Open Forum Infectious Diseases

NOVEL ID CASES

Clinical Cure of a Difficult-to-Treat Resistant *Pseudomonas aeruginosa* Ventriculitis Using Cefiderocol: A Case Report and Literature Review

Cristina Marcelo,[1] Alejandro de Gea Grela,[2] María Martínez Palazuelos,[3] Javier Veganzones,[3] David Grandioso,[4] and Beatriz Díaz-Pollán[1,5]

[1]Infectious Disease Unit, Internal Medicine Department, La Paz Institute for Health Research, La Paz University Hospital, Madrid, Spain, [2]Internal Medicine Department, La Paz University Hospital, Madrid, Spain, [3]Anesthesiology and Resuscitation Department, La Paz University Hospital, Madrid, Spain, [4]Microbiology Department, La Paz University Hospital, Madrid, Spain, and [5]Centro de Investigación Biomédica en Red de Enfermedades Infecciosas, Instituto de Salud Carlos III, Madrid, Spain

Ventriculitis is a complication of meningitis (community-acquired or nosocomial) or other central nervous system (CNS) infections such as brain abscess. They are associated with a different spectrum of microorganisms, from resistant gram-negative bacilli to staphylococci, that can lead serious illness with high mortality. Difficult-to-treat resistance (DTR) gram-negative bacilli may increase to 20% of deaths respective to susceptible isolates of the same bacteria. We present the first report of a clinical cured case of DTR *Pseudomonas aeruginosa* ventriculitis in which cefiderocol penetration into the CNS has been confirmed in blood and cerebrospinal fluid. Cefiderocol might be considered for difficult-to-treat CNS infections in view of the recent new cases published as well as our case.

Keywords. cefiderocol; central nervous system infections; multidrug resistance; *Pseudomonas aeruginosa*; ventriculitis.

Cefiderocol is a new siderophore cephalosporin approved for the treatment of carbapenem-resistant gram-negative bacterial infections, including carbapenemase-resistant Enterobacterales and nonfermentative gram-negative bacilli such as *Acinetobacter* spp, *Pseudomonas* spp, and *Stenotrophomonas* spp, being one of the main alternative therapies in these cases [1]. Difficult-to-treat resistance (DTR) gram-negative bacilli are those that show resistance to all β-lactams, including combinations with β-lactamase inhibitors and carbapenems and quinolones [2]. The European Medicines Agency has approved the use of cefiderocol for patients who have limited treatment options, based on pharmacokinetic/pharmacodynamic analyses and on limited clinical data from the CREDIBLE-CR and APEKS-NP clinical trials [3–5]. There are currently no recommendations in European guidelines on how to use cefiderocol in severe infections caused by carbapenem-resistant *Pseudomonas aeruginosa* [6]. Furthermore, the latest update of the Infectious Diseases Society of America (IDSA) [7] guidance on the treatment of DTR *P. aeruginosa* infections only includes the indication of this drug in urinary tract infections.

The lack of evidence for cefiderocol central nervous system (CNS) activity becomes more apparent when pivotal trials are reviewed. Phase 2 and 3 studies systematically excluded patients with CNS infections, so there is no indication in the technical datasheet for the use of cefiderocol in these patients [4, 5, 8]. However, there are inconclusive data on its use in CNS infections; clinical experience in treating these infections is limited [9], and the article from Kawaguchi et al on pharmacokinetics and pharmacodynamics of cefiderocol does not even mention CNS infections [10]. Recently, a few sporadic cases of ventriculitis by DTR *P. aeruginosa* have been reported [11, 12], in which cefiderocol was used as treatment, being only effective in some of them. As we are already aware, ventriculitis is a difficult-to-treat CNS infection associated with poor clinical outcomes [13], with an even worse prognosis if it is caused by a DTR bacteria [14, 15].

CASE REPORT

We describe a 63-year-old man with frontal craniotomy surgery for recurrence of right frontotemporal meningioma with enlargement of previous margins with complete tumor dissection and DTR *P. aeruginosa* ventriculitis in October 2021.

