REVIEW

Machines that help machines to help patients: optimising antimicrobial dosing in patients receiving extracorporeal membrane oxygenation and renal replacement therapy using dosing software

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Abstract

Intensive care unit (ICU) patients with end-organ failure will require specialised machines or extracorporeal therapies to support the failing organs that would otherwise lead to death. ICU patients with severe acute kidney injury may require renal replacement therapy (RRT) to remove fluid and wastes from the body, and patients with severe cardiorespiratory failure will require extracorporeal membrane oxygenation (ECMO) to maintain adequate oxygen delivery whilst the underlying pathology is evaluated and managed. The presence of ECMO and RRT machines can further augment the existing pharmacokinetic (PK) alterations during critical illness. Significant changes in the apparent volume of distribution (V_d) and drug clearance (CL) for many important drugs have been reported during ECMO and RRT. Conventional antimicrobial dosing regimens rarely consider the impact of these changes and consequently, are unlikely to achieve effective antimicrobial exposures in critically ill patients receiving ECMO and/or RRT. Therefore, an in-depth understanding on potential PK changes during ECMO and/or RRT is required to inform antimicrobial dosing strategies in patients receiving ECMO and/or RRT. In this narrative review, we aim to discuss the potential impact of ECMO and RRT on the PK of antimicrobials and antimicrobial dosing requirements whilst receiving these extracorporeal therapies. The potential benefits of therapeutic drug monitoring (TDM) and dosing software to facilitate antimicrobial therapy for critically ill patients receiving ECMO and/or RRT are also reviewed and highlighted.

Keywords: Antimicrobial, Dosing software, Extracorporeal membrane oxygenation, Pharmacokinetics, Renal replacement therapy, Therapeutic drug monitoring

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Introduction

Critically ill patients with life-threatening conditions often require specialised machines or extracorporeal therapies as part of care provided in the intensive care unit (ICU). Such patients may develop end-organ damage (due to acute and/or chronic disease) or in extreme cases, multiple organ dysfunction syndrome [1]. This syndrome can include cardiorespiratory and/or renal dysfunction, which necessitates extracorporeal therapies

to support the failing organs that would otherwise lead to death. ICU patients with severe acute kidney injury may require renal replacement therapy (RRT) to remove fluid and wastes from the body, and patients with severe cardiorespiratory failure will require extracorporeal membrane oxygenation (ECMO) to maintain adequate oxygen delivery whilst the underlying pathology is evaluated and managed. As ECMO and RRT do not resolve the underlying cause of organ failure by themselves, effective pharmacotherapy is crucial to reverse the cause of critical illness for such patients [2]. For example, in patients with sepsis or septic shock, both of which are common in ECMO and RRT patients in the ICU, therapeutic outcomes will heavily rely on whether effective antimicrobial therapy is delivered to these patients. However, antimicrobial dosing is challenging in these patients as both extracorporeal devices are hypothesised to further exacerbate existing physiological derangements during critical illness [2]. Conventional drug dosing which rarely considers these extreme homeostatic changes has a higher likelihood to fail in this patient population [3–5]. Aggressive antimicrobial dosing regimens (e.g. beta-lactam antimicrobials) appear to now be more common in many ICUs to account for this phenomenon leading to increasing reports of excessive drug exposure and toxicity in this patient population over the last 10 years [6]. Therefore, an in-depth understanding on potential pathophysiological and pharmacokinetic (PK) changes during ECMO and/or RRT is required to inform drug dosing strategies in critically ill patients receiving these extracorporeal machines/devices. Indeed, use of dosing software, an increasingly used technology, may facilitate optimised antimicrobial therapy.

We aim to review the potential impact of ECMO and RRT on the PK of antimicrobials and how these extracorporeal devices influence drug dosing requirements in critically ill adult patients receiving each. Although ECMO and RRT can influence the PK of many important drugs (e.g. sedatives and analgesics), this review will mostly focus on the PK, and dosing requirements of antimicrobials as instructive data are currently available for this drug class. We also highlight potential solutions to dosing challenges during ECMO and/or RRT in the form of individualised and optimised dosing strategies, supported by therapeutic drug monitoring (TDM) and dosing software.

Pharmacokinetic and pharmacodynamic issues in critically ill patients
Pharmacokinetic issues
Optimal pharmacotherapy is challenging in critically ill patients as they manifest extreme physiological derangements that are not commonly encountered in general

> **Take-home message**
>
> Extra-corporeal membrane oxygenation (ECMO) and renal replacement therapy (RRT) machines can further exacerbate existing pharmacokinetic alterations observed during critical illness complicating drug dosing, particularly for antimicrobials. Effective pharmacotherapy during ECMO and/or RRT can be achieved with the support of therapeutic drug monitoring and dosing software.

ward environments [7]. These dosing challenges have been reviewed in detail previously [8–11]. Critical illness is typically characterised by marked pathophysiological changes that can be driven by both the natural underlying disease process (e.g. sepsis) and the medical interventions provided (e.g. aggressive intravenous fluid and vasoactive infusions). These patients may also have pre-existing chronic co-morbidities which can reduce their physiological reserves even further. Additionally, the presence of extracorporeal therapies/machines (e.g. ECMO and/or RRT) can further exacerbate the existing pathophysiological changes during critical illness [2, 12, 13]. The interplay of these factors may significantly alter drug PK in critically ill patients and can be broadly considered in terms of altered apparent volume of distribution (V_d) and drug clearance (CL). Significant V_d and CL alterations leading to altered drug exposures have been reported for many important drugs during ECMO and RRT [13–15]. Conventional dosing regimens rarely consider the impact of the altered PK phenomenon and consequently, are unlikely to achieve effective drug exposures in a considerable proportion of critically ill patients receiving ECMO and/or RRT [3–5, 16]. Importantly, suboptimal drug dosing in this patient population may lead to therapeutic failure and/or drug toxicity [8].

