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REVIEW

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A narrative review on antimicrobial dosing in adult critically ill patients on extracorporeal membrane oxygenation

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Abstract

The optimal dosing strategy of antimicrobial agents in critically ill patients receiving extracorporeal membrane oxygenation (ECMO) is unknown. We conducted comprehensive review of existing literature on effect of ECMO on pharmacokinetics and pharmacodynamics of antimicrobials, including antibacterials, antifungals, and antivirals that are commonly used in critically ill patients. We aim to provide practical guidance to clinicians on empiric dosing strategy for these patients. Finally, we discuss importance of therapeutic drug monitoring, limitations of current literature, and future research directions.

Keywords Antimicrobial dosing, Extracorporeal membrane oxygenation, Pharmacokinetics, Therapeutic drug monitoring

Background

Extracorporeal membrane oxygenation (ECMO) is being increasingly used to provide hemodynamic and/or ventilatory support to critically ill patients for a variety of indications. According to the 2022 Extracorporeal Life Support Organization (ELSO) Registry Report, the utilization of ECMO has been steadily increasing every year [1]. With increasing usage, concerns related to the effect of both ECMO and critical illness on the pharmacokinetics (PK) and pharmacodynamics (PD) of antimicrobial agents is even more topical, with the potential for suboptimal dosing and preventable poor patient outcomes. Understanding the principles of these complex interactions is key to guiding antimicrobial dosing in critically ill people on ECMO.

With many components of an ECMO circuit including cannulas, pump, membrane, and tubing, there are several changes to drug delivery and concentration that may impact appropriate dosing as compared to other critically ill patients. Both the veno-arterial (VA-ECMO) and veno-venous (VV-ECMO) configuration require a large surface area of the circuit, which can lead to sequestration of drugs and substantial variations in PK including an increased volume of distribution (Vd), decreased drug clearance, and increased elimination half-life [2, 3]. Components and coatings of the circuit may also adsorb antimicrobials decreasing drug concentration; lipophilic drugs are more likely to be sequestered in the circuit, typically until binding sites become saturated [3]. For these agents, dosing is especially difficult, as when a circuit component is changed, more binding sites become

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available again and thus change the amount of agent available for its antimicrobial effect. Degree of protein binding also affects circuit drug recovery, as highly protein-bound drugs can be more significantly sequestered in ECMO circuits [4]. However, this theoretical prediction has limitations; PK/PD values observed in the patients are often discordant with values from in vitro or ex vivo studies or what we expect from known lipophilicity and protein binding of the drug. An additional consideration is that ECMO circuit can also include a renal replacement therapy (RRT) circuit, or critically ill patients on ECMO are often on independent RRT support, leading to more PK/PD complexities. Finally, flow rate is a parameter that has been hypothesized to affect drug delivery, but studies have shown minimal impact of flow rates on drug concentrations [5, 6]. The increasing accessibility of therapeutic drug monitoring (TDM) has the potential to guide individualized and responsive dosing approaches in these complex and dynamic situations.

Not only can the circuit affect drug delivery, but physiologic changes in patients requiring ECMO can be substantial and may require alternative dosing strategies. Patients receiving ECMO frequently have increased Vd secondary to their critical illness, and the associated fluid resuscitation, fluid retention, and low protein states [7–10]. Low protein state leads to increase in the fraction of unbound drug, which makes these drugs more available for elimination and distribution [7]. Kidney and liver failure can also affect drug metabolism and excretion, further complicating effective antimicrobial management [7, 9, 10]. Patients who are receiving ECMO have significant immune activation and may have a suboptimal response to antimicrobials leading to more adverse outcomes with decreased antimicrobial exposure [9–11]. These patient factors are dynamic and can change rapidly. Implications of the infection itself, including the site, causative microorganism(s), and ability of the drug to achieve adequate concentration at the site also must be considered, adding further complexity beyond the circuit and patient considerations.

Understanding these complexities and optimizing antibiotic management is key to successful patient outcomes. However, there is currently limited evidence and no specific guidelines to direct optimal antimicrobial dosing on ECMO, most data are based on case series and limited observational data. We review the recent clinical evidence supporting antimicrobial dosing on ECMO and summarize our recommendations for adult patients based on the strength of supporting evidence.

The variable nature of the literature for different drugs makes it challenging to form generalized statements summarizing each antimicrobial classifications. Hence, we urge the reader to attempt to read and understand drugs in an individual context. For ease, we will include a summary statement at the end of each drug. Throughout this article, the term "standard dosing" refers to a dose of antimicrobials used for a patient with normal organ function and normal range of weight indicated for the infection(s) that the antimicrobial agent is used for.

Methods

We searched PubMed for articles published in English from 1988 to July 2024. Search terms included "(ECMO) AND Pharmacodynamics" and "(ECMO) AND Pharmacokinetics." The types of studies we evaluated included ex vivo and in vivo studies, case reports, case series, and clinical trials. Due to inherent differences between Vd between adult patients and pediatrics patients, we excluded studies that specifically evaluated pediatric population when formulating our recommendations. Consensus for dosing recommendations was reached after the authors reviewed and discussed the articles. We graded strength of evidence guided by Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence document [12]. Table 1 shows level of recommendations based on the strength of supporting evidence and abbreviations used in summary tables.

Antifungals

Echinocandins

Echinocandins have a high degree of protein binding with low-to-moderate lipophilicity. Several PK studies showed conflicting data regarding how ECMO affects clearance of echinocandins. Two ex vivo PK

Table 1 Classification used in this review based on strength of existing literature

Strength of literature	Level of recommendation	Abbreviation in tables
≥ 3 prospective clinical studies with total number of patients ≥ 25	Recommend	PR25
1–2 prospective clinical studies or case reports with concordant results	Suggest	PR1/2
1–2 clinical case reports or discordant clinical results	Consider	CR
In vitro or ex vivo data only or no existing data	No recommendation	EV

model studies demonstrated significant reduction of caspofungin level in ECMO circuit [4, 13]. This was contradicted by another ex vivo study that showed no significant loss of caspofungin in the ECMO circuit [14]. Additionally, in two case reports, ECMO had little effect on PK of anidulafungin and caspofungin, respectively [15, 16]. Larger case series have found similar conclusions, such as a study in lung transplant patients receiving caspofungin, which compared 12 ECMO patients with 7 non-ECMO patients, and patients after ECMO weaning as self-controls, and found no significant differences in PK parameters between ECMO and non-ECMO groups [17]. Similarly, the ASAP ECMO study also demonstrated similar caspofungin PK parameters in ECMO patients, but with large inter-individual variations [18]. While these studies show target attainment at standard doses in ECMO, in another case report, caspofungin did not achieve therapeutic level even when it was given at a higher dose considering the patient's critical illness [19]. Given the conflicting and limited data along with high safety profile, is reasonable to consider an increased dosing strategy for caspofungin and anidulafungin with patients on ECMO. In terms of micafungin, two ex vivo studies suggested significant loss of the drug in ECMO circuit [14, 20]. A case report described a case of *Candida glabrata* fungemia successfully treated with increased dose of micafungin (150 mg every 24 h) while on ECMO[21]. Therefore, it is reasonable to consider an increased dosing strategy in micafungin.

Azoles

Fluconazole is a hydrophilic and has low protein binding. Ex vivo studies suggested that fluconazole is not significantly sequestered in the ECMO circuit [4, 20]. In ovine models, fluconazole had similar Vd and clearance on ECMO [22]. The limited clinical data in patients suggests otherwise; PK analysis in 40 infants on ECMO showed that Vd was increased, requiring a higher loading dose, however some of these were also receiving continuous renal replacement therapy (CRRT) [23]. Similarly, in PK analysis done in an adult patient, 40% increase in Vd was observed [24], implying that slightly more aggressive treatment dosing with a loading dose is reasonable. In this study, a dose of 6 mg/kg adequately met area under the curve (AUC) target for prophylaxis on ECMO [24]. ASAP ECMO study performed on eight critically ill patients receiving concomitant ECMO and CRRT showed that loading dose of 12 mg/kg followed by 6 mg/kg every 24 h achieved > 90% probability of target attainment, only when fluconazole MIC was equal to or less then 1 mg/L [25]. Therefore, for treatment we suggest a loading dose (12 mg/kg or double the usual maintenance dose), followed by standard maintenance dosing. While ELSO guidelines do not recommend routine antimicrobial prophylaxis for ECMO patients [26] and this strategy is not robustly studied, some retrospective reviews have implemented prophylaxis in specific populations [27, 28]. In the lack of strong evidence, if antifungal prophylaxis is desired, it is reasonable to consider the use of standard doses of fluconazole.

Voriconazole is lipophilic and exhibits a moderate to high degree of protein binding, likely leading to sequestration of drug on the ECMO membrane. Three ex vivo PK model studies reported drastic loss of voriconazole in ECMO circuit [14, 29, 30], while one ex vivo study reported only 9% loss of voriconazole based on calculated $AUC_{0\text{-}24}$ [13]. Possible explanations from the discordant results include differing oxygenator and tubing characteristics in these studies. Two retrospective observational cohort studies, each including 66 and 9 ECMO patients, consistently demonstrated significantly lower voriconazole levels in ECMO patients as compared to non-ECMO patients [31, 32]. In addition, several case reports documented reduced voriconazole exposure leading to dose escalation on ECMO [19, 33–35]. A case report described a phenomenon where voriconazole plasma concentration significantly decreased after each time the ECMO circuit was changed, necessitating temporary increase in the voriconazole dose [36]. This study also reported that after two to three weeks of membrane use, voriconazole plasma concentrations stabilized, implying that membrane became saturated by voriconazole [36]. It may be reasonable to consider a loading dose to be given for a longer duration (2 days) and to be repeated after oxygenator exchange. Along with this loading strategy, TDM is necessary for the use of voriconazole in ECMO to prevent over and underdosing. A retrospective study of 69 patients demonstrated that large proportions of critically ill patients had subtherapeutic voriconazole concentrations regardless of ECMO status with extensive inter- and intrasubject variability [37]. The importance of TDM is highlighted by a case report where a higher dose of voriconazole was administered considering that the patient was on ECMO, which led to unexpected supratherapeutic level and subsequent liver toxicity [16].

As expected with high lipophilicity and high protein binding, an ex vivo study demonstrated significant sequestration of posaconazole in blood primed ECMO (30.6% loss based on calculated $AUC_{0\text{-}24}$) [13]. A prospective study including six patients who received IV posaconazole as prophylaxis for invasive aspergillosis while on ECMO, all had measured trough concentrations that reached target (≥ 0.7 mg/dL), but simulation data suggested less than 90% attainment of treatment target (> 1.0 mg/dL) [38]. While lacking clinical data for therapeutic dose of posaconazole, it is reasonable to consider

increased empiric dose for treatment and adjusting the therapy with TDM. For prophylaxis, we recommend using standard doses. There is the least amount of data for isavuconazole. A study of seven individuals on ECMO showed standard dosing was sufficient and not affected by the membrane oxygenator [39]. Another case series on four patients reported highly variable drug concentration of isavuconazole, and authors discussed the challenge of differentiating the effect of ECMO versus critical illness [40]. Therefore, standard dosing can be considered for isavuconazole.