Figure 1 shows a visual timeline of antimicrobial administration in our case.

On day 20 after surgery, he presented an external fistula of cerebrospinal fluid (CSF), and a lumbar bypass catheter was placed. Twenty-four hours later, he was febrile and the

Received 01 June 2022; editorial decision 27 July 2022; accepted 29 July 2022; published online 1 August 2022

Correspondence: Beatriz Díaz Pollán, MD, Infectious Disease Unit, Internal Medicine Department, La Paz Institute for Health Research, Paseo de la Castellana 261, Madrid 28046, Spain (bdiazp14124@gmail.com).

Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofac391

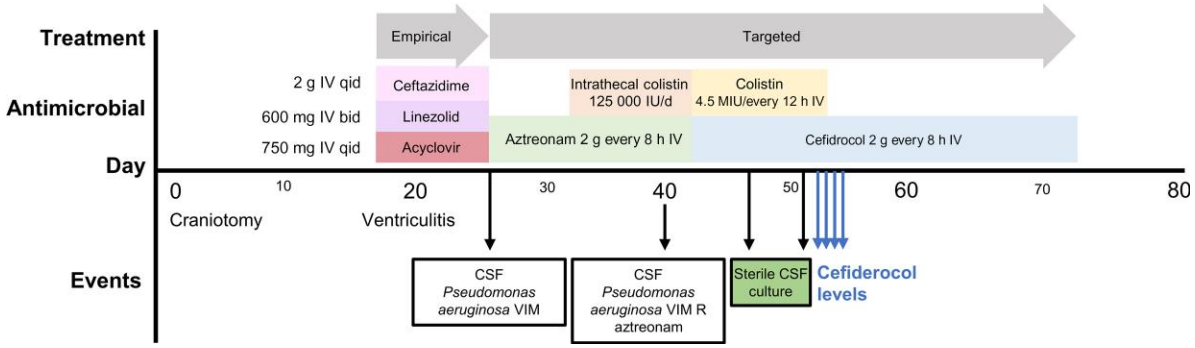

Figure 1. Timeline of antimicrobial administration periods and events in our case. Abbreviations: bid, twice daily; CSF, cerebrospinal fluid; IV, intravenous; qid, 4 times daily; R, resistant; VIM, carbapenemase VIM.

requirements for vasoactive drugs were increased. We started empirical antimicrobial therapy with ceftazidime (2 g intravenous [IV] 3 times daily), linezolid (600 mg IV twice daily), and acyclovir (750 mg IV 4 times daily), and performed CSF cultures without microbiological isolation. Nonetheless, he continued with a persistent fever, and we performed an analysis of CSF. It showed an abnormal CSF leukocyte count (183 cells/mm^3) with 67% polymorphonuclear cell predominance, an increase of total protein (110 mg/dL), and a normal lactate concentration (3.6 mmol/L) and glucose (80 mg/dL). We obtained new CSF cultures with VIM carbapenemase–producing *P. aeruginosa* isolation, susceptible (increased exposure) to aztreonam with a minimum inhibitory concentration (MIC) of 16 mg/L, and susceptible to colistin with an MIC ≤0.5 mg/L, based on European Committee on Antimicrobial Susceptibility Testing clinical breakpoints [16] (Table 1). Thereafter, we diagnosed a secondary nosocomial ventriculitis based on the IDSA guideline for healthcare-associated ventriculitis and meningitis [14]. On day 26 after craniotomy surgery, we modified treatment to aztreonam (2 g IV 4 times daily) administered in extended infusion after those results. He remained febrile and VIM carbapenemase–producing *P. aeruginosa* continued to be isolated in CSF cultures, so we added treatment with intrathecal colistin (125 000 IU daily) on day 32 after surgery (day 7 after isolation).

