JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlaf066

JAC-Antimicrobial Resistance

Feasibility of 24 h continuous-infusion cefiderocol administered by elastomeric pump in attaining an aggressive PK/PD target in the treatment of NDM-producing *Klebsiella pneumoniae* otomastoiditis

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Received 24 January 2025; accepted 15 April 2025

Objectives: Cefiderocol has emerged as a key treatment for managing MDR infections, and its time-dependent pharmacodynamics are optimized by prolonged infusion to maintain time above the MIC ($T_{>MIC}$). Whereas recent stability studies have shown cefiderocol remains stable up to 72 h in elastomeric pumps, its use in 24 h continuous infusions (CIs) for outpatient parenteral antibiotic therapy (OPAT) is undocumented. This case highlights its suitability for 24 h CI via elastomeric pumps in an OPAT setting, supported by therapeutic drug monitoring (TDM) to ensure optimal treatment efficacy.

Patient/case description: A 31-year-old male developed right-sided otomastoiditis caused by *Klebsiella pneumoniae* producing New Delhi MBL (NDM). Given the resistance profile and the need for prolonged therapy, cefiderocol was initiated at a daily dose of 6 g, administered by 24 h CI using an elastomeric pump. TDM was performed on Days 17 and 45 to assess plasma concentrations.

Results: TDM confirmed steady-state concentrations (C_{ss} 25.2–28.1 mg/L), achieving optimal pharmacokinetic/pharmacodynamic (PK/PD) target attainment such as 100% $T_{>4–6\ MIC}$ (free [*f*]C_{ss}/MIC 10.58–11.80). Significant clinical improvement avoided the need for planned surgery, with no adverse events reported from the venous catheter, antibiotic therapy or elastomeric pump.

Conclusions: This approach underscores the feasibility and efficacy of cefiderocol administered by 24 h CI by means of an elastomeric pump and supported by real-time TDM in achieving an aggressive PK/PD target for the treatment of otomastoiditis due to NDM-producing *K. pneumoniae*.

Introduction

Cefiderocol, a siderophore cephalosporin, has emerged as a critical option for managing infections caused by MDR Gram-negative bacteria.[1,2] Its efficacy is closely tied to time-dependent pharmacodynamics, with prolonged infusion being essential to maintain time above the MIC ($T_{>MIC}$).[3,4] However, beyond the limited clinical evidence, there is also a lack of pre-marketing studies addressing the chemical, microbiological, and physical stability of cefiderocol over periods longer than 6 h recommended in the technical data sheet to support its use by continuous infusion (CI).[5] Although recent stability studies have shown cefiderocol concentrations remaining stable up to 72 h at 25°C in elastomeric pumps,[6] its use in such devices, especially in a single dilution lasting 24 h, has never been documented. Moreover, its use in the outpatient parenteral antibiotic therapy (OPAT) setting remains poorly explored.[7]

Here, we present a novel case highlighting the suitability of cefiderocol for 24 h CI when administered via elastomeric pump supported by therapeutic drug monitoring (TDM).