Amphotericin B

The literature on dosing of liposomal amphotericin B in ECMO patients is limited to a few case reports with conflicting observations. Two case studies reported that liposomal amphotericin B maintained similar therapeutic levels and other PK parameters at usual dosage in the patients on ECMO [19, 41]. In contrast, there is one case report where failure of ECMO circuit was attributed to liposomal amphotericin B causing occlusion and damage to the ECMO filter [42]. In this case, a trough amphotericin B level was undetectable, and therapy was changed to amphotericin B deoxycholate 1 mg/kg/day with a subsequent adequate trough level. Another case report described significant decrease in C_{max} with ECMO when liposomal amphotericin B was used [43]. Based on these observations on liposomal amphotericin B, it is reasonable to consider higher doses with adjustments based on clinical response. Data on amphotericin B deoxycholate in ECMO is scant. An ex vivo study found no loss of amphotericin B deoxycholate at 4 and 12 h in the ECMO circuit [44]. For amphotericin B deoxycholate, considering standard doses is reasonable with close monitoring for effectiveness.

Table 2 summarizes dosing recommendations for antifungal agents.

Antibacterials

Beta-lactams

Anti-staphylococcal penicillins

Nafcillin and oxacillin are both lipophilic and highly protein bound. One ex vivo study which looked at oxacillin and observed significant differences of rate of concentration decease in ECMO circuit and controls [45]. One case report showed that when standard dose of oxacillin (2 g IV infused over 30 min every 4 h) was used on a patient on ECMO, it achieved time above minimum inhibitory concentration (MIC) of 58% where MIC was 0.5 mg/dL [46]. This study also noted that if MIC was ≥ 1 mg/dL, the goal of time above MIC > 50% would not have been met. Both for nafcillin and oxacillin, it is reasonable to consider dosing on the higher end of the normal dosing range and closely monitor clinical response.

Broad-spectrum penicillins

Ampicillin

An ex vivo study suggests significant sequestration is possible for ampicillin in the ECMO circuit [29]. Recently, Kim et al. reported treatment experience for two patients who received ampicillin while on ECMO [47]. Both patients achieved the target of time above MIC at 100% at doses at the higher end and dynamically adjusted for renal function and RRT status, ranging from 2 g every 12 h to 2 g every 4 h. Based on these data, it is reasonable to consider dosing on the higher end of the normal dosing range.

Piperacillin-tazobactam

Multiple prospective observational PK studies offered mixed data on the effect of ECMO on piperacillin-tazobactam. Some studies reported no substantial differences of PK parameters between critically ill patients on ECMO or not on ECMO [48–51]. Other prospective studies showed contradicting results, that patients receiving ECMO were less likely to achieve target attainment with piperacillin-tazobactam [6, 18, 52, 53]. A retrospective study that analyzed 85 blood samples found that 5 of them had insufficient C_{min}, however there was no non-ECMO control group [54]. Multiple studies suggested that continuous infusion or extended infusion strategies can improve target attainment rate [49, 52, 53]. Therefore, we recommend using high end of dosing range with extended infusion protocol with assistance of TDM if feasible to maximize time above MIC when giving piperacillin-tazobactam.

Cephalosporins

Cephalosporins have various degree of lipophilicity and protein binding, and mixed data exists to suggest more aggressive dosing. For cefazolin, Mehta et al. and Wildschut et al. reported around 20% of drug loss in in vitro ECMO circuit [29, 55], while Kato et al. found no significant decrease of cefazolin concentration in in vitro ECMO circuit [56]. A case report suggested that cefazolin PK was not affected by ECMO therapy [57]. Based on these studies, use of standard doses can be considered for bacterial prophylaxis while on ECMO, as Shah et al. showed the use of standard doses of cefazolin as prophylaxis did not increase infection rate compared to broad-spectrum antibiotics [27]. When used for treatment of infection, dosing on the higher end of the normal dosing range could be considered.

Ceftriaxone appeared not to be lost significantly in ex vivo ECMO circuit [45]. Gijsen et al. [58] reported

Table 2 Summary of recommendations for antifungals

Drug	Pertinent PK parameters[a]	Dosing recommendation[b]	Comments	Proposed strength of evidence[c]
Echinocandins				
Anidulafungin	> 99% protein bound LogP[d] = 2.3	Increase dose from 200 mg once followed by 100 mg q24h to 200 mg q24h	One case report suggests minimal effect on PK	CR
Caspofungin	97% protein bound LogP = 0.3	Increase dose from 70 mg once followed by 50 mg q24h to 70 mg q24h	Mixed data with high safety profile suggest increased doses are reasonable	CR
Micafungin	> 99% protein bound LogP = -1.6	Increase dose to 150 mg q24h	Ex vivo studies suggest drug loss in ECMO circuit, a case report suggest using higher doses	CR
Azoles				
Fluconazole	11–12% protein bound LogP = 0.4	Prophylaxis: use standard doses Treatment: Administer a loading dose (12 mg/kg or double the usual treatment dose) and use standard treatment doses thereafter	Data supports being slightly more aggressive with treatment dosing	PR25
Voriconazole	58% protein bound LogP = 1.5	Increase loading dose duration. Start at 6 mg/kg q12h for 2 days (or after oxygenator change) and then reduce dose to 3–4 mg/kg	Use TDM to guide dosing	CR
Posaconazole	> 98% protein bound LogP = 4.6	Prophylaxis: use standard doses Treatment: Consider increased doses (DR or IV formulation 400 mg q24h)	Use TDM to guide dosing. An ex vivo study showed significant sequestration; along with a high safety profile, increased empiric treatment doses are reasonable	CR
Isavuconazole	> 99% protein bound Log P = 3.5	Use standard doses	A single patient PK study showed standard dosing is sufficient	CR
Amphotericin B				
Liposomal	Unclear protein binding High lipophilicity	Consider increased doses (5–8 mg/kg q24h or higher)	Mixed data exist. Consider increased dosage with close monitoring of clinical response	CR
Deoxycholate	90% protein bound LogP = 0.8	Use standard doses	Less likely to be affected by ECMO than liposomal formulation. Monitor for increased toxicity	CR

PK pharmacokinetic(s), *LogP* $LogP_{octanol/water}$, *q24h* every 24 h, *q12h* every 12 h, *TDM* therapeutic drug monitoring, *ECMO* extracorporeal membrane oxygenation, *DR* delayed release, *IV* intravenous

[a] All protein binding and logP values were obtained from PubChem

[b] Dosing recommendations in this table are for normal organ function and body weight. Further dose adjustments may be needed for organ impairment, renal replacement therapies, or body weight

[c] Abbreviations correspond to level of recommendation defined in Table 1

[d] Lipophilicity of the drug is represented by $LogP_{octanol/water}$, which is a log value of proportion between concentration of drug in octanol phase and concentration of drug in water phase. Increasing positive values representing lipophilic drugs and increasingly negative values representing hydrophilic drugs

ceftriaxone PK data of two patients; ECMO did not significantly affect unbound PK and target attainment. Similarly, in a prospective study with 14 patients, Cheng et al. [59] suggested that ECMO does not significantly influence ceftriaxone pharmacokinetics. Therefore, we suggest ceftriaxone dosing similar to other critically ill patients on the higher end of the normal dosing range [60].

For ceftaroline, minimal data exists. An ex vivo study suggested significant loss of ceftaroline in ECMO circuit [61], which support using a higher dose, such as 600 mg every 8 h. However, as there are no published clinical cases to guide management, we have no recommendation for its use in ECMO.

For cefepime, ceftazidime, and ceftazidime-avibactam, we suggest using standard doses. Cefepime showed insignificant change in PK parameters both ex vivo and in patient PK samples [45, 54, 62–64]. Ceftazidime also showed reliable drug recovery in ex vivo study and similar PK parameters in clinical data [6, 45, 54]. In a retrospective observational study on 14 patients on ECMO receiving ceftazidime-avibactam, Curtiaud et al. showed that trough levels for both ceftazidime and avibactam were above predefined targets of European Committee

on Antimicrobial Susceptibility Testing (EUCAST) breakpoints in most patients, and concluded that dose modification may not be necessary [65].

For ceftolozane-tazobactam, one ex vivo study demonstrated significant loss of the drug in the circuit [66], whereas another ex vivo, porcine in vivo study and two case reports suggested the ECMO has minimal effect on ceftolozane-tazobactam PK [67–69]. Due to these studies, it is reasonable to consider standard dosing when using ceftolozane-tazobactam.

Ceftobiprole was studied in one retrospective cohort comparing 28 patients on ECMO and 7 patients not on ECMO [70]. Ceftobiprole blood concentrations were similar in two groups and was more affected by renal clearance and RRT than ECMO status [70]. Therefore, we suggest standard dosing with renal adjustment for ceftobiprole.

Cefiderocol is a new siderophore cephalosporin which is active against multiple antibiotic resistant infections. It is moderately protein bound (40 to 60%) and hydrophilic in nature. Cefiderocol sequestration was assessed in an ex vivo ECMO circuit versus a glass jar control. After 24 h, the percent drug reduction was similar between the ECMO circuit and control (50% ± 13 vs. 50% ± 9, $p = 1.0$) [71]. Similarly, a case report observed that there was no significant drug loss and the AUC of the drug was in fact, higher than expected [72]. Hence it is reasonable to consider cefiderocol standard doses in patients on ECMO.

Carbapenems

Meropenem is one of the most clinically studied antibiotics in terms of dosing in ECMO. A notable feature of meropenem is it is easily degraded in physiologic conditions, as shown in ex vivo studies [3, 14, 73]. In addition, Shekar et al., and Zhang et al., reported further loss of meropenem in ECMO circuit ex vivo [3, 14]. So far there are 12 clinical prospective studies on meropenem dosing in ECMO patients in adult patients [6, 18, 50, 58, 74–77]. These studies consistently demonstrated challenges of maintaining therapeutic time above MIC for meropenem in critically ill patients in general, while the use of ECMO did not seem to affect PK of meropenem significantly. The studies emphasized importance of utilizing extended or continuous infusion with guidance of TDM to meet therapeutic goal, especially if aggressive target of time above MIC is desired. Therefore, we recommend to dose on the higher end of the normal dosing range and consider an extended infusion dosing protocol for meropenem.

In 2015, Welsch et al. reported high variability in trough concentrations of imipenem-cilastatin in two patients on VV-ECMO and suggested dosing regimen of 1 g every 6 h [78]. Subsequently, two prospective PK studies, each performed on 10 patients, both showed poor target attainment with usual dosing and suggested 1 g every 6 h may be required for adequate serum concentration [5, 48]. A large retrospective population PK study on 247 patients showed that blood concentrations of imipenem in ECMO patients were lower than that of non-ECMO patients and suggested higher dose of imipenem-cilastatin 750 mg every 6 h [79]. Therefore, we recommend 1 g every 6 h of imipenem-cilastatin for the patients on ECMO. For imipenem-cilastatin-relebactam, which is co-formulation with beta-lactamase inhibitor relebactam, a population PK study on 7 patients suggested that a standard dose of 1.25 g every 6 h achieved sufficient drug exposure [80]. It is reasonable to consider standard dosing for imipenem-cilastatin-relebactam.

