergillus spp. co-infection	11 (9.1)	4 (6.1)	7 (13)	0.20
Gram-positive co-infection	27 (22)	13 (20)	14 (25)	0.45
VAP relapse	16/111 (14)	8/60 (13)	8/51 (16)	0.73
Microbiological failure	35/87 (40)	15/49 (31)	20/38 (53)	0.038
28-day mortality	68 (56)	44 (67)	24 (44)	0.011
28-day IMV	12/53 (23)	1/22 (4.5)	11/31 (35)	0.008
Adverse effects				
AKI	16 (13)	11 (17)	5 (9.1)	0.22
LFTs > 2 UNL	2 (1.7)	1 (1.5)	1 (1.8)	>0.99

AKI, acute kidney injury; CAD, coronary artery disease; HF, heart failure; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; CVD, cerebrovascular disease; CKD, chronic kidney disease; IMV, invasive mechanical ventilation; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; FDC, cefiderocol; LFTs, liver function tests; UNL, upper normal limit.

[a]Median (IQR) or frequency (%).

[b]Wilcoxon rank-sum test; Pearson's Chi-squared test; Fisher's exact test.

Of 121 patients included in the study, 28 (23%) were female, and the median age (IQR) was 66 (59, 72). All patients were affected by COVID-19, and 12/121 (9.9%) were immunocompromised. The median Charlson comorbidity index (CCI) was 4 (3, 6), and the median SOFA score was 8 (5, 10). Death on day 28 occurred in 68 (56%) patients. 28-day mortality significantly differed between patients who received an FDC-containing regimen and those without FDC (44% versus 67%, $P=0.011$).

Table 2. Survivors versus non-survivors characteristics

Characteristic	Overall, $N=121$[a]	Mortality		P value[b]
		Survivors, $N=53$[a]	Non-survivors, $N=68$[a]	
Age	66 (59, 72)	63 (58, 68)	69 (62, 74)	0.002
Female sex	28 (23)	14 (26)	14 (21)	0.45
BMI ≥ 30 kg/m^2	48 (40)	20 (38)	28 (41)	0.70
SARS-CoV-2 vaccination	15 (12)	9 (17)	6 (8.8)	0.18
Dexamethasone therapy	103 (85)	43 (81)	60 (88)	0.28
CAD	22 (18)	8 (15)	14 (21)	0.44
HF	16 (13)	1 (1.9)	15 (22)	0.001
COPD	19 (16)	4 (7.5)	15 (22)	0.029
Peptic ulcer disease	0 (0)	0 (0)	0 (0)	
PAD	6 (5.0)	1 (1.9)	5 (7.4)	0.23
CVD	5 (4.1)	3 (5.7)	2 (2.9)	0.65
Dementia	2 (1.7)	1 (1.9)	1 (1.5)	>0.99
Hemiplegia	5 (4.1)	4 (7.5)	1 (1.5)	0.17
Connective tissue disease	6 (5.0)	3 (5.7)	3 (4.4)	>0.99
Diabetes mellitus	31 (26)	13 (25)	18 (26)	0.81
Liver disease	3 (2.5)	2 (3.8)	1 (1.5)	0.58
Moderate to severe CKD	8 (6.6)	2 (3.8)	6 (8.8)	0.46
Malignancy	5 (4.1)	3 (5.7)	2 (2.9)	0.65
Lymphoma/leukaemia	5 (4.1)	1 (1.9)	4 (5.9)	0.38
AIDS	2 (1.7)	1 (1.9)	1 (1.5)	>0.99
CCI	4 (3, 6)	4 (3, 5)	5 (3, 6)	0.030
Immunocompromised	12 (9.9)	5 (9.4)	7 (10)	0.88
Days in hospital before VAP	16 (12, 27)	17 (11, 30)	16 (12, 24)	0.67
Days in ICU before VAP	11 (7, 20)	12 (8, 23)	11 (6, 18)	0.17
Days on IMV before VAP	10 (6, 19)	11 (7, 22)	8 (5, 15)	0.070
Tracheostomy before VAP	28 (23)	17 (32)	11 (16)	0.040
SOFA score	8 (5, 10)	5 (4, 9)	9 (6, 10)	<0.001
Septic shock	36 (30)	7 (13)	29 (43)	<0.001
CRRT	17 (14)	4 (7.5)	13 (19)	0.069
ECMO	4 (3.3)	1 (1.9)	3 (4.4)	0.63
Polymicrobial infection	61 (50)	28 (53)	33 (49)	0.64
CRAB-BSI	20 (17)	10 (19)	10 (15)	0.54
Duration of targeted antibiotic therapy	10.0 (7.0, 13.0)	11.0 (10.0, 14.0)	8.0 (4.0, 12.5)	<0.001
Aspergillus spp. co-infection	11 (9.1)	4 (7.5)	7 (10)	0.75
Gram-positive co-infection	27 (22)	11 (21)	16 (24)	0.72
VAP relapse	16/111 (14)	11/53 (21)	5/58 (8.6)	0.069
Cefiderocol treatment	55 (45)	31 (58)	24 (35)	0.011
Adverse effects				
AKI	16 (13)	8 (15)	8/63 (12)	0.59
LFTs > 2 UNL	2 (1.7)	1 (1.9)	1 (1.5)	>0.99

