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MAJOR ARTICLE

Real-life Data on Cefiderocol Efficacy and Safety to Treat Multidrug-Resistant *Acinetobacter baumannii* Infections

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Background. The objective of this study was to expand *real-life* data on cefiderocol efficacy to treat multidrug-resistant *Acinetobacter baumannii* infections.

Methods. This was a retrospective monocentric study including patients hospitalized (>24 hours) at Policlinico Tor Vergata, Rome, Italy, between May 1, 2021, and September 1, 2022, treated with cefiderocol (>48 hours). The primary objective was early clinical improvement at 48–72 hours from cefiderocol start; secondary objectives were clinical success (composite outcome of infection resolution and 14-day survival), breakthrough infection, overall 30-day mortality, and cefiderocol-related adverse events.

Results. Eleven patients were enrolled; 91% males (10/11), with a median age (interquartile range [IQR]) of 69 (59–71) years, 91% had ≥1 comorbidity, and 72.7% (8/11) were hospitalized in internal medicine wards. Six patients with bloodstream infection (54.5%; 4 primary, 2 central line–associated), 2 with pneumonia (18.2%), 2 with urinary tract infections (18.2%), and 1 with intra-abdominal infection (9.1%) were treated. Four patients (36.3%) presented with septic shock at cefiderocol start. Cefiderocol was used as monotherapy in 3/11 patients (27.3%), was combined with colistin in all the other 8 cases, and was used in triple combination with tigecycline in 2 patients. The median duration of treatment (IQR) was 12 (10–14) days. Early clinical improvement was documented in 8/11 patients (72.7%), clinical success in 8/11 patients (72.7%). Overall 30-day mortality was 27.3% (3/11), with death occurring a median (IQR) of 19 (17.5–20.5) days after the start of therapy. No cefiderocol-related adverse events were documented.

Conclusions. Cefiderocol seems to be a safe and effective option for multidrug-resistant *Acinetobacter baumannii* infections.

Keywords. *Acinetobacter baumannii*; antimicrobial resistance; cefiderocol; gram-negative; real-life.

Acinetobacter baumannii infections are characterized by high morbidity and mortality [1, 2]. In Europe, the majority of isolates are multidrug-resistant, and in Italy >80% of the *Acinetobacter baumannii* isolated in 2021 were carbapenem-resistant [3]. Few treatment options exist for this difficult-to-treat pathogen, with conflicting recommendations from the latest infectious diseases society guidelines [1, 2]. In recent years, cefiderocol (CFD), a new antibiotic active in gram-negative microorganisms, has been developed [4, 5]. CFD uses a peculiar mechanism of action named "Trojan horse," based on iron active transporters, overcoming common resistance mechanisms developed by gram-negative pathogens [6]. A randomized clinical trial that compared cefiderocol treatment with the best available therapy to treat carbapenem-resistant gram-negative infections showed higher mortality in the cefiderocol-treated group, mainly driven by *Acinetobacter baumannii* infections [7], hindering enthusiasm for this antibiotic and exposing crucial knowledge gaps on the best clinical approach for carbapenem-resistant *A. baumannii* (CRAB) infections. Indeed, the latest guidelines published by the European and American societies of infectious diseases recommend against CFD use in CRAB infections [1], or suggest using it only as salvage strategy, as part of a combination regimen [2]. However, subsequent real-life observational data reported high efficacy and safety of cefiderocol to treat severe CRAB infections [8–13]. The aim of this study was to collect real-life data on CFD efficacy and safety in treating carbapenem-resistant *Acinetobacter baumannii* infections.

