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REVIEW ARTICLE

Antifungal Dosing in Critically Ill Patients on Extracorporeal Membrane Oxygenation

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Abstract

Extracorporeal membrane oxygenation (ECMO) is an established advanced life support system, providing temporary cardiac and/or respiratory support in critically ill patients. Fungal infections are associated with increased mortality in patients on ECMO. Antifungal drug dosing for critically ill patients is highly challenging because of altered pharmacokinetics (PK). PK changes during critical illness; in particular, the drug volume of distribution (V_d) and clearance can be exacerbated by ECMO. This article discusses the available literature to inform adequate dosing of antifungals in this patient population. The number of antifungal PK studies in critically ill patients on ECMO is growing; currently available literature consists of case reports and studies with small sample sizes providing inconsistent findings, with scant or no data for some antifungals. Current data are insufficient to provide definitive empirical drug dosing guidance and use of dosing strategies derived from critically patients not on ECMO is reasonable. However, due to high PK variability, therapeutic drug monitoring should be considered where available in critically ill patients receiving ECMO to prevent subtherapeutic or toxic antifungal exposures.

Key Points

Robust guidelines for dosing of antifungal drugs in critically ill adult patients receiving ECMO are lacking.

Most ECMO pharmacokinetic studies are limited in that they do not include a non-ECMO comparator group although pharmacokinetic variability of antifungals is very high relative to other patient groups.

Dosing should be optimised using therapeutic drug monitoring to avoid therapeutic failure as well as drug accumulation and toxicity.

1 Introduction

Extracorporeal membrane oxygenation (ECMO) is an established advanced life support system which allows for prolonged temporary cardiopulmonary support in patients with life-threatening respiratory and/or cardiac failure refractory to maximal medical management [1, 2]. On its own, ECMO is not a disease-modifying intervention but a supportive therapy by providing temporary cardiorespiratory support while underlying pathologies, such as infection, are evaluated and treated. ECMO can also be used to bridge the patient to either organ recovery or lung or heart transplantation or to a long-term ventricular assist device. The two most common modalities of conventional ECMO are venoarterial (VA) or venovenous (VV) ECMO. In both modalities, the blood is drained from the venous system and oxygenated outside the body through an oxygenator. In VV ECMO, the blood is returned to the venous system driven by the patients' own heart function, thereby maintaining pulsatile blood flow, providing respiratory support only, while in VA ECMO the blood is returned to the arterial system, bypassing both the heart and the lungs, hence supporting both respiratory and cardiac function.

ECMO is a highly invasive treatment with a number of associated complications, including infections, bleeding, thrombosis and renal failure [3]. Infection is a significant problem in this patient group and is associated with increased mortality and morbidity, especially in patients with sepsis [4–6]. Critically ill patients with ECMO support are at a higher risk of developing nosocomial infection [7–9], and this increases with prolonged duration of ECMO support [4, 5, 10]. The

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prevalence and incidence of hospital-acquired and bloodstream infections during ECMO ranges from 10–12% in registry data to 9–65% in single-centre studies [3, 4, 6, 7, 10–14]. These commonly are bacterial infections, including those caused by coagulase-negative staphylococci, *Pseudomonas aeruginosa* and Enterobacteriaceae, but also include life-threatening fungal infections caused by *Aspergillus* spp. and *Candida* spp. [15, 16]. Early work from the Extracorporeal Life Support Organisation registry found a higher mortality in neonates on ECMO with fungal as compared with bacterial infections (57.7 versus 30.6%, $p = 0.007$) [17]. Fungal infections, aspergillosis and candidaemia in patients on ECMO have been associated with increased mortality [15, 16, 18, 19].