For ertapenem, clinical data is lacking. We recommend considering usage of meropenem or imipenem-cilastatin instead which have more published data and are less protein bound.

Daptomycin

Limited data on daptomycin dosing suggests that use of standard doses may be appropriate in ECMO patients. Two studies using ex vivo PK models showed that daptomycin levels were maintained in conventional ECMO circuit over 24 h [56, 61]. A case report described successful treatment of vancomycin-resistant *Enterococcus faecium* bacteremia with standard 10 mg/kg every 24 h doses of daptomycin [21]. A recent prospective PK study on 36 patients showed that creatinine clearance significantly affects the clearance of daptomycin while ECMO has no significant effect on PK parameters [81]. Therefore, we suggest standard dosing for daptomycin in ECMO patients with routine adjustments based on creatinine clearance and MIC.

Tetracyclines

Doxycycline has an important role in management of infections such as scrub typhus, leptospirosis, and malaria that can present with acute respiratory distress syndrome (ARDS) as a complication, necessitating the use of ECMO. Doxycycline is a highly protein bound and lipophilic molecule and therefore, could be sequestered into the ECMO circuit. Despite extensive use of doxycycline, the variation in PK in patients on ECMO has not been studied. However, A single case report observed that the ECMO circuit did not decrease the peak and trough concentrations and the standard dosing at 100 mg every 12 h may be sufficient in such case [82]. Thus, it is reasonable to consider use of standard doses of doxycycline in ECMO patients. For tigecycline, an ex vivo PK model study reported no significant loss of drug in ECMO circuit [14]. Similarly, in a case report in a patient

on VV-ECMO with centrifugal pump, ECMO did not have effect on PK of tigecycline [83]. Therefore, it is reasonable to consider using standard doses of tigecycline in ECMO patients.

Glycopeptides

A number of population PK, observational, and matched cohort studies described PK of vancomycin in ECMO patients [18, 84–91]. Consistent findings are that the PK parameters of vancomycin were largely consistent with that of critically ill patients not on ECMO, emphasizing that vancomycin dosing in ECMO patients should be in alignment with a general approach for critically ill patients [84–86, 88]. These include administration of a loading dose [90] with consideration for renal function and status of renal replacement therapy [85]. The importance of TDM is paramount when using vancomycin in ECMO patients. We recommend a loading dose of 20 to 30 mg/kg (maximum loading dose: 3000 mg) as in other critically ill patients, followed by standard maintenance doses guided by TDM.

Teicoplanin is a hydrophilic molecule that is highly protein bound. In presence of renal dysfunction, many clinicians outside of the United States prefer using teicoplanin for relatively easier dose adjustments and better side effect profile than vancomycin. Wi et al. developed a population PK model for dose optimization of teicoplanin [92]. The study suggested a loading dose of 600 mg (instead of 6 mg/kg) and a maintenance dose of 400 mg for mild to moderate infections and a loading dose of 1,000 mg and a maintenance dose of 800 mg for severe infections [92]. Similarly, another study observed that a regimen with 4 loading doses of 12 mg/kg was effective in achieving a median trough level above 10 mg/L in 100% cases and above 15 mg/L in 90.9% cases [93]. Based on these studies, we suggest higher than standard doses.

Linezolid

Minimal and conflicting data exists regarding linezolid dosing in ECMO. In ex vivo PK model, linezolid level was maintained at 91% after 24 h in the ECMO circuit [4]. However, a case series on three patients demonstrated that MIC values > 1 mg/dL for methicillin-resistant *Staphylococcus aureus* (MRSA) predicted subtherapeutic AUC/MIC [94]. Another case report observed subtherapeutic AUC/MIC at a higher dose of 600 mg every 8 h when used for MRSA even at MIC of 1 mg/dL [95]. In a prospective observational study, nine patient receiving continuous infusion of linezolid while on ECMO were studied, and authors found high rates of target attainment failure (35% vs. 15% in non-ECMO) when the target was defined as serum concentrations fourfold above the MIC [6]. Therefore, when using linezolid for patients on ECMO, high dose of 600 mg every 8 h may be considered especially for treatment of severe infection, accompanied by monitoring for adverse effect. If suboptimal clinical response is noted, an alternative antimicrobial agent should be considered.

Fluoroquinolones

It was demonstrated in multiple studies (ex vivo PK models and observational studies in patients) that ciprofloxacin concentrations and PK parameters are minimally affected by ECMO circuit [3, 96, 97]. The ASAP ECMO study demonstrated large between-subject variability in PK parameters of ciprofloxacin in ECMO patients as in other antimicrobials included in this study, emphasizing consideration of other factors when approaching critically ill patients [18]. An in vitro model using heparin coated ECMO circuit showed that the concentration of levofloxacin did not decrease significantly over 24 h [56]. We recommend a standard dosing approach for critically ill patients as appropriate for both ciprofloxacin and levofloxacin.

Azithromycin

One case series reported no significant difference in C_{max}, C_{min}, and AUC of azithromycin in three patients who received standard dose of IV azithromycin while on ECMO [98]. Standard dosing can be considered for azithromycin.

Aminoglycosides

Aminoglycosides are hydrophilic molecules with low protein binding. Most PK studies on aminoglycosides are performed on amikacin. For gentamicin, there is some early literature in infants and neonates [2, 99–104], and for tobramycin, there is no clinical data. In two prospective observation studies on adult patients, ECMO did not have a significant effect on peak and trough plasma amikacin levels [105, 106]. In two other prospective studies on adult patients, subtherapeutic amikacin peak levels were observed in 39% (41/106 patients) and 67% (4/6 patients), respectively [48, 107]. However, variability of amikacin levels in critically ill patients is a well described challenge even without the use of ECMO [108–111]. Overall, it appears that ECMO has minimal effect on PK of aminoglycosides. We recommend the same approach to aminoglycoside dosing in ECMO patients as in non-ECMO critically ill patients, which includes consideration for renal function, clinical indication, MICs, and most importantly, drug level monitoring.

Polymyxins

Polymyxins include colistin and polymyxin B. While colistin is administered as a prodrug (colistimethate

sodium), polymyxin B is administered in its active form. Both the drugs are moderately protein bound and possess both hydrophilic and lipophilic moieties [112]. Generally, these drugs are less likely to be sequestered in the ECMO circuit. Suk et al. studied the effect of ECMO on colistin concentrations in two patients and did not observe any reduction in drug concentrations [113]. In fact, they reported the levels to be higher than the average concentrations [113]. Another case report also reported similar findings with no significant differences in the trough and peak concentrations of the drug with ECMO [114]. In a study evaluating the PK profile of polymyxin B in critically ill patients on ECMO, the median area under the concentration–time curve over 12 h ($AUC_{0-12\ h}$) for the total drug and the free drug was not different when compared to non-ECMO patients. The authors concluded that current dosing strategies for polymyxin B are sufficient for patients on ECMO and dose modifications may not be necessary [115]. Similarly, Ye et al. [116] observed that the impact of ECMO on polymyxin B is likely to be minimal. Given this data indicating minimal impact of ECMO on polymyxins, we suggest use of standard dosing for both colistin and polymyxin B.

Metronidazole

Metronidazole has very low-grade protein binding (< 20%) and is hydrophilic, thus its PK is unlikely to be affected by ECMO. While lacking any literature, we have no recommendation for any alternative dosing strategy for ECMO patients.

Sulfamethoxazole-trimethoprim

A case report on a patient who was treated with IV sulfamethoxazole-trimethoprim at the dose of 100 mg/kg/day and 20 mg/kg/day for *Pneumocystis jirovecii* pneumonia while on VV-ECMO showed that PK parameters were not significantly affected by ECMO therapy [117]. It is reasonable to consider using standard initial doses with TDM given the high protein binding and lipophilicity of both sulfamethoxazole and trimethoprim components.

Fosfomycin

With increasing prevalence of multidrug resistant infections, intravenous fosfomycin, either alone or in combination is often used in critically ill patients outside of the United States. No study has assessed the PK of fosfomycin in patients on ECMO support. However, this drug is hydrophilic and has negligible protein binding, which suggests it would not likely be sequestered in the ECMO circuit [118]. With lack of data for use in ECMO, we have no recommendation for any alternative dosing strategy in patients receiving ECMO.

Table 3 summarizes dosing recommendations for antibacterial agents.

Antivirals

The literature on the use of ganciclovir on ECMO is limited to one case report in an adult patient with acquired immunodeficiency syndrome (AIDS) [24]. This study showed that ganciclovir at standard dosing achieved AUC target on ECMO [24]. In the absence of sufficient literature, given the hydrophilicity and low protein bindings of the drug, it is reasonable to consider using ganciclovir at standard doses with implementation of TDM if available.

Three small open label, prospective studies evaluated the PK parameters of oseltamivir in critically ill patients [119–121]. These studies consistently showed that ECMO itself did not change C_{max} and AUC of oseltamivir carboxylate, which is an active metabolite of oseltamivir. Only when the patient had renal dysfunction or was on concomitant continuous renal replacement therapy, oseltamivir carboxylate showed accumulation. ASAP ECMO study observed poor target attainment of oseltamivir in 3 out of 9 patients, however, it is not clear if these patients with poor target attainment had augmented or normal renal function compared to the patients who achieved the PK target [18]. We therefore recommend using standard, renally adjusted doses of oseltamivir in the patient on ECMO.

For peramivir, an ex vivo study demonstrated no significant loss of peramivir in the ECMO circuit regardless of the presence of the oxygenator [122]. Without any clinical data, we have no recommendation for alternative dosing strategies in patients receiving ECMO.

