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A descriptive case series of pharmacokinetic/pharmacodynamic target attainment and microbiological outcome in critically ill patients with documented severe extensively drug-resistant *Acinetobacter baumannii* bloodstream infection and/or ventilator-associated pneumonia treated with cefiderocol

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ABSTRACT

Objectives: The aim of this study was to explore the relationship between cefiderocol pharmacokinetic/pharmacodynamic (PK/PD) target attainment and microbiological outcome in critically ill patients affected by extensively drug-resistant *Acinetobacter baumannii* (XDR-AB) bloodstream infection (BSI) and/or ventilator-associated pneumonia (VAP).

Methods: Patients who received compassionate use of cefiderocol to treat documented XDR-AB infections at the intensive care unit of the IRCCS Azienda Ospedaliero–Universitaria of Bologna and who underwent therapeutic drug monitoring (TDM) from 15 March 2021 to 30 April 2021 were retrospectively assessed. Cefiderocol trough concentration (C_{min}) was determined at steady-state, and the free fraction (fC_{min}) was calculated according to a plasma protein binding of 58%. The fC_{min}/MIC ratio was selected as a pharmacodynamic parameter of cefiderocol efficacy and was defined as optimal if ≥4, quasi-optimal if between 1 and 4, and suboptimal if <1. The association between fC_{min}/MIC and microbiological outcome was assessed.

Results: A total of 13 patients treated with cefiderocol for the management of XDR-AB infections (6 BSI plus VAP, 5 VAP and 2 BSI) were retrieved. fC_{min}/MIC ratios were suboptimal in 3 cases (23%) and quasi-optimal or optimal in 5 cases each (38%). Microbiological failure occurred in seven cases (54%; six with VAP and one with VAP plus BSI). Microbiological failure occurred in 80% of patients with suboptimal fC_{min}/MIC compared with 29% of those achieving optimal or quasi-optimal fC_{min}/MIC ratio.

Conclusion: Suboptimal attainment of PK/PD targets of cefiderocol may lead to microbiological failure of treatment with cefiderocol of critically ill patients affected by XDR-AB VAP.

Introduction

Extensively drug-resistant *Acinetobacter baumannii* (XDR-AB) represents a major cause of healthcare-associated infections, accounting for more than 12% of bloodstream infections (BSIs) and for a remarkable proportion of late-onset pneumonia in the intensive care unit (ICU) [1]. The emergence of isolates resistant to commonly available antibiotics makes the management of XDR-AB infections quite challenging and may lead to high failure rates and increased mortality among critically ill patients [1].

Cefiderocol is a novel siderophore cephalosporin that is active in vitro against carbapenem-resistant isolates of Enterobacteriaceae, *Pseudomonas aeruginosa, Stenotrophomonas maltophilia* and

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A. baumannii [2]. It is approved for the treatment of infections caused by multidrug-resistant aerobic Gram-negative organisms in adults with limited treatment options [2]. In a surveillance study, the overall in vitro susceptibility of carbapenem-resistant *A. baumannii* isolates to cefiderocol was 96.0%, with MIC_{50} and MIC_{90} values of 0.12 mg/L and 1 mg/L, respectively [3].

The efficacy of cefiderocol in the management of XDR-AB infections has been questioned by the CREDIBLE-CR trial showing that both microbiological failure and mortality rates were higher in patients treated with cefiderocol compared with those treated with best available therapy [4]. Conversely, some real-world clinical data suggested that cefiderocol may have good efficacy in the treatment of infections caused by XDR-AB [5,6]. However, real-world data assessing attainment of the pharmacokinetic/pharmacodynamic (PK/PD) target of cefiderocol in patients affected by carbapenem-resistant *A. baumannii* infections are limited to only one case [7].

The aim of this study was to explore the relationship between PK/PD target attainment and microbiological outcome in a case series of critically ill patients affected by documented severe XDR-AB infections and treated with cefiderocol.

Materials and methods

Patients who received compassionate use of cefiderocol for the management of documented XDR-AB infections at the ICU of IRCCS Azienda Ospedaliero–Universitaria of Bologna between 15 March 2021 and 30 April 2021 and who underwent therapeutic drug monitoring (TDM) of cefiderocol were retrospectively analysed. Demographic and clinical/laboratory data were extracted for each single patient. Type/site of infection, cefiderocol dosage, treatment duration, eventual co-treatment with other antibiotics, and the minimum inhibitory concentration (MIC) of cefiderocol against *A. baumannii* were also collected. The definition of XDR-AB was based on the classification proposed by Magiorakos et al. who stated as XDR those clinical isolates that were non-susceptible to at least one agent in all but two or fewer antimicrobial categories [8]. Documented BSI was defined as the isolation of *A. baumannii* from blood cultures, whereas documented ventilator-associated pneumonia (VAP) was defined as the presence of an *A. baumannii* bacterial load $\geq 10^4$ CFU/mL in the bronchoalveolar lavage (BAL) fluid culture documented after more than 48 h of endotracheal intubation and initiation of mechanical ventilation [9]. Cefiderocol was administered at the scheduled dosage of 2 g every 8 h (q8h) as a 3-h intravenous infusion. Dosage adjustments for renal impairment were performed according to the manufacturer's recommendations.

