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SEPSIS IN THE ICU (J LIPMAN, SECTION EDITOR)

Applying Antimicrobial Pharmacokinetic Principles for Complex Patients: Critically Ill Adult Patients Receiving Extracorporeal Membrane Oxygenation and Renal Replacement Therapy

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Abstract

Purpose of Review Extracorporeal membrane oxygenation (ECMO) is establishing itself as the standard of care for managing critically ill patients who have exhausted conventional treatment in many adult ICUs around the world. The integration and combined extracorporeal effects of this device with renal replacement therapy (RRT) have not been well studied. This is especially challenging in the pursuit of achieving optimal antimicrobial exposures in this group of critically ill patients. The objective of this review is to discuss the available literature to support clinicians in navigating dosing challenges in this clinical scenario.

Recent Findings The number of antimicrobial pharmacokinetic (PK) studies in patients on RRT and ECMO is growing. However, very few studies have been designed to describe the combined effects of the concurrent use of two extracorporeal circuits. Currently available literature consists of studies with small sample sizes and provides inconsistent findings. Nevertheless, it is clear that it is not a simple sum of the independent RRT- and ECMO-induced PK changes in addition to the PK changes arising from severe physiological derangement associated with a critical illness. Preliminary data suggest that improvements in target attainment may be achieved through understanding the potential PK changes secondary to specific drug physicochemical properties and the extracorporeal circuits. Thus, the availability of therapeutic drug monitoring plays a key role in this complex patient group to recognise ineffective and toxic serum antimicrobial concentrations.

Summary The data available to clinicians are insufficient to guide appropriate empirical drug dosing in patients on concurrent ECMO and RRT. Future studies should be designed and powered to evaluate specific RRT settings and relevant covariates within the ECMO population. Until further data becomes available, therapeutic drug monitoring is recommended to prevent subtherapeutic and toxic concentrations of antimicrobials in this patient population.

Keywords Antimicrobial dosing · Extracorporeal membrane oxygenation · Pharmacokinetics · Antibiotics · Acute kidney injury · Renal replacement therapy

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Introduction

Extracorporeal membrane oxygenation (ECMO) is a life-sustaining device used in the intensive care unit (ICU) to provide temporary cardiorespiratory support while the underlying pathology can be treated. Patients on ECMO are often the sickest in the healthcare system and are highly susceptible to multiorgan failure, including acute kidney failure (AKI) requiring renal replacement therapy (RRT) support [1•]. RRT is a common technique to maintain fluid balance and manage the accumulation of metabolic waste and electrolyte imbalances in these patients. Both ECMO and RRT are extracorporeal devices, which in addition to the pathophysiology of critical illness can independently or collectively alter the pharmacokinetics (PK) of certain drugs, subsequently altering drug exposures [2, 3]. This review summarises the most relevant literature available on the PK and dosing recommendations of antimicrobials for critically ill adult patients on concurrent ECMO and RRT. This paper will report the key PK differences between patients on concomitant ECMO and RRT and ECMO alone.

Epidemiology, Outcome and Management of AKI and Sepsis

Sepsis has been reported to be the most frequent aetiology for AKI, with a reported prevalence of 40–50% in critically ill patients with AKI [4, 5]. Newly developed AKI in critically ill patients has been attributed to sepsis or septic shock in 11–50% of cases [6–8]. The incidence of AKI is positively correlated with the severity of sepsis with a prevalence of approximately 19% and 51% in patients with sepsis and septic shock, respectively [9]. In a multicentre study across 57 Australian ICUs, the overall hospital mortality in patients with sepsis-associated AKI was reported to be 70%, with septic AKI patients having a longer duration of stay in both ICU and hospital than those with nonseptic AKI [6].

RRT has become an indispensable management strategy in patients with severe AKI [10••]. RRT can often be divided into four modalities: continuous, prolonged, intermittent and peritoneal dialysis. Continuous and prolonged (over 6–14-h duration) forms of RRT are often used in ICU and will be the focus of this paper. Intermittent (over 3–4-h duration) is globally less commonly used in ICUs. The predominant form of RRT use in the ICU is continuous RRT (CRRT) [11, 12], but an increasing body of evidence is emerging for the use of more intense forms of dialysis, such as prolonged intermittent RRT (PIRRT) including sustained/slow low-efficiency dialysis (SLED) in the ICU [13, 14]. Although RRT is prescribed to remove waste solutes, the application of RRT significantly complicates drug dosing as it is nonspecific in its function and may enhance the removal of drug treatments. For example, an area of concern is the unintentional removal of antimicrobials to treat pathogens causing sepsis, thus reducing drug exposure and may lead to therapeutic failure.

