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Short Communication

Cefiderocol for compassionate use in the treatment of complicated infections caused by extensively and pan-resistant *Acinetobacter baumannii*

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ABSTRACT

Objective: This study presents real-life experience with cefiderocol used on a compassionate basis for treatment of three patients with severe infections caused by extensively/pan-drug resistant (XDR/PDR) *Acinetobacter baumannii* (Ab).
Methods: Serum bactericidal activity was determined and considered as a surrogate of cefiderocol susceptibility.
Results: Clinical improvement and microbiological eradication of *A. baumannii* were observed in all three patients, who were affected by extremely complex conditions either for type of infection, adverse effect or resistance profile of *A. baumannii*.
Conclusion: Cefiderocol for XDR/PDR-Ab infections might be reconsidered, especially in light of the recent disappointing results of the CREDIBLE-CR study.

1. Introduction

Cefiderocol is a novel siderophore cephalosporin exhibiting potent activity against multi-drug-resistant (MDR) Gram-negative microorganisms [1–4]. The efficacy of cefiderocol in the setting of extensively resistant *Acinetobacter baumannii* (XDR-Ab) infection has been questioned by the recent CREDIBLE-CR study, which showed a higher rate of clinical failure in patients receiving cefiderocol versus best available therapy (BAT) to treat carbapenem-resistant Gram-negative infections, especially those caused by XDR-Ab [5]. Nevertheless, favourable experience with use of cefiderocol for treatment of XDR Gram-negative bacterial infections including *A. baumannii* has been reported recently [6–8].

Herein, we share our real-life experience with use of cefiderocol on a compassionate basis for treatment of severe infections caused by XDR and pan-drug resistant (PDR)-Ab.

2. Method

The VITEK-2 (Bio-Merieux, Marcy l'Etoile, France) automated system was used to perform identification and antimicrobial susceptibility testing (AST). As it was not possible to perform AST for cefiderocol, we determined the serum bactericidal activity (SBA) as a potential substitute of cefiderocol susceptibility, according to the method described by Stratton [9]. Briefly, two-fold serial dilutions of the test samples in human serum were prepared in microtitre plates. For each strain, exponentially growing cultures were diluted to $\sim 10^6$ CFU/mL in Mueller-Hinton broth supplemented with Mg^{2+} and Ca^{2+} and 50 μL of the bacterial suspension was distributed into each well to give a final bacterial concentration of 5×10^5 CFU/mL. Aliquots of 10 μL each were withdrawn from the wells that did not show visible growth and sub-cultured on trypticase soy agar supplemented with blood. A colony count was performed after 48 h of incubation at 35 °C. SBA was defined as the highest dilution of each sample that reduced the initial inoculum by ≥99.9% [9]. A target peak bactericidal titre of >1:8 and a trough >1:2 were considered predictive of efficacy or associated with a more favourable clinical outcome [10]. An inherent limitation of SBA testing is the low turnaround time, which might contribute to affect the final outcome of patients.

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Table 1
Cefiderocol for compassionate use in the treatment of complicated infections caused by extensively and pan-resistant *Acinetobacter baumannii*.

