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Real-life experience with compassionate use of cefiderocol for difficult-to-treat resistant *Pseudomonas aeruginosa* (DTR-P) infections

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Objectives: To describe our real-life experience with cefiderocol in XDR and difficult-to-treat resistant *Pseudomonas aeruginosa* (DTR-P) infections without any other available treatment options.

Methods: We included patients with a proven infection due to an XDR/DTR-P, who had failed on previous regimens, and were treated with cefiderocol, following them prospectively to day 90 or until hospital discharge or death.

Results: Seventeen patients treated for >72 h with cefiderocol were included: 14 receiving combination regimens (82.4%) and 3 receiving monotherapy (17.6%). Fourteen patients were males (82%) with a median age of 64 years (IQR 58–73). Fifteen patients (88.2%) were admitted to the ICU and five had septic shock (29%). Seven cases (41.2%) were ventilator-associated pneumonia, of which 71% (5/7) occurred in COVID-19 patients. Four were complicated intrabdominal infections, one ecthyma gangrenosum, one nosocomial pneumonia and one empyema, one osteomyelitis, one primary bacteraemia, and one nosocomial external ventricular drainage meningitis. Clinical cure and microbiological cure rates were 70.6% and 76.5%, respectively. There were six deaths (35.3%) after a median of 8 days (IQR 3–10) from the end of treatment, but only two of them (11.7%) were associated with *P. aeruginosa* infection progression.

Conclusions: Our experience collecting this large case series of DTR-P treated with cefiderocol may help clinicians consider this new option in this hard-to-manage setting. Our results are even more relevant in the current scenario of ceftolozane/tazobactam shortage. Importantly, this is the first study providing real-life data indicating adequate cefiderocol concentrations in CSF.

Introduction

Cefiderocol is a new siderophore cephalosporin that exploits iron transport systems to penetrate bacterial cells and that has been developed to meet the treatment challenge of carbapenem-resistant Gram-negative bacteria (CRGNB).[1] It has shown potent *in vitro* activity against carbapenem-resistant Enterobacteriaceae (CRE), such as strains producing KPC and metallo-β-lactamases (NDM, VIM and IMP), and against carbapenem-resistant non-fermenting Gram-negative bacteria (*Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*).[2]

Two randomized controlled trials (RCTs) have highlighted the efficacy of cefiderocol compared with regimens including carbapenems in complicated urinary tract infections (cUTI; APEKS-cUTI)[3] and nosocomial pneumonia (APEKS-NP),[4] while the CREDIBLE-CR study demonstrated its efficacy in the treatment of CRGNB when compared with best available therapy (BAT).[5,6] Nevertheless, in this latter randomized study, the prevalence of *P. aeruginosa* in the cefiderocol group was only 15%, and real-life studies exploring this specific setting are currently limited. Our aim was to further evaluate the role of cefiderocol in extensively drug resistant (XDR) and difficult-to-treat

resistant *P. aeruginosa* (DTR-P) infections[7] unresponsive to the BAT or without any other available treatment options.

Patients and methods

We conducted a prospective, observational study enrolling all the patients treated with compassionate use of cefiderocol admitted to two large tertiary-care hospitals in Northern Italy (the University Hospitals of Modena and Brescia) from February 2020 to May 2021. We included patients with a proven infection due to an XDR/DTR-P who failed previous treatment regimens or without any other available antibiotic option. Cefiderocol was administered at a standard dose of 2 g every 8 h, each given as a 3 h infusion, with a renal adjustment dose according to the manufacturer recommendations, unless otherwise noted. The patients were prospectively followed from start of cefiderocol to day 90 or until hospital discharge or death. Clinical cure was defined as a resolution, or an improvement of baseline signs and symptoms related to the infection; microbiological cure was defined as the absence of the same CRGNB isolates, both assessed after 7 days from the end of treatment (EOT) with cefiderocol. We also evaluated the occurrence and the time onset of relapse of the clinical signs and/or symptoms (referred to hereafter as 'relapse') or the microbiological recurrence of the baseline pathogen from an appropriate specimen (referred to hereafter as 'recurrence'), in those patients who previously reached clinical and microbiological cure. Thirty and 90 day all-cause mortality rates were also recorded.

