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BRIEF REPORT

Cefiderocol for Extensively Drug-Resistant Gram-Negative Bacterial Infections: Real-world Experience From a Case Series and Review of the Literature

Sandra Zingg,[1,a] G. Jacopo Nicoletti,[2,a] Sabine Kuster,[1] Milena Junker,[2] Andreas Widmer,[1] Adrian Egli,[3,4] Vladimira Hinic,[3] Parham Sendi,[1,5] Manuel Battegay,[1] Veronika Bättig,[1] Nina Khanna,[1] and Sarah Tschudin-Sutter[1,6]

[1]Division of Infectious Diseases & Hospital Epidemiology, University Hospital Basel and University of Basel, Basel, Switzerland, [2]Division of Internal Medicine, University Hospital Basel, Basel, Switzerland, [3]Division of Clinical Bacteriology and Mycology, University Hospital Basel, Basel, Switzerland, [4]Applied Microbiology Research, Department of Biomedicine, University of Basel, Basel, Switzerland, [5]Department of Orthopaedics and Traumatology, University Hospital Basel, University of Basel, Basel, Switzerland, and [6]Department of Clinical Research, University Hospital Basel, Basel, Switzerland

Cefiderocol is a new siderophore cephalosporin with activity against carbapenem-resistant gram-negative bacteria. Data on its clinical efficacy are limited to complicated urinary tract infections. We present a series of 3 patients successfully treated with cefiderocol for complicated health care–associated infections and review published case reports.

Keywords. carbapenemase; case series; cefiderocol; drug-resistant gram-negatives; review.

Cefiderocol is a new siderophore cephalosporin with activity against carbapenem-resistant gram-negative bacteria, including *Enterobacterales* [1] and nonfermenters [2]. Its novel bacterial cell wall penetration mechanism overcomes all classes of carbapenemases [3], porin channel mutations, and efflux pump overexpression [4]. Data on the clinical efficacy of cefiderocol are limited mainly to complicated urinary tract infections [5]. Based on the results of a phase II trial [5], cefiderocol was granted US Food & Drug Administration (FDA) approval for the treatment of adult patients with complicated urinary tract infections (UTIs) caused by susceptible gram-negative bacteria with limited or no alternative treatment options in November 2019 (https://www.fda.gov/news-events/press-announcements/fda-approves-new-antibacterial-drug-treat-complicated-urinary-tract-infections-part-ongoing-effort). Clinical data on the efficacy of cefiderocol for treatment of multidrug-resistant bacterial infections involving other body sites are lacking. We present a series of 3 consecutive patients treated with cefiderocol for complicated health care–associated infections and review published clinical case reports.

The University Hospital of Basel is a tertiary care center with ~670 beds, admitting around 35 000 adult patients annually. It serves as a referral center for patients requiring specialized medical care in the northwestern part of Switzerland. We applied to Shionogi's cefiderocol compassionate use program for 3 patients hospitalized at our institution between 12/2018 and 12/2019. Susceptibility testing for cefiderocol was performed with disk diffusion testing according to the company's instructions. The susceptibility patterns of all other agents were reported according to the 2018 European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations, or the 2018 Clinical and Laboratory Standards Institute (CLSI) Performance Standards for Antimicrobial Susceptibility Testing if EUCAST recommendations were not available. Susceptibility testing for cefiderocol was interpreted according to the company's instructions. Results, as well as cefiderocol inhibition zone diameters, are presented in Table 1. Carbapenemase-encoding genes were confirmed through molecular diagnostics (Easyplex SuperBug CPE Assay, Amplex BioSystems, Giessen, Germany).

To identify clinical reports of cefiderocol treatment beyond the setting of clinical trials, we searched Embase and Medline for all reports published up to January 7, 2020, using the search terms "cefiderocol" or "S-649266."

All patients included in this report are part of an ongoing cohort study on patients with carbapenemase-producing bacteria at our institution (ClinicalTrials.gov Identifier: NCT04098133), which has been approved by the local ethics committee (Ethikkommission Nordwest-und Zentralschweiz, Project-ID 2019-01548). The main characteristics of the 3 cases treated at our institution, as well as the cases identified by the literature search, are summarized in Table 2 and Supplementary Table 1. The standard dose of cefiderocol (2 g 3 times daily) was initiated in all 3 patients with normal baseline creatinine levels.