Patient, age, sex and comorbidities	Reason for hospitalization	Preceding infection (s)	Current infection(s)	Susceptibility of *A. baumannii*	Previous therapy	Reason for cefiderocol use	Dosage of cefiderocol[§]	Duration of cefiderocol therapy, d	SBA*	Clinical and microbiological outcome
#1, 60 y male, hypertension	Haemorrhagic cardiac tamponade	VAP	Carbapenem and CAZ-AVI resistant Kp ST; PDR-Ab breakthrough bacteraemia	Pan-drug resistant (colistin MIC > 2 μg/mL); tygecicline MIC = 4 μg/mL	TMP/SMX	TMP/SMX induced myelotoxicity; PDR-Ab breakthrough bacteraemia	1.5 g bid (CVVHD)	14	–	Clinical improvement and clearance of XDR-Ab from the blood; death for acute cardiac failure after 30 d in absence of infection relapse
#2, 70 y female, type II diabetes mellitus	Septic shock caused by *K. oxytoca* and right suppurative pyelonephritis	Secondary BSI caused by *K. oxytoca*	XDR-Ab persistent BSI; XDR-Pa breakthrough bacteraemia	Susceptible only to colistin (MIC = 0.5 μg/mL); tygecicline MIC = 4 μg/mL	Colistin	Persistently XDR-Ab positive BCs	2.0 g tid (CVVHDF)	14	1:64 (trough) against XDR-Ab; 1:16 (trough) against XDR-Pa	Clinical improvement and clearance of XDR-Ab from the blood; absence of XDR-Pa clearance from the blood; death for HSV-1 disseminated infection after 14 d
#3, 55 y female, severe scoliosis	Spinal fusion for scoliosis along the entire spine	Spinal implant infection and lung empyema caused by MRSA	XDR-Ab spondylodiscitis	Susceptible only to colistin (MIC = 0.5 μg/mL); tygecicline MIC = 2 μg/mL	Colistin; HD tygecicline°	Colistin renal toxicity; tygecicline-induced severe coagulopathy	2.0 g tid (normal renal function)	21	1:256 (peak)^; 1:128 (trough)^	Clinical cure at 9-month follow-up; clearance of XDR-Ab from the bone
Trecarichi et al. [7], adult male	Severe H1N1 influenza virus complicated by bilateral pneumonia	Bilateral pneumonia	XDR-Ab and KPC-Kp VAP and BSI	Susceptible only to colistin (MIC ≤ 0.5 μg/mL); tygecicline MIC = 1 μg/mL. Cefiderocol disc diffusion testing 23 mm[§]	Colistin; fosfomycin; tygecicline; ampicillin/sulbactam; ceftazidime/avibactam; rifampicin	Colistin toxicity; persistence of fever and worsening of lung infiltrates	Not specified	14	–	Clinical and microbiological cure
Dagher et al. [8], 57 y, male, type 2 diabetes mellitus and hypertension	Worsening of left leg pain after external fixation and debridements for open comminuted left tibia and fibula fracture	None	Polymicrobial osteomyelitis (*XDR-Ab*, *Enterococcus faecalis*, *Corynebacterium striatum*)	Susceptible to colistin (MIC ≤ 2 μg/mL), fosfomycin (17 mm), intermediate to minocycline (14 mm). Cefiderocol disc diffusion testing 23 mm[§]	Polymyxin B; intravenous minocycline; tigecycline; meropenem	Polymyxin B renal toxicity; minocycline toxicity; persistence of XDR-Ab from intra-operative cultures	2.0 g tid	109	–	Clinical and microbiological cure
Zingg et al. [6], Case#1, 29 y, male	Early postoperative implant-associated polymicrobial wound infection after external fixation of a 3rd degree open fracture of the tibia	None	Acute polymicrobial osteomyelitis (VIM-producer *P. aeruginosa*, OXA-23 *A. baumannii*, KPC producer *Enterobacter cloacae*)	Susceptible to colistin, tygecicline, fosfomycin. Cefiderocol disc diffusion testing 23 mm[§]	Not specified	–	Not specified	14	–	Clinical and microbiological cure
Zingg et al. [6], Case#2, 64 y male	Vertebral stabilization and external fixation of the femur	None	Early postoperative implant-associated infection of the spine (OXA-40 and NDM-producer *A. baumannii*)	Susceptible only to colistin. Cefiderocol disc diffusion testing 18 mm[§]	Not specified	–	1.5 g tid (after adjustment for renal clearance)	54	–	Clinical cure

Table 1 (*Continued*)

Patient, age, sex and comorbidities	Reason for hospitalization	Preceding infection (s)	Current infection(s)	Susceptibility of *A. baumannii*	Previous therapy	Reason for cefiderocol use	Dosage of cefiderocol[§]	Duration of cefiderocol therapy, d	SBA*	Clinical and microbiological outcome
Zingg et al. [6], Case#3, 62 y, male	Blunt thoracic trauma with injury of the lung parenchyma, haemothorax and serial rib fractures	Kp and XDR-Ab HAP	Left-sided pleural empyema with XDR-Ab and *C. striatum*; subsequent acute osteomyelitis and urinary tract infection caused by XDR-Ab	Susceptible to colistin; intermediate to amikacin. Cefiderocol disc diffusion testing 20 mm[§]	Not specified	–	1.5 g tid (after adjustment for renal clearance)	42	–	Clinical and microbiological cure