Remdesivir is a pro-drug which converts into its active metabolite GS-441524. It is a highly protein bound molecule and therefore may get sequestered in the circuit [123]. Carina et al. examined the interactions between circuits and drugs in closed-loop ex vivo ECMO and CRRT setups. The mean recovery of remdesivir at 6 h post-dosing was notably low in both ECMO (33.3% [2.0]) and CRRT (3.5% [0.4]) circuits. Conversely, the recovery of GS-441524 at the 6-h mark was substantial in the ECMO circuit (75.8%), but undetectable in the CRRT circuit. The significant loss of both molecules, particularly in the CRRT setup, indicates potential need for remdesivir dosing adjustments especially in patients undergoing both ECMO and CRRT support [124]. Similarly, Dhanani et al. [125] observed decreased drug recoveries in ex vivo ECMO circuits than control jars. Ide et al. assessed the effect of ECMO circuit in a patient with severe coronavirus disease 2019 (COVID-19) with normal renal function. The plasma concentrations of remdesivir and GS-441524 4 h after administration were lower than the

Table 3 Summary of recommendations for antibacterials

Drug	Pertinent PK parameters[a]	Dosing recommendation[b]	Comments	Proposed strength of evidence[c]
Beta-lactams				
Nafcillin	90% protein bound LogP[d] = 2.9	Dose on the higher end of the normal dosing range	Highly protein bound and lipophilic drugs may be sequestered by ECMO	CR
Oxacillin	94% protein bound LogP = 2.4	Dose on the higher end of the normal dosing range	Highly protein bound and lipophilic drugs may be sequestered by ECMO, and a case report suggested aggressive dosing	CR
Ampicillin	15–18% protein bound LogP = − 1.1	Dose on the higher end of the normal dosing range	PK data in one patient suggest advantage of aggressive dosing	CR
Piperacillin-tazobactam	Piperacillin: 26–33% protein bound, LogP = 0.5; Tazobactam: 30% protein bound, LogP = − 2.0	Dose on the higher end of the normal dosing range. Consider extended infusions to maximize time above MIC, TDM if available	Mixed data exist but literature consistently show benefit of extended infusion	PR25
Cefazolin	80% protein bound LogP = − 0.6	Prophylaxis: use standard doses Treatment: dose on the aggressive side of the normal dosing range	In vitro studies suggested significant sequestration but a case report minimal effect on PK	CR
Cefepime	20% protein bound LogP = − 4 to -0.4	Use standard dose. Consider extended infusions to maximize time above MIC, TDM if available	Insignificant PK changes in both ex vivo and patient studies	PR1/2
Cefiderocol	40–60% protein bound LogP = 1	Use standard doses	An ex vivo study and a case report suggest no significant drug loss	CR
Ceftaroline	20% protein bound LogP = − 0.8 to 2.3	Consider a dose of 600 mg q8h or an alternative agent	Minimal data exist; an ex vivo study suggests significant loss of drug in the circuit	EV
Ceftazidime	< 10% protein bound LogP = 0.4	Use standard doses	Insignificant PK changes in both ex vivo and patient studies	PR1/2
Ceftazidime-avibactam	Ceftazidime: see above Avibactam: 5–8% protein bound, LogP = 1.8	Use standard doses	A retrospective clinical study suggested dose adjustment is not necessary	PR1/2
Ceftolozane-tazobactam	Ceftolozane: 16–21% protein bound LogP = − 3.2; Tazobactam: 31–30% protein bound LogP = − 2.0	Use standard doses	Minimal data exist; two case reports minimal PK effect	CR
Ceftobiprole	16% protein bound LogP = − 2.4	Use standard doses	A retrospective study suggested dose adjustment are not necessary	PR1/2
Ceftriaxone	85–95% protein bound LogP = − 1.7	Dose on the higher end of the normal dosing range	Clinical data suggest dosing similar to other critically ill patients	PR1/2
Meropenem	2% protein bound LogP = − 0.6	Dose on the higher end of the normal dosing range. Consider extended or continuous infusions with TDM	Carbapenems are innately unstable and the full impact of ECMO is unknown. However, literature consistently show benefit of extended infusion	PR25

Table 3 (continued)

Drug	Pertinent PK parameters[a]	Dosing recommendation[b]	Comments	Proposed strength of evidence[c]
Ertapenem	85–95% protein bound LogP = 0.3	Consider using an alternative agent such as meropenem	No clinical data	EV
Imipenem-cilastatin	20% protein bound LogP = − 0.7	Increase dose to 1 g q6h	Large retrospective and prospective studies suggest increased dosing	PR25
Imipenem-cilastatin-relebactam	Imipenem: see above Relebactam: 22% protein bound LogP = − 3.6	Use standard doses	A retrospective study suggested dose adjustment are not necessary	CR
Cyclic lipopeptides				
Daptomycin	84–93% protein bound LogP = − 5.1	Use standard doses	Data suggest minimal effect on PK	PR1/2
Tetracyclines				
Doxycycline	90% protein bound LogP = − 0.7	Use standard doses	A single case report minimal PK effect	CR
Tigecycline	71–89% protein bound LogP = 1.1	Use standard doses	An ex vivo study and a case report showed no PK effect	CR
Glycopeptides				
Vancomycin	50% protein bound LogP = − 2.6	Loading dose of 20–30 mg/kg (maximum: 3000 mg) followed by standard doses guided by TDM	Literature consistently shows PK is consistent with that of non-ECMO critically ill patients	PR25
Teicoplanin	> 90% protein binding LogP = 0.5	Loading dose of 600–1000 mg followed by maintenance doses of 400–800 mg	Clinical data suggests use of higher dose	PR1/2
Oxazolidinones				
Linezolid	< 35% protein bound LogP = 0.7	May use standard doses, but consider a dose of 600 mg q8h or an alternative agent for severe infection or if a suboptimal response is noted	Minimal, conflicting data exist	CR
Fluoroquinolones				
Ciprofloxacin	20–40% protein bound LogP = − 1.1	Use standard doses	Data suggest minimal effect on PK	PR25
Levofloxacin	24–38% protein bound LogP = − 0.4	Use standard doses	Data suggest minimal effect on PK	PR25
Macrolides				
Azithromycin	7–51% protein bound LogP = 3–4	Use standard doses	A case series showed minimal PK changes	CR
Aminoglycosides				
Amikacin	< 10% protein bound LogP = − 7.9	Use standard doses with TDM	Literature suggests dosing similar to other critically ill patients	PR25

Table 3 (continued)

Drug	Pertinent PK parameters[a]	Dosing recommendation[b]	Comments	Proposed strength of evidence[c]
Gentamicin	< 30% protein bound LogP = − 4.1	Use standard doses with TDM	No adult patient data	EV
Tobramycin	Negligibly protein bound LogP = − 6.2	Use standard doses with TDM	No data	EV
Polymyxins				
Colistin	50% Protein bound LogP = − 3.3	Use standard doses	Minimal PK effect	PR1/2
Polymyxin B	58–98% Protein bound LogP = no data in literature	Use standard doses	Minimal PK effect	PR1/2
Others				
Metronidazole	< 20% protein bound LogP = 0	Use standard doses	No clinical data	EV
Sulfamethoxazole-trimethoprim	Sulfamethoxazole: 70% protein bound LogP = 0.9 Trimethoprim: 44% protein bound LogP = 0.9	Use standard doses with TDM	A case report suggested use of standard dose	CR
Fosfomycin	Not bound to plasma proteins Log P = − 1.4	Use standard doses	No clinical data	EV

PK pharmacokinetic(s), *LogP* $LogP_{octanol/water}$, *ECMO* extracorporeal membrane oxygenation, *q8h* every 8 h, *q12h* every 12 h, *TDM* therapeutic drug monitoring

[a] All protein binding and logP values were obtained from PubChem

[b] Dosing recommendations in this table are for normal organ function and body weight. Further dose adjustments may be needed for organ impairment, renal replacement therapies, or body weight

[c] Abbreviations correspond to level of recommendation defined in Table 1

[d] Lipophilicity of the drug is represented by $LogP_{octanol/water}$, which is a log value of proportion between concentration of drug in octanol phase and concentration of drug in water phase. Increasing positive values representing lipophilic drugs and increasingly negative values representing hydrophilic drugs

concentrations reported in normal individuals [126]. Notably, the patient had also gained 20 kg of extracellular fluid weight during the hospitalization which likely also affected the PK resulting in lower serum levels. While clinical evidence is scarce, standard dosing may be considered for remdesivir.

Table 4 summarizes dosing recommendations for antiviral agents.

Discussion

Optimizing drug exposure in patients requiring ECMO remains challenging. Concerns with circuit sequestration of lipophilic and highly protein bound molecules and an expanded volume of distribution of hydrophilic molecules have yielded mixed findings in the above reviewed literature. The conflicting nature of literature existing in this sphere makes interpretation very challenging and strong recommendations are sparse. The severe degree of critical illness that necessitates exposure to ECMO circuitry very frequently carries additional perturbations to PK that, in themselves, can also affect drug exposure [2, 3, 7, 8]. Most of the comparative data suggests antimicrobial exposure for several agents did not differ in critically ill patients requiring ECMO versus those not requiring ECMO [17, 31, 37, 50, 51, 76, 84, 85, 89–91, 98, 105, 108, 114, 116, 121]. In contrast, some studies do suggest decreased drug exposure in ECMO patients compared to non-ECMO patients [6, 53, 99, 100], highlighting the need to further elucidate the interplay of the ECMO circuit and critical illness in individual drugs. While the circuit and critical illness cause PK alterations as described in this article, there is limited data on PD and patient outcomes, which is essential information to improve clinical outcomes for the patients receiving ECMO.

While in vitro and ex vivo studies are important first steps to understand the PK effects of the ECMO circuit on the antimicrobials, there are several challenges to these study designs. Aside from the concerns of removing the human compartment, in vitro and ex vivo circuit models used in sequestration studies may be performed under conditions not broadly generalizable to contemporary practice, including differences in membrane oxygenator composition, type and length of tubing, tubing coatings, choice of priming fluid, and abridged duration of circuit exposure. Theoretical concerns regarding saturation of binding sites are difficult to quantify but also may not be captured in these analyses. Ideally, PK studies in pre-clinical models can complement clinical observations, However, given the limitations of in vitro and ex vivo sequestration studies and that results frequently do not align with PK studies, use of clinical PK studies in real world settings when available is preferable. For the majority of antimicrobials discussed above, individual case reports and case series evaluating PK data are the strongest level, and only a few have studies with a non-ECMO comparator arm.

End-organ dysfunction occurs frequently in this population, with some reports of concomitant acute kidney injury occurring in over 50% of cases [127]. Concomitant use of CRRT is commonly employed in these patients and can often be done using the same circuit. Presence of renal dysfunction and accompanying renal replacement therapies will further alter antimicrobial dosing needs of some antimicrobials beyond that of ECMO alone. In general, CRRT most efficiently removes antimicrobials with

Table 4 Summary of recommendations for antivirals

Drug	Pertinent PK parameters[a]	Dosing recommendation[b]	Comments	Proposed strength of evidence[c]
Ganciclovir	1–2% protein bound LogP[d] = −2.5	Use standard doses with TDM	Insufficient clinical data	CR
Oseltamivir	42% protein bound LogP = 1.1	Use standard doses	Prospective studies suggest standard dosing	PR25
Peramivir	< 30% protein bound LogP = 0	Use standard doses	No clinical data	EV
Remdesivir	90% protein bound LogP = 1.9	Use standard doses	1 case report suggest possible decreased plasma concentration with multiple confounding factors	CR

PK pharmacokinetic(s), *LogP* $LogP_{octanol/water}$, *TDM* therapeutic drug monitoring

[a] All protein binding and logP values were obtained from PubChem

[b] Dosing recommendations in this table are for normal organ function and body weight. Further dose adjustments may be needed for organ impairment, renal replacement therapies, or body weight

[c] Abbreviations correspond to level of recommendation defined in Table 1

[d] Lipophilicity of the drug is represented by $LogP_{octanol/water}$, which is a log value of proportion between concentration of drug in octanol phase and concentration of drug in water phase. Increasing positive values representing lipophilic drugs and increasingly negative values representing hydrophilic drugs

low protein binding, low volumes of distribution, and those that are more hydrophilic with predominately renal elimination (characteristics that are largely the opposite to those most potentially affected by ECMO)[128, 129]. Other publications exist to provide guidance on dosing for CRRT and should also be referenced for patients receiving this in addition to ECMO [129–132]. Each patient's individual scenario needs to be comprehensively evaluated to determine appropriate dosing strategies, ideally guided by TDM if feasible. Also, it should be noted that while the dosing suggestions in this article are for ECMO, it was not always possible to cleanly separate out publications and study data with regards to whether concomitant CRRT was employed, and that is a limitation of this paper.