METHODS

Study Design and Population Selection

This was a single-center, retrospective, observational study, performed at the Policlinico Tor Vergata University Hospital of Rome, Italy, involving adult patients (≥18 years) hospitalized

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from May 1, 2021, to September 1, 2022, for >24 hours receiving CFD treatment for ≥48 consecutive hours for a carbapenem-resistant *Acinetobacter baumannii* infection. The patient list was derived from the hospital pharmacy registry. Patients who died or were discharged within 24 hours of hospitalization were excluded; patients who received CDF within the expanded access program (compassionate use) or with microbiological isolates that showed resistance to CFD were excluded. Patients with polymicrobial gram-negative infection, defined as isolation of another gram-negative pathogen in the same specimen with *Acinetobacter baumannii*, were excluded. The study was approved by the local ethics committee (experimentation register number 25.22). Given the retrospective nature of the study, written informed consent was waived by the ethics committee, in accordance with local legislation. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Outcomes

The primary outcome was to evaluate the early clinical improvement rate, defined as the achievement of ≥1 of the following at 48–72 hours from cefiderocol start:

- resolution of signs/symptoms of infection;
- suspension of inotropic agents if needed at antibiotic start;
- absence of fever for ≥48 consecutive hours;
- reduction of procalcitonin (PCT) levels of ≥80% of the maximal value or PCT <0.5 ng/mL [14, 15];
- reduction of C-reactive protein values of ≥75% of the maximal value [16].

Secondary outcomes were:

- clinical success (composite end point of absence of signs and symptoms of *Acinetobacter baumannii* infection and 14-day survival after CFD discontinuation);
- breakthrough infections (re-isolation of the same pathogen >72 hours after CFD start);
- microbiological relapse (re-isolation of the same pathogen within 30 days after CFD treatment suspension);
- overall 30-day mortality, evaluated at 30 days after antibiotic treatment initiation;
- CFD-related adverse events.

Data Collection

An ad hoc electronic database was created to collect clinical data, including demographic, comorbidity, laboratory, and microbiological data. Clinical data were directly registered from clinical charts; laboratory data were extracted from the electronic hospital software. All blood tests were performed in the central laboratory of Policlinico Tor Vergata University Hospital, following standard procedures. Site of infection was defined according to the Centers for Disease Control and Prevention's National Healthcare Safety Network (NHSN) definitions, version January 2021 [17]. Antibiotic initiation by the infectious diseases specialist to treat CRAB isolate would classify as infection. For bloodstream infections (BSIs), central line–associated BSIs were defined by ≥1 blood culture positive for CRAB being drawn from a central line (CL; including midline).

Antimicrobial Susceptibility Testing and CFD Administration

Antimicrobial susceptibility testing was performed using ITGN Micronaut panels (Diagnostika Gmbh, Bornheim, Germany, now Bruker Daltonics) run on MICRO MIB (Bruker Daltonics, Billerica, MA, USA) and interpreted following the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoint, version 9.0. Cefiderocol susceptibility was performed using Cefiderocol MTS (MIC Test Strip), FDC 0.016–256 μg/mL (Liofilchem, Abruzzo, Italy). MTS consists of special porous paper impregnated with a predefined concentration gradient of an antimicrobial agent (reported on the strip), used to determine the minimum inhibitory concentration (MIC) in μg/mL of antimicrobial agents against bacteria as tested on agar media using overnight incubation and manual reading procedures. MIC value corresponds to the number reported on the strip where the edge of the inhibition ellipse intercepts the strip itself. MTS strips were applied on iron-depleted Mueller Hinton II agar plates (Liofilchem, Abruzzo, Italy) with the isolated pathogen and incubated for 16–20 hours at 37°C. After the required incubation period, MIC values were read (where the relevant inhibition ellipse intersects the strip); the MIC end point was read at complete inhibition of growth. Following the EUCAST guidelines, the following breakpoints were used: ≤2 μg/mL susceptible, >2 μg/mL resistant.

CFD was administered at the standard dosage of 2 g every 8 hours ("full dose"), with adjustment of dosage for renal impairment according to the manufacturer's recommendations [18]. If the dose had to be reduced for >48 hours during the whole treatment course, it was labeled "reduced CFD dose."