All collected isolates were identified by MALDI-TOF MS using VITEK MS (bioMérieux, Marcy ÍEtoile, France) following the manufacturer's instructions. Antimicrobial susceptibility testing was performed by VITEK MS (bioMérieux) and for cefiderocol by broth microdilution panel YEUMDROF [Thermo Fisher Diagnostics S.p.A., Rodano (MI), Italia]. *P. aeruginosa* ATCC 27853 was used as QC strain. MICs were interpreted according to the EUCAST breakpoints, Version 11.0, 2021.[8]

Each *P. aeruginosa* isolate was classified according to the Magiorakos *et al*.[9] criteria as MDR, XDR or pandrug resistant (PDR) and further characterized according to Kadri *et al*.[7] as difficult-to-treat resistance (DTR).

Finally, we performed therapeutic drug monitoring (TDM) in the case of meningitis. Cefiderocol concentrations were determined by means of a validated liquid chromatography-tandem mass spectrometry method, using cefiderocol-d12 at a concentration of 10 ppm as internal standard working solution.[10] The lower limit of quantification for cefiderocol was 0.25 mg/L.

Ethics

According to the Early Access Program of Shionogi & Co. Ltd (closed on 26 April 2021), each single request for cefiderocol compassionate use was approved by the Institutional Ethics Committee of Modena and Brescia University hospitals.

Results

Table 1 shows the MIC values of the *P. aeruginosa* isolates.

A total of 17 patients were treated for >72 h with cefiderocol, 14 with combination regimens (82.4%) and 3 with monotherapy (17.6%). All the XDR/DTR-P were susceptible to cefiderocol (MIC ≤2 mg/L, MIC was not available for three strains). The median duration of therapy was 14 days (IQR 12–21). Cefiderocol was administered in all but one patient as a rescue therapy after experiencing failure of previous treatment regimens. Median time to switch was 3 days (IQR 2–5).

Fourteen patients were males (82%) with a median age of 64 years (IQR 58–73). Fifteen patients (88.2%) were admitted to ICU, five had septic shock (29%) and 13/17 (76.5%) underwent endotracheal intubation (ETI). Seven cases (41.2%) were ventilator-associated pneumonia (VAP) of which 71% (5/7) occurred in COVID-19 patients, one of them complicated with bacteraemia. Four cases were complicated intrabdominal infections: two peritonitis with retroperitoneal abscess following an acute necrotic-haemorrhagic pancreatitis and a pancreatectomy, one cholangitis in cholangiocarcinoma and one aortic graft infection with associated tertiary peritonitis. Finally, there was one osteomyelitis, one ecthyma gangrenosum, one nosocomial pneumonia, one recurrent thoracic empyema, one primary bacteraemia and one nosocomial external ventricular drainage meningitis. Patient characteristics, type of infections, pathogens and therapies are described in Table 2.

In most cases XDR/DTR *P. aeruginosa* was the only pathogen isolated, while three cases were polymicrobial: one with a PDR *A. baumannii*, one with *S. maltophilia* and one with a carbapenem and ceftazidime/avibactam-resistant KPC-producing *Klebsiella pneumoniae*.

In the whole population, clinical cure was observed in 12/17 patients (70.6%), all but one of them also obtained microbiological cure (13/17; 76.5%). We did not observe breakthrough infections during therapy with cefiderocol. Clinical relapse was observed in three patients (17.6%). The median time from cefiderocol discontinuation to relapse/recurrence was 10 days (IQR 10–12). Unfortunately, we were able to re-test cefiderocol in only one case (P3), in which the MIC increased from 0.25 to 1 mg/L.

Considering only patients with XDR/DRT-P HAP or VAP, the clinical and microbiological cure rates were respectively 62.5% (5/8) and 75% (6/8).

