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Ceftriaxone exposure in patients undergoing extracorporeal membrane oxygenation

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Sir,

Extracorporeal membrane oxygenation (ECMO) has the potential to further increase the pharmacokinetic (PK) variability of antimicrobial drugs in critically ill patients, potentially leading to either therapeutic failure or drug toxicity. Studies in *ex vivo* ECMO circuits have identified greater degree of lipophilicity (characterized by the octanol/water partition coefficient, LogP) and plasma protein binding (PPB) as key determinants for drug sequestration within the ECMO circuit.[1, 2] Ceftriaxone, an antimicrobial agent frequently used in the intensive care unit (ICU) in patients admitted with community-acquired pneumonia in standard dosing regimens of 1g or 2g q12h or q24h, is a moderately hydrophilic drug (Log P=-1.7) but shows extensive, albeit variable PPB (83-95%). Recent *ex vivo* studies reported conflicting results on the influence of ECMO on ceftriaxone PK.[1, 2] Hence, it is possible that ceftriaxone PK is affected by ECMO and dose adjustments may be necessary to ensure therapeutic exposure.

To the best of our knowledge, we present the first report of ceftriaxone total and unbound concentrations in two critically ill patients receiving ECMO support. Informed consent was obtained from the patients' closest relative, in accordance with the local ethics committee policy.

Both patients were admitted to the ICU with overwhelming respiratory failure associated with community-acquired pneumonia, for which they were treated with intravenous ceftriaxone and supported by ECMO. Neither patient required renal replacement therapy. Patient characteristics and ECMO details are shown in Table 1.

Ceftriaxone plasma samples were taken immediately before the start of infusion (over 30 minutes), at 0.5h, 1h, 2h, 6h, 12h and before the next dose (trough). Patient 1 received 2g q12h because of possible central nervous system (CNS) co-infection, hence the trough level was taken at 12h. Patient 2 received 2g q24h. Total concentrations were measured for each sample, unbound concentrations were measured for the sample at 0.5h and the trough level. Unbound fractions were determined by equilibrium dialysis (HTD96b, HTDialysis, USA). Ceftriaxone concentrations were measured by liquid chromatography and tandem mass spectrometry (Supplementary Methods).

Ceftriaxone PK parameters, calculated by non-compartmental analysis, are shown in Table 1. The unbound fractions at 0.5h and at trough were 22% and 18% for patient 1, and 19% and 19% for patient 2, respectively. Considering the non-species related clinical MIC breakpoint for ceftriaxone (i.e. 2 mg/L) recommended by the European Committee on Antimicrobial Susceptibility Testing (<http://www.eucast.org>), both frequently recommended pharmacokinetic/pharmacodynamic targets for β -lactam agents (i.e. $100\%fT_{>MIC}$ and $100\%fT_{>4\times MIC}$; based on unbound ceftriaxone concentrations) were met.

Although highly protein-bound, there does not seem to be a significant alteration in ceftriaxone unbound PK, compared to non-ECMO ICU patients, probably because of its hydrophilicity (thus lower tendency for sequestration in the ECMO circuit). The clearance (CL_{unbound}), volume of distribution ($V_{\text{d,unbound}}$) and unbound fractions are in accordance with previously published values for non-ECMO ICU patients.[3] If relevant drug sequestration would have occurred due to ECMO, it does not seem to have a significant impact on exposure >48-72h (which might be due to saturation of ceftriaxone adsorption within the first 48h of ECMO). Therefore, in similar cases, ceftriaxone dosing as in non-ECMO patients could be considered acceptable.

Nevertheless, although ECMO may not significantly alter ceftriaxone PK, ICU clinicians need to be aware that standard dosing regimens might not achieve target attainment in every ICU patient. Recently, Heffernan *et al.*[4] recommended a standard dose of 2g q24h to achieve therapeutic exposure in >90% of septic patients admitted to the emergency department. It should be noted that, with abovementioned dosing regimen of 2g q24h, the first patient would probably not have met the $100\% fT_{>4 \times \text{MIC}}$ target due to augmented renal clearance (ARC) and possibly due to loss of drug in the ECMO circuit. In the second patient, decreased renal clearance of drugs may have a cancelling effect on any increased clearance of the drug due to circuit sequestration. As shown before, estimated kidney function is a major determinant for ceftriaxone CL_{unbound} . [3] Our results suggest that, regardless of ECMO, kidney function should be taken into account when dosing ceftriaxone in critically ill patients. Recently, the use of an estimated kidney function cut-off value with high sensitivity – which is desirable in ECMO patients – has been suggested to detect ARC in critically ill patients (i.e. $\text{CKD-EPI}=87.3 \text{ ml/min/1.73m}^2$). [5] Accordingly, this cut-off might have alerted the ICU clinician to increase ceftriaxone dosing in the first patient – if dosing had not already been increased due to CNS involvement. Hence, our findings are in line with previous results from non-ECMO patients suggesting that a 2g q24h dosing regimen may lead to subtherapeutic exposure in patients with normal or increased renal function[3].

To the best of our knowledge, this is the first published report of ceftriaxone unbound PK in ECMO patients. The two cases presented here suggest that ECMO does not significantly affect unbound PK and pharmacokinetic/pharmacodynamic target attainment of ceftriaxone. In agreement with dosing recommendations for non-ECMO ICU patients, ceftriaxone dosing should be informed mainly by kidney function. Although drug sequestration and significant PK alterations, possibly resulting in subtherapeutic exposure, within 24-48h after initiating ECMO could not be ruled out. More robust evidence to inform the clinician about antimicrobial dosing in ECMO patients is underway.

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Declarations

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Competing Interests: None declared.

Ethical Approval: Approval for the present study was obtained from the EC of the University Hospitals Leuven (S54509). This research has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from the patients' closest relative.

Supplementary data

Supplementary Methods.

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Table 1. Patient characteristics, ECMO details, and ceftriaxone pharmacokinetic parameters.

	Patient 1	Patient 2
Gender	Man	Woman
Age, years	61	51
Body weight, kg	108	58
Body mass index, kg/m ²	38.3	20.1
Serum albumin, g/L	34.6	25.5
eGFR _{CKD-EPI} , mL/min/1.73m ²	91	51
ECMO modality	Veno-venous	Veno-arterial
Total ECMO duration, days	6.6	5.1
Number of ECMO days at first sample, days	2.5	2.8
ECMO oxygenator	Medos 7000LT	Medos 7000LT
ECMO blood pump	Jostra Rota Flow	Medos DP3
APACHE II on admission	29	24
SOFA	11	14
Ceftriaxone dosing regimen	2g q12h	2g q24h
Number of ceftriaxone days at first sample, days	4	4
AUC ₀₋₂₄ , unbound, mg*h/L	498	434
C _{min, total} , mg/L	66.1	55.9
C _{min, unbound} , mg/L	11.9	10.6
CL _{unbound} , L/h	8	4.6
V _{d unbound} , L	29.7	32.9
Concentration-time profile

eGFR_{CKD-EPI}: estimated glomerular filtration rate according to the Chronic Kidney Disease epidemiology equation; ECMO: extracorporeal membrane oxygenation; APACHE II: acute physiology and chronic health evaluation II score; SOFA: sequential organ failure assessment score; AUC₀₋₂₄: area under the curve over 24 hours; C_{min, total}: total trough concentration; C_{min, unbound}: unbound trough concentration; CL_{unbound}: clearance of the unbound fraction; V_{d unbound}: distribution volume of the unbound fraction