Data Presentation

Continuous data are presented as median with interquartile range (IQR), while categorical data are presented as absolute frequency and percentage. Data representation was performed using the software JASP (version 0.11.1; JASP Team, 2019).

RESULTS

In the study period, CFD was prescribed to 43 patients and administered to 38 patients, 17 of whom (44.7%) had infections due to *Acinetobacter baumannii* (Figure 1). Three patients were excluded because they had a gram-negative polymicrobial infection, and CFD resistance was documented in 2 cases. One patient received CFD only for 1 day, to complete the treatment

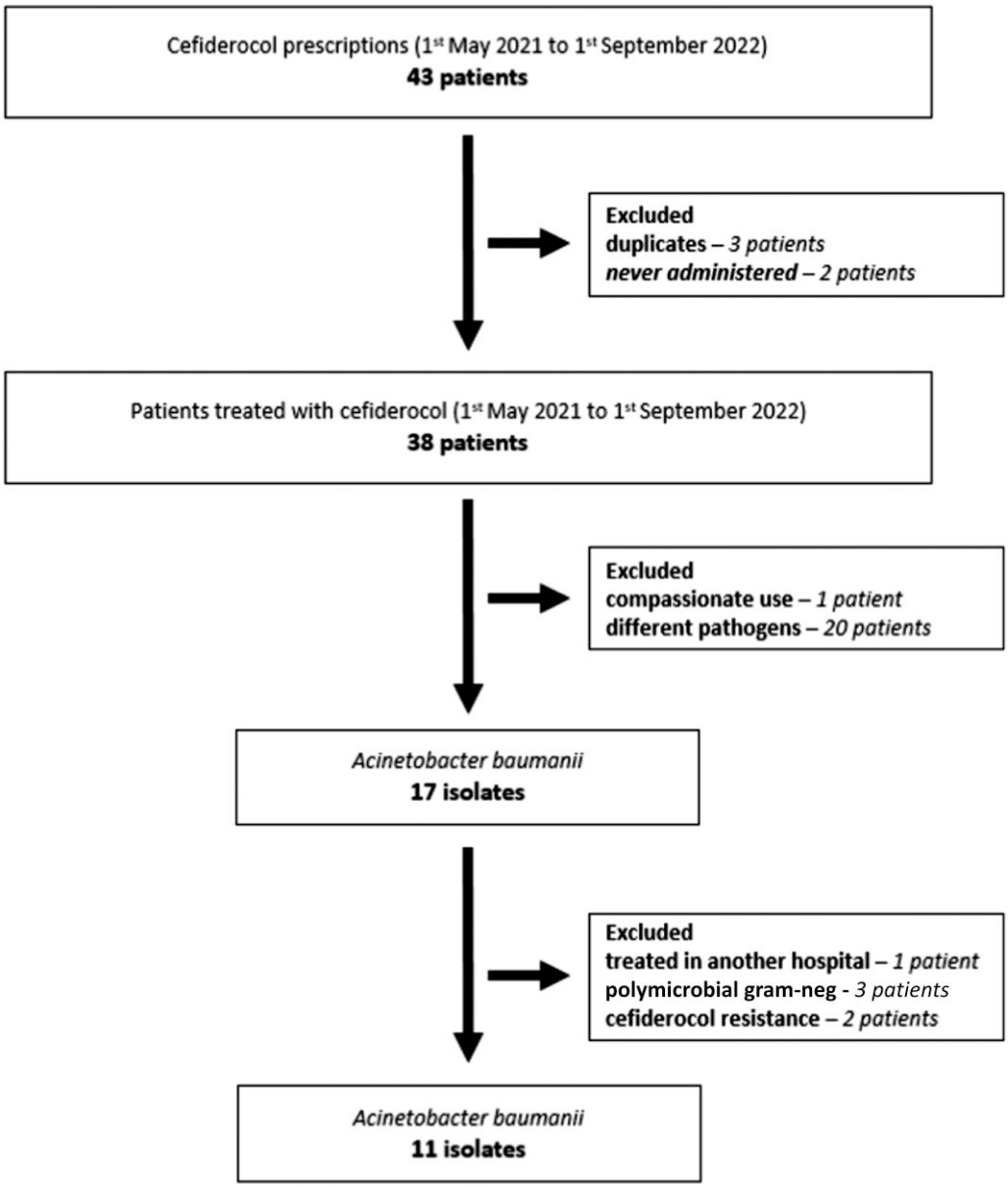

Figure 1. Population selection criteria.

for *Acinetobacter baumannii* infection started in another facility, just before being transferred to Tor Vergata Hospital. Finally, 11 patients were included in the study. The characteristics of the population are reported in Table 1. The majority of the enrolled patients were males (10/11, 91%), with a median age (IQR) of 69 years (59.00–71.00), mainly admitted in internal medicine wards (8/11, 72.7%). Ten patients (91%) had ≥1 comorbidity, mainly cardiovascular disease (9/11, 81.9%) and SARS-CoV-2 coinfection, at hospital admission (4/11, 36.3%); the median Charlson comorbidity score index (IQR) was 5 (2.5–5.5). The median time from hospital admission to *Acinetobacter baumannii* infection (IQR) was 19 (12–42.5) days. The included infections were bloodstream infections (BSIs) in 6 patients (54.5%, 4 primary BSI, 2 central line–associated, with positive blood cultures from the central line), urinary tract infections in 2 cases (18.2%), ventilator-associated pneumonia in 2 patients (18.2%), and intra-abdominal infection in 1 case (9.1%). Four patients (36.3%) presented with septic shock at infection onset.