The management of sepsis is supported by guidelines with treatment recommendations on initial resuscitation, maintenance of haemodynamic parameters, source control and timely administration of appropriately dosed antimicrobials [15]. The latest update from the Surviving Sepsis Campaign has recommended the administration of an effective intravenous antimicrobial agent as soon as possible after recognition and within 1 h for both sepsis and septic shock [16]. However, the difficulty is often in selecting the right dose of the right antimicrobial agent in patients with complicated medical histories and extreme pathophysiological derangements and further effects of extracorporeal devices such as RRT and ECMO.

Epidemiology, Outcome and Management of Sepsis and Cardiorespiratory Failure

Mortality rates for critically ill adult patients with conventional management of severe acute respiratory distress syndrome (ARDS) have been reported to exceed 60% [17] and 40–50% for patients with cardiogenic shock [18]. It is often when conventional treatment options have been exhausted that clinicians use ECMO as a life-sustaining technique. ECMO, by itself, is not a disease-modifying intervention but an adjuvant that facilitates organ support through the provision of tissue oxygenation while the primary pathology is evaluated or managed.

The ECMO circuit configuration is dependent on the kind of cardiorespiratory support required. The two most common forms of ECMO configurations are venovenous (VV) ECMO where blood is drained from and oxygenated blood returned to the venous system, and venoarterial (VA) ECMO, where blood is drained from the venous system and oxygenated blood returned to the arterial system. VV ECMO is predominantly used for patients with respiratory failure, while VA ECMO provides an additional artificial cardiac output that can be used in both cardiorespiratory and/or respiratory failure.

Epidemiology of AKI and RRT Use in ECMO

A single-centre ICU study reported the incidence of AKI in adult ECMO patients post-cardiotomy was 81% [19]. While another single-centre study reported a similar incidence of AKI in their cardiovascular surgery ECMO patients to be 78% [20]. A recent meta-analysis reported a pooled estimated incidence of AKI among adult patients on ECMO to be 62.8% [21]. The indications prompting the initiation of RRT in the adult ECMO population have been reported to primarily be

for the treatment and prevention of fluid overload and the management of waste secondary to AKI [22]. The causative relationship between ECMO and AKI has not been well explained [23]. However, AKI in critically ill patients has been postulated to be predominately due to sepsis, ischaemia, cardiorespiratory failure and the use of nephrotoxic drugs [1•]. The Extracorporeal Life Support Organisation (ELSO) Registry data reports that up to 38% of the patient on VV ECMO and 48% of VA ECMO may require some form of RRT during ECMO [24]. A single-centre retrospective study conducted by Dado et al. in adult ECMO patients reported that over 50% of ECMO patients received CRRT. Furthermore, the authors reported a mortality rate of 39.5% with combined ECMO/CRRT use when compared with 31.4% of those receiving ECMO only [3]. This was further supported by reported mortality rates of 60–100% in several single-centre studies looking at combined CRRT and ECMO use [19, 22, 25, 26]. Despite the prevalent use of concurrent ECMO and RRT devices, there is a dearth in the literature providing robust evidence on preferential configuration, modalities, extracorporeal device settings and ultimately drug dosing in this select group of patients.

Principles of Drug Dosing in Concurrent RRT and ECMO

With the high prevalence of sepsis contributing to the mortality of critically ill patients, appropriate antimicrobial exposures are essential for optimal treatment. While the majority of drug effects can be guided by clinical surrogates (such as heparin by activated partial thromboplastin time (APTT); sedatives by the Richmond Agitation–Sedation Scale (RASS) scoring; or bispectral index (BIS) monitoring and inotropes by heart rate and blood pressure, mixed venous oxygen saturation and serum lactate), the lack of a useful bedside clinical endpoint for antimicrobial efficacy makes dosing very challenging. Consequently, clinicians must resort to recommendations from generic product information that do not account for the physiology and PK differences in this critically ill patient cohort. A significant body of research has therefore been undertaken to investigate the PK alterations that may occur during critical illness [27] while receiving extracorporeal therapies [28••, 29, 30•]. Several studies have explored the PK alterations induced by ECMO [31–35] and RRT separately [30•, 36], but very few studies have described the collective impact of concurrent ECMO and RRT use [37]. Improving the understanding of these potential PK alterations will increase the likelihood of achieving safe and efficacious antimicrobial concentrations and exposures leading to effective antimicrobial therapy in this patient population.