The next CSF cultures showed in vitro resistance to aztreonam (MIC ≥64 mg/L) (Table 2). We did not observe a synergistic effect in the laboratory between aztreonam and ceftazidime-avibactam; cefiderocol was in vitro susceptible (MIC = 0.5 mg/L); and colistin MIC remained unchanged (Table 3). After these results, on day +42 after surgery (day 17 after isolation), we changed to IV colistin (4.5 MIU every 12 hours, given as a 1-hour infusion) and we started cefiderocol (2 g IV 4 times daily, in a 3-hour infusion) despite the low evidence of its penetration from the brain-blood barrier (BBB). The neurosurgery team removed the lumbar drainage catheter and placed an external shunt; subsequently, the patient presented clinical improvement with repeated sterile CSF cultures. The patient required sporadic renal replacement therapy by continuous venovenous hemodiafiltration because he had oliguria, but without antimicrobial therapy dose adjustment needed, with a urine creatinine clearance from 90 mL/minute to 120 mL/minute. We stopped IV colistin on day 11 of prescription (day 53 after surgery) and maintained cefiderocol 3 weeks since the first sterile culture, with clinical, neurological, and inflammatory laboratory data improvement. After 3 months of hospital admission, the infection did not relapse.

Table 1. Initial *Pseudomonas aeruginosa* Susceptibility Testing Using an Automated Broth Microdilution System (VITEK 2)

Antimicrobial	MIC, mg/L	Interpretation
Ceftazidime	≥64	Resistant
Cefepime	≥32	Resistant
Ceftolozane-tazobactam	≥32	Resistant
Ceftazidime-avibactam	≥64	Resistant
Piperacillin-tazobactam	≥128	Resistant
Tobramycin	≥16	Resistant
Gentamycin	≥16	Resistant
Amikacin	≥64	Resistant
Aztreonam	16	Susceptible (increased exposure)
Imipenem	≥16	Resistant
Meropenem	≥16	Resistant
Ciprofloxacin	≥4	Resistant
Colistin	≤0.5	Susceptible

MICs interpreted by European Committee on Antimicrobial Susceptibility Testing clinical breakpoints.

Abbreviation: MIC, minimum inhibitory concentration.

We tested drugs levels, obtaining samples of CSF through the external shunt drainage on 4 consecutive days (Figure 1), and we also analyzed 2 simultaneous plasma samples. We took peak (2 hours after infusion) and trough (immediately before infusion) samples on days 10–13 from the start of cefiderocol (Table 3).

We found detectable levels of cefiderocol in CSF in 2 of the 4 samples. We quantified a decrease of 1_{log} in plasma concentration between peak and trough, as well as decrease of 1_{log} between plasma and CSF trough test.

Table 2. Consecutive *Pseudomonas aeruginosa* Susceptibility Testing Using an Automated Broth Microdilution System (VITEK 2) That Showed In Vitro Development of Aztreonam Resistance

Antimicrobial	MIC, mg/L	Interpretation
Ceftazidime	≥64	Resistant
Cefepime	≥32	Resistant
Ceftolozane-tazobactam	≥32	Resistant
Ceftazidime-avibactam	≥64	Resistant
Cefiderocol	0.5	Susceptible
Piperacillin-tazobactam	≥128	Resistant
Tobramycin	≥16	Resistant
Gentamycin	≥16	Resistant
Amikacin	≥64	Resistant
Aztreonam	≥64	Resistant
Imipenem	≥16	Resistant
Meropenem	≥16	Resistant
Ciprofloxacin	≥4	Resistant
Colistin	≤0.5	Susceptible

MICs interpreted by European Committee on Antimicrobial Susceptibility Testing clinical breakpoints.

Abbreviation: MIC, minimum inhibitory concentration.

Table 3. Cefiderocol Levels Achieved in Cerebrospinal Fluid (CSF) (Samples 1 and 2) and CSF Simultaneously With Plasma (Samples 3 and 4)

Days of Cefiderocol	Sample No.	Matrix	Cefiderocol Concentration, μg/mL
10	1 (peak)	CSF	3.628
11	2 (peak)	CSF	No peak
12	3 (peak)	CSF	No peak
		Serum	219.2
13	4 (trough)	CSF	1.586
		Serum	40.18

Abbreviation: CSF, cerebrospinal fluid.