Pharmacokinetic/pharmacodynamic issues
Effective use of some drugs during ECMO and/or RRT can be more challenging than for some other drugs. For example, although sedatives and vasoactive agents can be titrated to the desired pharmacological response, there are no reliable or timely clinical markers to guide antimicrobial therapy. However, each antimicrobial/antimicrobial class exhibits different pharmacokinetic/pharmacodynamic (PK/PD) indices that are associated with increased effectiveness [17], and achieving these concentration exposures increases the likelihood of therapeutic of response. Clear relationships have been described for most antimicrobials linking plasma PK/PD exposures with clinical efficacy [8, 18] and for some drugs, toxicity [8, 18]. Therefore, antimicrobial dosing that can achieve and maintain plasma antimicrobial concentrations within this therapeutic exposure range increases the likelihood of therapeutic clinical efficacy whilst limiting the

probability of toxicity in patients receiving ECMO and/or RRT. However, most studies defining these therapeutic exposures are based on studies of plasma concentrations, and do not always reflect concentrations at the site of infection (e.g. epithelial lining fluid in pneumonia) which may be highly variable. Therefore, although these ranges provide strong guidance, pharmacokinetic outliers may not be represented by a plasma derived therapeutic range meaning that clinical judgement still needs to be provided. Further research is needed in this area and the application of TDM and dosing software are meant only to supplement, and not to supersede, clinical judgement during decision making.

Minimum inhibitory concentration considerations

As minimum inhibitory concentration (MIC) is an integral component of antimicrobial PK/PD, failure to consider both PK and MIC differences may lead to suboptimal antimicrobial dosing and therapeutic failure. This is especially important when TDM is performed in "high-risk" patient populations (e.g. critically ill ECMO and/or RRT patients), which are more likely to be infected by pathogens with reduced antimicrobial susceptibility (i.e. higher MICs) when compared with any other population (e.g. patients in the general wards) [19]. Additionally, TDM- and software-guided dosing adjustments need to consider MIC variation, specifically in the context of MIC determination method (broth microdilution versus Etest®), assay variation, species identification and wild-type distributions [20]. Importantly, an individual MIC measurement should not be regarded as a "true" value but only an estimate of pathogen susceptibility.

Renal replacement therapy

Variability in RRT modalities and techniques

RRT is typically provided as continuous renal replacement therapy (CRRT) or as standard intermittent haemodialysis (IHD). Alternatives, such as slow extended haemodialysis (SLED), prolonged intermittent renal replacement therapy (PIRRT) or peritoneal dialysis (PD), are used less often [21].

CRRT remains dominant in Europe and most countries around the world [22]. However, with lower dialysate and blood flow rates compared to IHD, PIRRT is now used in some centres, especially in the subacute phase of illness [23]. Advantages of PIRRT include increased patient mobility, more opportunities for physical and occupational therapy as compared with CRRT and greater haemodynamic stability than IHD. Thus, the dichotomy of CRRT versus IHD is to some extent artificial. Modern CRRT machines can deliver therapy that resembles IHD, and IHD treatments can be slowed to deliver therapy over 10–12 h as SLED or PIRRT. Therefore, CRRT and standard IHD represent extremes of a continuum with associated variable effects on drug removal and dosing requirements.

The two main mechanisms of solute and drug removal are diffusion and convection, whereas ultrafiltration is utilised for fluid removal. Diffusion is the movement of solutes across the membrane across a concentration gradient and is the main mechanism of removal for small molecules in dialysis. Convection is the movement of solutes across the membrane along with water as pressure is applied (known as "solvent drag") and is the main mechanism of removal for small and middle molecules in haemofiltration. Conventional IHD, continuous veno-venous haemodialysis (CVVHD), and SLED primarily utilise diffusion, whereas continuous veno-venous haemofiltration (CVVH) primarily utilises convection. Finally, continuous veno-venous haemodiafiltration (CVVHDF) utilises both mechanisms [24].

All RRT modalities have specific advantages and disadvantages, and Supplementary Table 1 lists the major advantages and disadvantages of CRRT, IHD, PIRRT and PD when used in patients with AKI. In most cases, the choice of RRT is guided by the clinical condition of the patient and availability of devices, kits, and expertise. To date, there is no robust evidence that either modality is superior in terms of survival or renal recovery. However, individual patients may benefit more from one technique than other techniques at different phases of critical illness. Thus, the decision of which modality to use, both between individual patients and within the same patient over time, may vary during the course of a patient's illness.

Effect of RRT settings on antimicrobial drug PK

RRT support may increase drug CL, affect drug dosing, and contribute to clinical failure and/or the development of resistance in the case of antimicrobials [25]. Clinicians must ensure that the appropriate drug is selected, and adequate dose is delivered whilst accounting for RRT CL and the altered PK in critical illness. As there are different modalities of RRT, there is not one single approach to optimising antimicrobial drug dosing.