ECMO: the Device and PK Considerations

Regardless of the configuration, modern ECMO circuitry consists of a centrifugal blood pump, an artificial membrane oxygenator and a heat exchanger, which are connected via conduit tubing. Each of these components provides a surface for potential interactions with drug molecules. The degree of these adsorptive interactions has been attributed to various circuit materials [38–41], ECMO flow rate and the drug's physicochemical properties [34, 35]. Ex vivo studies with ECMO circuits have demonstrated that drugs with a high lipophilicity or octanol–water partition coefficient (log *P*) and those with a higher affinity to plasma protein (e.g. fentanyl and ceftriaxone, respectively) are more likely to be sequestered into the circuit [34, 35, 41, 42]. The findings from the mechanistic studies have also been found in neonatal and paediatric studies and have been hypothesised to be due to circuit sequestration and haemodilution. These studies suggested that ECMO increases the V_d and may also alter the clearance (CL) of drugs [43–45]. Several clinical studies have looked into the translatability of this phenomenon in the adult clinical setting. Several studies have reported on the differences in the probability of attaining target concentrations and exposures, but the findings so far have been inconsistent [31, 46–48]. The body of evidence for dosing in ECMO has been building, and the Antibiotic, Sedatives and Analgesic Pharmacokinetics during Extracorporeal Membrane Oxygenation (ASAP ECMO) study has been designed to provide clinicians with clear dosage recommendations in this patient group [28••].

RRT: the Device and PK Considerations

As CRRT is the most common modality of RRT used in the critically ill population on ECMO, this section will mainly focus on CRRT and briefly discuss PIRRT.

CRRT is usually provided as continuous venovenous haemofiltration (CVVH), continuous venovenous haemodialysis (CVVHD) or a combination of the two, continuous venovenous haemodiafiltration (CVVHDF) [29].

Similar to ECMO, researchers have endeavoured to use the physicochemical properties of a drug to determine the potential degree of extracorporeal drug removal and the subsequent dosing adjustment required. Generally, studies suggest that drugs with large V_d ($\geq$1 L/kg) such as ciprofloxacin (V_d of 1.5 L/kg) and drugs exhibiting high degrees of protein binding (>80%) such as ceftriaxone (85–95%) are poorly eliminated by CRRT [49]. However, drug physicochemical properties alone do not predict dialytic drug loss, and additional factors such as renal elimination characteristics, degree of nonrenal elimination, dose of CRRT, blood flow rate, filter material and surface area need to be considered [10••, 50]. It is therefore

imperative to discuss the different modalities of CRRT separately.

Haemofiltration utilises a hydrostatic pressure gradient to drag solute along with water across a filter membrane to achieve CL by the principles of convection. Most antimicrobials are small enough that the convective transport across commonly used membranes (pore sized 10,000–30,000 Da) is unimpeded [51, 52]. The ability of a solute to pass through the membrane is expressed as the sieving coefficient (S_c): the ratio of drug concentration in the ultrafiltrate to plasma. S_c has been demonstrated to be determined by the drug's degree of protein binding, rate of predilution fluid, membrane material and flux properties [53–55]. Consequently, antimicrobials with high degrees of protein binding, such as ceftriaxone, will not be extensively eliminated by haemofiltration irrespective of albumin concentrations [56].

Haemodialysis CL is determined by the diffusion across the filter membrane. This has been reported to be dependent on the molecular weight of the drug, the blood flow and the dialysate flow [29]. However, as CVVHD and CVVHDF are performed with a relatively low dialysate flow rate compared with the blood flow rate, neither blood flow nor molecular size are important determinants in the CL of commonly use antimicrobials. The saturation coefficient S_d (the ability of a solute to diffuse through the filter membrane) and the dialysate flow rate are therefore the two key determinates in the dialytic CL of drugs in haemodialysis.

Haemodiafiltration is the combination of both the convection and diffusion CL to eliminate solutes, and drug CL in CVVHDF is estimated by the summation of the two processes.