Antimicrobial susceptibility testing for cefiderocol was performed by the broth microdilution method with iron-depleted cation-adjusted Mueller–Hinton broth (ID-CAMHB) as previously described [10]. Briefly, ID-CAMHB was prepared by removing divalent cations with a cation-binding Chelex® 100 resin (Bio-Rad Laboratories, Hercules, CA, USA). The iron-depleted broth was filtered through a 0.2-μm pore size filter and was subsequently autoclaved and supplemented with 20–25 mg/L $CaCl_2$, 10–12.5 mg/L $MgCl_2$ and 0.5–1.0 mg/L $ZnSO_4$. Cefiderocol powder (Shionogi & Co., Ltd.) was dissolved and diluted in sterile normal saline. The microdilution panel was inoculated with a standardised inoculum at a final concentration of 1×10^5 CFU/mL and was incubated for 20 h at 35 ± 1°C.

The MIC of cefiderocol was determined according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines by evaluating the relative growth reduction (button of <1 mm) in comparison with the ID-CAMHB growth control well. Whenever the cefiderocol MIC was ≥2 mg/L, confirmation of resistance to cefiderocol was provided by means of disk diffusion susceptibility testing according to EUCAST standard methodology for non-fastidious organisms on regular Mueller–Hinton agar.

Blood samples for assessing plasma cefiderocol trough concentrations (C_{min}) were collected 15 min before one of the daily administrations after achieving steady-state conditions. Steady-state was considered achieved after the administration of at least four prior doses of cefiderocol. Samples were centrifuged and, after separation, plasma cefiderocol concentrations were determined by means of a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method using cefiderocol-d12 at a concentration of 10 ppm as internal standard working solution [11]. The lower limit of quantification was 0.25 mg/L.

As only total cefiderocol concentrations were measured, the free fraction (f) was calculated by taking into account the plasma protein binding reported in the literature of 58% [2].The fC_{min}/MIC ratio was selected as the best pharmacodynamic parameter for describing cefiderocol efficacy in terms of microbiological outcome. The fC_{min}/MIC ratio was defined as optimal if ≥4, quasi-optimal if between 1 and 4, and suboptimal if <1. Thresholds were selected according to preclinical models showing that a C_{min}/MIC ≥ 4 may be associated with suppression of emergence of resistance to β-lactams [12,13]. Microbiological failure was defined as the persistence of XDR-AB in blood and/or BAL culture after ≥7 days from starting cefiderocol treatment, as previously reported [14]. Microbiological eradication was defined as the occurrence of negativity of BAL or blood cultures in at least two subsequent assessments.

Descriptive statistics were used. Continuous data were presented as the mean ± standard deviation (S.D.) or median and interquartile range (IQR), whereas categorial variables were expressed by count and percentage.

The study was approved by the local ethical committee. Informed written consent was waived due to the retrospective and observational nature of the study.

Results

Overall, during the study period 13 patients were treated with cefiderocol for the management of XDR-AB infections and had a TDM assessment of cefiderocol C_{min} performed (Table 1). Patients were admitted to the ICU owing to acute respiratory distress syndrome caused by severe COVID-19 (coronavirus disease 2019) pneumonia and all underwent invasive mechanical ventilation. The mean ± S.D. age was 62.2 ± 17.2 years with a slight male preponderance (62%). The mean ± S.D. body mass index (BMI) was 31.2 ± 8.6 kg/m^2. Most patients (69%) had septic shock. Four patients (31%) underwent extracorporeal membrane oxygenation (ECMO) and two required continuous venovenous haemodiafiltration (one with ECMO).

The types of infections were BSI (8/13) and VAP (11/13). In 6 of the 13 patients BSI and VAP occurred simultaneously. All infections were microbiologically documented as being caused by XDR-AB. Overall, XDR-AB isolates were fully susceptible to cefiderocol, the MIC for cefiderocol being of 0.5 mg/L in five cases and 1 mg/L in the other eight. Furthermore, all *A. baumannii* isolates were susceptible to colistin.