Case 1

A 29-year-old male patient was transferred to our hospital after being hospitalized in Colombia due to a polytrauma after a motorcycle accident. He underwent surgery with external fixation of a third-degree open fracture of the tibia. At the time of repatriation, an early postoperative implant-associated polymicrobial wound infection with carbapenemase-producing

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[a]Equal contribution

Correspondence: Sarah Tschudin-Sutter, MD, MSc, Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland (sarah.tschudin@usb.ch).

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Table 1. Susceptibility Patterns of Treated Gram-Negative Bacteria

	Cefepim	Ceftazidim	Aztreonam	Ceftazidim/ Avibactam	Meropenem	Imipenem	Ciprofloxacin	Tobramycin	Amikacin	Colistin	Tige cyclin	Fosfo mycin	Cefiderocol Inhibition Zone Diameter (Interpretation)
Case 1													
P. aeruginosa (VIM)	R	R	R	R	R	R	R	R	R	S	-	S	24 mm (S)
A. baumannii (OXA-23)	R	R	-	R	R	R	R	R	R	S	S	S	23 mm (S)
E. cloacae (KPC)	I	R	R	S	R	I	R	S	R	S	S	R	14 mm (R)
Case 2													
A. baumannii (OXA-40, NDM)	R	R	R	R	R	R	R	R	R	S	R	R	18 mm (S)
Case 3													
A. baumannii (OXA-23, OXA-58)	R	R	R	R	R	R	R	R	I	S	R	R	20 mm (S)

Abbreviations: I, intermediate; KPC, Klebsiella- pneumoniae-Carbapenemase; NDM, New-Delhi-Metallobetalactamase; OXA: oxacillinases; R, resistant; S, susceptible; VIM, Verona-Integron-Metallobetalactamase.

Pseudomonas aeruginosa (VIM), *Acinetobacter baumannii* (OXA-23), and *Enterobacter cloacae* (KPC) was diagnosed. He underwent multiple surgeries with removal of the external fixation and osteosynthesis of the tibia. Histopathology confirmed acute osteomyelitis. Cefiderocol was started after removal of all foreign implants and was continued for 2 weeks. In addition, ceftazidime-avibactam and colistin were administered and continued for 4 weeks. No significant adverse events were recorded during treatment. A minimal drop in neutrophil count (nadir 1.13 $\times 10^9$/L) was seen at the end of the therapy with cefiderocol, normalizing at a consecutive control. After an antibiotic-free interval of 2 weeks, bone biopsies showed no evidence for persistent infection. The patient underwent definite surgery with implantation of an internal fixation device after receiving preoperative antibiotic prophylaxis with single-dose colistin, ceftazidime-avibactam, and cefiderocol. By the time of hospital discharge, there was no clinical sign of recurrent infection, and blood chemistry results showed a normal C-reactive protein (CRP) level (<10 mg/L). After 8 months of follow-up, there were no clinical or radiological signs of recurrent infection at the surgical site.

Case 2

A 64-year-old male patient was transferred from a hospital in Serbia, where he was admitted with polytrauma after falling off a ladder. He underwent transpedicular stabilization Th11–L3 and external fixation of the femur. Later, internal fixation of a trans/subtrochanteric femoral fracture and osteosynthesis of a medial malleolus ankle fracture and of a periprosthetic fracture of the tibia were performed. At the time of repatriation, he was found to have an early postoperative implant-associated infection of the spine with *A. baumannii* (NDM, OXA-40). Cefiderocol in combination with colistin was started after surgical revision with removal of the osteosynthesis from the spine. On the 12th day of treatment, the patient developed acute renal injury (AKIN I; creatinine-increase from 70 µmol/L [0.8 mg/dL] at baseline to 140 µmol/L [1.6 mg/dL]). Colistin was stopped, and cefiderocol doses were adapted to a glomerular filtration rate of 44 mL/min (1.5 g 3 times daily). Within 1 week, renal function fully recovered. Cefiderocol was continued at a standard dose to complete 6 weeks of treatment for acute vertebral osteomyelitis. No further significant adverse events were recorded. After completion, the patient underwent osteosynthesis of the spine, and cefiderocol was discontinued on the 12th postoperative day as intraoperative biopsies remained negative. During treatment, a second episode of reversible acute kidney failure occurred, most likely associated with re-exposure to colistin, which was administered for preoperative prophylaxis. After 13 weeks of follow-up, no signs of recurrent infection at the spinal site were noted, the CRP value was normal, and radiological control revealed spinal stabilization without any signs of loosening.