Unfortunately, slight variations in the type of filter material, blood flow rate, pre- or post-dilution fluid replacements and effluent flow rate settings can substantially alter antimicrobial PK and, consequently, dosing requirements. It is therefore essential for clinicians to understand the implications of each individual factor and dose antimicrobials accordingly.

The growing adoption of the hybrid form of RRT, PIRRT, has led to several small single-centre studies investigating appropriate antimicrobial dosing in this subgroup [57–59]. PIRRT is a moderate intensity RRT applied over a period of 6–12 h daily. It is gaining popularity due to comparable haemodynamic stability with CRRT while reducing cost and the ability to promote early patient mobility. However, preliminary data suggests that the CL resultant from PIRRT is highly inconsistent and variable [57, 58]. Further robust multicentre studies are required to support clinicians in dosing antimicrobials secondary to the increasingly popular use of SLED in the ICU. The large changes in CL during and off SLED result in inconsistent drug CL across a 24-h period which is a phenomenon rarely considered in dosing regimen design and requires further elucidation.

ECMO and RRT: Overall Concept

The most commonly used modality in ECMO patients has been reported to be CRRT via the use of an in-line haemofilter or via a traditional CRRT device connected to the extracorporeal circuit [Figure 1] [22]. Configuration of the two extracorporeal devices can vary and is often institution and clinician dependent. In-line haemofilters are typically placed after the ECMO pump to provide forward blood flow through the haemofilter and before the oxygenator to maintain the oxygenator's use as a clot and air trap. Similarly, a CRRT machine can be connected in-line to the ECMO circuit. The CRRT machine is typically connected after the ECMO centrifugal pump to reduce the risk of air entrainment. Alternatively, ECMO and RRT circuits can also be utilised in parallel with separate circuits [60]. Regardless of configuration, the PK changes secondary to the integration of the two extracorporeal circuits have been shown to not be a simple summation of the two independent extracorporeal circuit-induced PK changes. Further comparative studies are required to better describe this complex relationship and therefore provide robust dosing advice to guide clinicians in this challenging clinical scenario.

Specific Antimicrobial/Antimicrobial Classes

Over the past 10 years, the body of literature emerging to better describe the PK of antimicrobials in ECMO is growing. However, most studies are designed and powered to explain ECMO variables alone. The serendipitous enrolment of patients receiving concurrent RRT often does not provide enough data points to explain the final effects of concurrent extracorporeal circuits. Table 1 summarises recent studies that have investigated PK of antimicrobials in patients receiving concurrent ECMO and RRT.

Aminoglycosides

Aminoglycosides are hydrophilic with a low V_d, a low degree of protein binding (<30%) and predominantly renally cleared. Optimal bactericidal activity has been reported to be concentration dependent which is represented by an area under the curve over minimum inhibitory concentration (MIC) ($AUC_{0–24}$/MIC) of total drug concentrations greater than 110 mg h/L [67, 68] and of free drug concentrations greater than 50 mg h/L [69]. Ruiz-Ramos et al. compared amikacin PK parameters among six groups of patients with various combinations of ECMO or ventricular assist device and CVVHDF with a control group. The ECMO group demonstrated a higher V_d than the ECMO/CVVHDF, CVVHDF and control groups (V_d of 0.346 L/kg, 0.304 L/kg, 0.261 L/kg and 0.288 L/kg,