Cefiderocol was administered at the full licensed dosage of 2 g q8h over 3 h in 11 patients and at the adjusted dose of 1.5 g q8h over 3 h in the other 2 patients according to the degree of renal impairment. No patient had augmented renal clearance. The median (IQR) duration of treatment was 10 days (8–13 days). Combination therapy was adopted in 3/13 cases (with ampicillin/sulbactam, fosfomycin, and ampicillin/sulbactam + colistin, respectively). The median (IQR) fC_{min} of cefiderocol was 2.39 mg/L (0.68–6.47 mg/L). The fC_{min}/MIC ratio was suboptimal in 3 cases (23%) and was quasi-optimal or optimal in 5 cases each (38%).

Table 1
Demographic and clinical features of critically ill patients affected by extensively drug-resistant *Acinetobacter baumannii* infections receiving cefiderocol

ID	Age/sex	BMI (kg/m^2)	Type of infection (bacterial load in BAL)	Cefiderocol MIC (mg/L)	Cefiderocol dosage (infused over 3 h)	fC_{min}/MIC [a]	Antibiotic co-treatment	CRRT/ECMO	ME BSI	ME VAP	30-day mortality
#1	55/F	27.1	BSI + VAP (>10^6)	0.5	1.5 g q8h	26.71	No	ECMO	Yes	No (>10^6)	No
#2	57/M	24.5	BSI	0.5	2 g q8h	3.11	No	ECMO	Yes	NA	Yes
#3	15/M	27.8	VAP (>10^6)	1	2 g q8h	6.89	No		NA	No (>10^6)	No
#4	75/F	32.7	BSI + VAP (>10^6)	0.5	2 g q8h	5.38		ECMO + CVVHDF CVVHDF	Yes	Yes	Yes
#5	54/M	31.6	BSI + VAP (>10^5)	1	2 g q8h	0.59	Colistin + SAM Fosfomycin	No	No	No (>10^6)	No
#6	67/F	31.3	BSI + VAP (10^6)	1	2 g q8h	2.94	No	No	Yes	No (10^6)	No
#7	65/M	29.4	BSI	0.5	2 g q8h	1.09	SAM	No	Yes	NA	Yes
#8	49/M	37.6	VAP (>10^6)	1	2 g q8h	2.39	No	ECMO	NA	No (>10^5)	No
#9	76/M	29.4	VAP (10^4)	1	2 g q8h	0.67	No	No	NA	No (>10^6)	No
#10	77/M	23.0	VAP (>10^6)	1	1.5 g q8h	2.35	No	No	NA	Yes	No
#11	68/F	27.1	BSI + VAP (10^5)	1	2 g q8h	0.63	No	No	Yes	No (10^5)	No
#12	72/F	56.9	BSI + VAP (10^6)	0.5	2 g q8h	28.39	No	No	Yes	Yes	No
#13	78/M	27.8	VAP (10^5)	1	2 g q8h	6.47	No	No	NA	Yes	Yes

BAL, bronchoalveolar lavage; BMI, body mass index; BSI, bloodstream infection; C_{min}, trough concentration; CRRT, continuous renal replacement therapy; CVVHDF, continuous venovenous haemodiafiltration; ECMO, extracorporeal membrane oxygenation; *f*Cmin, plasma cefiderocol trough concentration of the free fraction; ME, microbiological eradication; MIC, minimum inhibitory concentration; NA, not applicable; q8, every 8 h; SAM, ampicillin/sulbactam; VAP. ventilator-associated pneumonia.
[a] Estimated considering plasma protein binding of 58% [2].