Effective and early antibiotic therapy is a key to management of infection in critically ill patients; therefore, more aggressive dosing approaches in these patients could be considered in the context of severity of infection, individual patient comorbidities, and specific drug properties. Close monitoring and dosing adjustment is necessary to minimize the potential for antimicrobial toxicity. An understanding of antimicrobial PK and PD is essential in guiding effective and safe dosing, this requires support from informed clinical pharmacists and clinicians.

In this context, we recommend individualizing therapy for patients by TDM, when available. Limitations of TDM should not be overlooked, however, including a dearth of availability of assays for some of the commonly utilized antimicrobials at many institutions and in some cases. In the future, increased access to TDM and dosing software may also be impactful for individualizing effective therapy for these patients. The other limitation is a lack of consensus on optimal PK/PD targets for each drug. Beta-lactams, for example, have conflicting suggestions, depending on the citation, of time over MIC targets of 50–70% of the dosing interval to trough goals of greater than four times the MIC [133, 134]. For beta-lactams, we recommend the use of extended infusion when possible, as is commonly utilized in other critically ill patients to optimize PD, which is in concordance with 2021 international guidelines for management of sepsis [135].

In addition, it should be noted that for antimicrobials with oral administration options (e.g., azoles), precaution should be taken when adopting dosing strategies from these literature. Majority of PK studies that we reviewed are done with IV formulation of antimicrobials, and oral absorption of drugs may be erratic in critically ill patients [136].

The strength of our paper is that we performed comprehensive and extensive review of the most up-to-date literature. This review carries high clinical relevance thus provides practical guidance to clinicians and pharmacists. Finally, we adopted semi-quantitative method to assess the level of evidence as outlined in Table 1.

Looking forward, there are many opportunities to improve our understanding of antimicrobial exposure in these complex patients. Clinical outcomes studies may be difficult to perform and interpret in this population given the high underlying mortality risk, lack of standard definition for infections during ECMO support [137], and different ECMO systems and cannulations strategies used among centers. However additional studies comparing drug levels in ECMO patients to matched non-ECMO cohorts would help elucidate whether the PK changes are truly secondary to presence of the ECMO circuit or if the profound degree of critical illness and the associated physiological changes are the main driver. More data on the interplay of ECMO and CRRT on dosing needs would also be beneficial. As new circuits are developed, it is possible that they may affect antimicrobials in ways that are different from previously studied circuits, and application of these dosing strategies should be interpreted with caution. Lastly, expanded access to antimicrobial assays and further clarification of goal ranges would also be of utility for future studies in efforts to optimize efficacy and minimize toxicity.

Conclusion

Effective antimicrobial use in patients on ECMO requires careful consideration of the complex interplay between patient, circuit, and antimicrobial factors. Recently there has been significant progress in understanding these complexities and emerging clinical data to support antimicrobial dosing recommendations in these complex, critically ill patients on ECMO. However robust prospective clinical studies centered to patient outcomes beyond the scope of PK/PD parameters are needed. TDM should be utilized when feasible to improve outcomes in these complex, critically ill patients.

Abbreviations

AIDS	Acquired immunodeficiency syndrome
ARDS	Acute respiratory distress syndrome
AUC	Area under the curve
C_{max}	Peak concentration
C_{min}	Trough concentration
CMV	Cytomegalovirus
COVID-19	Coronavirus disease 2019
ECMO	Extracorporeal membrane oxygenation
ELSO	Extracorporeal Life Support Organization
EUCAST	European Committee on Antimicrobial Susceptibility Testing
HHV-6	Human herpesvirus-6
IV	Intravenous
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
PK	Pharmacokinetic(s)
PD	Pharmacodynamic(s)
Vd	Volume of distribution
RRT	Renal replacement therapy

CRRT	Continuous renal replacement therapy
TDM	Therapeutic drug monitoring
VA-ECMO	Veno-arterial extracorporeal membrane oxygenation
VV-ECMO	Veno-venous extracorporeal membrane oxygenation

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MK, MM, LLE, NJM, and AM conducted literature review and writing of the original draft. JWW and JEM provided review and editing and supervision of the project. CRO conducted literature review and editing of the original draft. AS conducted review and editing, supervision of the project, and project administration.

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References

1. Tonna JE, Boonstra PS, MacLaren G, Paden M, Brodie D, Anders M, Hoskote A, Ramanathan K, Hyslop R, Fanning JJ, et al. Extracorporeal life support organization registry international report 2022: 100,000 survivors. ASAIO J. 2024;70(2):131–43.
2. Buck ML. Pharmacokinetic changes during extracorporeal membrane oxygenation: implications for drug therapy of neonates. Clin Pharmacokinet. 2003;42(5):403–17.
3. Shekar K, Roberts JA, McDonald CI, Fisquet S, Barnett AG, Mullany DV, Ghassabian S, Wallis SC, Fung YL, Smith MT, et al. Sequestration of drugs in the circuit may lead to therapeutic failure during extracorporeal membrane oxygenation. Crit Care. 2012;16(5):R194.
4. Shekar K, Roberts JA, McDonald CI, Ghassabian S, Anstey C, Wallis SC, Mullany DV, Fung YL, Fraser JF. Protein-bound drugs are prone to sequestration in the extracorporeal membrane oxygenation circuit: results from an ex vivo study. Crit Care. 2015;19(1):164.
5. Jaruratanasirikul S, Vattanavanit V, Wongpoowarak W, Nawakitrangsan M, Samaeng M. Pharmacokinetics and Monte Carlo dosing simulations of imipenem in critically ill patients with life-threatening severe infections during support with extracorporeal membrane oxygenation. Eur J Drug Metab Pharmacokinet. 2020;45(6):735–47.
6. Kuhn D, Metz C, Seiler F, Wehrfritz H, Roth S, Alqudrah M, Becker A, Bracht H, Wagenpfeil S, Hoffmann M, et al. Antibiotic therapeutic drug monitoring in intensive care patients treated with different modalities of extracorporeal membrane oxygenation (ECMO) and renal replacement therapy: a prospective, observational single-center study. Crit Care. 2020;24(1):664.
7. Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, Hope WW, Farkas A, Neely MN, Schentag JJ, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis. 2014;14(6):498–509.
8. Varghese JM, Roberts JA, Lipman J. Pharmacokinetics and pharmacodynamics in critically ill patients. Curr Opin Anaesthesiol. 2010;23(4):472–8.
9. Morales Castro D, Dresser L, Granton J, Fan E. Pharmacokinetic alterations associated with critical illness. Clin Pharmacokinet. 2023;62(2):209–20.
10. Dzierba AL, Abrams D, Brodie D. Medicating patients during extracorporeal membrane oxygenation: the evidence is building. Crit Care. 2017;21(1):66.
11. Millar JE, Fanning JP, McDonald CI, McAuley DF, Fraser JF. The inflammatory response to extracorporeal membrane oxygenation (ECMO): a review of the pathophysiology. Crit Care. 2016;20(1):387.
12. Howick J, Chalmers I, Glasziou P, Greenhalgh T, Heneghan C, Liberati A, Moschetti I, Phillips B, Thornton H, Goddard O, Hodgkinson, M. OCEBM table of evidence working group: The Oxford 2011 levels of evidence. OCEBM Levels of Evidence Working Group. [http://www.cebm.net/index.aspx?o=5653]
13. Lyster H, Pitt T, Maunz O, Diamond S, Roberts JA, Brown D, Mills J, Armstrong-James D, Gerovasili V, Carby M, et al. Variable sequestration of antifungals in an extracorporeal membrane oxygenation circuit. ASAIO J. 2023;69(3):309–14.
14. Zhang Y, Hu H, Zhang Q, Ou Q, Zhou H, Sha T, Zeng Z, Wu J, Lu J, Chen Z. Effects of ex vivo extracorporeal membrane oxygenation circuits on sequestration of antimicrobial agents. Front Med (Lausanne). 2021;8:748769.
15. Aguilar G, Ferriols R, Carbonell JA, Ezquer C, Alonso JM, Villena A, Puig J, Navarro D, Alos M, Belda FJ. Pharmacokinetics of anidulafungin during venovenous extracorporeal membrane oxygenation. Crit Care. 2016;20(1):325.
16. Spriet I, Annaert P, Meersseman P, Hermans G, Meersseman W, Verbesselt R, Willems L. Pharmacokinetics of caspofungin and voriconazole in critically ill patients during extracorporeal membrane oxygenation. J Antimicrob Chemother. 2009;63(4):767–70.
17. Wang Q, Zhang Z, Liu D, Chen W, Cui G, Li P, Zhang X, Li M, Zhan Q, Wang C. Population pharmacokinetics of caspofungin among extracorporeal membrane oxygenation patients during the postoperative period of lung transplantation. Antimicrob Agents Chemother. 2020;64(11):10–1128.
18. Shekar K, Abdul-Aziz MH, Cheng V, Burrows F, Buscher H, Cho YJ, Corley A, Diehl A, Gilder E, Jakob SM, et al. Antimicrobial exposures in critically ill patients receiving extracorporeal membrane oxygenation. Am J Respir Crit Care Med. 2023;207(6):704–20.
19. Ruiz S, Papy E, Da Silva D, Nataf P, Massias L, Wolff M, Bouadma L. Potential voriconazole and caspofungin sequestration during extracorporeal membrane oxygenation. Intensive Care Med. 2009;35(1):183–4.
20. Watt KM, Cohen-Wolkowiez M, Williams DC, Bonadonna DK, Cheifetz IM, Thakker D, Benjamin DK Jr, Brouwer KLR. Antifungal extraction by the extracorporeal membrane oxygenation circuit. J Extra Corpor Technol. 2017;49(3):150–9.
21. Cabanilla MG, Villalobos N. A successful daptomycin and micafungin dosing strategy in veno-venous ECMO and continuous renal replacement. J Clin Pharm Ther. 2022;47(2):251–3.
22. Shekar K, Roberts JA, Barnett AG, Diab S, Wallis SC, Fung YL, Fraser JF. Can physicochemical properties of antimicrobials be used to predict their pharmacokinetics during extracorporeal membrane oxygenation? Illustrative data from ovine models. Crit Care. 2015;19:437.
23. Watt KM, Gonzalez D, Benjamin DK Jr, Brouwer KL, Wade KC, Capparelli E, Barrett J, Cohen-Wolkowiez M. Fluconazole population pharmacokinetics and dosing for prevention and treatment of invasive candidiasis in children supported with extracorporeal membrane oxygenation. Antimicrob Agents Chemother. 2015;59(7):3935–43.
24. Dhanani JA, Lipman J, Pincus J, Townsend S, Livermore A, Wallis SC, Abdul-Aziz MH, Roberts JA. Pharmacokinetics of fluconazole and ganciclovir as combination antimicrobial chemotherapy on ECMO: a case report. Int J Antimicrob Agents. 2021;58(5): 106431.
25. Novy E, Abdul-Aziz MH, Cheng V, Burrows F, Buscher H, Corley A, Diehl A, Gilder E, Levkovich BJ, McGuinness S, et al. Population pharmacokinetics of fluconazole in critically ill patients receiving extracorporeal membrane oxygenation and continuous renal replacement therapy: an ASAP ECMO study. Antimicrob Agents Chemother. 2024;68(1):e0120123.