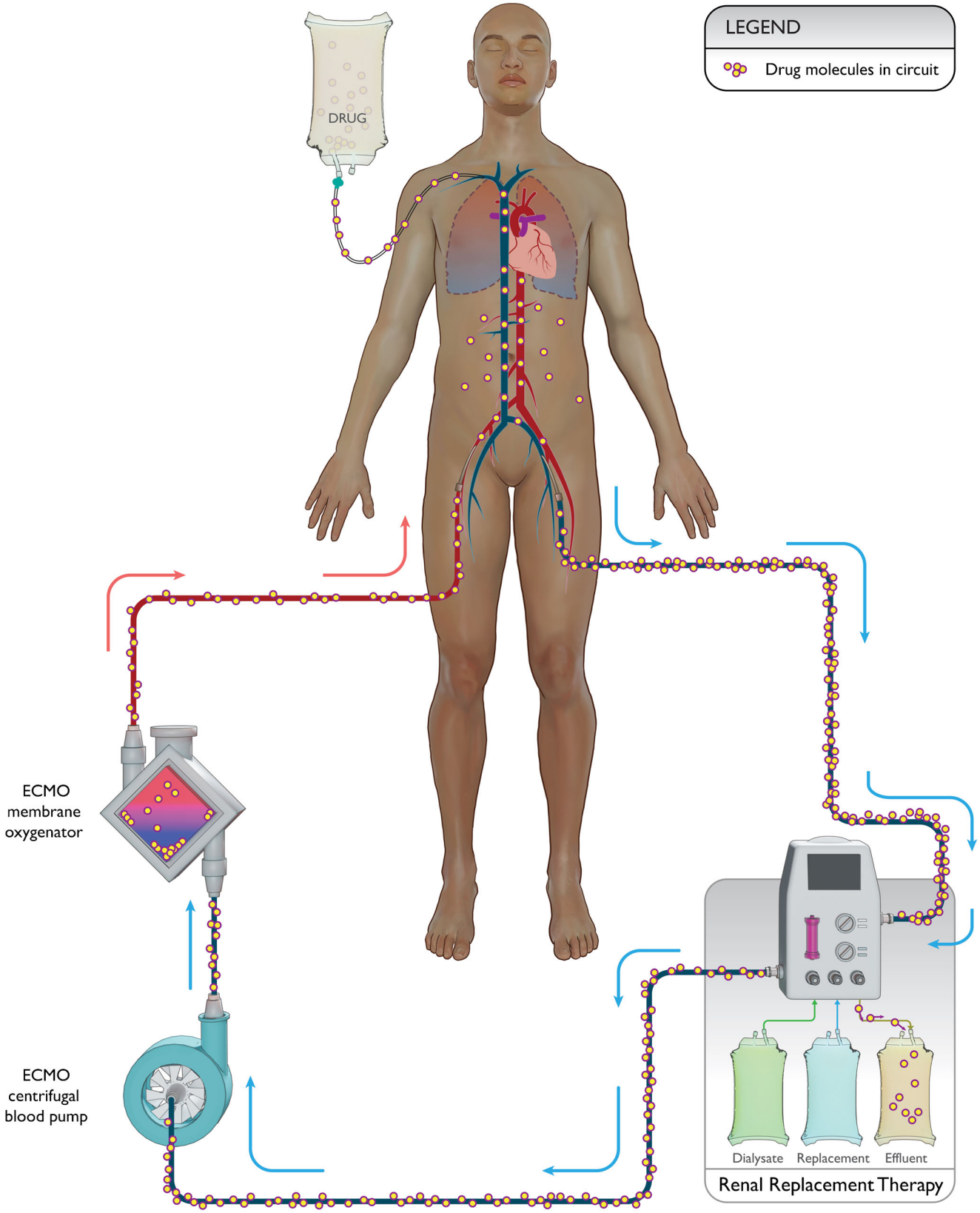

Fig. 1 Potential sites of distribution/sequestration for vulnerable drugs in a critically ill patients requiring concurrent ECMO and CRRT

Table 1 Clinical pharmacokinetic studies conducted over the last 12 years describing antimicrobial PK in critically ill adult patients receiving ECMO and RRT

