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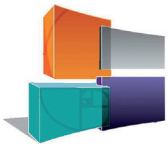

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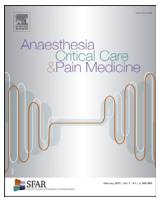

Editorial

Antimicrobial therapy during ECMO – customised dosing with therapeutic drug monitoring: The way to go?

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Extracorporeal membrane oxygenation (ECMO) can provide temporary cardiac and/or respiratory support for critically ill patients who have failed maximal conventional medical management [1]. ECMO does not resolve the underlying cause of cardiorespiratory failure by itself, but it stabilises severely ill patients and sustains life whilst the underlying pathology is being evaluated and managed. It provides an important bridge to either organ transplantation (e.g., heart or lung transplantation), long-term support devices or to full organ recovery. Although this life support technique is traditionally being used more often in the neonatal and paediatric populations, the use of ECMO has evolved and increased exponentially in critically ill adults since the H1N1 flu pandemic and publication of the Conventional Ventilatory Support versus ECMO for Severe Adult Respiratory Failure (CESAR) trial in 2009 [2].

As ECMO is only "supportive" in nature, optimal pharmacotherapy to reverse the underlying cause of cardiorespiratory failure and minimise complications of ECMO is critical to ensure therapeutic success for the patient. However, it is commonly recognised that optimal drug therapy is challenging in such patients and may be complicated by extreme physiological derangements leading to altered pharmacokinetics (PK) and drug exposure [3]. ECMO is hypothesised to further exacerbate the PK alterations that occur during critical illness and may potentially impact therapeutic outcomes [4,5]. The introduction of ECMO may influence the PK of "vulnerable drugs" by: (a) circuit sequestration; (b) increased volume of distribution (V_d) and (c) altered drug clearance (CL). Significant alterations in the primary PK parameters (i.e., V_d and CL) of analgesics, antibiotics, antiepileptic drugs and sedatives have been described in neonatal and paediatric ECMO studies [5]. Although the extent of such alterations remain poorly elucidated in adult ECMO patients, emerging data are suggesting that similar phenomena are highly-likely, at least theoretically, and drug dosing that does not compensate for these alterations has a higher likelihood of failure in this population.

ECMO carries several risks and complications, a major one associated with this extracorporeal life support being nosocomial infection. Critically ill patients on ECMO commonly develop nosocomial infections during hospital stay (range: 8 – 60%), which are associated with prolonged ECMO and ventilator support, as well as poor mortality outcomes [1]. As ECMO is not a disease-modifying intervention on its own, therapeutic outcomes of critically ill patients with severe infections on ECMO will heavily rely on whether optimal antibiotic therapy is delivered to these patients. An in-depth knowledge on ECMO and critical illness-related PK changes is required to inform antibiotic dosing in these patients and thankfully, important breakthroughs have been made in this area of research. An emerging body of literature over the last 10 years describes the PK of antibiotics in critically ill adult patients on ECMO support (Table 1) [6–17]. These clinical PK data, in combination with existing *ex vivo* and *in vivo* animal model data [4,5], outline four key findings in relation to ECMO and antibiotic PK: (a) physicochemical properties of drugs influence the degree of drug loss/sequestration in ECMO circuits whereby lipophilic (e.g., fentanyl) and highly-protein bound drugs (e.g., ceftriaxone) would be most vulnerable to these losses; (b) earlier neonatal and paediatric PK data cannot be extrapolated to the critically ill adult population; (c) modern ECMO circuitry has minimal adsorption and impact on the PK of most antibiotics and; (d) altered PK changes in ECMO patients are more reflective of critical illness rather than ECMO itself. Therefore, antibiotic dosing in this patient population should generally align with the recommended dosing strategies for critically ill patients without ECMO support [5]. However, the intrinsic PK variability in this patient population may mean that some patients will still receive sub-optimal antibiotic exposures with variable clinical responses despite receiving customised antibiotic dosing.

