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(Article begins on next page)

1 **Highly-adsorptive removal of cefiderocol during continuous venovenous hemodiafiltration equipped**
2 **with oXiris filter in an orthotopic liver transplant recipient having septic shock caused by VIM-**
3 **producing *Klebsiella pneumoniae***

4
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24 Sir,
25 continuous renal replacement therapy (CRRT) is a technique useful in critically ill patients at replacing the
26 lost kidney blood-filtering function in presence of severe renal dysfunction.¹ In recent years, CRRT emerged
27 also as valuable approach for removing inflammatory cytokine burden in the early phase of septic shock.² In
28 this scenario, equipping CRRT with oXiris hemofilter in critical septic patients was shown to enhance either
29 inflammatory cytokine adsorption or to reduce organ damage and mortality rate.² Unfortunately, under these
30 circumstances also therapeutic drugs may be consistently removed.

31 In regard to beta-lactams, current evidence on pharmacokinetic (PK) alterations during CRRT
32 equipped with oXiris hemofilter is quite limited.³ Here, we describe the PK alterations concerning
33 cefiderocol in a orthotopic liver transplant (OLT) recipient who, while being treated with continuous
34 infusion (CI) cefiderocol because having septic shock caused by VIM-producing *Klebsiella pneumoniae*,
35 underwent continuous venovenous hemodiafiltration (CVVHDF) before with traditional AN-69 ST150 filter
36 and subsequently with highly-adsorptive oXiris filter.

37 A 51-years-old male underwent OLT because of complicated alcoholic cirrhosis (Model for End-
38 Stage Liver Disease score 20). The post-operative course was complicated by acute kidney injury requiring
39 CVVHDF, rectal colonization by VIM-producing Kp, and liver failure caused by post-traumatic thrombosis
40 of the suprahepatic vein. The patient needed liver re-transplantation on day 7, and on days 11-27 and 35-44,
41 suffered from bloodstream infection and VAP caused by VIM-producing Kp. In these occasions, treatment
42 courses with CI ceftazidime-avibactam plus CI aztreonam were given. Unfortunately, on day 45, the patient
43 needed a second re-transplantation because of graft rejection. On day 52, clinical conditions suddenly
44 worsened, and septic shock as a complication of VIM-producing Kp related VAP occurred ($>10^6$ cfu/mL).
45 Being clinical isolate susceptible to cefiderocol (tested by disc-diffusion as suggested by EUCAST and
46 interpreted according to clinical breakpoint, namely $MIC \leq 2$ mg/L),⁴ treatment with a 2g loading dose
47 cefiderocol followed by a 2g q8h over 8-h (CI) maintenance dose was started, according to previous findings
48 concerning cefiderocol PK behavior during CVVHDF.⁵ Cefiderocol exposure was optimized by means of a
49 real-time therapeutic drug monitoring (TDM)-guided approach with the intent of maximizing aggressive
50 pharmacokinetic/pharmacodynamic (PK/PD) target attainment against all of the susceptible pathogens. The
51 desired target was a free steady-state concentrations (fC_{ss}) of > 8 mg/L, corresponding to a fC_{ss} -to-MIC ratio

52 >4 against pathogens with an MIC value up to the clinical breakpoint of 2 mg/L.⁵ For this purpose,
53 cefiderocol total plasma C_{ss} were measured by means of a validated liquid chromatography tandem mass
54 spectrometry method,⁶ and the free moiety (fC_{ss}) were calculated by considering a 42% of the total C_{ss} ,
55 based on a plasma protein binding of 58%.⁷ Cefiderocol plasma C_{ss} were measured on real-time at day 53,
56 55, 60, and 63, and prompt TDM-guided advices of cefiderocol dosing at each occasion were provided.⁸ At
57 each TDM assessment, cefiderocol total clearance (CL_{tot}) was calculated by means of the following formula:
58 CL_{tot} (L/h) = infusion rate (mg/h) / C_{ss} (mg/L). Data on cefiderocol PK features, PK/PD target attainment and
59 CVVHDF operative conditions are summarized in **Figure 1**. Specifically, CVVHDF was performed by
60 means of a Prisma Flex System equipped with an AN69 high-flux ST-150 filter membrane and using citrate
61 as a regional anticoagulant. Blood flow rate, pre-blood pump flow rate, post-filter replacement fluid rate, and
62 dialysate flow rate were set in the range of 110-150 mL/min, 917-1,250 mL/h, 400-500 mL/h and 400-700
63 mL/h, so that the delivered CVVHDF dose was in the range of 30-35 mL/kg/h. The desired PK/PD target
64 was always attained. Unfortunately, after an initial clinical improvement, on day 60 the patient experienced a
65 further episode of septic shock requiring vasopressor support and mechanical ventilation. oXiris filter was
66 then adopted for further increasing removal of the inflammatory cytokine burden. Noteworthy, despite in this
67 latter phase the CVVHDF total effluent flow rate (Q_{ef}) was decreased by around 10%, the cefiderocol CL_{tot}
68 under oXiris filter increased by 49.6% compared to that under AN-69 ST150 filter (4.33 L/h versus 2.90
69 L/h). Unfortunately, BAL performed on day 65 yielded both VIM-producing Kp resistant to cefiderocol and
70 *Burkholderia cepacia*, so that treatment was switched to combination therapy with imipenem-relebactam
71 plus aztreonam.