BC = blood culture; BSI = bloodstream infection; CAZ-AVI = ceftazidime/avibactam; CVVHD = continuous veno-venous hemodialysis; CVVHDF = continuous veno-venous hemodiafiltration; HAP = hospital-acquired pneumonia; HD = high dosage; Kp = *Klebsiella pneumoniae;* KPC-Kp = carbapenemase-producing *Klebsiella pneumoniae;* MRSA = methicillin-resistant *Staphylococcus aureus;* PDR-Ab = pan-drug resistant *Acinetobacter baumannii;* SBA = serum bactericidal activity; ST = septic thrombosis; TMP/SMX = trimethoprim/sulphamethoxazole; VAP = ventilator-associated pneumonia; XDR-Ab = extensively resistant *Acinetobacter baumannii;* XDR-Pa = extensively resistant *Pseudomonas aeruginosa.*

[§]Dosage of cefiderocol according to renal function.

*SBA was performed after 5 d of cefiderocol therapy.

◦100 mg bid.

^SBA was performed after 5 and 12 d of cefiderocol therapy. At each time point (5th and 12th d of therapy) peak and trough measurements were performed.

[§]15 mm breakpoints for a 30 μg disc.

In the present report, the SBA results were available 72 h after serum collection.

3. Results

3.1. Case#1

A 65-y-old patient with hypertension was admitted for cardiac tamponade and underwent cardiothoracic surgery. He had a prolonged post-surgery course in the intensive care unit (ICU), which included septic thrombosis of the central veins caused by a ceftazidime/avibactam-resistant (MIC 12 μg/mL) carbapenemase-producing *K. pneumoniae* susceptible only to trimethoprim/sulphamethoxazole (TMP/SMX, MIC < 2 μg/mL as for TMP concentration). The patient improved on TMP/SMX but developed a PDR-Ab breakthrough bacteraemia (BB) and severe myelotoxicity. Thus, cefiderocol represented the only therapeutic option and was given at a dosage of 1.5 g every 12 h for a total of 14 d according to renal function with prompt favourable clinical and microbiological response (Table 1). He was then transferred to rehabilitation without signs of infection. Death occurred 30 d after discharge from acute cardiac failure with no apparent signs of infection relapse.

3.2. Case#2

A 70-y-old female with a history of diabetes mellitus was admitted to the ICU because of *Klebsiella oxytoca* septic shock associated with bacteraemic pyelonephritis requiring right nephrectomy. On day 21, she developed XDR and colistin-susceptible (0.5 μg/mL) Ab bacteraemia persisting despite appropriate colistin therapy, and her clinical course was further complicated by XDR *P. aeruginosa* (XDR-Pa) BB. Given the persistence of positive blood cultures irrespective of appropriate in vitro therapy, cefiderocol for compassionate use was requested and then administered at a dosage of 2 gr every 8 h. On day 5 of cefiderocol therapy, trough SBA 1:64 and 1:16 titres were obtained against XDR-Ab and XDR-Pa, respectively [9]. On subsequent days, microbiological eradication was obtained for XDR-Ab; conversely, XDR-Pa persisted (Table 1). Death occurred on day 14 of cefiderocol from an intercurrent disseminated HSV-1 infection.

3.3. Case#3

A 56-y-old female was hospitalized for *Staphylococcus aureus* spinal implant infection requiring vacuum-assisted-closure along the entire spine. On treatment, the patient developed wound superinfection and spondylodiscitis with bone cultures (obtained by biopsy) growing XDR *A. baumannii* (colistin MIC = 0.5 μg/mL; tygecicline MIC = 2 μg/mL): targeted therapy was complicated by acute renal failure during colistin and tigecycline-induced severe coagulopathy [11]. Additionally, control bone cultures remained persistently positive for XDR-Ab and therefore cefiderocol was started. She clinically improved with bone microbiological eradication with a 21 d cefiderocol treatment course, which provided peak/trough SBA titres of 1:256/1:128, respectively. The patient concluded 6 weeks of oral minocycline treatment and no infection relapse after a 9-month follow-up was observed (Table 1).