Different factors affect antimicrobial PK in patients receiving RRT and these relationships are summarised in Table 1. They are the main determinants of antimicrobial dose adjustments. Factors related to RRT system properties are key. They first include the RRT modality factor. For example, CRRT provides constant drug CL whilst PIRRT and IHD present two distinct PK phases characterised by inter and intra-dialytic elimination that may require different dosing adjustments. Comparing equal effluent doses in CRRT, techniques combining convection and diffusion (CVVHDF) may

Table 1 Relevant factors that can influence antimicrobial pharmacokinetics in patients receiving renal replacement therapy

Patient-specific factors	
Critical illness	V_d ↑
	CL ↑ or ↓ based on renal function or RRT settings
Residual renal function	CL ↑ compared to anuric patients
Hypoalbuminemia	Free drug concentrations ↑
	CL ↑ for highly protein bound drugs
	V_d ↑
Drug-specific factors	
Solubility	Hydrophilic drugs more likely to be affected by RRT-related CL
	Lipophilic drugs potentially affected by membrane adsorption
Molecular weight	CL ↑ for low molecular weight drugs
	This may not be a major determinant of drug removal due to the use of high flux hemofilters with large pore size
Protein binding	CL ↑ for low protein bound drugs
Electric charge	CL ↑ for anionic antibiotics (e.g. cefotaxime and ceftazidime) compared to cationic antibiotics (e.g. aminoglycosides) retained in plasma by negatively charged molecules like albumin (Gibbs–Donnan effect)
PK/PD target	RRT-related CL influences maintenance dose for time-dependent antibiotics (e.g. 100%/$\mathbf{T}_{>1-4 \times MIC}$)
	RRT-related CL influences dosing frequency for concentration-dependent antibiotics (C_{max}/MIC)
	RRT-related CL influences maintenance dose and/or dosing frequency for time- and concentration-dependent antibiotics (AUC/MIC)
RRT-specific factors	
RRT modality: Continuous versus Intermittent	Variable elimination rates depending on intra and inter-dialytic phases for IHD
	Relatively constant drug CL depending on RRT intensity for CRRT
RRT technique: Convective versus Diffusive	Higher CL of high molecular weight drugs with convection technique
	Combining convection and diffusion (i.e. CVVHDF) often results in greater drug CL than by convection or diffusion alone at equal RRT doses
Effluent flow rate	Higher CRRT effluent rates resulting in higher CL
Blood flow rate	CL ↑ with high blood flow rate
	Negligible clinical impact for CRRT
Dilution mode	CL ↓ in pre-dilution mode
	Negligible clinical impact
Membrane type/adsorption	Polyacrylonitrile membranes more likely to be associated with drug adsorption (e.g. amikacin, levofloxacin, echinocandins in particular)
	Saturable effect
Hemofilter life span	CL ↓ over time unless circuit components are replaced regularly
Down time	CL ↓ if prolonged circuit downtime

AUC area under the concentration–time curve, *CL* clearance, *C_max* maximal drug concentration during a dosing interval, *CRRT* continuous renal replacement therapy, *CVVHDF* continuous veno-venous hemodiafiltration, *IHD* intermittent hemodialysis, *MIC* minimum inhibitory concentration, *RRT* renal replacement therapy, *PK/PD* pharmacokinetic/pharmacodynamics, *V_d* volume of distribution

provide higher drug CL for beta-lactam antimicrobials and linezolid [26, 27].

Another RRT system factor is the effluent flow rate factor. Drug removal is strongly influenced by dialysate and ultrafiltration flow rates [28]. Thus, higher RRT effluent flow rates lead to greater drug CL requiring higher antimicrobial doses to achieve the same plasma concentrations as with lower flow rates. Additionally, high ultrafiltration rates may result in greater removal of larger molecular weight drugs such as vancomycin.

Finally, residual renal function may significantly affect antimicrobial drug dosing. Patients with residual renal function have been shown to require increased dosing/dosing frequency of linezolid and meropenem when compared with anuric patients [29, 30].

Pharmacological considerations for antimicrobials are also important. Altered protein binding may

be associated with drug CL changes because only the unbound fraction can be cleared across the hemofilter. During critical illness, albumin and α_1-acid glycoprotein concentrations can be altered impacting the PK of acidic and basic drugs, respectively. Typically, high protein-bound antimicrobials (e.g. cefazolin, ceftriaxone, and teicoplanin) are not significantly affected by RRT. However, wide variations in protein binding occur in critically ill patients, especially in the case of hypoalbuminemia, which has been commonly reported and studied thus far [7]. This can increase RRT-related CL and affect antibiotic exposure. The extent to which a drug is removed by dialysis is strongly influenced by the physicochemical properties of the drug and the apparent V_d [13]. In general, lipophilic drugs, such as macrolides, quinolones, and echinocandins, which exhibit large apparent V_d are less affected by RRT compared to hydrophilic drugs, such as beta-lactam antimicrobials and aminoglycosides, because a low proportion of the drug is present in the bloodstream from where clearance occurs. However, for echinocandins, significant adsorption could occur with highly adsorptive membranes (e.g. AN69 surface-treated and poly-methyl-methacrylate filters) and deserve further investigations to determine optimal dosing in CRRT patients.