Table 2. Characteristics of the 3 Cases Treated at our Institution, as Well as the Cases Identified by the Literature Search

Case	Age, y	Sex	Exposition	Diagnosis	Pathogen(s) and Carbapenemases	Days on Cefiderocol	Concomitant Antibiotic Therapy[a]	Adverse Events	Outcome
Case 1	29	M	Columbia	Acute osteomyelitis	*A. baumannii* (OXA-23) *E. cloacae* (KPC) *P. aeruginosa* (VIM)	14	Ceftazidim/ avibactam, colistin	None	Cured
Case 2	64	M	Serbia	Postoperative implant-associated surgical site infection	*A. baumannii* (OXA-40, NDM)	54	Ceftazidim/ avibactam (6d), colistin (14d)	None	Cured
Case 3	62	M	Thailand	Pleural empyema	*A. baumannii* (OXA-23, OXA-58)	42	Colistin	None	Cured
Stevens et al. [6]	46	M	USA	Tertiary peritonitis	*P. aeruginosa* (no carbapenemase detected)	28	None	None reported	Cured
Contreras et al. [7]	68	M	USA	Postoperative intra-abdominal infection	*K. pneumoniae* (2 strains; OXA-232, NDM-1, CTX-M-15)	13	Polymixin B, ceftazidim/ avibactam	None reported	Died[b]
Edgeworth et al. [8]	78	F	Kuwait	Native valve endocarditis	*P. aeruginosa* (no carbapenemase detected)	23	Colistin, meropenem (7d)	Neutropenia	Cured
Trecarichi et al. [9]	Adult	M	Italy	Ventilator-associated pneumonia	*A. baumannii* (no carbapenemase reported), *K. pneumoniae*	14	None	None reported	Cured
Alamarat et al. [10]	15	M	Nigeria	Chronic implant-associated osteomyelitis	*P. aeruginosa* (NDM-1)	95	Aztreonam (13d)	Neutropenia	Cured

Abbreviations: CTX-M-15, Cefotaximase Munich β-lactamase; d, days; F, female; KPC, *Klebsiella-pneumoniae*-Carbapenemase; M, male; NDM, New-Delhi-Metallobetalactamase; OXA, oxacillinases; VIM, Verona-Integron-Metallobetalactamase; y, years.

[a]Only compounds with activity against gram-negative bacteria are reported. When combination therapy was not continued during the entire course of cefiderocol treatment, the number of days of combination treatment is reported in brackets.

[b]Death attributed to polymicrobial infections with vancomycin-resistant enterococci, *Candida glabrata*, and *Clostridoides difficile*.