All isolates were resistant to carbapenemes, with preserved susceptibility to colistin only. A susceptibility test for CFD was performed in 8/11 cases; MIC value was available for 7 isolates, ranging from 0.094 to 1 μg/mL (Figure 2): 1 strain was reported as susceptible to CFD, although MIC value was not available.

CFD was used as first-line therapy in 4 cases (36.3%) and as second-line therapy in the remaining cases, due to clinical

Table 1. Characteristics of the Overall Population

Total patients, No.	11
Age, median [IQR], y	69 [59–71]
Sex (M/F)	10/1 (91/9)
Charlson comorbidity index, median [IQR]	5 [2.5–5.5]
Comorbidities	
≥1	10 (91)
Cardiovascular	9 (81.9)
SARS-CoV-2 coinfection	4 (36.3)
Psychiatric/dementia	3 (27.3)
Cerebrovascular disease	2 (18.2)
Hematologic malignancy	2 (18.2)
Respiratory disease	2 (18.2)
Diabetes	2 (18.2)
Chronic kidney disease	1 (9)
Days hospital admission/infection, median [IQR]	19 [12–42.5]
Ward infection detection	
Internal medicine	8 (72.7)
Intensive care unit	3 (27.3)
Surgical ward	0
Infection site	
BSI	4 (36.3)
CLABSI	2 (18.2)
Urinary tract	2 (18.2)
Ventilator-associated pneumonia	2 (18.2)
Intra-abdominal	1 (9.1)
Septic shock at CFD start	4 (36.3)
CVVHDF	0
Days from microbiologic isolate to CFD initiation, median [IQR]	5 [2.5–5.5]
CFD as first-line treatment	4 (36.3)
No. of treatments before CFD treatment, median [IQR]	1 [0–1]
CFD started due to	
Clinical failure	2/7 (28.6)
For better tolerability	2/7 (28.6)
Therapy optimization	3/7 (42.8)
Days of CFD therapy, median [IQR]	12 [10–14]
Full dose of CFD[a]	7 (63.3)
Monotherapy	3 (27.3)
Combination therapy	8 (72.7)
With colistin	5
With tigecycline	1[b]
With colistin and tigecycline	2[c]
Early clinical improvement	8 (72.7)
Clinical success	8 (72.7)
Death 30 d	3 (27.3)
Days from infection to death, median [IQR]	19 [17.5–20.5]
Microbiological relapse	0/5[d]
Breakthrough infection	1 (9)
Adverse events	0

Data reported as median [IQR] or absolute frequency (%), as appropriate.