AKI, acute kidney injury; CAD, coronary artery disease; HF, heart failure; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; CVD, cerebrovascular disease; CKD, chronic kidney disease; IMV, invasive mechanical ventilation; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; FDC, cefiderocol; LFTs, liver function tests; UNL, upper normal limit.

[a]Median (IQR) or Frequency (%).

[b]Wilcoxon rank-sum test; Pearson's Chi-squared test; Fisher's exact test.

Patients treated with an FDC-containing regimen were more frequently completely vaccinated against SARS-CoV-2 (24% versus 3%, $P<0.001$) and were younger [64 (55,70) versus 68 (61,74), $P=0.045$]. Patients in the FDC group had a higher rate of microbiological failure (53% versus 31%, $P=0.038$), while no difference was present regarding VAP relapse (16% versus 13%, $P=0.73$). Among 20 (10%) patients treated with FDC who had follow-up susceptibility testing, two patients developed resistance to it after exposure. Other characteristics of the two groups are reported in Table 1. The non-survivors versus survivors comparison is reported in Table 2. Standardized differences tables for the cohorts are available in Table S1 (available as Supplementary data

Table 3. Multiple logistic regression models for 28-day mortality

	Crude model		PS-adjusted model	
Characteristic	OR	95% CI	OR	95% CI
Cefiderocol	0.41	0.16, 0.99	0.35	0.14, 0.83
SARS-CoV-2 vaccine	0.49	0.11, 2.02	0.48	0.13, 1.47
SOFA score	1.33	1.12, 1.60	1.24	1.09, 1.57
CCI	1.37	1.09, 1.76	1.36	1.16, 1.78
CRRT	0.54	0.11, 2.83	0.93	0.09, 5.69
Septic shock	2.82	0.98, 8.78	3.71	1.44, 12.73
BMI ≥ 30 kg/m^2	1.00	0.41, 2.44	0.94	0.45, 2.21

CRRT, continuous renal replacement therapy.

at *JAC-AMR* Online). A comparison between monomicrobial and polymicrobial infections is reported in Table S2. The ITT-like complete analyses of patients immediately started on FDC-containing or -non-containing regimens are reported in Table S3 and S4. The diagnostic dates distribution is shown in Figure S1.

Antimicrobial treatments

The most representative regimens in the FDC-containing group were cefiderocol monotherapy in 12/55 cases (21.8%), cefiderocol + colistin in 18/58 (29%) and cefiderocol + colistin + tigecycline in 11/55 (20%). In the non-FDC-containing group, colistin + tigecycline + fosfomycin was the most frequent regimen in 48/66 cases (72.7%). Other therapies are reported in Table S5. All patients were also treated with high-dose nebulized colistimethate. The comparisons between patients treated with cefiderocol monotherapy and cefiderocol combination therapy and the Kaplan–Meier curves are reported in Table S6 and Figures S2, respectively.