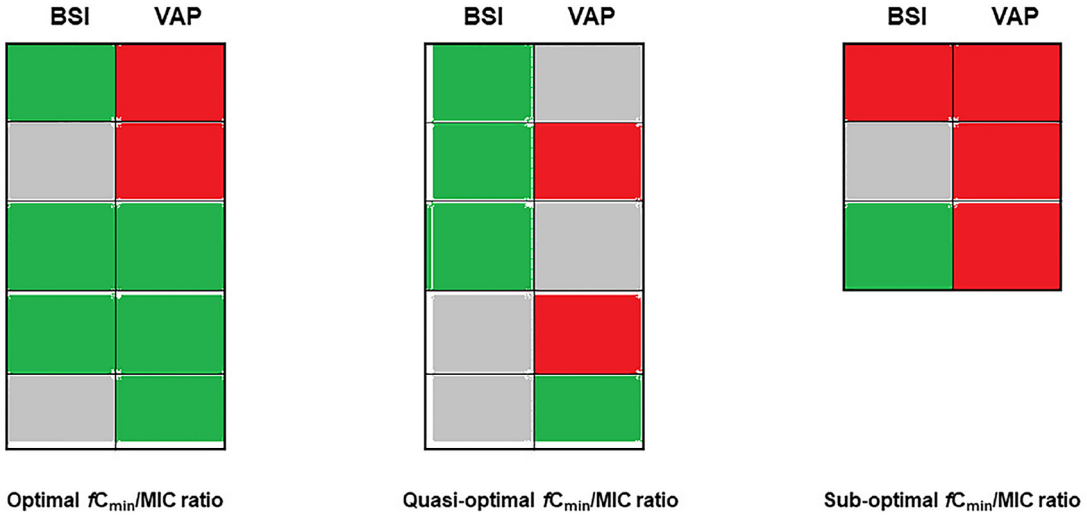

Fig. 1. Description of pharmacokinetic/pharmacodynamic target attainment (expressed as fC_{min}/MIC ratio) and microbiological outcome for cefiderocol. Green box, microbiological eradication; red box, microbiological failure; grey box, absence of the specific type of infection. Each row corresponds to a single patient. The fC_{min}/MIC ratio was defined as optimal if ≥4, quasi-optimal if between 1 and 4, and suboptimal if < 1. *f*Cmin, plasma cefiderocol trough concentration of the free fraction; MIC, minimum inhibitory concentration; BSI, bloodstream infection; VAP, ventilator-associated pneumonia.

The overall 30-day mortality rate was 31% (4/13). Microbiological failure occurred in 54% of patients (7/13), and concerned 6 VAP and 1 VAP plus BSI. Among those patients with microbiological failure, no changes in the *A. baumannii* susceptibility profile was observed on subsequent cultures compared with baseline. Microbiological failure occurred in 80% of patients with suboptimal fC_{min}/MIC compared with 29% of those with optimal or quasi-optimal fC_{min}/MIC ratio (Fig. 1). Interestingly, all patients with BSI who achieved optimal or quasi-optimal fC_{min}/MIC ratio had microbiological eradication (100% vs. 50%). Conversely, among patients with VAP, microbiological failure occurred in all three with suboptimal fC_{min}/MIC ratios (100% vs. 50%) and in two of the three with quasi-optimal fC_{min}/MIC ratios (83% vs. 40%).

Discussion

To the best of our knowledge, this is the first study assessing the feasibility and utility of TDM to evaluate achievement of the optimal PK/PD target of cefiderocol in critically ill patients affected by severe documented XDR-AB infections. Furthermore, the findings of PK/PD target attainment and microbiological outcome were described. Currently, real-world experience describing the role of cefiderocol in the management of *A. baumannii* infections are still limited. In previous studies, few patients affected by *A. baumannii* infections were included [5,6], and TDM of cefiderocol in patients with *A. baumannii* infection was applied only in one case without any evaluation of the correlation with microbiological outcome [7].

In our case series, microbiological failure in the treatment of XDR-AB infections with cefiderocol was quite frequent, exceeding 50% of cases, concerned mainly VAP, and approximately one-third of patients died. These findings are consistent with those of the CREDIBLE-CR trial that reported microbiological failure in the treatment of *A. baumannii* in 73% of cases and a mortality rate as high as 49% [4].

Noteworthy, our results showed that suboptimal and quasi-optimal cefiderocol PK/PD target attainment accounted for most of the cases with microbiological failure. Overall, the findings suggest a trend toward a proportional increase in microbiological failure of cefiderocol therapy in XDR-AB VAP when PK/PD target attainment shifted from optimal, to quasi-optimal and suboptimal,

respectively, although further confirmation of our hypothesis in larger prospective studies is required. However, these preliminary findings could support the utility of cefiderocol TDM in rapidly assessing achievement of the optimal PK/PD target.

The licensed dosing regimens of cefiderocol were based on achievement of a PK/PD target of 75–100%$fT_{>MIC}$ (corresponding to an fC_{min}/MIC of 0.75–1) in pivotal clinical trials, namely values that we defined as suboptimal in our study. Recent guidelines recommend that when dealing with severe Gram-negative bacterial infections in critically ill patients, a more aggressive PK/PD target should be achieved, namely 100%$fT_{>4–6\times MIC}$ [12,15]. This target has also been shown to be helpful in preventing the occurrence of resistance development [12,15]. Several preclinical data showed that achievement of a PK/PD target of C_{min}/MIC ≥ 4–6 (that is equivalent to 100%$fT_{>4–6\times MIC}$) was associated with the suppression of resistance occurrence with β-lactams in infections caused by Enterobacteriaceae and/or non-fermenting Gram-negative pathogens [12,13]. Notably, more than 70% of patients with microbiological failure of XDR-AB infections had cefiderocol fC_{min}/MIC < 4.