Case 3

A 62-year-old male patient was repatriated from a hospital in Bangkok, Thailand, where he initially was admitted following blunt thoracic trauma with injury of the lung parenchyma, hemothorax, and serial rib fractures after a fall. He received repeated surgery and required invasive ventilation. His course was further complicated by hospital-acquired pneumonia with *Klebsiella pneumoniae*, XDR *A. baumannii*, and the development of multiple pressure ulcers. At admission to our institution, the patient was found to have left-sided pleural empyema with XDR *A. baumannii* (OXA-23, OXA-58) and *Corynebacterium striatum*. He underwent multiple surgical revisions of the pleural cavity, with consecutive detection of *Candida albicans*, *Enterococcus faecalis*, and *Corynebacterium tuberculostearicum*, among others. Treatment with cefiderocol in combination with colistin was initiated and complemented with daptomycin and fluconazole. After 14 days of treatment, the patient developed acute renal injury (AKIN II, creatinine increase from 40 µmol/L [0.45 mg/dL] at baseline to 122 µmol/L [1.38 mg/dL]). Colistin was discontinued, and cefiderocol doses were adjusted to a glomerular filtration rate of 58 mL/min (1.5 g 3 times daily). Renal function fully recovered within 4 days. Cefiderocol was discontinued after 14 days. After surgery for the pressure ulcer on the back, the patient was found to have histopathologically confirmed acute osteomyelitis of the processus spinosus (Th12) with detection of XDR *A. baumannii*. At the same time, the patient developed fever attributed to a urinary tract infection with XDR *A. baumannii*. A second course of cefiderocol was initiated and continued for a total duration of 6 weeks. Clinical improvement was documented (resolution of fever, normalization of CRP and leukozyte count). After 6 weeks of follow-up, no radiological signs of recurrent infection of the pleural cavity, the spinal site, or the urinary tract occurred.

Review of Published Case Reports

Five case reports were identified (Table 2): Stevens et al. [6] reported the successful treatment of a 46-year-old polymorbid patient with a polymicrobial intra-abdominal abscess after colon perforation and detection of an XDR *P. aeruginosa*, susceptible only to amikacin and colistin. Cefiderocol monotherapy was administered for 28 days with resolution of the abscess. Contreras et al. [7] presented a 68-year-old patient with a bloodstream infection caused by NDM-1 and OXA-48 *K. pneumoniae*, only susceptible to colistin and tigecycline, and vancomycin-resistant *E. faecium*, originating from a postoperative abscess/hematoma complicating a kidney transplant from a deceased donor. Clinical response was noted with polymyxin B, ceftazidime-avibactam, and cefiderocol. The patient died due to complicating infections with vancomycin-resistant enterococci, *Candida glabrata*, and *Clostridoides difficile*. Edgeworth et al. [8] reported a 78-year-old woman from Kuwait with

hospital-acquired native aortic valve endocarditis with XDR *P. aeruginosa* following complications of hydronephrosis. She recovered while undergoing treatment with cefiderocol, colistin, and valve replacement. Trecarichi et al. [9] describe the case of an adult patient with glucose-6-phosphate dehydrogenase deficiency and Aarskog-Scott syndrome who was successfully treated with cefiderocol plus linezolid for hospital-acquired pneumonia with XDR *A. baumannii* and KPC *K. pneumoniae.* Finally, a first report of successful prolonged cefiderocol treatment for implant-associated chronic osteomyelitis with NDM-1 *P. aeruginosa* and ESBL *Klebsiella pneumoniae* in a 15-year-old boy was recently published by Alamarat et al. [10].

DISCUSSION

We present a single-center series of 3 consecutive patients treated within the cefiderocol compassionate use program for complicated health care–associated infections (without detected bloodstream infections) with MDR gram-negative organisms. After a median follow-up time of 13 weeks (range, 6–32 weeks), treatment response without recurrence was documented for all patients.

All 3 patients received cefiderocol in combination with colistin, possibly favorably influencing the patients' outcomes, as observed with other compounds in gram-negative infections [11]. Two patients developed acute kidney injury, which resolved after discontinuation of colistin but required dose adjustment of cefiderocol. Colistin-induced acute kidney injury is frequent, reported in ~30% of colistin-treated patients [12]. Whether combination therapy with cefiderocol represents an additional risk factor is unclear and warrants special attention. No further safety issues attributable to cefiderocol were recorded in any of the 3 cases, even after prolonged treatment of up to 54 days.

In line with our results, all case reports identified by the literature search reported cure of gram-negative infection with cefiderocol treatment. Although the results of further clinical trials investigating the efficacy of cefiderocol for treatment of severe infections with carbapenem-resistant gram-negative bacteria (NCT02714595), nosocomial pneumonia (NCT03032380), and bloodstream infections (NCT03869437) are pending, these results suggest that cefiderocol may constitute a promising treatment option for infections caused by extensively drug-resistant gram-negative bacteria, including complicated health care– and implant-associated infections.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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