The complexity of dosing antibiotics in critically ill patients during ECMO was somewhat characterised by the recent PHARMECMO study [18]. The PHARMECMO study was a prospective, observational single-centre PK study with an aim to determine whether contemporary antibiotic dosing in critically ill ECMO patients achieves the pharmacokinetic/pharmacodynamic (PK/PD) targets associated with maximal clinical outcomes. Forty-four patients who were receiving aminoglycosides, beta-lactam antibiotics, ciprofloxacin and/or vancomycin were recruited over a one-year period. Huge concentration variations were observed in this study, particularly for the beta-lactam antibiotics (up to 100-fold variations), and this phenomenon also led to variable antibiotic PK/PD target attainment (range: 4 – 100% of

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Table 1
Clinical studies conducted over the last 10 years describing antibiotic pharmacokinetics in critically ill adult patients receiving ECMO.

Study	Setting (Year)	Study design	Sample size	ECMO type		Antibiotic	PK estimates	
				VA	VV		ECMO	Non-ECMO
Jaruratanasirikul et al. [6]	Thailand (2019)	Prospective, open-labelled PK study	ECMO: 10 Non-ECMO: 18[a]	6	4	Imipenem	V_d: 0.54 L/kg CL: 0.15 L/hr/kg	V_d: 0.39 L/kg CL: 0.39 L/hr/kg
Hanberg et al. [8]	Denmark (2018)	Prospective, open-labelled PK study	10	NS	NS	Meropenem	V_d: 0.16 L/kg CL: 0.03 L/kg	NA
Ruiz-Ramos et al. [7]	Spain (2018)	Prospective, open-labelled PK study	ECMO: 9 Non-ECMO: 50[b]	NS	NS	Amikacin	V_d: 0.35 L/kg CL: 0.04 L/hr/kg	V_d: 0.29 L/kg CL: 0.04 L/hr/kg
Wi et al. [9]	S. Korea (2017)	Prospective, open-labelled PK study	ECMO: 10	10	0	Teicoplanin	V_d: 1.29 L/kg CL: 0.01 L/hr/kg	NA
Gelisse et al. [10]	France (2016)	Case report	ECMO: 50 Non-ECMO: 50	43	7	Amikacin	C_{max}: 71.7 mg/L AUC: 973 mg·h/L	C_{max}: 68.4 mg/L AUC: 921 mg·h/L
Moore et al. [11]	USA (2016)	Prospective, open-labelled PK study	14	12	2	Vancomycin	V_d: 0.59 L/kg CL: 0.03 L/hr/kg	NS
Turner et al. [12]	USA (2016)	Case report	ECMO: 3 Non-ECMO: NS[c]	0	3	Azithromycin	V_d: 19.80 L/kg CL: 0.48 L/hr/kg	V_d: 33.30 L/kg CL: 0.61 L/hr/kg
Wu et al. [13]	Taiwan (2016)	Prospective, open-labelled, matched-cohort PK study	ECMO: 11[d] Non-ECMO: 11[e]	7	3	Vancomycin	V_d: 0.84 L/kg CL: 0.07 L/hr/kg	V_d: 0.81 L/kg CL: 0.09 L/hr/kg
Donadello et al. [14]	Belgium (2015)	Retrospective, matched-cohort PK study	ECMO: 26 Non-ECMO: 41[f]	9	17	Meropenem Pip/Tazo	V_d: 0.46 L/kg CL: 7.50 L/hr V_d: 0.33 L/kg CL: 9.36 L/hr	V_d: 0.60 L/kg CL: 8.64 L/hr V_d: 0.31 L/kg CL: 8.04 L/hr
Park et al. [15]	S. Korea (2015)	Retrospective, case-control PK study	ECMO: 20[d] Non-ECMO: 60[g]	8	11	Vancomycin	V_d: 0.65 L/kg CL: 4.62 L/hr	V_d: 0.68 L/kg CL: 4.31 L/hr
Donadello et al. [16]	Belgium (2014)	Retrospective, matched-cohort PK study	ECMO: 11 Non-ECMO: 11[f]	5	6	Vancomycin	V_d: 1.41 L/kg CL: 0.03 L/hr/kg	V_d: 1.32 L/kg CL: 0.03 L/hr/kg
Shekar et al. [17]	Australia (2014)	Prospective, open-labelled, matched-cohort PK study	ECMO: 11 Non-ECMO: 10[h]	5	6	Meropenem	V_d: 0.45 L/kg CL: 7.90 L/hr	V_d: 0.41 L/kg CL: 11.70 L/hr