26. Extracorporeal Life Support Organization: Extracorporeal Life Support Organization (ELSO) general guidelines for all ECLS cases. In 2017
27. Shah A, Sampathkumar P, Stevens RW, Bohman JK, Lahr BD, Dhungana P, Vashistha K, O'Horo JC. Reducing broad-spectrum antimicrobial use in extracorporeal membrane oxygenation: reduce AMMO study. Clin Infect Dis. 2021;73(4):e988–96.
28. Sah R, Shah S, Subedi P, Kashyap A, Kc A, Wosti D, Sanghavi D, Bhattacharyya A, Guru P, Chaudhary S. Antibiotic prophylaxis in patients on extracorporeal membrane oxygenation: a systematic review. ASAIO J. 2024;70(8):e103–7.
29. Mehta NM, Halwick DR, Dodson BL, Thompson JE, Arnold JH. Potential drug sequestration during extracorporeal membrane oxygenation: results from an ex vivo experiment. Intensive Care Med. 2007;33(6):1018–24.
30. Raffaeli G, Cavallaro G, Allegaert K, Koch BCP, Mosca F, Tibboel D, Wildschut ED. Sequestration of voriconazole and vancomycin into contemporary extracorporeal membrane oxygenation circuits: An in vitro study. Front Pediatr. 2020;8:468.
31. Ye Q, Yu X, Chen W, Li M, Gu S, Huang L, Zhan Q, Wang C. Impact of extracorporeal membrane oxygenation on voriconazole plasma concentrations: A retrospective study. Front Pharmacol. 2022;13: 972585.
32. Ronda M, Llop-Talaveron JM, Fuset M, Leiva E, Shaw E, Gumucio-Sanguino VD, Diez Y, Colom H, Rigo-Bonnin R, Puig-Asensio M, et al. Voriconazole pharmacokinetics in critically ill patients and extracorporeal membrane oxygenation support: a retrospective comparative case-control study. Antibiotics (Basel). 2023;12(7):1100.
33. Mathieu A, Thiboutot Z, Ferreira V, Benoit P, Lapierre SG, Hetu PO, Halwagi A. Voriconazole sequestration during extracorporeal membrane oxygenation for invasive lung aspergillosis: a case report. ASAIO J. 2022;68(3):e56–8.
34. Peterson EL, Chittick PJ, Richardson CL. Decreasing voriconazole requirement in a patient after extracorporeal membrane oxygenation discontinuation: a case report. Transpl Infect Dis. 2021;23(3): e13545.
35. Vu T, Feih J, Juul J. Fluctuating voriconazole concentrations during extracorporeal membrane oxygenation. J Pharm Pract. 2023;36(4):998–1001.
36. Winiszewski H, Rougny AC, Lagoutte-Renosi J, Millon L, Capellier G, Navellou JC, Piton G, Clairet AL. The pharmacokinetic challenge of treating invasive aspergillosis complicating severe influenzae assisted by extracorporeal membrane oxygenation. Crit Care. 2018;22(1):355.
37. Van Daele R, Bekkers B, Lindfors M, Broman LM, Schauwvlieghe A, Rijnders B, Hunfeld NGM, Juffermans NP, Taccone FS, Coimbra Sousa CA, et al. A large retrospective assessment of voriconazole exposure in patients treated with extracorporeal membrane oxygenation. Microorganisms. 2021;9(7):1543.
38. Van Daele R, Bruggemann RJ, Dreesen E, Depuydt P, Rijnders B, Cotton F, Fage D, Gijsen M, Van Zwam K, Debaveye Y, et al. Pharmacokinetics and target attainment of intravenous posaconazole in critically ill patients during extracorporeal membrane oxygenation. J Antimicrob Chemother. 2021;76(5):1234–41.
39. Kriegl L, Hatzl S, Zurl C, Reisinger AC, Schilcher G, Eller P, Gringschl Y, Muhr T, Meinitzer A, Prattes J, et al. Isavuconazole plasma concentrations in critically ill patients during extracorporeal membrane oxygenation. J Antimicrob Chemother. 2022;77(9):2500–5.
40. Mertens B, Wauters J, Debaveye Y, Van Regenmortel N, Degezelle K, Meersseman P, Hermans G, Vandenbriele C, Van Daele R, Spriet I. The impact of extracorporeal membrane oxygenation on the exposure to isavuconazole: a plea for thorough pharmacokinetic evaluation. Crit Care. 2022;26(1):227.
41. Foulquier JB, Berneau P, Frerou A, Verdier MC, Saint-Marcoux F, Petitcollin A, Tron C, Bellissant E, Lemaitre F. Liposomal amphotericin B pharmacokinetics in a patient treated with extracorporeal membrane oxygenation. Med Mal Infect. 2019;49(1):69–71.
42. Branick K, Taylor MJ, Trump MW, Wall GC. Apparent interference with extracorporeal membrane oxygenation by liposomal amphotericin B in a patient with disseminated blastomycosis receiving continuous renal replacement therapy. Am J Health Syst Pharm. 2019;76(11):810–3.
43. Zhao Y, Seelhammer TG, Barreto EF, Wilson JW. Altered pharmacokinetics and dosing of liposomal amphotericin b and isavuconazole during extracorporeal membrane oxygenation. Pharmacotherapy. 2020;40(1):89–95.
44. Watt KM. Physiologically-based pharmacokinetics in critically ill children. 2016
45. Leven C, Fillatre P, Petitcollin A, Verdier MC, Laurent J, Nesseler N, Launey Y, Tattevin P, Bellissant E, Flecher E, et al. *Ex vivo* model to decipher the impact of extracorporeal membrane oxygenation on beta-lactam degradation kinetics. Ther Drug Monit. 2017;39(2):180–4.
46. Seddon MM, Busey KV, Kutner SB, Mejia RE, Bhattacharyya R. Oxacillin therapeutic drug monitoring in a patient on extracorporeal membrane oxygenation support. J Antimicrob Chemother. 2020;75(9):2699–700.
47. Kim S, Stucky NL, Drummond W, Elbarbry F, Footer BW. Pharmacokinetics of ampicillin during venovenous extracorporeal membrane oxygenation: a case report. Pharmacotherapy. 2023;43(8):864–8.
48. Bougle A, Dujardin O, Lepere V, Ait Hamou N, Vidal C, Lebreton G, Salem JE, El-Helali N, Petijean G, Amour J. PHARMECMO: Therapeutic drug monitoring and adequacy of current dosing regimens of antibiotics in patients on extracorporeal life support. Anaesth Crit Care Pain Med. 2019;38(5):493–7.
49. Cheng V, Abdul-Aziz MH, Burrows F, Buscher H, Cho YJ, Corley A, Diehl A, Gilder E, Jakob SM, Kim HS, et al. Population pharmacokinetics of piperacillin and tazobactam in critically ill patients receiving extracorporeal membrane oxygenation: an ASAP ECMO study. Antimicrob Agents Chemother. 2021;65(11): e0143821.
50. Donadello K, Antonucci E, Cristallini S, Roberts JA, Beumier M, Scolletta S, Jacobs F, Rondelet B, de Backer D, Vincent JL, et al. beta-Lactam pharmacokinetics during extracorporeal membrane oxygenation therapy: a case-control study. Int J Antimicrob Agents. 2015;45(3):278–82.
51. Fillatre P, Lemaitre F, Nesseler N, Schmidt M, Besset S, Launey Y, Maamar A, Daufresne P, Flecher E, Le Tulzo Y, et al. Impact of extracorporeal membrane oxygenation (ECMO) support on piperacillin exposure in septic patients: a case-control study. J Antimicrob Chemother. 2021;76(5):1242–9.
52. Hahn J, Min KL, Kang S, Yang S, Park MS, Wi J, Chang MJ. Population pharmacokinetics and dosing optimization of piperacillin-tazobactam in critically ill patients on extracorporeal membrane oxygenation and the influence of concomitant renal replacement therapy. Microbiol Spectr. 2021;9(3): e0063321.
53. Kim YK, Kim HS, Park S, Kim HI, Lee SH, Lee DH. Population pharmacokinetics of piperacillin/tazobactam in critically ill Korean patients and the effects of extracorporeal membrane oxygenation. J Antimicrob Chemother. 2022;77(5):1353–64.
54. Polain A, Gorham J, Romeo I, Belliato M, Peluso L, Partipilo F, Njimi H, Brasseur A, Jacobs F, Creteur J, et al. Prediction of insufficient beta-lactam concentrations in extracorporeal membranous oxygenation patients. Microorganisms. 2021;9(11):2219.
55. Wildschut ED, Ahsman MJ, Allegaert K, Mathot RA, Tibboel D. Determinants of drug absorption in different ECMO circuits. Intensive Care Med. 2010;36(12):2109–16.
56. Kato T, Enokiya T, Morikawa Y, Okuda M, Imai H. Sequestration of antimicrobial agents in xcoating and heparin-coated extracorporeal membrane oxygenation circuits: An in vitro study. ASAIO J. 2023;69(1):e23–7.
57. Dhanani JA, Lipman J, Pincus J, Townsend S, Livermore A, Wallis SC, Abdul-Aziz MH, Roberts JA. Pharmacokinetics of total and unbound cefazolin during veno-arterial extracorporeal membrane oxygenation: a case report. Chemotherapy. 2019;64(3):115–8.
58. Gijsen M, Annaert P, Shekar K, Roberts JA, Wauters J, Spriet I. Letter to the editor regarding: ceftriaxone exposure in patients undergoing extracorporeal membrane oxygenation. Int J Antimicrob Agents. 2021;57(5): 106326.
59. Cheng V, Abdul-Aziz MH, Burrows F, Buscher H, Cho YJ, Corley A, Gilder E, Kim HS, Lim SY, McGuinness S, et al. Population pharmacokinetics and dosing simulations of ceftriaxone in critically ill patients receiving extracorporeal membrane oxygenation (An ASAP ECMO Study). Clin Pharmacokinet. 2022;61(6):847–56.
60. Ollivier J, Carrie C, d'Houdain N, Djabarouti S, Petit L, Xuereb F, Legeron R, Biais M, Breilh D. Are standard dosing regimens of ceftriaxone adapted for critically ill patients with augmented creatinine clearance? Antimicrob Agents Chemother. 2019;63(3):10–1128.
61. Cies JJ, MooreGiliam WSN, Low T, Enache A, Chopra A. Oxygenator impact on ceftaroline in extracorporeal membrane oxygenation circuits. Pediatr Crit Care Med. 2018;19(11):1077–82.