Drug dosing for critically ill patients receiving RRT remains challenging. Thus, a rational approach to antibiotic dosing during RRT in ICU patients consists of high loading doses to avoid low concentrations associated with increased apparent V_d, adjustments of first maintenance dose based on the effluent flow rate (Table 2), and subsequent adjustment as guided by TDM and Bayesian dosing software. Additionally, the site of infection and minimum inhibitory concentration (MIC) of causative pathogens should be considered whilst choosing the optimal antimicrobial dosing regimen for patients on RRT.

Exposure and outcomes

A key question in antimicrobial drug dosing during RRT is whether a systematic approach leads to superior antimicrobial drug concentrations compared to clinical judgement. Such a systematic approach could be based on TDM, software-based PK calculations, or the administration via continuous infusion of those antimicrobial drugs for which bactericidal activity is dependent on the time above the minimal inhibitory concentration [4, 31–33]. The logic behind such methods is that the reality of critical illness and RRT is complex. Both, interventions and illness can change the apparent V_d. Similarly, events related to RRT (circuit clotting, progressive loss of functional membrane performance, cessation of therapy due to investigations, downtime due to circuit alarms) impact drug CL [8]. Thus, across ICUs worldwide, as

demonstrated by the SMARRT study, there is extreme variability in antimicrobial drug dosing and concentrations leading to variable clinical outcomes [4]. Cumulatively, these data support a careful personalised approach to dosing accounting for the drug, patient's underlying organ function, type of RRT used and the duration of RRT.

Extracorporeal membrane oxygenation

ECMO is an advanced life support system which allows for prolonged cardiopulmonary support in patients with life-threatening respiratory or cardiac failure [34, 35]. ECMO does not provide treatment of the underlying illness, it is purely a supportive strategy that is implemented whilst underlying co-morbidities such as infection are treated.

Pharmacokinetic determinants during ECMO

In general, the ECMO circuit consists of a centrifugal blood pump, an oxygenator, heat exchanger and tubing. The ECMO circuit is primed with combination of crystalloid, albumin, and blood. Essentially, the addition of an ECMO circuit may further alter the PK in a critically ill patient in three ways: (1) sequestration of the drug by the ECMO circuit; (2) increasing the apparent V_d; and (3) altered drug CL due to alteration in renal and liver blood flow, and altered plasma protein binding [36, 37]. The combined impact of ECMO- and critical illness-related factors on drug PK are summarised in Table 3. Importantly, drug dosing that does not consider these PK changes can lead to either therapeutic failure or toxicity.

Drug sequestration

Some drugs are sequestered onto the ECMO circuit which has a very large surface area due to its oxygenator and tubing; the degree of loss is influenced by both the drug physicochemical properties and circuit factors [37–41]. This sequestration is likely a result of non-specific binding of the drug onto the circuit components, with the degree of sequestration influenced by the surface area and the drugs affinity to it. This effect may decrease over time as the binding sites become saturated, so dosing should be regularly reviewed to avoid drug accumulation and toxicity [42]. However, the concept of reversible binding and saturation is still not understood.

In vitro or ex vivo experiments can help evaluate the extent of drug sequestration by the ECMO circuitry and have demonstrated that lipophilic drugs and those highly protein bound are sequestered to a greater degree [40, 41]. An ex vivo study investigated the influence of plasma protein binding on sequestration in the ECMO circuit and concluded that for drugs with similar lipophilicity, the extent of protein binding may determine the degree

Table 2 Example doses of antimicrobial drugs according to renal replacement therapy modality