Logistic regression of risk factors for 28-day mortality and survival analysis

A PS of receiving cefiderocol was calculated. Variables with a standardized difference >0.1 for both the exposure and outcome group included in the PS were: age, anti-SARS-CoV-2 complete vaccination, coronary artery disease, cerebrovascular disease, chronic obstructive pulmonary disease, hemiplegia, leukaemia/lymphoma, tracheostomy before VAP onset, non-haematological malignancy and SOFA score. The balance of PS covariates and the baseline comparison of the two exposure groups after applying the IPTW are reported in Figure S3. Although age and cerebrovascular disease were not balanced after PS estimation and with a standardized difference >0.25, the CCI variable was used due to its influence on the mortality outcome and multicollinearity concerns (Figure S4). Variables finally included in crude and adjusted models were: cefiderocol, CCI, anti-SARS-CoV-2 complete vaccination, SOFA score, continuous renal replacement therapy, septic shock at VAP presentation and BMI > 30 kg/m^2.

In the simple crude logistic regression model, the calculated OR for cefiderocol was 0.39 (95% CI, 0.18 to 0.80). The simple propensity-adjusted logistic regression model resulted in an OR for cefiderocol of 0.40 (95% CI, 0.14 to 0.84). In the crude multiple logistic regression model, cefiderocol [OR 0.41 (95% CI, 0.16 to 0.99)], the SOFA score [OR 1.33 (95% CI, 1.12 to 1.60)] and CCI [OR 1.37 (95% CI, 1.09 to 1.76)] were significantly associated with 28-day mortality. In the propensity-adjusted model, the use of cefiderocol [OR 0.35 (95% CI, 0.14 to 0.83)] was found to be predictive of 28-day survival, while CCI [OR 1.36 (95% CI, 1.16 to 1.78)], the SOFA score [OR 1.24 (95% CI, 1.09 to 1.57)] and septic shock presence [OR 3.71 (95% CI, 1.44 to 12.73)] were found to be significantly associated with 28-day mortality. The OR and 95% CI of both multiple logistic regression models are reported in Table 3. Performance model measures and variance inflation factors are shown in Table S7 and Figures S5. The ITT-like logistic regression balance and results are reported in Figure S6 and Table S8.

The crude and propensity-adjusted Kaplan–Meier curves comparing patients who received an FDC-containing regimen versus a non-FDC-containing regimen are reported in Figure 2. The log-rank test was $P = 0.022$.

Discussion

To our knowledge, this study includes the largest cohort of severe carbapenem-resistant *A. baumannii* infections treated with cefiderocol, and this is the first study directly focusing on VAP. The results showed that cefiderocol-containing-regimens are associated with a lower risk of 28-day mortality. Indeed, compared with patients treated with regimens without cefiderocol, patients treated with cefiderocol experienced a significant reduction in 28-day mortality in the crude analysis. Cefiderocol was also associated with a lower risk of 28-day mortality at the propensity-adjusted multiple logistic regression.

VAP represents a fearsome complication in the ICU, accounting for a high mortality rate,[18] especially when multi-drug resistant organisms are implicated. Specifically, severe CRAB infections have been associated with increased mortality rates in different studies.[25] Cefiderocol seems to display an interesting profile of safety[26] and pulmonary penetration.[27] Nonetheless, the role of this new cephalosporin has yet to be completely established. In the CREDIBLE-CR trial, higher mortality has been reported in the cefiderocol-treated CRAB infection subgroup, softening the expectations toward this drug.[9] However, patients in the cefiderocol arm of the CRAB subgroup were at higher mortality risk, probably due to a randomization imbalance between the two arms.[9] Moreover, the mortality rate of the best available therapy arm of the CREDIBLE-CR was 18%, notably less than in other studies addressing carbapenem-resistant *A. baumannii* infections, potentially being altered by the baseline severity of patients' conditions selected in the mentioned trial.[28] As a result, discrepancies exist in international guidelines; for instance, the IDSA guidance contemplates cefiderocol as a potential antimicrobial when treating CRAB,[15] whereas ESCMID guidelines conditionally recommend against cefiderocol[16] due to the limited information available. Regarding real-life experiences with cefiderocol, they mainly consist of a few observational studies with no significant conclusions in lower respiratory tract infection subgroups.[14,29] Other case series exist,[10–13] although with no or low number of VAP.