The 30 day and 90 day all-cause mortality rates were respectively 23.5% and 35.3%. The median time to death was 8 days (IQR 3–10) from the EOT. Importantly, only two deaths were associated with both clinical and microbiological failures.

There was no evidence of mild-to-moderate side effects, except for one case (P13) with a possible neurological drug-related adverse event (encephalopathy) requiring the discontinuation of cefiderocol (and amikacin) after 5 days of therapy.

Concerning the TDM for the meningitis case (P10), trough and peak cefiderocol serum levels were collected immediately before (–0.25 h) administration and at the end of 3 h infusion, respectively, resulting in concentrations of 105 mg/L (C_{min}) and 170 mg/L (C_{max}). CSF levels (13 mg/L) were measured 25 min before cefiderocol administration, concomitantly with serum trough concentrations, accounting for a C_{min} CSF/serum ratio of 12.4%. It is important to remark that P10 showed moderate renal impairment (creatinine clearance 44.8 mL/min) and was treated with high-dose cefiderocol (2000 mg q6h by 3 h infusion), to optimize drug penetration into the CSF, without developing adverse events despite the high dosage.

Discussion

Our study described a successful experience with the compassionate use of cefiderocol as rescue therapy in a series of 17 patients with severe infection due to XDR/DRT-P with no other antibiotic options available. We report a rate of clinical and microbiological success respectively of 70.6% and 76.5%. Although the rate of clinical cure reported in our study is in line with those previously reported in the larger RCTs, this result is relevant considering the

Table 1. MIC values and EUCAST breakpoints of the *P. aeruginosa* isolates

		MIC/EUCAST breakpoint (mg/L)													
Patient	Isolate	GEN	AMK	IPM	MEM	CIP	TZP	FEP	CAZ	CZA	C/T	FOF	ATM	CST	FDC
P1	*P. aeruginosa*	2/IE	4/16	>8/4	>8/8	0.5/0.5	16/16	16/8	16/8	8/8	1/4	NA	NA	≤0.5/2	≤2/2
P2[a]	*P. aeruginosa*	2/IE	≤32/16	>8/4	32/8	1/0.5	64/16	32/8	32/8	16/8	8/4	32	NA	2/2	1/2
P3	*P. aeruginosa*	≤1/IE	32/16	8/4	≥16/8	0.5/0.5	32/16	16/8	16/8	≥16/8	1/4	>64	128/16	NA	0.25/2
P4	*P. aeruginosa*	NA	4/16	>8/4	16/8	1/0.5	≥128/16	16/8	16/8	16/8	2/4	>64	32/16	2/2	0.5/2
P5[b]	*P. aeruginosa*	2/IE	4/16	2/4	2/8	2/0.5	32/16	8/8	2/8	2/8	1/4	NA	NA	<0.5/2	≤2/2
P6	*P. aeruginosa*	≤1/IE	2/16	>8/4	>8/8	0.12/0.5	>64/16	16/8	16/8	>8/8	8[d]/4	NA	NA	1/2	≤2/2
P7	*P. aeruginosa*	≤1/IE	≤1/16	>8/4	>8/8	>2/0.5	>64/16	NA/8	32/8	>8/8	2[d]/4	NA	NA	≤0.5/2	≤2/2
P8[c]	*P. aeruginosa*	≤1/IE	2/16	>8/4	32/8	1/0.5	32/16	16/8	16/8	16/8	1/4	128	>256/16	2/2	NA
P9	*P. aeruginosa*	>8/IE	8/16	>8/4	>8/8	>2/0.5	>64/16	>16/8	>32/8	>8/8	4/4	64	NA	≤0.5/2	≤2/2
P10	*P. aeruginosa*	2/IE	2/16	>8/4	64/8	0.5/0.5	16/16	>32/8	>32/8	8/8	2/4	32	8/16	NA	0.12/2
P11	*P. aeruginosa*	≤1/IE	2/16	NA	32/8	0.25/0.5	≥128/16	>32/8	≥64/8	≥16/8	8/4	64	>64/16	NA	0.5/2
P12	*P. aeruginosa*	4/IE	8/16	>8/4	64/8	1/0.5	≥128/16	≥32/8	≥64/8	>16/8	8/4	>256	>256/16	2/2	NA
P13	*P. aeruginosa*	≥16/IE	8/16	NA	16/8	≥4/0.5	32/16	≥32/8	≥64/8	>16/8	>16/4	>64	>16/16	1/2	1/2
P14	*P. aeruginosa*	4/IE	4/16	NA	>8/8	>2/0.5	32/16	NA	16/8	4/8	1[d]/4	128	NA	≤0.5/2	≤2/2
P15	*P. aeruginosa*	2/IE	4/16	>8/4	>8/8	0.5/0.5	>64/16	16/8	>32/8	>8/8	1[d]/4	NA	NA	2/2	≤2/2
P16	*P. aeruginosa*	>8/IE	4/16	>8/4	>8/8	>2/0.5	>64/16	16/8	8/8	2/8	1/4	64	NA	≤0.5/2	≤2/2
P17	*P. aeruginosa*	4/IE	4/16	>8/4	>8/8	0.12/0.5	>64/16	16/8	>32/8	>8/8	4/4	NA	NA	≤0.5/2	≤2/2