	Free fraction (%)	CVVH		CVVHDF		CVVHD		PIRRT
		Ultrafiltration rate 20–25 mL/kg/h	Ultrafiltration rate 35 mL/kg/h	Effluent flow rate 20–25 mL/kg/h	Effluent flow rate 35 mL/kg/h	Dialysate flow rate 20–25 mL/kg/h	Dialysate flow rate 35 mL/kg/h	
Beta-lactam antimicrobials								
Amoxicillin/ Clavulanate	80	ND		ND		ND		ND
Cefazolin	15–20	2 g q12h		ND		ND		ND
Cefepime	80	LD: 2 g MD:1.5 g q8h	LD: 2 g MD: 1.75 g q 8 h	LD: 2 g MD: 1.75 g q8h	ND	1.75 g q8h	2 g q8h	LD: 2 g MD: 1 g q6h
Cefiderocol	40	1.5 g q8–12 h		1.5 g q8–12 h[a]		1.5 g q8–12 h[a]		ND
Cefotaxime	60–80	LD: 2 g MD: CI 4 g q24h		ND		ND		ND
Ceftaroline	80	0.6 g q12h		ND		ND		ND
Ceftazidime	90	ND		LD: 2 g MD: CI 4 g/24 h		ND		2 g q12h
Ceftazidime/ Avibactam	90	ND		2.5 g q8h		ND		ND
Ceftolozane/ Tazobactam	80	1.5–3 g q8h[b]	ND	1.5–3 g q8h[b]	3 g q8h	1.5–3 g q8h[b]		ND
Ceftriaxone	10	2 g q24h or 1 g q12h		2 g q24h		2 g q24h		2 g q24h
Imipenem	80	ND		0.5 g q8h	1 g q8h	ND		0.5 g q6h
Meropenem	100	LD: 1 g MD:0.75 g q8h	LD: 1 g MD:1 g q8h	LD: 1 g MD: 1 g q12h		LD: 1 g MD: 0.75 g q8h	LD: 1 g MD: 1 g q8h	1 g q12h
Oxacillin	10	No adjustment		No adjustment		No adjustment		No adjustment
Piperacillin/ Tazobactam	70/80	LD: 4 g MD: CI 12 g q24h		LD: 4 g MD: CI 12 g q24h		LD: 4 g MD: CI 16 g q24h		4 g q8h or 4 g q12h following 2 g replacement dose post PIRRT
Aztreonam	45	1 g q8h		ND		2 g q8h		ND
Aminoglycosides								
Amikacin	>95	25 mg/kg ABW q48h		25 mg/kg ABW		25 mg/kg ABW		ND
Gentamicin	>95	8 mg/kg ABW		8 mg/kg ABW		8 mg/kg ABW		6–8 mg/kg ABW 1 h before PIRRT session
Tobramycin	90–100	8 mg/kg ABW		8 mg/kg ABW		8 mg/kg ABW		6–8 mg/kg ABW 1 h before PIRRT session
Glycopeptides								
Vancomycin	50	ND		LD: 30 mg/kg MD: 10 mg/kg q24h		ND		20–25 mg/kg followed by TDM
Teicoplanin	10–40	LD: 1200 mg MD: 600–1800 mg		ND		ND		ND
Oxazolidinones								
Linezolid	70	No adjustment		No adjustment		No adjustment		No adjustment
Tedizolid	10–30	No adjustment		No adjustment		No adjustment		No adjustment
Fluoroquinolones								
Ciprofloxacin	60–80	400 mg q8h		400 mg q8h		200 mg q8h		ND
Levofloxacin	60–75	250 mg/24 h	500 mg/24 h	ND		Consider alternative		250 mg q24h

Table 2 (continued)

	Free fraction (%)	CVVH Ultrafiltration rate 20–25 mL/kg/h	CVVH Ultrafiltration rate 35 mL/kg/h	CVVHDF Effluent flow rate 20–25 mL/kg/h	CVVHDF Effluent flow rate 35 mL/kg/h	CVVHD Dialysate flow rate 20–25 mL/kg/h	CVVHD Dialysate flow rate 35 mL/kg/h	PIRRT
Other classes								
Tigecycline	10–30	No adjustment		No adjustment		No adjustment		No adjustment
Colistin	60–75	LD: 9 MUI MD: 3 MUI q8h	MD: 4.5 MUI q8h	LD: 6–9 MUI MD: 1.5–2 MUI q8h		6 MUI q12h		3 MUI q8h
TMP-SMX		5 mg/kg q12h		ND		5 mg/kg q12h		15 mg/kg/24 h in 4 divided doses
Daptomycin	20	ND		6–8 mg/kg q24h		6–8 mg/kg q24h		6 mg/kg q24h
Antifungal Drugs								
Fluconazole	90	ND		LD: 800 mg MD: 400 mg q12h		ND		400 mg q12h
Voriconazole	40	4 mg/kg q12h Preferable oral route		4 mg/kg q12h Preferable oral route		4 mg/kg q12h Preferable oral route		ND
Isavuconazole	< 1	No adjustment		No adjustment		No adjustment		No adjustment
Caspofungin	3	No adjustment		No adjustment		No adjustment		No adjustment
Micafungin	< 1	No adjustment		No adjustment		No adjustment		No adjustment
Amphotericin B	10	No adjustment		No adjustment		No adjustment		No adjustment
Antiviral drugs								
Acyclovir	70–90	5–7.5 mg/kg q24h		5–7.5 mg/kg q24h		5–7.5 mg/kg q24h		ND
Ganciclovir	98	ND		ND		5 mg/kg q48h		ND
Oseltamivir	97	ND		75 mg q12h		ND		ND

ABW adjusted body weight; *CVVH* continuous veno-venous hemofiltration, *CVVHDF* continuous veno-venous hemodiafiltration, *ND* no data, *LD* loading dose, *MD* maintenance dose, *PIRRT* prolonged intermittent renal replacement therapy, *TMP-SMX* trimethoprim-sulfamethoxazole

As a general rule, the "loading dose" of a drug, is strictly dependent on V_d and does not require any adjustment in patients with renal failure, including those undergoing RRT for AKI. RRT intensity may influence maintenance doses as reported in Table 1 and suggestions were derived from the references listed in the Supplementary Materials and from the main guidelines for antimicrobial therapy during RRT

[a] Extrapolated from cefepime data

[b] Consider higher dosing regimens for deep seated infections or less susceptible isolates

of circuit loss and vice versa [41]. The same drug can be sequestered to a different extent depending on the oxygenator used, the type of tubing [39, 43], the pump [37], the age of the circuit [44], and the priming solution used [45].

Modern circuits have evolved to decrease the risks from ECMO and drug disposition. These developments include the use of hollow-fibre membrane oxygenators (replacing earlier silicone rubber membrane), centrifugal pumps (replacing roller-head) and integrating the heat exchanger. Although pre-coated polyvinyl chloride tubing are now widely used, it is not clear whether their use significantly decrease the absorption of drugs [43].