Abbreviations: BSI, bloodstream infection; CFD, cefiderocol; CLABSI, central line–associated bloodstream infection; CVVHDF, continuous veno-venous hemodiafiltration; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Full dose of CFD: 2 g every 8 h for the whole treatment.

[b]The patient started CFD in combination with tigecycline; after 6 d, treatment was switched to CFD + colistin, continued for another 6 d (tigecycline was switched to daptomycin due to a concomitant gram-positive infection).

[c]Colistin stopped after 6 d of treatment in 1 patient due to acute kidney injury.

[d]Number of patients with microbiological outcome evaluable (available cultures from infection site, from 1 to 30 d after CFD suspension).

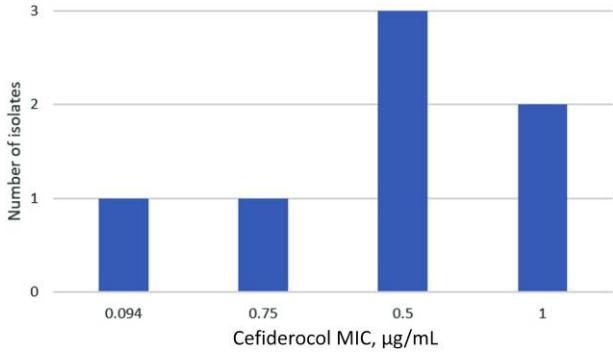

Figure 2. Cefiderocol MIC distribution. Susceptibility MIC reported for 7 patients; 1 isolate was reported as susceptible by the microbiology laboratory, but MIC value was not available. Abbreviation: MIC, minimum inhibitory concentration.

failure of the previous treatment (2/7, 28.6%, defined as fever persistence or clinical deterioration), for better tolerability (2/7, 28.6%, suspending colistin), or after obtaining CFD susceptibility results as part of combination therapy (3/7, 42.8%). Previous therapies included colistin, used in all cases either alone or in combination with tigecycline, meropenem, or fosfomycin. In the majority of cases (5/7), CFD replaced the associated antibiotic to colistin, and a combination of colistin and CFD was continued; in 2 cases, CFD introduction led to colistin suspension. The majority of patients received CFD as combination therapy (8/11, 72.7%), with colistin in 5 patients, tigecycline in 1 patient (switched to CFD and colistin after 6 days of treatment), and both colistin and tigecycline in 2 patients (1 patient developed acute kidney injury 6 days after colistin start; hence it was stopped, and the treatment was completed with CFD and tigecycline). Dosages of the antibiotics used in combination with CFD are specified in Table 2. The 3 patients treated with CFD monotherapy had urinary tract infections (2 patients) and intra-abdominal infection (1 patient). Overall, patients started CFD a median (IQR) of 5 (2.5–5.5) days after the microbiological isolate and received CFD for a median (IQR) of 12 (10.0–14.0) days.

Early clinical improvement was documented in 8 cases out of 11 (72.7%), who had ≥1 of the listed criteria. In the 3 patients who did not reach early clinical improvement, laboratory parameters did not meet the specified cutoffs of reduction after 48–72 hours from CFD start; furthermore, 1 of the 3 patients was still febrile 72 hours after CFD start. Clinical success was documented in 8/11 patients (72.7%). Among the 8 patients with clinical success, 5 had the CRAB strain tested and were susceptible to CFD, while 3 patients received CFD empirically, without a susceptibility test available. Overall 30-day mortality was 27.3% (3/11); death occurred a median (IQR) of 19 (17.5–20.5) days after infection onset. In the 4 patients presenting