Hence, this study may provide new evidence regarding the use of cefiderocol for treating *A. baumannii* VAP. These results could be helpful, considering the paucity of available data for

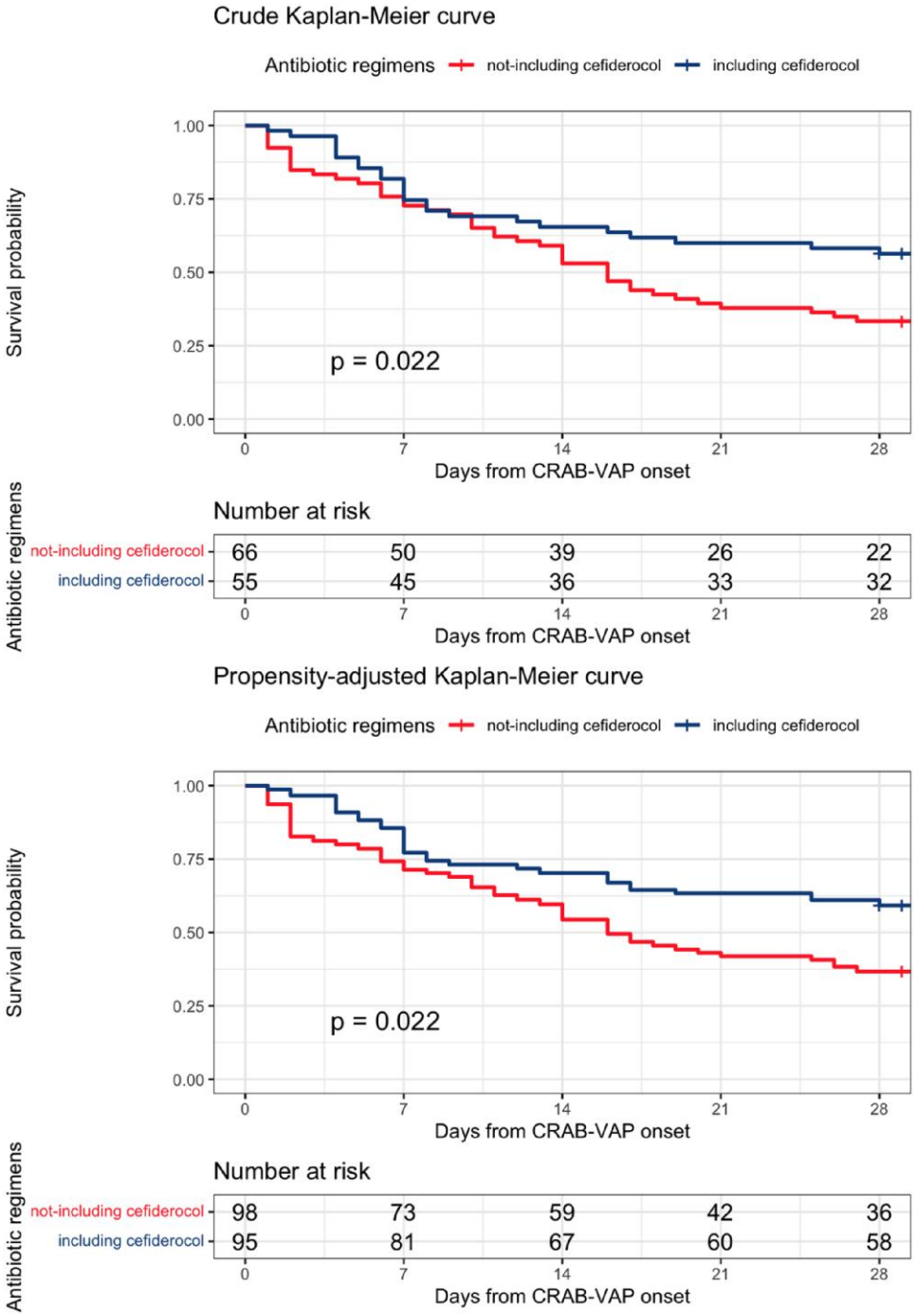

Figure 2. Crude and propensity-adjusted Kaplan–Meier curves.

pulmonary infections caused by this pathogen. The finding of resistance to cefiderocol is another important aspect highlighted in this work. We found resistance to cefiderocol in the follow-up susceptibility tests for 2/20 (10%) patients treated with cefiderocol. Cefiderocol resistance in *A. baumannii* has been reported. Several mechanisms have been implied, including the expression of PER-type ESBL, SHV-Type β-lactamases, siderophore receptor mutations[30] and the phenomenon of heteroresistance.[31] Moreover, two other characteristics emerged; a higher microbiological failure in the cefiderocol group was found, despite possibly being influenced by the higher survival rates of this group; and a trend of reduced acute kidney injury in the cefiderocol-containing group.