DISCUSSION

Although the penetration of β-lactam antibiotics through the BBB is variable [17], there were no data on cefiderocol beyond experimental studies performed in rats [18] at the time of our case. We decided to measure drug levels due to limited clinical experience with cefiderocol for CNS infections, with only few data from experiments conducted in the nervous system of animals [18].

We found detectable levels of cefiderocol in CSF in 2 of the 4 samples. CSF drug levels were probably undetectable in the other 2 samples because the patient was under sporadic renal replacement therapy by continuous venovenous hemodiafiltration, which would limit drug bioavailability. CSF cefiderocol trough levels corresponded to approximately 4% of the drug concentration simultaneously achieved in plasma, which was slightly lower than the results found for other β-lactams. Nau et al [19, 20] observed that the penetration ratio between plasma and CSF (area under the curve [AUC] CSF/AUC serum) without meningeal inflammation is usually <15% (ie, 2% in penicillins, 10% in cephalosporins, and 20% in carbapenems). However, an increase in the ratio (AUC CSF/AUC serum) was observed the greater the meningeal inflammation (20% in penicillins, 15% in cephalosporins, and 30% in carbapenems). A direct comparison of these findings with our results is unfeasible because we test punctual concentration data and lack continuous evolution. As an example of the complexity of comparing data in our case, the target trough total [C_{min}] CSF/serum ratio of 4% was lower than in the findings of Meschiari et al (C_{min} CSF/serum ratio of 12.4%) and Luque-Paz et al (AUC_{0-8h} ratio of 44%) [9, 12]. However, this ratio was not associated with survival as both our patient and Meschiari et al's patient survived, but not the patient of Luque-Paz et al.

Therapeutic options for the treatment of CNS infections caused by multidrug-resistant (MDR) bacteria are scarce due to the different penetration of antibiotics through the BBB that often requires clinicians to associate intrathecal therapies [17]. In 2020, Bavaro et al reported a case of a neurosurgical site infection with MDR *P. aeruginosa* successfully treated with cefiderocol [21]. In 2021, Meschiari et al reported 17 cases of complex DTR *P. aeruginosa* infections, including a case of nosocomial meningitis with a favorable evolution after treatment with cefiderocol [9]. However, in none of these cases did the authors quantify drug levels reached in blood or CSF. Recently, Luque-Paz et al published a case report of an MDR *P. aeruginosa* ventriculitis treated with cefiderocol, in which they measured CSF trough drug levels that were similar to levels found in our work, but peak drug levels were unknown [12]. Concurrently, another patient with a DTR *P. aeruginosa* ventriculitis was published with measured CSF cefiderocol levels [11]. The CSF levels found in both cases and ours were in the same range (1.22–24.4 μg/mL), although the doses of cefiderocol used in each case were different [11, 12]. Thus, Luque-Paz et al prescribed 2 g IV every 6 hours through 3-hour extended infusion after a 2-g bolus, Stevenson et al 1 g IV 4 times daily, and in our case 2 g IV 4 times daily through 3-hour extended infusion. These 4 well-known patients with complex meningitis have received combined treatment with colistin [9, 11, 12], but only our patient and Meschiari et al's patient have recovered.

Plasma and CSF drug levels and the bacterial clearance in CSF cultures after cefiderocol onset support the hypothesis of its penetration in BBB and the probable effect in CNS infections, although the coadministration with colistin, first intrathecal and then IV, might also play a significant role. Further research is necessary to understand the individual effect of these 2 drugs, but given the severity of these infections, the use of new antibiotics such as cefiderocol opens new therapeutic options.

CONCLUSIONS

Our work adds to previous case reports showing the penetration of cefiderocol through the BBB, suggesting the future

possibility of its use for CNS infections by MDR microorganisms. Given that patients with clinical pictures such as the one presented in this case are not represented in clinical trials, we provide information that could be relevant when designing treatments for infections by MDR bacteria in the CNS.

Notes

Acknowledgments. We acknowledge all healthcare professionals for their outstanding efforts and dedication to the care of the patient. We dedicate this work to our patient and his family. The authors also acknowledge Erhard Berndes and Dr Martina Kinzig for support cefiderocol levels.