Extrapolating from some of the earlier ex vivo studies is challenging as they differ in circuit materials used compared with the improved ECMO technology in the modern era [46]. Hence, ongoing study of drug–ECMO circuit interactions for new machines and consumables remains important.

Increased apparent V_d

The physiological changes associated with critical illness, such as systemic inflammatory response syndrome (SIRS), fluid shifts, altered blood pH and organ dysfunction, are common in this patient group and result in increased apparent V_d of hydrophilic drugs. The addition of an ECMO circuit may further increase apparent V_d by drug sequestration and hemodilution from the priming solution. Drugs with a large apparent V_d (e.g. ciprofloxacin) would be less effected by haemodilution than those with low V_d (e.g. beta-lactam antimicrobials). The significance of haemodilution is more pronounced in neonates and infants, than in older children and adults as this

Table 3 The interrelationship of lipophilicity, hydrophilicity and protein binding and the impact of critical illness, extra-corporeal membrane oxygenation (ECMO) and renal replacement therapy (RRT) on drug pharmacokinetics

	Lipophilic	Hydrophilic	Protein bound (PB)
General pharmacokinetics	High V_d & hepatic CL	Low V_d & renal CL	Low V_d & hepatic or renal CL
Critical illness	V_d unchanged	↑ V_d	V_d & CL—as per lipophilicity or hydrophilicity and plasma protein
	CL ↑or↓ based on hepatic function	CL ↑ or ↓based on renal function	
ECMO	↑ V_d	Low or slightly ↑ V_d	↑ or low V_d for lipophilicity + PB drugs
	CL ↑or↓ based on hepatic function	CL ↑ or ↓based on renal function	CL ↓or ↑ based on renal or hepatic function
RRT	↓CL as high V_d	↓CL as low V_d	↓ CL—if less free drug
Critical illness + ECMO + RRT	↑↑V_d & ↓↓CL	↑V_d & ↓ CL	↑V_d & CL ↓↑ based on renal or hepatic function
	↓↓CL CRRT as ↑↑V_d	↓CL CRRT as ↑V_d	
	Hepatic dysfunction can ↓ CL	↓ CL if renal function ↓	
Examples	Fluoroquinolones	Aminoglycosides beta-lactams	Ceftriaxone
	Lincosamides	Colistin	
	Macrolides	Glycopeptides	Clindamycin
	Tigecycline	Linezolid	

ECMO extracorporeal membrane oxygenation, *CL* drug clearance, *PB* protein binding, *CRRT* continuous renal replacement therapy, *RRT* renal replacement therapy, V_d apparent volume of distribution

represents a greater proportion of their circulating blood volume.

Altered drug CL

Drug CL in general is decreased in ECMO, likely due to of reduced renal and hepatic perfusion and hypoxia; in addition, the SIRS response seen in patients on ECMO decreases the expression and function of drug-metabolising enzymes [1, 47].

Pharmacokinetic changes during combined ECMO and RRT support

Almost 50% of patients on ECMO require RRT [48], the indications of which are multifactorial similar to other critically ill patients. RRT whilst on ECMO adds increasing complexity to the PK of drugs because the presence of two extracorporeal circuits can make the estimation of PK parameters more difficult [2]. The effects may cancel each other and are dependent on the physicochemical properties of the drug, in particular its lipophilicity and protein binding. The most common RRT used in combination with ECMO is CRRT, and the resultant PK changes are not a simple sum of both independent changes and requires further studies. The potential PK alterations of common antimicrobials during ECMO are summarised in Table 4.

Clinical studies and future directions

There are several clinical PK studies in patients with ECMO; the majority were performed in neonates and children showed significant changes in the PK of antimicrobials [49–52]. These results cannot be confidently extrapolated to adults due to significant body composition differences and the physiological processes that affect absorption, distribution, metabolism, and excretion are not fully developed and are thus different to those in adults.

The absence of real-time measurable PD endpoints for infection as well as the importance of optimised therapy has meant recent adult ECMO PK studies have focussed on this class of drugs (Table 4) [53–63]. A recent comprehensive review of clinical PK studies of antimicrobial dosing in ECMO concluded that most PK changes are more reflective of critical illness rather than the ECMO device [14].

An integrated approach combining the mechanistic ex vivo experiments together with clinical PK studies is necessary to provide evidence-based dosing guidance. Examples include the ECMO PK project, an incremental research approach to integrate ex vivo experiments, PK studies in ovine models and a clinical PK study (ASAP ECMO study) [36, 41, 56, 57, 59, 60, 64–68]. Others incorporate the sequestration impact from the ex vivo ECMO experiments with physiologically-based pharmacokinetics (PBPK) modelling [38, 49].