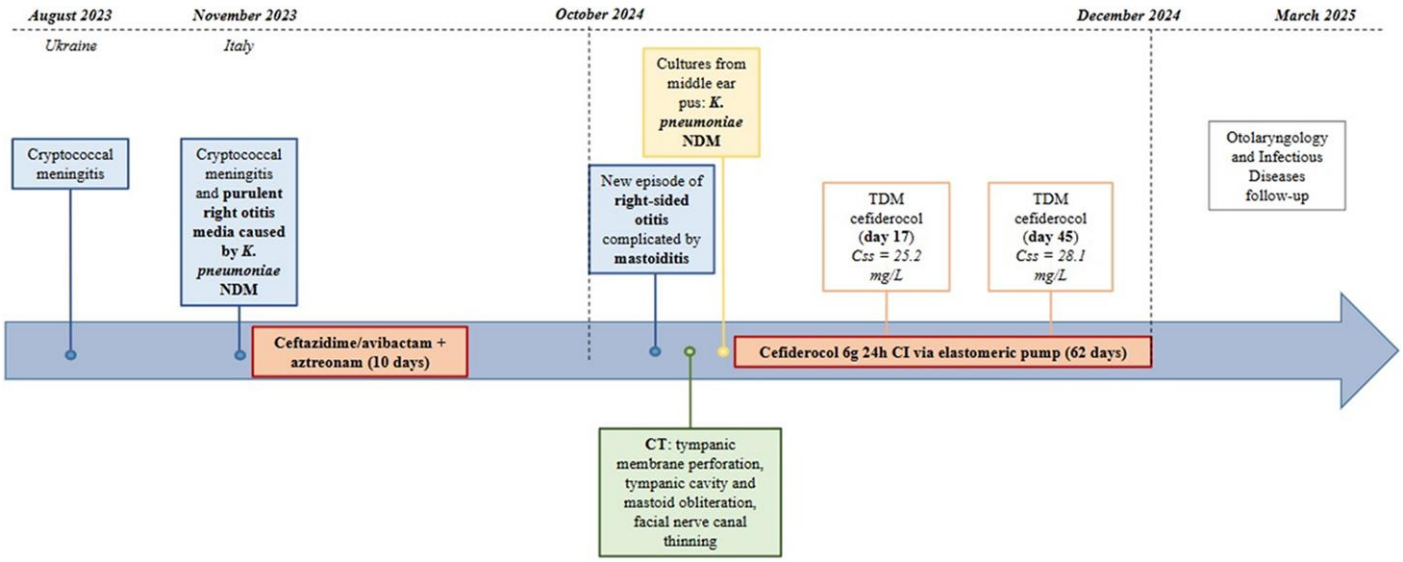

Figure 1. Timeline of the clinical case, illustrating key events and antibiotic therapy.

Patient and methods

Our patient, a 31-year-old male from Ukraine, was diagnosed with cryptococcal meningitis in a late-presenting HIV infection in August 2023. He migrated to Italy due to the ongoing war in Ukraine in November 2023 and he was admitted to the Infectious Diseases Unit of Trieste for cryptococcal meningitis and purulent right otitis media caused by *Klebsiella pneumoniae* producing New Delhi MBL (NDM). During this admission, the purulent otitis media was managed with a combination of IV ceftazidime/avibactam and aztreonam for 10 days. A detailed timeline of the medical history is presented in Figure 1.

In October 2024, following a period of apparent well-being during maintenance therapy for cryptococcal meningitis and nearly 14 months of persistent HIV viral suppression, the patient developed a new episode of right-sided otitis, which was complicated by mastoiditis. CT scans revealed tympanic membrane perforation, obliteration of the tympanic cavity and mastoid air cells with soft tissue density material and thinning of the facial nerve canal. Microbiological cultures, collected from middle ear pus, yielded *K. pneumoniae* NDM. Given the pathogen's resistance profile and the need for prolonged therapy, cefiderocol was initiated at a daily dose of 6 g, administered by 24 h CI using an elastomeric pump (INFUSOR LV; product code 2C2063K, 10 mL/h; Baxter), diluted in 240 mL of 0.9% normal saline solution. The drug was reconstituted according to the manufacturer's technical data sheet, immediately loaded into the elastomeric pump, and directly administered to the patient.[5]

The identification of NDM-producing *K. pneumoniae* was performed using the GeneXpert Carba-R assay (Cepheid, USA).

The MIC of cefiderocol was 1 µg/mL as determined by broth microdilution in iron-depleted Mueller–Hinton broth (according to EUCAST).[8] Notably, the pathogen demonstrated resistance to ceftazidime/avibactam.

Laboratory monitoring, including complete blood count, liver function tests, serum creatinine, electrolytes, C-reactive protein and albumin, was performed every 2 weeks, with samples collected immediately before TDM assessments.

Baseline clinical and laboratory data included a BMI of 26.8 kg/m^2, normal renal (serum creatinine: 0.86 mg/dL on Day 17, 0.81 mg/dL on Day 45) and liver function tests, and albumin (4.5 g/dL). Home medications at presentation included prednisone 25 mg daily, fluconazole 200 mg daily, prophylactic trimethoprim/sulfamethoxazole thrice weekly, calcium folinate, and bictegravir/emtricitabine/tenofovir alafenamide 50/200/25 mg daily. The patient's written consent was obtained.

Cefiderocol TDM was performed randomly at Days 17 and 45 by means of a validated HPLC/MS-MS method.[9] TDM was performed on peripheral blood samples collected independently of the infusion line. The first sample was obtained immediately before elastomeric pump replacement; the second, 2 h after the new infusion had started, to assess potential variations in drug concentration during CI.

TDM results revealed total steady-state concentrations (C_{ss}) of 25.2 and 28.1 mg/L, respectively. In order to achieve optimal pharmacokinetic/pharmacodynamic (PK/PD) target attainment, such as 100% $T_{>4\text{–}6\ MIC}$ at the site of infection and considering both the high plasma protein binding of cefiderocol of 58% and the specific deep-seated infection,[10] the observed plasma concentration yielded an free (f)C_{ss}/MIC of 10.58–11.80, which was deemed adequate for treating the patient's clinical condition. An aggressive PK/PD target (i.e. at least 100% $fT_{>4\text{–}5\times MIC}$) was selected according to clinical evidence reporting a significantly higher clinical cure rate, and lower risk of microbiological failure or resistance development with the attainment of aggressive β-lactam PK/PD targets compared with conservative PK/PD targets.[11] The cefiderocol dose of 6 g daily by CI was confirmed at both TDM sessions up to the end of therapy.