62. Green DJ, Watt KM, Fish DN, McKnite A, Kelley W, Bensimhon AR. Cefepime extraction by extracorporeal life support circuits. J Extra Corpor Technol. 2022;54(3):212–22.
63. Zheng L, Alshaer MH, Peloquin C, Venugopalan V, Alnuaimat HM, Converse M. Cefepime pharmacokinetics in adult extracorporeal membrane oxygenation patients. Pulm Pharmacol Ther. 2024;84: 102271.
64. Kois AK, Gluck JA, Nicolau DP, Kuti JL. Pharmacokinetics and time above the MIC exposure of cefepime in critically ill patients receiving extracorporeal membrane oxygenation (ECMO). Int J Antimicrob Agents. 2022;60(1): 106603.
65. Curtiaud A, Petit M, Chommeloux J, Pineton Chambrun M, Hekimian G, Schmidt M, Combes A, Luyt CE. Ceftazidime/avibactam serum concentration in patients on ECMO. J Antimicrob Chemother. 2024;79(5):1182–6.
66. Cies JJ, MooreGiliam WSN, Low T, Enache A, Chopra A. Oxygenator impact on ceftolozane and tazobactam in extracorporeal membrane oxygenation circuits. Pediatr Crit Care Med. 2020;21(3):276–82.
67. Arena F, Marchetti L, Henrici Angelis L, Maglioni E, Contorni M, Cassetta MI, Novelli A, Rossolini GM. Ceftolozane-tazobactam pharmacokinetics during extracorporeal membrane oxygenation in a lung transplant recipient. Antimicrob Agents Chemother. 2019;63(3):10–1128.
68. Argudo E, Riera J, Luque S, Los-Arcos I, Lopez-Meseguer M, Sandiumenge A, Nuvials X, Grau S, Ferrer R. Effects of the extracorporeal membrane oxygenation circuit on plasma levels of ceftolozane. Perfusion. 2020;35(3):267–70.
69. Mane C, Delmas C, Porterie J, Jourdan G, Verwaerde P, Marcheix B, Concordet D, Georges B, Ruiz S, Gandia P. Influence of extracorporeal membrane oxygenation on the pharmacokinetics of ceftolozane/tazobactam: an ex vivo and in vivo study. J Transl Med. 2020;18(1):213.
70. Coppens A, Zahr N, Chommeloux J, Bleibtreu A, Hekimian G, Pineton de Chambrun M, LeFevre L, Schmidt M, Robert J, Junot H, et al. Pharmacokinetics/pharmacodynamics of ceftobiprole in patients on extracorporeal membrane oxygenation. Int J Antimicrob Agents. 2023;61(4):106765.
71. Berry AV, Conelius A, Gluck JA, Nicolau DP, Kuti JL. Cefiderocol is not sequestered in an ex vivo extracorporeal membrane oxygenation (ECMO) circuit. Eur J Drug Metab Pharmacokinet. 2023;48(4):437–41.
72. Riera J, Domenech L, Garcia S, Pau A, Sosa M, Domenech J, Palmada C, Torrella P, Sanchez A, Lamora A, et al. Pharmacokinetics of cefiderocol during extracorporeal membrane oxygenation: a case report. Perfusion. 2023;38:40–3.
73. Honeycutt CC, McDaniel CG, McKnite A, Hunt JP, Whelan A, Green DJ, Watt KM. Meropenem extraction by ex vivo extracorporeal life support circuits. J Extra Corpor Technol. 2023;55(4):159–66.
74. Hanberg P, Obrink-Hansen K, Thorsted A, Bue M, Tottrup M, Friberg LE, Hardlei TF, Soballe K, Gjedsted J. Population pharmacokinetics of meropenem in plasma and subcutis from patients on extracorporeal membrane oxygenation treatment. Antimicrob Agents Chemother. 2018;62(5):10–1128.
75. Lee JH, Lee DH, Kim JS, Jung WB, Heo W, Kim YK, Kim SH, No TH, Jo KM, Ko J, et al. Pharmacokinetics and Monte Carlo simulation of meropenem in critically ill adult patients receiving extracorporeal membrane oxygenation. Front Pharmacol. 2021;12: 768912.
76. Lee DH, Kim HS, Park S, Kim HI, Lee SH, Kim YK. Population pharmacokinetics of meropenem in critically ill korean patients and effects of extracorporeal membrane oxygenation. Pharmaceutics. 2021;13(11):1861.
77. Shekar K, Fraser JF, Taccone FS, Welch S, Wallis SC, Mullany DV, Lipman J, Roberts JA, Investigators AES. The combined effects of extracorporeal membrane oxygenation and renal replacement therapy on meropenem pharmacokinetics: a matched cohort study. Crit Care. 2014;18(6):565.
78. Welsch C, Augustin P, Allyn J, Massias L, Montravers P, Allou N. Alveolar and serum concentrations of imipenem in two lung transplant recipients supported with extracorporeal membrane oxygenation. Transpl Infect Dis. 2015;17(1):103–5.
79. Chen W, Zhang D, Lian W, Wang X, Du W, Zhang Z, Guo D, Zhang X, Zhan Q, Li P. Imipenem population pharmacokinetics: Therapeutic drug monitoring data collected in critically ill patients with or without extracorporeal membrane oxygenation. Antimicrob Agents Chemother. 2020;64(6):10–1128.
80. Fratoni AJ, Kois AK, Gluck JA, Nicolau DP, Kuti JL. Imipenem/relebactam pharmacokinetics in critically ill patients supported on extracorporeal membrane oxygenation. J Antimicrob Chemother. 2024;79(5):1118–25.
81. Zhang LC, Li QY, Zhang YQ, Shan TC, Li Y, Li YH, Han H, Qin WD, Guo HP, Zhao W, et al. Population pharmacokinetics of daptomycin in critically ill patients receiving extracorporeal membrane oxygenation. J Antimicrob Chemother. 2024;79(7):1697–705.
82. Mehta T, Vindenes T, Beaulac K, Roberts R. Pharmacokinetics of doxycycline in extracorporeal membrane oxygenation. Open Forum Infect Dis. 2015;2:804.
83. Veinstein A, Debouverie O, Gregoire N, Goudet V, Adier C, Robert R, Couet W. Lack of effect of extracorporeal membrane oxygenation on tigecycline pharmacokinetics. J Antimicrob Chemother. 2012;67(4):1047–8.
84. Cheng V, Abdul-Aziz MH, Burrows F, Buscher H, Cho YJ, Corley A, Diehl A, Gilder E, Jakob SM, Kim HS, et al. Population pharmacokinetics of vancomycin in critically ill adult patients receiving extracorporeal membrane oxygenation (an ASAP ECMO Study). Antimicrob Agents Chemother. 2022;66(1): e0137721.
85. Donadello K, Roberts JA, Cristallini S, Beumier M, Shekar K, Jacobs F, Belhaj A, Vincent JL, de Backer D, Taccone FS. Vancomycin population pharmacokinetics during extracorporeal membrane oxygenation therapy: a matched cohort study. Crit Care. 2014;18(6):632.
86. Ferre A, Giglio A, Zylbersztajn B, Valenzuela R, Van Sint Jan N, Fajardo C, Reccius A, Dreyse J, Hasbun P. Analysis of vancomycin dosage and plasma levels in critically ill adult patients requiring extracorporeal membrane oxygenation (ECMO). J Intensive Care Med. 2024; 8850666241243306.
87. Jung Y, Lee DH, Kim HS. Prospective cohort study of population pharmacokinetics and pharmacodynamic target attainment of vancomycin in adults on extracorporeal membrane oxygenation. Antimicrob Agents Chemother. 2021;65(2):10–1128.
88. Moore JN, Healy JR, Thoma BN, Peahota MM, Ahamadi M, Schmidt L, Cavarocchi NC, Kraft WK. A Population pharmacokinetic model for vancomycin in adult patients receiving extracorporeal membrane oxygenation therapy. CPT Pharmacometrics Syst Pharmacol. 2016;5(9):495–502.
89. Mulla H, Pooboni S. Population pharmacokinetics of vancomycin in patients receiving extracorporeal membrane oxygenation. Br J Clin Pharmacol. 2005;60(3):265–75.
90. Park SJ, Yang JH, Park HJ, In YW, Lee YM, Cho YH, Chung CR, Park CM, Jeon K, Suh GY. Trough concentrations of vancomycin in patients undergoing extracorporeal membrane oxygenation. PLoS ONE. 2015;10(11): e0141016.
91. Wu CC, Shen LJ, Hsu LF, Ko WJ, Wu FL. Pharmacokinetics of vancomycin in adults receiving extracorporeal membrane oxygenation. J Formos Med Assoc. 2016;115(7):560–70.
92. Wi J, Noh H, Min KL, Yang S, Jin BH, Hahn J, Bae SK, Kim J, Park MS, Choi D, et al. Population pharmacokinetics and dose optimization of teicoplanin during venoarterial extracorporeal membrane oxygenation. Antimicrob Agents Chemother. 2017;61(9):10–1128.
93. Chen GJ, Lin SW, Tsai IL, Kuo CH, Wang JT, Hsieh SM. Therapeutic drug monitoring of the teicoplanin trough level after the loading doses in patients receiving venoarterial extracorporeal membrane oxygenation. J Formos Med Assoc. 2020;119(6):1086–92.
94. De Rosa FG, Corcione S, Baietto L, Ariaudo A, Di Perri G, Ranieri VM, D'Avolio A. Pharmacokinetics of linezolid during extracorporeal membrane oxygenation. Int J Antimicrob Agents. 2013;41(6):590–1.
95. Nikolos P, Osorio J, Mohrien K, Rose C. Pharmacokinetics of linezolid for methicillin-resistant Staphylococcus aureus pneumonia in an adult receiving extracorporeal membrane oxygenation. Am J Health Syst Pharm. 2020;77(11):877–81.
96. Cheng V, Abdul-Aziz MH, Burrows F, Buscher H, Corley A, Diehl A, Levkovich BJ, Pellegrino V, Reynolds C, Rudham S, et al. Population pharmacokinetics of ciprofloxacin in critically ill patients receiving extracorporeal membrane oxygenation (an ASAP ECMO study). Anaesth Crit Care Pain Med. 2022;41(3): 101080.
97. Sinnah F, Shekar K, Abdul-Aziz MH, Buscher H, Diab SD, Fisquet S, Fung YL, McDonald CI, Reynolds C, Rudham S, et al. Incremental research approach to describing the pharmacokinetics of ciprofloxacin