This issue is remarkable considering that 15% of the carbapenem-resistant pathogens isolated at baseline (almost one-half of which were *A. baumannii*) in the CREDIBLE-CR trial had a four-fold or even higher increase of MICs with cefiderocol treatment [4]. This suggests that the worse results found in the *A. baumannii* subgroup could be related to the achievement of inadequate cefiderocol PK/PD target, as shown in our case series.

In this regard, it could be speculated that the pharmacodynamic targets of cefiderocol needed for eradicating *A. baumannii* could be higher compared with those needed for eradicating Enterobacteriaceae or *P. aeruginosa*. Although no specific data on cefiderocol currently exist, some preclinical studies could support this hypothesis. One study showed that the pharmacodynamic targets of colistin required to achieve a 1-$\log_{10}$ and 2-$\log_{10}$ kill were higher against *A. baumannii* (*f*AUC/MIC = 6.98–42.1 and 17.5–95, respectively) than against *P. aeruginosa* (*f*AUC/MIC = 5.07–27.1 and 6.81–35.7, respectively) [16,17]. Likewise, the pharmacodynamic target required for meropenem to achieve a 2-$\log_{10}$ kill was slightly higher against *A. baumannii* compared to extended-spectrum β-lactamase-producing Enterobacteriaceae or *P. aeruginosa* (47.5%$fT_{>MIC}$ vs. 40%$fT_{>MIC}$) [18,19].

Based on these assumptions, implementation of a cefiderocol dosing strategy focused at achieving a PK/PD target of fC_{min}/MIC ≥ 4 could allow both to obtain microbiological eradication and to minimise the risk of resistance development in patients affected by XDR-AB infections [15].

It should not be overlooked that most of the microbiological failures occurred in patients with XDR-AB VAP. This suggests that microbiological eradication may be especially difficult in these deep-seated infections, as previously shown with other novel β-lactams [14]. This could be explained by the limited penetration rate of cefiderocol into the epithelial lining fluid (ELF), as suggested by the low cefiderocol ELF to total/free plasma ratios documented in healthy volunteers (0.1/0.24, respectively) [20].

Overall, these considerations support the rationale of more intensified dosages of cefiderocol (e.g. 2 g every 6 h) coupled with administration by continuous infusion as an approach that, by leading to better achievement of the aggressive PK/PD targets, could maximise cefiderocol exposure in critically ill patients with VAP.

We recognise that our case series is limited and that the study design was retrospective and monocentric. Additionally, only total cefiderocol concentrations were measured, thus potential variability in protein binding commonly encountered in critically ill patients could impact on cefiderocol free levels. However, this is the first real-life experience that explored and found a relationship between PK/PD target attainment of cefiderocol and microbiological outcome in the treatment of XDR-AB infections among critically ill patients.

In conclusion, we believe that the low eradication rate of XDR-AB during treatment of VAP with cefiderocol in our critically ill patients could be at least partially explained by suboptimal attainment of PK/PD targets, thus highlighting the potentially relevant role of cefiderocol TDM in this challenging scenario. Higher PK/PD targets could be desirable in XDR-AB VAP considering the low microbiological eradication and the limited penetration of cefiderocol into ELF. Additional larger clinical studies are warranted for confirming this hypothesis and for exploring whether new altered dosing strategies could be helpful in maximising cefiderocol efficacy in the treatment of XDR-AB infections.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

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None.

Competing interests

FP has participated in speakers bureaus for Angelini, Basilea Pharmaceutica, bioMérieux, Gilead, Hikma, Merck Sharp & Dohme, Nordic Pharma, Pfizer and Sanofi Aventis and on advisory boards for Angelini, Basilea Pharmaceutica, BeiGene, Gilead, Hikma, Merck Sharp & Dohme, Nordic Pharma, Novartis, Pfizer, Shionogi and Thermo Fisher; PV has participated in speakers bureaus for Correvio, Gilead, Merck Sharp & Dohme and Nordic Pharma and on advisory boards for bioMérieux, Gilead, Merck Sharp & Dohme, Nabriva, Nordic Pharma, Pfizer, Thermo Fisher and Venatorx. All other authors declare no competing interests.

Ethical approval

This study was approved by the local ethical committee [no. 442/2021/Oss/AOUBo]. Informed written consent was waived due to the retrospective and observational nature of the study.

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