72 To the best of our knowledge, this is the first case reporting cefiderocol PK features during
73 CVVHDF equipped with oXiris membrane filter. Notably, equipping CVVHDF with this filter membrane
74 resulted in a consistent increase of cefiderocol removal compared to the traditional AN-69 ST150 filter
75 membrane. Overall, considering that the CVVHDF dose under oXiris treatment was partially decreased
76 compared with that under AN-69 ST150 treatment, we are quite confident that the net effect on decreasing
77 C_{ss} under oXiris treatment could be likely attributed mainly to an adsorptive removal by the oXiris
78 membrane filter. Noteworthy, it could be speculated that the multilayer linear structure cationic complex
79 resulting from the polyethyleneimine and heparin coatings of the oXiris membrane filter might have caused

80 relevant adsorption of cefiderocol, being this a negatively charged molecule,⁹ similarly to what just
81 previously shown for other negatively charged molecules.² Our findings are in agreement with a previous
82 population PK study conducted among 12 critically ill patients showing that the meropenem CL_{tot} during
83 CVVHDF equipped with oXiris filter was higher than reported during CVVHDF equipped with AN-69
84 filter.³

85 Consequently, clinicians should be aware that during cefiderocol treatment, potential dosage increase
86 could be needed for granting optimal exposure when shifting CVVHDF equipment from the traditional AN-
87 69 ST150 filter to the highly adsorptive oXiris filter. In these cases, adopting a real-time TDM-guided
88 strategy may be helpful for promptly implementing dosing adaptation in relation to the evolving
89 pathophysiological and/or iatrogenic conditions in order to attain cefiderocol aggressive PK/PD targets.
90 Further larger prospective studies are warranted for testing our hypothesis.

91

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96 **Transparency declarations**

97 M.G. reports grant from Angelini, and participated in advisory board for AdvanzPharma and Viatris, outside
98 the submitted work. P.V. has served as a consultant for bioMérieux, Gilead, Merck Sharp & Dohme,
99 Nabriva, Nordic Pharma, Pfizer, Thermo-Fisher, and Venatorx, and received payment for serving on the
100 speaker's bureaus for Correvio, Gilead, Merck Sharp & Dohme, Nordic Pharma, and Pfizer, outside the
101 submitted work. F.P. participated in speaker bureau for Angelini, BeiGene, Gilead, InfectoPharm, Menarini,
102 Merck Sharp & Dohme, Pfizer, and Shionogi, and in advisory board for BeiGene, Merck Sharp & Dohme,
103 Pfizer, and Viatris, outside the submitted work. The other authors report no potential conflicts of interest for
104 this work.

105 **Ethical approval**

106 The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the
107 local ethical committee (CE AVEC: 272/2024/Sper/AOUBo on 16 May 2024). Signed informed consent was
108 collected from the included patient.

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139

140 **Figure 1** – Cefiderocol PK features and CVVHDF operative conditions at each TDM assessment

141 BAL: bronchoalveolar lavage; CI: continuous infusion; CL: clearance; CVVHDF: continuous veno-venous hemodiafiltration; FDC: cefiderocol; Kp: *Klebsiella*
142 *pneumoniae*; OLT: orthotopic liver transplantation; PBP: pre-blood pump flow rate; Q_b: blood flow rate; Q_d: dialysate flow rate; Q_{ef}: total effluent flow rate

143

144 * percentage variation in FDC CL between average CL during AN-69 ST150 (2.90 L/h) and oXiris filter membrane (4.33 L/h) equal to 49.6%, and calculated
145 according to the following equation: $[(\text{FDC CL during oXiris} - \text{average FDC CL during AN-69 ST150}) / (\text{average FDC CL during AN-69 ST150})] * 100\%$

146