Table 2. Patients' Characteristics and Outcomes

	Age	Sex	Ward of Infection	Type of Infection	Septic Shock	Previous Therapy, No.	CFD Reason to Start	CFD Dosage	Mono/Combo Therapy	Combo Dosage[c]	CFD Days	Early Clinical Improvement	Clinical Success	Outcome (30-Day Death)
1	69	M	Internal medicine	BSI	Yes	1	Prevent toxicity	2 g q 8h	Combo	Tige → switch to colistin after 6 d	12	Yes	No	Dead
2	51	M	Internal medicine	BSI	Yes	1	Therapy optimization	2 g q 8h	Combo	Colistin (after 5 d→3.5MU q12h)	12	Yes	Yes	Survived
3	67	M	Internal medicine	BSI	No	1	Therapy optimization	2 g q 8h	Combo	Colistin	14	No	Yes	Survived[b]
4	70	M	Internal medicine	BSI	No	1	Therapy optimization	2 g q 8h (3 d) →1 g q8h (7 d)	Combo	Tige colistin (stop after 6 d: AKI)	10	Yes	Yes	Survived
5	64	M	Intensive care unit	CLABSI	Yes	1	Clinical failure	2 g q 8h	Combo	Tige (100 mg q12h) colistin	14	Yes	Yes	Survived
6	49	M	Internal medicine	CLABSI	No	0	Targeted therapy	2 g q 8h	Combo	Colistin (8.5MU LD, 3MU q12h)	7	Yes	Yes	Survived
7	89	M	Internal medicine	UTI	No	1	Prevent toxicity	1.5 g q8h	Mono	/	6	Yes	Yes	Survived
8	84	M	Internal medicine	UTI	No	0	Targeted therapy	1 g q 8h	Mono	/	14	Yes	No	Dead
9	72	M	Intensive care unit	VAP	Yes	0	Targeted therapy	1.5 g q8h	Combo	Colistin	21	Yes	Yes[a]	Survived
10	54	M	Intensive care unit	VAP	No	1	Clinical failure	2 g q 8h	Combo	Colistin[d]	13	No	No	Dead
11	70	F	Internal medicine	IAI	No	0	Rational therapy	2 g q 8h	Mono	/	10	No	Yes	Survived

Abbreviations: AKI, acute kidney injury; BAS, bronchial aspirate; BSI, bloodstream infection; CFD, cefiderocol; combo, CFD used in combination with another antibiotic; CLABSI, central line–associated bloodstream infection; CVVHDF, continuous veno-venous hemodiafiltration; IAI, intra-abdominal infection; ICU, intensive care unit; IQR, interquartile range; LD, loading dose; mono, CFD used as monotherapy; MU, million unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Breakthrough infection during treatment (BAS persistently positive), but then microbiological eradication, continuing CFD.

[b]Transferred to ICU in another hospital due to septic shock caused by *Escherichia coli* >30 d after *A. baumannii* infection.

[c]When not specified, tigecycline was administered at 100-mg loading dose, followed by 50 mg q12 h; colistin 9 MU as loading dose, then 4.5 MU q12 hours.

[d]Dosage unknown.

with septic shock, early clinical improvement was documented in all cases (4/4, 100%), and clinical success was achieved in 3 patients (75%). Among patients treated for BSI (6/11, 54.5%), early clinical improvement was documented in 5/6 patients (83.3%), clinical success in 5/6 (83.3%).

There was 1 breakthrough infection in a patient treated for ventilator-associated pneumonia, with re-isolation of *Acinetobacter baumannii* from bronchial aspirate 5 days into CFD treatment. CFD therapy was continued, leading to clinical success and microbiological eradication. CFD susceptibility testing was not performed on either CRAB isolate. Overall, no microbiological relapses due to CRAB were documented after CFD suspension. No CFD-related adverse events were recorded. A more detailed description of the enrolled patients is presented in Table 2.