Manufacturer's data showed that cefiderocol was stable in saline solution for up to 6 h at 25°C.[12] Thus, prolonging the infusion could compromise stability and hence antimicrobial efficacy. However, a recent stability test of antipseudomonal β-lactams

for outpatient therapy reported cefiderocol concentrations in elastomeric pump devices >90% up to 72 h at 25°C and up to 24 h at 32°C at a dilution of 12 g/L.[6] A higher cefiderocol concentration was selected in our case considering the availability of elastomeric pump devices with a maximum volume of 240 mL and according to a recent stability study reporting that cefiderocol was stable up to 24 h at a concentration of 62.5 g/L in polypropylene syringes.[13]

Based on this, along with a recent case series showing PK/PD target attainment in six patients treated with quasi-continuous cefiderocol infusion (2 g every 8 h with infusions of 8 h) for XDR Gram-negative bacteria,[4] we decided to dilute the entire reconstituted cefiderocol solution in an elastomeric pump allowing for 24 h CI administration.

The patient underwent frequent infectious disease and otolaryngological evaluations, which revealed a marked improvement in his clinical condition, ultimately leading to the decision to forgo the initially planned surgical intervention. Therapy was completed on Day 62, with no adverse events reported related to the midline venous catheter, the antibiotic or the elastomeric pump. Laboratory monitoring showed no abnormalities or significant alterations throughout therapy, nor any signs of anaemia, as observed in the case reported by Schellong *et al.*[7] The patient remains under follow-up to monitor his clinical progress and ensure the sustained resolution of the infection.

Results and discussion

The implications of this approach are promising: CI via elastomeric pump in OPAT improves patient adherence, minimizes healthcare resource utilization, and facilitates outpatient management, as seen in our patient, who avoided prolonged hospitalization and maintained quality of life.[14,15]

It is important to note that although drug stability is often discussed in terms of percentage degradation, these values must be interpreted within the context of therapeutic outcomes. A significant loss of the active drug would clearly compromise efficacy, but smaller percentages are unlikely to have meaningful clinical implications, provided the drug concentration remains within the therapeutic range. This is particularly relevant in the context of antibiotics used in the treatment of severe MDR infections. In such cases, TDM plays a crucial role not only for confirming whether pharmacodynamic targets are achieved despite potential minor degradation during infusion, but also for addressing the clinical opportunity of using cefiderocol in OPAT settings where CI via elastomeric pumps may be required. Moreover, TDM allows for the optimization of drug dosing, ensuring that specific PK/PD targets based on pathogen MIC are achieved.[16]

Although concerns have been raised regarding potential toxicity with aggressive β-lactam PK/PD targets, it should be noted that the ceiling dose is only determined by the threshold for toxicity without involving MIC values.[17] Currently, no specific toxicity threshold has been established for cefiderocol. However, total cefiderocol concentrations (i.e. 25.2–28.1 mg/L) retrieved in our patient were well below the average concentrations of 72 mg/L reported in the product information for patients with a creatinine clearance >60 mL/min, with no occurrence of concentration-dependent toxicity, thus supporting the fact that no toxicity could be expected with similar cefiderocol exposure levels.

The discrepancy between FDA/CLSI (≤4 mg/L) and EUCAST (≤2 mg/L) susceptibility breakpoints may impact clinical decisions, particularly for MICs near the threshold. In our case, the MIC was 1 mg/L, well within both limits, but caution is warranted at higher values. Though not always available, TDM provides an additional safeguard in tailoring cefiderocol therapy to individual patient needs. When unavailable, the adoption of a CI administration strategy remains a key tool to maximize aggressive PK/PD target attainment with novel β-lactams.[18]

Recent reports have highlighted a growing incidence of MDR infections in the context of the ongoing war in Ukraine.[19,20] Armed conflicts and humanitarian crises create conditions that facilitate the spread of antimicrobial resistance. Our case further supports these epidemiological findings, underscores the clinical challenges posed by MDR infections in the current geopolitical landscape, and highlights the need to consider the increased prevalence of NDM-producing pathogens in patients with infections originating from these geographical areas.

In conclusion, this case underscores the feasibility and efficacy of cefiderocol administered by 24 h CI by means of an elastomeric pump and supported by real-time TDM in achieving an aggressive PK/PD target for the treatment of otomastoiditis due to NDM-producing *K. pneumoniae*.

Acknowledgements

We would like to thank the medical, nursing and laboratory staff involved in the patient's care for their professional support and collaboration.

Funding

This study was conducted as part of our routine work. We acknowledge Shionogi SRL (Italian affiliate of Shionogi & Co., Ltd, Japan) for the unconditional financial support for the publication process.

Transparency declarations

The authors declare no conflicts of interest related to this publication.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

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