Study	Setting (year)	Study design	Sample size	Antimicrobial	PK parameters	Findings and recommendations
Kang et al. [61]	Korea (2020)	Prospective, open-label, population PK study	ECMO alone: 9 ECMO/CVVHDF: 5	Cefpirome	ECMO and ECMO/CVVHDF together: V_c 10.3 L, V_p 19.5 L, CL 3.6 L/h	Not enough information to describe the role of CVVHDF with ECMO
Kuhn et al. [62]	Germany (2019)	Prospective, open-label, observational TDM study	ECMO alone: 14 ECMO/CVVHD: 16	Piperacillin, meropenem and linezolid	N/A	Not enough information to describe the role of CRRT with ECMO.
Hanberg et al. [63]	Denmark (2018)	Prospective, open-label, population PK study	ECMO alone: 1 ECMO/CRRT: 9	Meropenem	ECMO and ECMO/CRRT together: V_c 8.31 L, V_p 6.99 L, CL 0.046 mL/min	Not enough information to describe the role of CRRT with ECMO. But as a majority of this population was on CRRT, significantly lower CL and V_d were exhibited compared with other studies
Ruiz-Ramos et al. [64]	Spain (2018)	Prospective, open-label PK study	ECMO alone: 7 ECMO/CVVHDF: 2	Amikacin	ECMO alone: V_d 0.346 L/kg, CL 0.040 L/h/kg ECMO and CVVHDF: V_d 0.304 L/kg, CL 0.041 L/h/kg	Concurrent ECMO and RRT patients demonstrated a slightly lower V_d but similar CL to ECMO alone
Strunk et al. [65]	Germany (2016)	Case report	ECMO and EDD/IHD	Ethambutol and rifampicin	N/A	EDD eliminates ethambutol effectively and to a larger extent than regular IHD. Rifampicin was found in the spent dialysate. ECMO did not remove either drug
Donadello et al. [32]	Belgium (2015)	Retrospective, matched-cohort PK study	ECMO alone: 17 ECMO/CRRT: 9	Piperacillin and meropenem	ECMO and ECMO/CRRT together: Piperacillin V_d 0.33 L/kg, CL 156 mL/min Meropenem V_d 0.46 L/kg, CL 125 mL/min	Not enough information to describe the role of CRRT with ECMO
Shekar et al. [37]	Australia (2014)	Prospective, open-label matched-cohort PK study	ECMO alone: 6 ECMO/EDD-f: 5	Meropenem	ECMO alone: V_c 18.7 L, V_p 13.2 L, CL 1.89*108 L/h ECMO and ECMO/EDD-f together: V_c 18.7 L, V_p 13.2 L, CLrrt 5.1 L/h	EDD-f only partially compensates decreased CL in AKI, higher concentrations observed compared with ECMO alone
Donadello et al. [33]	Belgium (2014)	Retrospective, matched-cohort PK study	ECMO alone: 4 ECMO/CRRT: 7	Vancomycin	ECMO alone: V_c 31.8 L, V_p 57.1 L, CL 3.7 L/h ECMO and CRRT: V_c 31.8 L, V_p 57.1 L, CL 2.22 L/h	Total CL during ECMO/CRRT was lower than in patients on ECMO alone. Lower doses should be used
Lemaitre et al. [66]	France (2010)	Prospective, open-label PK study	ECMO alone: 4 ECMO/CVVHDF: 3	Oseltamivir	ECMO alone: C_{max} 5.3 ng/mL · mg, AUC_{0-12} 0.044 mcg · h/mL · mg ECMO and CVVHDF: C_{max} 13.9 ng/mL · mg, AUC_{0-12} 0.143 mcg · h/mL · mg	CVVHDF and ECMO patients had a much 4- to 5-fold increase in peak concentration and AUC when compared with patients on ECMO alone

ECMO, extracorporeal membrane oxygenation; *EDD-f*, extended daily haemodiafiltration; *CL*, clearance; *AKI*, acute kidney injury; *PK*, pharmacokinetics; *CRRT*, continuous renal replacement therapy; *CVVHDF*, continuous venovenous haemodiafiltration; V_d, volume of distribution; V_c, central volume of distribution; V_p, peripheral volume of distribution; *CVVHD*, continuous venovenous haemodialysis; *EDD*, extended daily dialysis; *IHD*, intermittent haemodialysis; C_{max}, peak concentration; *AUC*, area under the curve

respectively). CL was similar in the ECMO and the ECMO/CVVHDF groups with values reported to be 0.040 L/h/kg and 0.041 L/h/kg, respectively. However, it is important to note that the ECMO/CVVHDF group consisted of only two patients, which is often insufficient in adequately describing PK parameters in this highly heterogenous group [64]. Overall, the introduction of ECMO and CVVHDF appears to significantly alter the PK of amikacin. Without further research into this hypothesis, it is difficult to differentiate among critical illness-related PK changes, ECMO-induced PK effects and the interpatient differences in these two groups of patients. Until large-scale studies are available, therapeutic drug monitoring (TDM) should be used to maximise target attainment in these groups of critically ill patients.

Beta-Lactams

Beta-lactam antimicrobials are hydrophilic and most have a low-to-moderate degree of protein binding. These antimicrobials demonstrate low V_d and are predominately cleared renally. Penicillins demonstrate time-dependent bactericidal activity which is optimised when the duration of time that the free drug concentration remains above the MIC ($\%fT_{>MIC}$) is at least 50% [70]. Donadello et al. investigated the effects of ECMO on the PK of piperacillin in a descriptive PK study using TDM concentration data. The serendipitous recruitment of nine patients on CRRT allowed the authors to comment on the differences of target attainment in the ECMO alone and ECMO/CRRT groups. Although the authors concluded that the introduction of ECMO did not significantly change the PK parameters of piperacillin and rates of target attainment, the study was insufficiently powered to assess the influences of CRRT [32].