DISCUSSION

This real-life study showed clinical success of CFD therapy in 72.7% of patients treated for CRAB infections, with particular success in the majority of bloodstream infections (83.3%).

In vitro efficacy of CFD, confirmed in multinational surveillance studies for a wide range of multidrug-resistant (MDR) gram-negative pathogens including nonfermenters, suggests an encouraging clinical role for this antibiotic [16–19]. However, these data were hindered by in vivo results of 1 clinical randomized controlled trial (RCT) on CFD, the CREDIBLE-CR, which reported increased mortality in the CFD group, compared with best available therapy in carbapenem-resistant gram-negative infections [7]. A subanalysis showed that the increase in mortality in the CFD group was mainly due to CRAB infections [7], leading to the release of cautious and conflicting recommendations on CFD use for CRAB in the latest guidelines published by the American and European societies of infectious diseases [1, 2]. Nevertheless, subsequent real-life studies showed different results, reporting promising efficacy of CFD for the treatment of CRAB infections [8–13]. In our study, mortality rates were lower than in the CREDIBLE-CR study [7]. This might be due to differences in the study populations: first of all, the number of included patients. In the CREDIBLE-CR study, the majority of patients had pneumonia (45% vs 2 patients in our group), and 50% of the patients were ventilated at randomization. Furthermore, in CREDIBLE-CR, a higher proportion of patients in the CRAB subgroup presented with shock or were in intensive care unit (ICU) ward at randomization, suggesting a higher baseline mortality risk, as stated by the authors. A multicenter retrospective observational study by Pascale et al. including patients hospitalized for coronavirus disease 2019 (COVID-19) pneumonia in the ICU who developed a secondary CRAB superinfection compared CFD compassionate use treatment (42 patients) with other antibiotic therapies (65 patients), reporting an overall comparable 28-day mortality of 55% [13]. Interestingly, CFD was always used in monotherapy, while its comparator was colistin, used in combination therapy in 85% of cases, mainly with meropenem. The higher clinical success documented in our cohort could be related to the different hospital setting, with the majority of our patients being admitted to the internal medicine ward (72.7%) compared with the ICU in the study by Pascale et al., where COVID-19 may have adversely affected the outcome.

Another sizable real-life study by Falcone et al. retrospectively collected data on *A. baumannii* infections, comparing CFD-based (47 patients) and colistin-based regimens (77 patients); the authors reported a significantly reduced 30-day mortality rate and risk of toxicity in the CFD-treated group (34% vs 55.8% 30-day mortality in CFD vs colistin-based treatment groups, respectively) [8]. As in our study, a better outcome, with a substantial reduction in both 14- and 30-day mortality, was observed in patients treated for BSI. Less benefit was shown in patients with pneumonia, making the authors speculate on a lower penetration of CFD in the epithelial lung fluid. The available in vivo studies describe an adequate plasma CFD concentration with standard dosing, with few data on epithelial lung fluid (ELF) concentration. Overall, CFD seems to have a good ELF penetration, effective for pathogens with a MIC <4 mg/L; nonetheless, there is an increased risk of microbiological failure with suboptimal CFD exposure [20–22]. Large clinical studies should be encouraged to explore whether new dosing strategies are needed to maximize CFD efficacy for CRAB pneumonia.

Different factors might have contributed to the discrepancy between RCT and real-life data about CFD treatment for CRAB, such as the recently hypothesized undetected heteroresistance of *A. baumanni* isolates toward CFD [23–25]. Heteroresistance refers to subpopulations with different antibiotic susceptibilities coexisting in the same bacterial colonies, with subgroup of cells having higher minimum inhibitory concentrations (MICs) than the main population. In *Acinetobacter baumannii*, the existence of heteroresistance has been demonstrated for different antibiotics, including colistin, tigecycline, and meropenem [26–28]. Choby et al. identified the presence of heteroresistance to CFD in all the analyzed *Enterobacterales* and CRAB isolates collected through different American surveillance systems and suggested that this phenomenon could have contributed to the increased mortality in the CREDBILE-CR study [26]. Other in vitro and in vivo studies have reinforced the existence of heteroresistance to CFD in CRAB, supporting the use of combination therapy as a strategy to overcome this resistance mechanism [28].