Another aspect of this study is the use of multiplex PCR assays for the timing of empiric therapy. Timely initiation of anti-CRAB treatment may improve survival rates for VAP, and molecular methods may assist in this aim.[21] All patients enrolled were

initially started on anti-CRAB regimens based on the results of the molecular assays, confirming the therapy only if *A. baumannii* grew in cultures. This fact is of valuable interest since the prompt start of an appropriate empiric regimen is crucial for VAP in ICU,[32] and CRAB is only sometimes covered.

Nevertheless, our study should be interpreted considering some limitations. First, its observational nature is not the most appropriate study design when evaluating drug treatments. Indeed, albeit the use of PS weighting assisted in reducing selection bias, the imbalance of the two cohorts together with unmeasured confounders remains a matter of concern, affecting the interpretation of the results. Second, all patients were affected by critical SARS-CoV-2 infection; for this reason, it could be challenging to assess the impact of antibiotic therapy on mortality.[33] This might be mainly due to the similar clinical presentation of both VAP and COVID-19 pneumonia, for which no valid criteria currently exist. However, patient worsening and unstable ventilatory parameters occurring more than one week after ICU admission for viral pneumonia may account for bacterial aetiology, although no conclusive diagnosis could be made. Moreover, more patients were vaccinated against SARS-CoV-2 in the cefiderocol group. Even though no difference in mortality was found in the comparison between vaccinated versus non-vaccinated patients, the standardized difference's value suggests the vaccine's influence on the mortality outcome. Ultimately, most cases of cefiderocol occurred in the final phase of the study, when the Omicron variant was probably prevalent. Hence, establishing the weight of COVID-19-related or bacterial VAP mortality can be especially challenging. Third, nearly half of the infections were polymicrobial, possibly confusing the sole contribution of *A. baumannii* in terms of virulence in establishing the severity of infection. Indeed, this pathogen is known to colonize the respiratory tract and understanding its pathogenic role in VAP might be challenging. Despite this, the disease severity and the related high mortality risk make most healthcare providers cover it in the prescribed regimen. Moreover, even RCTs faced similar issues; for instance, 22% of patients had a polymicrobial infection in the CREDIBLE-CR.[9] Fourth, microbiological susceptibility tests were only sometimes available for all cases due to the commercial absence of the kit to test cefiderocol MIC during the study period; this could have led to an inaccurate report of resistance development rate. Additionally, the AST was performed through the disc-diffusion method instead of the broth microdilution reference method, potentially altering a definitive susceptibility categorization. Fifth, many different regimens were used, and some cefiderocol combination regimens also contain colistin, the base of a non-cefiderocol-containing regimen. However, in our experience, colistin was frequently removed after 3 or 4 days of appropriate targeted therapy. Nonetheless, these facts might complicate the results' interpretation, considerably limiting the finding of a possible cefiderocol benefit. Sixth, as all patients were in ICU, these results may not be generalizable to patients hospitalized in ordinary wards. Even so, this work may help researchers address unsolved questions about the cefiderocol role in CRAB-VAP and frame future studies based on the encountered caveats. Understanding the intrinsic limitation of the study design is crucial, and randomized controlled trials are encouraged and urgently necessary to establish the cefiderocol efficacy for *A. baumannii* infection.

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Author contributions

Study concept and design, E.R.; acquisition of data, E.R., F.S., S.L.C., E.S.T.; statistical analysis, E.R.; interpretation of data, E.R., S.L.C, F.G. G.D.P.; drafting the manuscript, E.R.; microbiology contribution, G.D.A.; critical revision of the manuscript, G.D.P., M.F., R.M., M.A.; study supervision, G.D.P, M.F., R.M., M.A., All authors have reviewed and approved the final version of the manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Supplementary data

Figures S1 to S6 and Tables S1 to S8 are available as Supplementary data at *JAC-AMR* Online.

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