Practical dosing recommendations

Currently, there are a lack of robust guidelines for dosing of drugs in critically ill adult patients receiving ECMO. The physicochemical properties of drugs can be used to predict PK changes and determine loading dose adjustments and subsequent maintenance dosing in this patient group [36, 41, 66, 69] (Table 3). Drugs with high protein binding (e.g., > 70%) and highly lipophilic (e.g. Log P > 2) are likely to be sequestered on the

Table 4 Potential pharmacokinetic changes in adult critically patients on extracorporeal membrane oxygenation (ECMO) for commonly used antimicrobials

Drug	Log P	Protein binding (%)	Volume of distribution	Expected ECMO sequestration effect	General dosing guidance
Antimicrobials					
Meropenem	− 0.69	2	0.25 L/kg	Minimal circuit loss V_d: increased	Dosing similar to critically ill not on ECMO TDM-guided dosing
Piperacillin/tazobactam	0.67	30	0.243 L/kg	Minimal circuit loss V_d: increased	Dosing similar to critically ill not on ECMO TDM-guided dosing
Vancomycin	− 4.4	50	0.4–1 L/kg	Minimal circuit loss V_d: increased	Dosing similar to critically ill not on ECMO TDM-guided dosing
Aminoglycosides: gentamicin, tobramycin, amikacin	< 0	< 30	0.2–0.3 L/kg	Minimal circuit loss V_d: increased CL: decreased	Insufficient data TDM-guided dosing
Antifungals					
Fluconazole	0.56	12	Approx. to total body water	Minimal circuit loss V_d: increased	Insufficient adult data May require increased LD
Voriconazole	2.56	58	4.6 L/kg	Moderate to significant circuit loss	Conflicting data Dosing similar to critically ill not on ECMO TDM-guided dosing
Caspofungin	− 2.8	97	NA	Moderate circuit loss V_d: increased	Insufficient and conflicting data

ECMO extracorporeal membrane oxygenation, *CL* drug clearance, *LD* loading dose, *NA* not available, *V_d* volume of distribution

circuit and may require an increase in their dose, or frequency of administration [15]. As the PK changes of increased apparent V_d and altered CL may both be seen concurrently in critical illness, the use of dosing strategies derived from critically ill adult patients not on ECMO is acceptable for empiric dosing of most other drugs [56, 57, 59, 60, 64].

Dosing software

Acute pathophysiological changes that occur during critical illness including when receiving life-saving RRT and ECMO machines are used, can lead to difficult-to-predict antimicrobial concentrations in plasma and other body compartments, including at the site of infection. Furthermore, lower pathogen susceptibility observed in the ICU means that there may be PK/PD considerations that also need to be taken into account when seeking to achieve adequate antimicrobial exposure in these patients [70].

In the light of these challenges, dose optimisation strategies may play a key role to improve PK/PD target attainment. TDM is one such strategy that has traditionally been used to minimise the risk of exposure-related toxicity, particularly in antimicrobials with a narrow therapeutic index, such as the aminoglycosides and glycopeptides. With growing evidence linking sub-therapeutic

antimicrobial concentrations with treatment failure [16, 71, 72], the role of TDM has now expanded to ensure therapeutic effectiveness is maximised [73, 74].

When TDM is performed, biological samples (usually plasma) are transported to an analysis laboratory with a turnaround time of approximately 30-min to 48 h, depending on the drug and availability of assay. Given the importance of prompt effective antimicrobial therapy in sepsis management [75, 76], a reduction in this turnaround time so that corresponding antimicrobial dose adjustments could be initiated in a timely manner would potentially be of great benefit. Another limitation of current TDM practices revolves around the minimal set of antimicrobial assays currently available in most laboratories that service healthcare facilities. Given the above challenges, there is a real need to develop innovative technologies that overcome the current shortcomings of conventional TDM processes. In this vein, development of real-time TDM sensor monitoring appears to be a promising tool, with biosensor research attracting enormous interest within healthcare services [77]. Basic requirements for this technological innovation include: (1) transduction, including target identification in human matrices; (2) continuous sample collection e.g. through the use of interstitial fluid sampling techniques, such as

microneedle biosensors; and (3) real-time signal processing of assay results [78].

Several biosensor techniques are presently being tested, such as aptamer-based electrochemical and electronic sensors. One of these technologies is derived from particle mobility, based on a so-called 'competition assay' [79]. The assay detects a binding event by a sudden decrease in particle mobility due to interactions between a particle and a sensor surface. Because these are mediated by weak biological interactions, they are reversible and can be monitored continuously. The transitions between these unbound and bound states are recorded over time for many hundreds of particles simultaneously by bright field optical microscopy, enabling the accurate determination of concentrations [79]. Key parameters to improve biosensor robustness include selectivity, sensitivity, reproducibility, reusability and long-term stability. There also needs to be a focus on validating the new technology against the golden standard of mass spectrometry. Attention to data confidentiality is an important consideration given the vast amount of data captured, processed, and managed during clinical use. Artificial intelligence (AI) may be able to facilitate data analysis and exposure prediction, so may play a significant future role in implementation of real-time biosensors [80].

The ability of computers to perform complex mathematical modelling and statistical analysis has allowed for published antimicrobial population PK models to be integrated with relevant patient-specific data, such as renal function, weight and TDM sample measurements (if using Bayesian forecasting). Termed model-informed precision dosing (MIPD), these types of software can generate a priori dosing recommendations required for initiation of empiric-based therapy. If using a Bayesian component, these software may also provide a posteriori PK parameter estimates that potentially improve future dosing recommendation accuracy. Additionally, some MIPD software have the ability to input pathogen MIC so that variations in pathogen susceptibility can be accounted for.

One issue of particular relevance to the ECMO and RRT population sub-groups of critically ill patients is the generalisability of existing PK models available in MIPD software. As many of these published models have been developed within specific patient populations, caution must be applied when extrapolating MIPD dosing recommendations to other critically ill sub-groups with external validation strongly suggested.