A better microbiologic efficacy of CFD when used in combination therapy seems to emerge from the study by Falcone et al., previously mentioned [8]. In this study, in spite of a significantly lower mortality in CFD-treated patients compared with colistin-treated subjects, microbiological failure was more frequent in patients treated with cefiderocol, especially

with CFD monotherapy. In our cohort, the majority of patients received CFD as part of a combination therapy (72.7%), mainly with colistin. No definitive data are available on this issue, and the potential optimal companion drug for CFD has yet to be identified, even if the synergistic effect of tigecycline in both CFD-susceptible and CFD-resistant isolates and colistin has been reported [29–32]. At the expense of theh epidemiological advantage and high tolerability of cefiderocol, treating severe MDR infections with more than 1 antibiotic might increase the possibility of having ≥1 effective drug promptly started, reducing mortality in these serious infections. In our population, CFD was started a median of 5 days after infection onset, while awaiting susceptibility results. Given the absence of automatized susceptibility testing for CFD and the complexity of the infections treated, it might be reasonable to start with a combination therapy including CFD until susceptibility results are available. More robust data are needed to plan an effective treatment strategy, with de-escalation criteria.

Limitations

The main limitation of our study is the small sample, deriving from a single center, limiting statistical analysis and logic inferring. It was a retrospective data collection; some patients had incomplete data, and follow-up cultures were often lacking, hindering evaluation of microbiologic outcomes. CRAB isolates were not stored; hence no further microbiology analysis could be performed (eg, heteroresistance studies in patients with unfavorable outcomes and documented CFD susceptibility). The study also has some strengths: being a real-life pathogen-driven study on CFD post-marketing use, excluding patients treated within compassionate use programs, and focusing on CRAB infections.

CONCLUSIONS

In conclusion, our findings reinforce the existing data and literature on the tolerability and efficacy of CFD to treat infections caused by carbapenem-resistant *Acinetobacter baumannii*, particularly for bloodstream infections. Robust multicenter studies should be encouraged to further address the suitableness of CFD for monotherapy and its place in treating MDR gram-negative infections.

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Prior presentation. Data were presented at the 33rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); April 15–18, 2023; Copenhagen, Denmark.

Patient consent. The study was approved by the local ethics committee (Comitato Etico Indipendente Fondazione PTV Policlinico Tor Vergata, experimentation register number 25.22). Given the retrospective nature of the study, written informed consent was waived by the ethics committee, in accordance with local legislation.

Potential conflicts of interest. L.C. received honoraria for lectures from MICOM Srl and research grants from Gilead Italia. E.T. received honoraria for lectures from AbbVie, Gilead, MSD, and Jannsen; participated in advisory boards for Jannsen and Gilead Science; and received a research grant from Gilead Sciences. M.I. received honoraria for lectures from Biogen Italia, AIM Educational, andMICOM srl and research grants from Gilead Italia and Roche; M.I. also participated in an advisory board for BD Biosciences. M.A. received funding for participation in advisory boards, for the preparation of educational materials, for research and educational grants, for participation in speaker panels, and for support for travel to conferences from Gilead Sciences, Janssen-Cilag, Viiv Healthcare, Merck Sharp and Dohme, AbbVie, Angelini, Pfizer, GSK, Menarini, Astra Zeneca, and Moderna. L.S. received a research grant from Gilead and fees for lectures and expertise from Merck, Gilead, and Pfizer. The other authors declare no conflicts of interest.

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