In terms of cephalosporins, the optimal $\%fT_{>MIC}$ has been reported to be 60–70% [70]. To the best of our knowledge, only one study has investigated the concurrent effect of ECMO and RRT in cephalosporins. Cefpirome PK was investigated in a single-centre population PK study conducted by Kang et al., with the authors concluding that the presence of ECMO increased both CL and central volume of distribution (V_c). The authors of the paper did not comment on the ultimate effects of V_d ($V_p + V_p$) and the subsequent need to modify the loading dose. However, CRRT was not supported as a covariate in the final model as it did not statistically improve the robustness of the final PK model [61]. The authors suggested that the reason for this may have been due to the CL relating to serum creatinine used in the model was unable to differentiate between native renal and dialytic CL.

For carbapenems, the optimal $\%fT_{>MIC}$ for the antimicrobial class has been reported to be 40% [71, 72]. Shekar et al. conducted a multicentre population PK meropenem study investigating the concurrent effects of ECMO and a form of PIRRT, extended daily diafiltration (EDD-f) [37]. The authors reported numerically higher plasma meropenem concentrations in the ECMO/RRT group (C_{max} 59 mg/L) compared with the patients with preserved renal function on ECMO alone (C_{max} 42 mg/L) following a 3-g daily dose. Overall, it appears that the concurrent use of ECMO and RRT is associated with higher meropenem serum concentrations compared to patients on ECMO alone. Consequently, future studies should aim to better describe the impact of native renal clearance in patients on ECMO alone and the combined effects of resolving native clearance and dialytic clearance in ECMO/RRT patients. This will allow for the quantification of the combined effects of ECMO and RRT variables on target attainment and provide dosing advice for this specific patient group. Until this data becomes available, TDM should be utilised to guide the dosing of antimicrobials in this complex clinical scenario.

Glycopeptides

Vancomycin is a relatively hydrophilic glycopeptide antimicrobial agent with optimal bactericidal activity represented by the ratio of the area under the concentration-time curve during a 24-h period ($AUC_{0–24}$) to MIC greater than 400 [73]. Donadello et al. reported from a retrospective single-centre study a vancomycin CL of 3.7 L/h and 2.22 L/h in the ECMO alone and ECMO/RRT groups, respectively. The authors recommended that dosing adjustment should be considered in concomitant extracorporeal therapy to avoid drug accumulation [33].

Others

A case study conducted by Strunk et al. found that extended daily dialysis removed considerable amounts of both ethambutol and rifampicin in a patient on ECMO, with dialyser plasma clearance ranging between 37–95 and 39–53 mL/min, respectively. The authors suggest that therapeutic monitoring should be used to guide dosing drugs, such as ethambutol which exhibit moderate protein binding of 20–30% and a relatively large V_d of 1.6–3.2 L/kg [65]. The PK of the hydrophilic antiviral oseltamivir was reported in a small PK study where the authors reported patients with concurrent CVVHDF and ECMO produced a 4- to 5-fold higher peak serum concentration and AUC than in ECMO patients alone [66]. The authors recommend lower doses be used in patients undergoing concurrent therapy.

Therapeutic Drug Monitoring

Before robust dosing guidelines specific for this patient group become available, dosing should be in line with the recommendations for the critically ill population. Until the literature gaps in dosing for patients on concomitant ECMO and RRT are met, the most useful tool to guide dosing remains to be TDM. TDM-based dosing adjustment is clinically useful for antimicrobials with significant PK variability and is strongly recommended to guide safe and efficacious antimicrobial treatment pending definitive clinical PK data. In such a case, it would be prudent to choose an antimicrobial agent that can be supported by local TDM services.

Conclusion

The data currently available to guide clinicians to safely dose efficacious antimicrobials in critically ill adults receiving concurrent ECMO and RRT remains to be insufficient. Future studies will need to be designed and powered to investigate the specific RRT parameters and the subsequent effects in patients receiving ECMO. Until more robust data becomes available, clinicians should use TDM to guide dosing to ensure antimicrobial concentrations are within the efficacy and toxicity thresholds.

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Compliance with Ethical Standards

Conflict of Interest The authors have no conflicts of interest to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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