Patient consent. Our study does not include factors necessitating patient consent.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Syed YY. Cefiderocol: a review in serious gram-negative bacterial infections. Drugs **2021**; 81:1559–71.
2. Kadri SS, Adjemian J, Lai YL, et al. Difficult-to-treat resistance in gram-negative bacteremia at 173 US hospitals: retrospective cohort analysis of prevalence, predictors, and outcome of resistance to all first-line agents. Clin Infect Dis **2018**; 67:1803–14.
3. European Medicines Agency. Fetroja (cefiderocol). https://www.ema.europa.eu/en/medicines/human/EPAR/fetcroja. Accessed 25 May 2022.
4. Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. Lancet Infect Dis **2021**; 21:226–40.
5. Wunderink RG, Matsunaga Y, Ariyasu M, et al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis **2021**; 21:213–25.
6. Paul M, Carrara E, Retamar P, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant gram-negative bacilli (endorsed by European Society of Intensive Care Medicine). Clin Microbiol Infect **2022**; 28:521–47.
7. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, Van Duin D, Clancy CJ. Infectious Diseases Society of America guidance on the treatment of extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*). Clin Infect Dis **2021**; 72: e169–83.
8. Portsmouth S, van Veenhuyzen D, Echols R, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. Lancet Infect Dis **2018**; 18:1319–28.
9. Meschiari M, Volpi S, Faltoni M, et al. Real-life experience with compassionate use of cefiderocol for difficult-to-treat resistant *Pseudomonas aeruginosa* (DTR-P) infections. JAC Antimicrobial Resist **2021**; 3:dlab188.
10. Kawaguchi N, Katsube T, Echols R, Wajima T. Population pharmacokinetic and pharmacokinetic/pharmacodynamic analyses of cefiderocol, a parenteral siderophore cephalosporin, in patients with pneumonia, bloodstream infection/sepsis, or complicated urinary tract infection. Antimicrob Agents Chemother **2021**; 65:1–13.
11. Stevenson DR, Cherian BP, Kinzig M, Sörgel F, Wareham DW. P44 nosocomial neurosurgical meningitis due to XDR *Pseudomonas aeruginosa*: clinical experience with cefiderocol. JAC Antimicrobial Resist **2022**; 4:dlac004.043.
12. Luque-Paz D, Bennis Y, Jaubert P, Dubée V, Wolff M, Mortaza S. Cerebrospinal fluid concentrations of cefiderocol during the treatment of extensively drug-resistant *Pseudomonas aeruginosa* ventriculitis. J Antimicrob Chemother **2022**; 77:1787–9.
13. Luque-Paz D, Revest M, Eugène F, et al. Ventriculitis: a severe complication of central nervous system infections. Open Forum Infect Dis **2021**; 8:ofab216.
14. Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. Clin Infect Dis **2017**; 64:e34–65.
15. Cassini A, Högberg LD, Plachouras D, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis **2019**; 19:56–66.
16. European Committee on Antimicrobial Susceptibility Testing. Clinical breakpoints and dosing of antibiotics. https://www.eucast.org/clinical_breakpoints/. Accessed 28 May 2022.
17. Heffernan AJ, Roberts JA. Dose optimisation of antibiotics used for meningitis. Curr Opin Infect Dis **2021**; 34:581–90.
18. Takemura M, Kanazawa S, Kohira N, et al. Evaluation of penetration of cefiderocol into cerebrospinal fluid using a rat meningitis model. Open Forum Infect Dis **2021**; 8(Suppl 1):S645.
19. Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clin Microbiol Rev **2010**; 23:858–83.
20. Nau R, Blei C, Effert H. Intrathecal antibacterial and antifungal therapies. Clin Microbiol Rev **2020**; 33:e00190-19.
21. Bavaro DF, Romanelli F, Stolfa S, et al. Recurrent neurosurgical site infection by extensively drug-resistant *P. aeruginosa* treated with cefiderocol: a case report and literature review. Infect Dis (Lond) **2021**; 53:206–11.