during extracorporeal membrane oxygenation. Crit Care Resusc. 2017;19(1):8–14.
98. Turner RB, Rouse S, Elbarbry F, Wanek S, Grover V, Chang E. Azithromycin pharmacokinetics in adults with acute respiratory distress syndrome undergoing treatment with extracorporeal-membrane oxygenation. Ann Pharmacother. 2016;50(1):72–3.
99. Bhatt-Mehta V, Johnson CE, Schumacher RE. Gentamicin pharmacokinetics in term neonates receiving extracorporeal membrane oxygenation. Pharmacotherapy. 1992;12(1):28–32.
100. Cohen P, Collart L, Prober CG, Fischer AF, Blaschke TF. Gentamicin pharmacokinetics in neonates undergoing extracorporal membrane oxygenation. Pediatr Infect Dis J. 1990;9(8):562–6.
101. Dodge WF, Jelliffe RW, Zwischenberger JB, Bellanger RA, Hokanson JA, Snodgrass WR. Population pharmacokinetic models: effect of explicit versus assumed constant serum concentration assay error patterns upon parameter values of gentamicin in infants on and off extracorporeal membrane oxygenation. Ther Drug Monit. 1994;16(6):552–9.
102. Moffett BS, Morris J, Galati M, Munoz FM, Arikan AA. Population pharmacokinetic analysis of gentamicin in pediatric extracorporeal membrane oxygenation. Ther Drug Monit. 2018;40(5):581–8.
103. Munzenberger PJ, Massoud N. Pharmacokinetics of gentamicin in neonatal patients supported with extracorporeal membrane oxygenation. ASAIO Trans. 1991;37(1):16–8.
104. Southgate WM, DiPiro JT, Robertson AF. Pharmacokinetics of gentamicin in neonates on extracorporeal membrane oxygenation. Antimicrob Agents Chemother. 1989;33(6):817–9.
105. Gelisse E, Neuville M, de Montmollin E, Bouadma L, Mourvillier B, Timsit JF, Sonneville R. Extracorporeal membrane oxygenation (ECMO) does not impact on amikacin pharmacokinetics: a case-control study. Intensive Care Med. 2016;42(5):946–8.
106. Ruiz-Ramos J, Gimeno R, Perez F, Ramirez P, Villarreal E, Gordon M, Vicent C, Remedios Marques M, Castellanos-Ortega A. Pharmacokinetics of amikacin in critical care patients on extracorporeal device. ASAIO J. 2018;64(5):686–8.
107. Touchard C, Aubry A, Eloy P, Brechot N, Lebreton G, Franchineau G, Besset S, Hekimian G, Nieszkowska A, Leprince P, et al. Predictors of insufficient peak amikacin concentration in critically ill patients on extracorporeal membrane oxygenation. Crit Care. 2018;22(1):199.
108. de Montmollin E, Bouadma L, Gault N, Mourvillier B, Mariotte E, Chemam S, Massias L, Papy E, Tubach F, Wolff M, et al. Predictors of insufficient amikacin peak concentration in critically ill patients receiving a 25 mg/kg total body weight regimen. Intensive Care Med. 2014;40(7):998–1005.
109. Galvez R, Luengo C, Cornejo R, Kosche J, Romero C, Tobar E, Illanes V, Llanos O, Castro J. Higher than recommended amikacin loading doses achieve pharmacokinetic targets without associated toxicity. Int J Antimicrob Agents. 2011;38(2):146–51.
110. Roger C, Nucci B, Molinari N, Bastide S, Saissi G, Pradel G, Barbar S, Aubert C, Lloret S, Elotmani L, et al. Standard dosing of amikacin and gentamicin in critically ill patients results in variable and subtherapeutic concentrations. Int J Antimicrob Agents. 2015;46(1):21–7.
111. Taccone FS, Laterre PF, Spapen H, Dugernier T, Delattre I, Layeux B, De Backer D, Wittebole X, Wallemacq P, Vincent JL, et al. Revisiting the loading dose of amikacin for patients with severe sepsis and septic shock. Crit Care. 2010;14(2):R53.
112. Nation RL, Velkov T, Li J. Colistin and polymyxin B: peas in a pod, or chalk and cheese? Clin Infect Dis. 2014;59(1):88–94.
113. Suk P, Rychlickova J. Pharmacokinetics of colistin during extracorporeal membrane oxygenation. J Antimicrob Chemother. 2022;77(8):2298–300.
114. Peng D, Zhang F, Lv P, Chen Y, Yang J, Zhu W, Zhu S, Shao H. Plasma concentrations of colistin sulfate in a patient with septic shock on extracorporeal membrane oxygenation and continuous renal replacement therapy: a case report. Ann Transl Med. 2022;10(10):614.
115. Surovoy YA, Burkin MA, Galvidis IA, Bochkov PO, Oganesyan AV, Tsarenko SV. Comparative polymyxin B pharmacokinetics in patients receiving extracorporeal membrane oxygenation. J Antimicrob Chemother. 2022;77(5):1379–84.
116. Ye Q, Wang Q, Chen W, Zhang R, Chen Z, Li P, Zhang X, Zhan Q, Wang C. The population pharmacokinetics and dose optimization of polymyxin B in critically ill patients with or without extracorporeal membrane oxygenation. J Clin Pharm Ther. 2022;47(10):1608–18.
117. Dhanani JA, Lipman J, Pincus J, Townsend S, Livermore A, Wallis SC, Pandey S, Abdul-Aziz MH, Roberts JA. Pharmacokinetics of sulfamethoxazole and trimethoprim during venovenous extracorporeal membrane oxygenation: a case report. Pharmacotherapy. 2020;40(7):713–7.
118. Roussos N, Karageorgopoulos DE, Samonis G, Falagas ME. Clinical significance of the pharmacokinetic and pharmacodynamic characteristics of fosfomycin for the treatment of patients with systemic infections. Int J Antimicrob Agents. 2009;34(6):506–15.
119. Eyler RF, Heung M, Pleva M, Sowinski KM, Park PK, Napolitano LM, Mueller BA. Pharmacokinetics of oseltamivir and oseltamivir carboxylate in critically ill patients receiving continuous venovenous hemodialysis and/or extracorporeal membrane oxygenation. Pharmacotherapy. 2012;32(12):1061–9.
120. Lemaitre F, Luyt CE, Roullet-Renoleau F, Nieszkowska A, Zahr N, Corvol E, Fernandez C, Antignac M, Farinotti R, Combes A. Impact of extracorporeal membrane oxygenation and continuous venovenous hemodiafiltration on the pharmacokinetics of oseltamivir carboxylate in critically ill patients with pandemic (H1N1) influenza. Ther Drug Monit. 2012;34(2):171–5.
121. Mulla H, Peek GJ, Harvey C, Westrope C, Kidy Z, Ramaiah R. Oseltamivir pharmacokinetics in critically ill adults receiving extracorporeal membrane oxygenation support. Anaesth Intensive Care. 2013;41(1):66–73.
122. Cies JJ, Moore WS 2nd, Marino D, Deacon J, Enache A, Chopra A. Oxygenator impact on peramivir in extra-corporeal membrane oxygenation circuits. Perfusion. 2023;38(3):501–6.
123. Humeniuk R, Mathias A, Kirby BJ, Lutz JD, Cao H, Osinusi A, Babusis D, Porter D, Wei X, Ling J, et al. Pharmacokinetic, pharmacodynamic, and drug-interaction profile of remdesivir, a SARS-CoV-2 replication inhibitor. Clin Pharmacokinet. 2021;60(5):569–83.
124. Imburgia CE, Rower JE, Green DJ, McKnite AM, Kelley WE, Reilly CA, Watt KM. Remdesivir and GS-441524 extraction by ex vivo extracorporeal life support circuits. ASAIO J. 2022;68(9):1204–10.
125. Dhanani JA, Shekar K, Parmar D, Lipman J, Bristow D, Wallis SC, Won H, Sumi CD, Abdul-Aziz MH, Roberts JA. COVID-19 drug treatments are prone to sequestration in extracorporeal membrane oxygenation circuits: An *ex vivo* extracorporeal membrane oxygenation study. ASAIO J. 2024;70(6):546–52.
126. Ide S, Saito S, Akazawa T, Furuya T, Masuda J, Nagashima M, Asai Y, Ogawa T, Yamamoto R, Ishioka H, et al. Extracorporeal membrane oxygenation may decrease the plasma concentration of remdesivir in a patient with severe coronavirus disease 2019. IDCases. 2021;26: e01343.
127. Thongprayoon C, Cheungpasitporn W, Lertjitbanjong P, Aeddula NR, Bathini T, Watthanasuntorn K, Srivali N, Mao MA, Kashani K. Incidence and impact of acute kidney injury in patients receiving extracorporeal membrane oxygenation: a meta-analysis. J Clin Med. 2019;8(7):981.
128. Choi G, Gomersall CD, Tian Q, Joynt GM, Freebairn R, Lipman J. Principles of antibacterial dosing in continuous renal replacement therapy. Crit Care Med. 2009;37(7):2268–82.
129. Hoff BM, Maker JH, Dager WE, Heintz BH. Antibiotic dosing for critically ill adult patients receiving intermittent hemodialysis, prolonged intermittent renal replacement therapy, and continuous renal replacement therapy: an update. Ann Pharmacother. 2020;54(1):43–55.
130. Corona A, Cattaneo D, Latronico N. Antibiotic therapy in the critically ill with acute renal failure and renal replacement therapy: a narrative review. Antibiotics (Basel) 2022; 11(12)
131. Jang SM, Infante S, Abdi Pour A. Drug dosing considerations in critically ill patients receiving continuous renal replacement therapy. Pharmacy (Basel). 2020;8(1):18.
132. Li L, Li X, Xia Y, Chu Y, Zhong H, Li J, Liang P, Bu Y, Zhao R, Liao Y, et al. Recommendation of antimicrobial dosing optimization during continuous renal replacement therapy. Front Pharmacol. 2020;11:786.
133. Gatti M, Cojutti PG, Pea F. Impact of attaining aggressive vs. conservative PK/PD target on the clinical efficacy of beta-lactams for the treatment of Gram-negative infections in the critically ill patients: a systematic review and meta-analysis. Crit Care. 2024;28(1):123.
134. Scharf C, Liebchen U, Paal M, Taubert M, Vogeser M, Irlbeck M, Zoller M, Schroeder I. The higher the better? Defining the optimal beta-lactam

target for critically ill patients to reach infection resolution and improve outcome. J Intensive Care. 2020;8(1):86.
135. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, McIntyre L, Ostermann M, Prescott HC, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11):1181–247.
136. Forsberg J, Bedard E, Mahmoud SH. Bioavailability of orally administered drugs in critically ill patients. J Pharm Pract. 2023;36(4):967–79.
137. Marcus JE, Shah A, Peek GJ, MacLaren G. Nosocomial infections in adults receiving extracorporeal membrane oxygenation: a review for infectious diseases clinicians. Clin Infect Dis. 2024;79(2):412–19.

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