Abbreviations: GEN, gentamicin; AMK, amikacin; IPM, imipenem; MEM, meropenem; CIP, ciprofloxacin; TZP, piperacillin/tazobactam; FEP, cefepime; CAZ, ceftazidime; CZA, ceftazidime/avibactam; C/T, ceftolozane/tazobactam; FOF, fosfomycin; ATM, aztreonam; CST, colistin; FDC, cefiderocol; NA, not available; IE, insufficient evidence.
[a]Coinfected with PDR *A. baumannii*.
[b]Coinfected with MDR *S. maltophilia*.
[c]Coinfected with *K. pneumoniae* KPC.
[d]C/T available in that period.

peculiarity of our population. First of all, the prevalence of DRT-P infections was much higher than in previous studies: the rate was only 15% in the CREDIBLE-CR (including also MDR *P. aeruginosa*)[5,6] and in the study by Bavaro *et al.*,[11] while no cases were reported by Falcone *et al.*[12] Only Bleibtreu *et al.*[13] reported 9 of 12 cases (75%) of XDR *P. aeruginosa*, and 5 of them were non-susceptible to cefiderocol at baseline, contributing to the 55% overall clinical failure. Second, the clinical pictures of patients included were particularly challenging. Indeed, our series included difficult-to-treat-infections (meningitis, aortic prosthetic graft infections, osteomyelitis with prosthetic joint infection, acute necrotic-haemorrhagic pancreatitis and thoracic empyema) that are characterized by poor penetration of antibiotics, inadequate source control and inadequate host defence/cellular response. All these factors could affect the antibiotic pharmacodynamic and pharmacokinetic aspects and may influence clinical outcome. Finally, these favourable outcomes are even more relevant since almost 90% of the patients were admitted to intensive care and they all had an extended follow-up of 90 days, significantly longer than other published case series,[11,13] and 30% of our cases were critically ill COVID-19 patients with a VAP due to XDR/DRT-P, associated *per se* with a significantly increased 28 day mortality rate.[14]

Concerning mortality, there is still an open debate after the alarming results reported by the CREDIBLE-CR study, in which the authors reported numerically more deaths in the cefiderocol group, especially in patients affected by *Acinetobacter* spp. infections.[5,6] In our series, six patients died (35.3%) but only two of them reported both clinical and microbiological failure. The first case was a COVID-19 patient (P4) with a DTR-P VAP who died during cefiderocol therapy after 18 days and after 40 days of extracorporeal membrane oxygenation (ECMO). The second one, P9, with a prosthetic joint infection and osteomyelitis, died while waiting for joint replacement.