Use of MIPD software may result in dosing recommendations that are more likely to achieve PK/PD targets [81]; however, the clinical outcome benefits of these software applications are yet to be quantified in critically ill patients with sepsis. Future studies will firstly need to examine comparative predictive accuracy of dosing

Fig. 1 Future approach to therapeutic drug monitoring and use of dosing software in the ICU
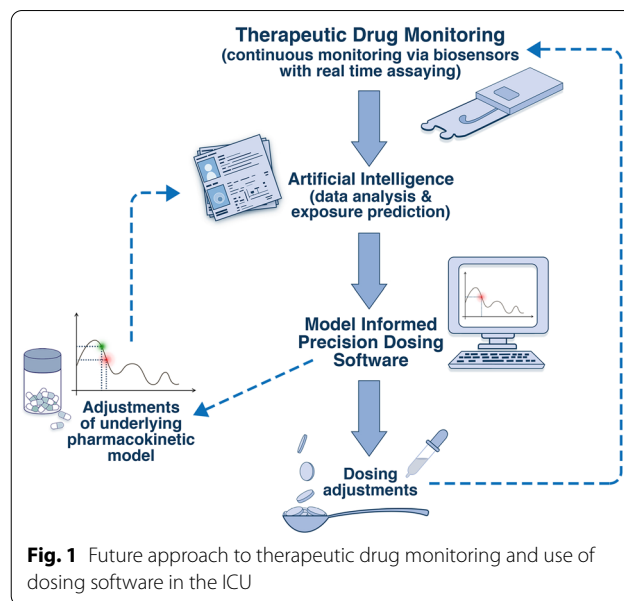
recommendations before second, the design of the most sensitive interventions from clinical advantages (if any) of MIPD can occur.

When a patient is connected to an extracorporeal circuit/machine, the implementation of real-time TDM biosensors informing MIPD software will have several advantages. Firstly, all circuits are dynamic processes, and real-time monitoring will make it possible to react to the dynamics of the systems as soon as possible. This is of paramount importance as interruptions and/or fluctuations in extracorporeal treatment modalities are very common during clinical care of patients. Secondly, the information collected via the sensor will allow for the MIPD tool to efficiently optimise antimicrobial dosing. For example, a severe acute kidney injury patient commencing RRT will have an increase in drug CL and the corresponding change in plasma drug concentrations can be detected and dosing can be adjusted more efficiently. Third, as TDM information is gathered at a faster pace with potentially more intensive sampling, there is a possibility for these data to inform and fine-tune population PK models used in MIPD software, making these applications "smarter" in dosing accuracy (Fig. 1). As we are still limited in our knowledge of the impact of extracorporeal circuits on drug exposure, there is scope for TDM biosensors to be used in the future research, especially when novel therapeutics are first administered to patients on extracorporeal treatments. Most importantly, clinical implementation of innovations such as MIPD relies heavily on improving clinician understanding of PK/PD concepts and principles. Without this underlying knowledge, clinicians may not fully appreciate the

complexities of how changes in drug exposure are influenced by extracorporeal treatment modalities, such as ECMO or RRT, and will likely not be equipped to maximise the use of these technologies.

In our opinion, ICU monitoring of antibiotic exposure has the capacity for significant progress in the near future. As a first step, MIPD software will need validated models that can help predict antibiotic exposure in critically ill patients on ECMO and RRT. However, as there are many variables that may influence drug exposure in these patients, and these variables change continuously, we know that MIPD alone is somewhat limited in its ability to improve attainment of target exposures. To this extent, although TDM remains the central tool to adapt antimicrobial dosing in most centres, TDM processes will need to become streamlined so that the time-lag between analysis and reporting is greatly reduced. Therefore, the ideal picture in 10–15 years would be that, in addition to MIPD software incorporated into the patient dossier, real-time TDM of antimicrobials in these patients can be achieved through a validated and in situ secured biosensor (either via micro-dialysis or the skin). Output data can be used and interpreted by a team composed of a clinical pharmacist/pharmacologist and intensive care specialist (with input from infectious diseases clinicians if required) to optimise antimicrobial doses accordingly. Alternatively, antimicrobial dosing could be automatically corrected by the system through use of smart antibiotic pumps that can adjust infusion rates. These infusor devices, however, would still need operator controlled and clinician overriding mechanisms in place at all times.

Conclusion

ECMO and RRT machines can further exacerbate existing PK alterations observed during critical illness potentially leading to therapeutic failure and/or drug toxicity. The combined use of ECMO and RRT is common in the ICU, and this further complicates drug dosing, particularly for antimicrobials. Poor antimicrobial exposure (either sub-therapeutic or supra-therapeutic exposures) is a recurrent theme that is associated with worse patient outcomes and is a worrying trend in critically ill patients, with or without the two extracorporeal devices. Optimised dosing strategies supported by other 'machines', and routine TDM (where possible) would be advantageous to prevent sub-therapeutic and toxic drug exposures in critically ill patients receiving ECMO and/or RRT.

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Author contributions
The idea and design of the paper were conceptualised by JAR. Literature review and data analysis were performed by all authors. The first draft of the paper was jointly written by all authors according to the assigned sections. All authors critically revised and commented on subsequent versions of the manuscript. All authors read and approved the final version of the paper.

Declarations

Conflicts of interest
All authors declare no conflict of interest in relation to this paper.

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