4. Discussion

Severe infections caused by XDR/PDR-Ab are associated with high mortality rate and therapeutic failure, possibly related to colistin-induced toxicity or resistance, as occurred in our cases [12,13]. In this setting cefiderocol, a novel siderophore cephalosporin exhibiting a unique mode of action with activity against carbapenem-resistant Gram-negative bacteria including

nonfermenters might represent a promising option [1,14–17]. Although the efficacy of cefiderocol in the setting of carbapenem-resistant Gram-negative infections, and especially those caused by *A. baumannii,* has been doubted by the CREDIBLE-CR study, no specific reason for the difference in mortality could be found, suggesting that additional investigations are needed [5]. On the other hand, recent real-life reports showed clinical and microbiological effectiveness of cefiderocol for the treatment of XDR-Ab infections [6–8] (Table 1). In fact, Trecarichi et al. described a patient with severe H1N1 influenza further complicated by ventilator-associated pneumonia and bloodstream infection caused by XDR-Ab and carbapenemase-producing *Klebsiella pneumoniae* successfully treated with cefiderocol for a total of 14 d [7], whereas Dagher et al. described the successful use of cefiderocol as a rescue treatment adjuvant to surgical debridement for polimicrobial osteomyelitis containing also XDR *A. baumannii* [8] (Table1). Of note, a marked safety profile of cefiderocol was observed as no adverse events were noted after 109 d of treatment, in line with the CREDIBLE-CR study which reported lower rates of drug-related acute renal injury in patients receiving cefiderocol compared to BAT [5,18]. Zingg and colleagues presented a series of three patients treated with cefiderocol for complicated XDR-Ab infections, including a postoperative implant-associated polymicrobial wound infection, a spine infection and a hospital-acquired pneumonia [6] (Table 1). Again, no significant adverse events were observed.

Although only a case series, our report seems to confirm the efficacy of cefiderocol against XDR/PDR-Ab [6–8]. Clinical improvement and microbiological eradication of *A. baumannii* were observed in all patients, who were affected by extremely complex conditions either for type of infection, adverse effect observed during the course of targeted therapy or resistance profile of *A. baumannii*.

The effect of cefiderocol was remarkable in microbiological eradication of XDR-Ab from the bone in Case#3, corroborating recent reports on its efficacy in treatment of osteomyelitis [6,8,19]. The unique mode of action of cefiderocol on bacterial iron-transport system might explain the observed effectiveness against biofilm-associated infections such as osteomyelitis [8].

Our clinical findings are consistent with SBA values, which have been used in the present cases as a surrogate marker of cefiderocol susceptibility as it was not possible to perform in vitro susceptibility testing [9,20]. Of note, the lower SBA titres against XDR-Pa corresponded with the absence of bacteraemia clearance in Case#2, persistence of which might have contributed to the final fatal outcome. These findings confirm the recent results which showed that SBA, although labour-intensive, have prognostic value for identifying patients at high risk for treatment failure during Gram-negative infections [21]. Furthermore, it should be noted that high peak SBA titres (i.e. > 1:64) would be required to achieve higher target exposures proposed for more severely ill patients or reduce the risk of resistance [21,22]; therefore, the unfavourable outcome of patient #2 could be also attributed to low peak SBA titres, which, unfortunately, were not measured.

In conclusion, taking our cases together with the available data from the literature, the use of cefiderocol for treatment of severe and complex infections resulting from XDR/PDR-Ab might be reconsidered, especially in light of the recent disappointing results of the CREDIBLE-CR study. Further investigation is required to understand the real role of cefiderocol for serious infections caused by XDR/PDR Gram-negative bacilli.

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Competing interests

None declared.

Ethical approval

The local Ethical Committee approved the requests and each patient signed a written informed consent to receive cefiderocol (Shionogi & Co. Ltd., Osaka, Japan) on a compassionate basis.

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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