Therefore, our study, in agreement with previous studies,[12,13] confirms that inadequate source control together with failing to achieve adequate drug exposure still represents a crucial risk factor for death related to infection. To date, no real-world evidence regarding the administration of cefiderocol during ECMO exists and optimizing the drug dosage in this emerging clinical scenario could be extremely difficult.

Notably, this is the first study providing real-life data on CSF and plasma cefiderocol concentrations. Our findings suggest that high-dose cefiderocol could allow adequate CSF concentrations to be achieved. However, further confirmation through the assessment of AUC CSF:plasma ratio will be required.

Lastly, in our series, cefiderocol has been mostly used in combination therapy. The main combinations were with colistin (often by inhalation for VAP), fosfomycin, ceftazidime/avibactam and amikacin. It is important to highlight that two out of three patients treated with cefiderocol monotherapy experienced microbiological relapse and one of them (P3) reported an MIC creep. Currently, there is still no agreement about how to use cefiderocol, whether in monotherapy[12] or in combinations,[11,15] and further studies are needed.

Table 2. Description of patient characteristics, type of infections, pathogens and therapies

Patient	Age (years)/ sex	Underlying conditions	ICU	ETI	CRRT/ ECMO	Type of infection	Septic shock	Pathogens	Combination therapy with FDC	FDC MIC (mg/L)	FDC dose	Days of therapy	FDC Adverse events	Previous/ empirical treatment regimen	Outcome (after 7 days from EOT)	Death (days after EOT)	Relapse/ recurrence (days after EOT)
P1	66/M	Haematologic cancer with neutropenia	No	No	No	HAP	No	XDR/DTR-P	FDC+CST	≤2	2 g q8h	21	No	TZP+CST (aerosol)	CC, MC	No	No
P2	73/M	Rhino-pharyngeal cancer	Yes	Yes	No	VAP	No	XDR/DTR-P, *A. baumannii* PDR	FDC+CST (aerosol)	NA	2 g q8h	5	No	CST (aerosol) +TGC+SAM	CF, NA	Yes (9)	No
P3	64/M	COVID-19	Yes	Yes	CRRT	VAP	No	XDR/DTR-P	FDC	0.25	2 g q12h	13	No	None	CC, MC	No	Yes (recurrence+ relapse, 12)
P4	51/M	COVID-19	Yes	Yes	ECMO	VAP	Yes	XDR/DTR-P	FDC+FOF	0.5	2 g q6h (ECMO)	18	No	CZA+FOF	CF, MF	Yes (0)	No
P5	53/M	COVID-19	Yes	Yes	No	VAP	No	*P. aeruginosa* MDR, *S. maltophilia*	FDC+CST (aerosol) +MXF	≤2	2 g q8h	13	No	MEM	CC, MC	No	No
P6	53/M	Left upper sleeve lobectomy in thoracotomy, poorly differentiated adenocarcinoma	Yes	Yes	No	VAP	No	XDR/DTR-P	FDC+CST	≤2	2 g q8h	14	No	MEM+FOF+ C/T+CIP	CC, MC	No	No
P7	62/M	COVID-19	Yes	Yes	No	VAP	Yes	XDR/DTR-P	FDC+CST (aerosol+ev)	≤2	2 g q8h	16	No	C/T+CST (aerosol)	CC, MC	No	No
P8	74/M	COVID-19	Yes	Yes	CRRT	VAP, BSI	Yes	XDR/DTR-P, *K. pneumoniae* KPC	FDC+CZA+FOF	NA	1 g q8h	7	No	CZA+FOF	CF, MC	Yes (7)	No
P9	70/F	Relapsing infections in hip replacement	Yes	Yes	No	Osteomyelitis with PJI	No	XDR/DTR-P	FDC+CST	≤2	2 g q8h	25	No	TEC+RIF+TZP	CF, MF	Yes (10)	No
P10	77/M	Craniotomy after cerebellar AVM bleeding	Yes	Yes	No	Nosocomial external ventricular drainage meningitis	No	XDR/DTR-P	FDC+FOF+CZA	0.12	2 g q6h	14	No	CZA+FOF +ATM	CC, MC	No	No
P11	64/F	Recurrent cholangitis, cholangiocarcinoma	Yes	Yes	No	Cholangitis	Yes	XDR/DTR-P	FDC+FOF	0.5	2 g q8h (CRRT)/1 g q8h	12	No	CZA+AMK +ATM	CF, MC	Yes (3)	No
P12	74/M	Rupture abdominal aortic aneurysm, colon perforation	Yes	Yes	No	Aortic graft infection, peritonitis	Yes	XDR/DTR-P	FDC+CZA	NA	1.5 g q8h	15	No	CZA+FOF +AMK	CC, MC	No	No
P13	73/M	Multiple myeloma	No	No	No	cSSTI (ecthyma gangrenosum)	No	XDR/DTR-P	FDC+AMK	1	2 g q8h	5	Yes	MEM+FOF	CC, MF	No	Yes (relapse, 10)
P14	64/M	Mesothelioma	Yes	No	No	Recurrent thoracic empyema	No	XDR/DTR-P	FDC	≤2	2 g q8h	28	No	C/T+GEN	CC, MC	No	No
P15	50/F	Acute necrotic-haemorrhagic pancreatitis	Yes	Yes	No	Peritonitis and retroperitoneal abscess	No	XDR/DTR-P	FDC+CIP	≤2	2 g q8h	21	No	C/T+CIP +AMK	CC, MC	Yes (23)	No
P16	58/M	Pancreatic cancer, pancreatectomy	Yes	No	CRRT	Peritonitis and retroperitoneal abscess, BSI	No	XDR/DTR-P	FDC+TGC+RIF	≤2	1.5 g q8h (10), 2 g q8h (13)	23	No	CZA+TGC	CC, MC	No	No
P17	77/M	Endocarditis with cerebral embolization by *E. faecalis*	Yes	Yes	No	Primary bacteraemia	No	XDR/DTR-P	FDC	≤2	2 g q8h	12	No	TZP+AMK	CC, MC	No	Yes (relapse, 10)