AUC: area under the concentration-time curve; CL: clearance; Cmax: maximal drug concentration; ECMO: extracorporeal membrane oxygenation; NS: not specified; NP: not available; Pip/Tazo: piperacillin/tazobactam; PK: pharmacokinetic; VA: venoarterial ECMO; V_d: volume of distribution; VV: venovenous ECMO.
[a] Non-ECMO controls were critically ill patients with ventilator-associated pneumonia and serious bacteraemia.
[b] Non-ECMO controls were critically ill patients with normal renal function.
[c] Non-ECMO controls were hospitalised patients with community-acquired pneumonia and healthy volunteers
[d] One patient received hybrid VA and VV ECMO.
[e] Non-ECMO controls were ICU patients matched by age, gender and creatinine clearance.
[f] Non-ECMO controls were ICU patients matched by dosing regimen, renal function, total body weight, SOFA score and age.
[g] Non-ECMO controls were critically ill patients receiving vancomycin in medical ICU.
[h] Non-ECMO controls were critically ill patients with normal renal function ($N = 5$) and critically ill patients receiving continuous renal replacement therapy ($N = 5$).

target attainment rate). Whilst the majority of patients who received cefotaxime and piperacillin achieved the desired PK/PD targets, those receiving aminoglycosides and imipenem demonstrated poor target attainment rates despite receiving "standard ICU dosing", with or without altered dosing methods (e.g., continuous or extended infusion). The PHARMECMO findings of variable antibiotic concentrations and inconsistent PK/PD target attainment rates are in-line with what have been previously described in critically ill patients [19]. The consequences following these may be severe for critically ill ECMO patients, as sub-optimal antibiotic exposures have been linked to poor clinical outcomes and the emergence of bacterial resistance [3]. As patients on ECMO are often regarded as the "sickest of the sickest" population, the high mortality rate in this study (50%) is therefore not surprising. An optimised approach to antibiotic dosing during ECMO is clearly needed to maximise therapeutic outcomes.

Although altered dosing methods such as continuous and extended beta-lactam infusion can improve antibiotic exposure, the extreme PK variability in this patient population means that some patients may still receive insufficient antibiotic exposure leading to variable clinical outcomes. However, the number of affected patients is likely to be reduced and lower in comparison to standard dosing based on Product Information leaflet. Therapeutic drug monitoring (TDM) is the only effective and safe way to ensure that all critically ill patients achieve therapeutic antibiotic exposures during ECMO. Pending more robust clinical PK data to guide antibiotic dosing in this patient population, TDM appears highly necessary not only to prevent sub-optimal dosing but also to minimise the likelihood of adverse events during ECMO [4,5]. TDM-guided dosing has been shown to be meritorious for various antibiotics [20], antifungals [21] and antivirals [22]. Additionally, emerging data have described the utility of TDM and its potential benefits in guiding antibiotic therapy in critically ill paediatric patients during ECMO [23,24]. Therefore, the PHARMECMO findings further strengthen the need for antibiotic TDM in critically ill adult patients receiving ECMO.

As a conclusion, ECMO is a relatively complex therapy that is delivered over days and weeks, and therapeutic outcomes in this heterogeneous population may be determined by various inter-

linked factors. Appropriate patient selection, optimal timing and ECMO application, adequate staff training, availability of bridging options (e.g., mechanical support devices and/or transplantation) in cases of non-recovery, as well as the volume and experience in ECMO centres may influence ECMO-related outcomes. Hence, it will always be challenging to characterise the morbidity and mortality related to sub-optimal antibiotic dosing on ECMO in clinical trials. This should not discourage clinicians from striving for optimal pharmacotherapy, which is one of the basic tenets of medicine. Dosing antibiotics during ECMO can be challenging, as these drugs cannot be titrated to clinical effect in real time, contrary to sedatives and analgesics. Importantly, these challenges are likely to be further escalated for antibiotics for which TDM is not readily available. It is therefore important to apply the existing knowledge of critical illness-related PK changes and the emerging knowledge of altered PK in ECMO patients to ensure optimal pharmacotherapy can be delivered during ECMO. International collaboration is the key to conduct adequately powered high-quality clinical trials in ECMO, and organisations such as the International ECMO Network (www.internationalecmonetwork.org) can play an important role in this regard.

Disclosure of interest

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The author Abdul–Aziz declares that he has no competing interest.

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