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

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Sir,

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

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

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

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

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

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

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

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Transparency declarations

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Ethical approval

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

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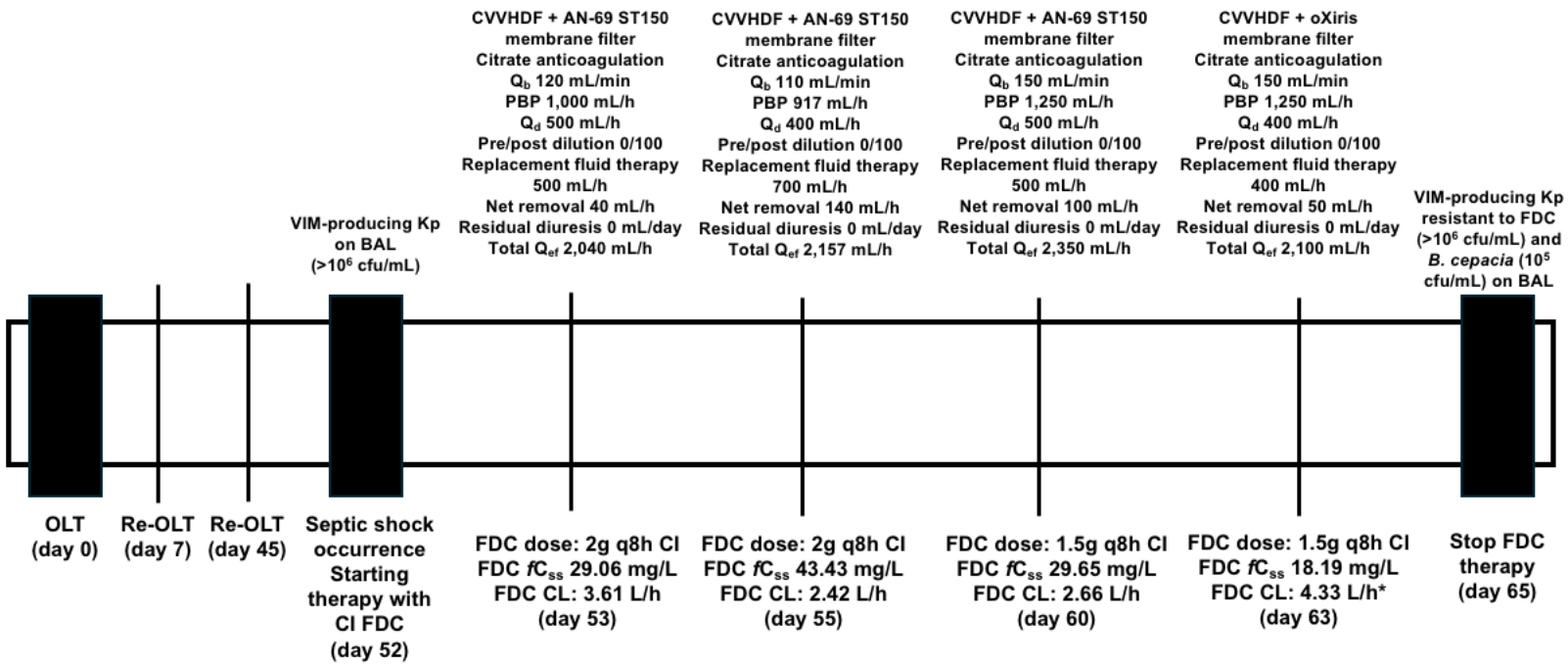
Figure 1 – Cefiderocol PK features and CVVHDF operative conditions at each TDM assessment

BAL: bronchoalveolar lavage; CI: continuous infusion; CL: clearance; CVVHDF: continuous veno-venous hemodiafiltration; FDC: cefiderocol; Kp: *Klebsiella 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

* 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 according to the following equation: [(FDC CL during oXiris – average FDC CL during AN-69 ST150) / (average FDC CL during AN-69 ST150)] * 100%


CVVHDF + AN-69 ST150
membrane filter
Citrate anticoagulation
Q_b 120 mL/min
PBP 1,000 mL/h
Q_d 500 mL/h
Pre/post dilution 0/100
Replacement fluid therapy
500 mL/h
Net removal 40 mL/h
Residual diuresis 0 mL/day
Total Q_{ef} 2,040 mL/h
CVVHDF + AN-69 ST150
membrane filter
Citrate anticoagulation
Q_b 110 mL/min
PBP 917 mL/h
Q_d 400 mL/h
Pre/post dilution 0/100
Replacement fluid therapy
700 mL/h
Net removal 140 mL/h
Residual diuresis 0 mL/day
Total Q_{ef} 2,157 mL/h
CVVHDF + AN-69 ST150
membrane filter
Citrate anticoagulation
Q_b 150 mL/min
PBP 1,250 mL/h
Q_d 500 mL/h
Pre/post dilution 0/100
Replacement fluid therapy
500 mL/h
Net removal 100 mL/h
Residual diuresis 0 mL/day
Total Q_{ef} 2,350 mL/h
CVVHDF + oXiris
membrane filter
Citrate anticoagulation
Q_b 150 mL/min
PBP 1,250 mL/h
Q_d 400 mL/h
Pre/post dilution 0/100
Replacement fluid therapy
400 mL/h
Net removal 50 mL/h
Residual diuresis 0 mL/day
Total Q_{ef} 2,100 mL/h
VIM-producing Kp on BAL
(>10^6 cfu/mL)
VIM-producing Kp resistant to FDC (>10^6 cfu/mL) and *B. cepacia* (10^5 cfu/mL) on BAL
OLT (day 0)
Re-OLT (day 7)
Re-OLT (day 45)
Septic shock occurrence
Starting therapy with CI FDC
(day 52)
FDC dose: 2g q8h CI
FDC fC_{ss} 29.06 mg/L
FDC CL: 3.61 L/h
(day 53)
FDC dose: 2g q8h CI
FDC fC_{ss} 43.43 mg/L
FDC CL: 2.42 L/h
(day 55)
FDC dose: 1.5g q8h CI
FDC fC_{ss} 29.65 mg/L
FDC CL: 2.66 L/h
(day 60)
FDC dose: 1.5g q8h CI
FDC fC_{ss} 18.19 mg/L
FDC CL: 4.33 L/h*
(day 63)
Stop FDC therapy
(day 65)

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