Abbreviations: ICU, intensive care unit; ETI, endotracheal intubation; CRRT, continuous renal replacement therapies; ECMO, extracorporeal membrane oxygenation; MIC, minimal inhibitory concentration; EOT, end of treatment; F, female; M, male; COVID-19, coronavirus disease 2019; AVM, arteriovenous malformation; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; BSI, bloodstream infection; PJI, prosthetic joint infection; cSSTI, complicated skin and soft tissue infection; MDR, multidrug-resistant; XDR, extensively drug-resistant; PDR, pandrug-resistant; DTR-P, difficult-to-treat resistant *Pseudomonas aeruginosa*; KPC, *Klebsiella pneumoniae* carbapenemase; NA, not available; FDC, cefiderocol; CST, colistin; TZP, piperacillin/tazobactam; FOF, fosfomycin; SAM, ampicillin/sulbactam; TGC, tigecycline; CZA, ceftazidime/avibactam; MXF, moxifloxacin; MEM, meropenem; C/T, ceftolozane/tazobactam; CIP, ciprofloxacin; TEC, teicoplanin; RIF, rifampicin; ATM, aztreonam; AMK, amikacin; GEN, gentamicin; CC, clinical cure; MC, microbiological cure; CF, clinical failure; MF, microbiological failure.

Our study has several limitations. The limited sample size from only two Italian centres does not allow us to draw universal and definitive conclusions. Moreover, information about molecular mechanisms of *P. aeruginosa* resistance and about *in vivo* development of cefiderocol resistance observed in other real-life series are lacking in our study and need future investigations.[11–13,16]

In conclusion, our experience describing a large number of cases of DTR-P susceptible to cefiderocol allows us to provide promising data that may help clinicians with the use of cefiderocol in this hard-to-manage setting. Our results are even more relevant in the current scenario of ceftolozane/tazobactam shortage.

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Transparency declarations

None to declare.

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