Critically ill patients can manifest altered pharmacokinetics (PK) such as increased volume of distribution (V_d) and altered clearance (CL) with many drugs [20, 21]. ECMO may also further exacerbate these PK changes; ex vivo experiments have suggested that drugs which are lipophilic and are highly protein bound are likely to be sequestered within the ECMO circuit [22]. Acute kidney injury (AKI) during ECMO is associated with a poor outcome, with approximately 50% of patients requiring concomitant renal replacement therapy (RRT) [23]. In critically ill patients receiving RRT, no dosing adjustment is required for most antifungal agents commonly used to treat invasive fungal infections except for fluconazole, itraconazole and flucytosine [24]. Estimating antifungal PK changes in those patients receiving both ECMO and RRT support can be challenging. It is not simply additive, as the effects may cancel each other and are dependent on the drug's physicochemical properties. It is crucial that critically ill ECMO patients receive the right antifungal dosing regimen; suboptimal dosing strategies can lead to both underdosing and supratherapeutic concentrations causing potential antifungal resistance and adverse drug effects, respectively [20]. Most antifungal drugs are lipophilic and/or highly protein bound, hence raising concerns regarding their ability to reach their target pharmacokinetic/pharmacodynamic (PK/PD) exposure which may in turn affect therapeutic outcomes in patients receiving ECMO.

The aims of this review are to discuss the potential impact of ECMO on the PK of antifungals and to describe how it may influence drug dosing requirements in critically ill adult patients receiving ECMO. Optimised antifungal dosing regimens in this patient population are also suggested based on available literature.

2 Methods

We performed a structured literature review by searching PubMed (1988–July 2022). Search terms included "pharmacokinetics AND/OR dosing", "Extracorporeal Membrane Oxygenation AND/OR ECMO", AND/OR "antifungal" AND/OR "fluconazole" AND/OR "itraconazole" AND/OR "isavuconazole" AND/OR "posaconazole" AND/OR "voriconazole" AND/OR anidulafungin" AND/OR caspofungin" AND/OR micafungin" AND/OR amphotericin". Articles included in vitro and ex vivo studies, clinical PK studies and case reports. Animal studies and studies in languages other than English were excluded. References from searched articles and other research known to authors were also considered if they met the above criteria.

3 Pharmacokinetic Determinants During ECMO

There are several patient factors related to critical illness and ECMO which can affect the PK of drugs, and these include renal or hepatic impairment, and alterations in fluid regulation [20]. The ECMO circuit consists of five main components: large arterial and venous cannulas, gas exchange membrane oxygenator, blood tubing, heat exchanger and a pump. 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, increasing the apparent V_d as a result of drug sequestration onto the ECMO circuit, and altering drug CL due to changes in renal and liver blood flow and altered plasma protein binding [25, 26].

3.1 Increased Apparent V_d

3.1.1 Critical Illness-Related Physiological Changes

Patients with critical illness often have a number of physiological changes, including fluid shifts, altered blood pH, organ dysfunction and systemic inflammatory response syndrome (SIRS). These changes are associated with an apparent increase in the volume of distribution (V_d) of hydrophilic drugs [20]. Secondary to drug sequestration to the circuitry and haemodilution from the priming solution, the inclusion of an ECMO circuit could further increase the apparent V_d in critically ill patients, especially in neonates and young infants [25, 27, 28].

3.1.2 Drug Sequestration

Data suggests that certain drugs have the potential to be sequestered onto the ECMO circuit, likely due to the large surface area of the membrane oxygenator and tubing that drug can be adsorbed on [25, 26, 29]. The extent of drug loss or sequestration is dependent on both the physicochemical properties of the drug and factors related to the circuit itself [26, 29–32]. The degree to which a

drug is sequestered can vary depending on several factors, such as the type of oxygenator [29, 33], tubing [29, 34] and pump used in the ECMO circuit [26], as well as the age of the circuit [35], and the priming solution used [36]. Hence, the same drug may exhibit different levels of sequestration under different conditions. In vitro and ex vivo experiments have shown lipophilic action, and highly protein-bound drugs are significantly sequestered to a greater degree in the circuit [31, 32]. As the binding sites on the circuit become saturated with drugs, the sequestration effect may diminish over time. However, it remains unclear whether the ECMO circuit may function as a drug reservoir, with drugs potentially leaching back into the circulation understood [37].

Importantly, over the years the improvement of ECMO circuits has decreased the complications associated with ECMO use, such as clotting. Also, the increasing use of other therapies that may result in drug sequestration such as concomitant cytokine absorption therapies, e.g., Cytosorb® and/or RRT with ECMO need to be studied to understand any impact on drug PK.

3.1.3 Haemodilution

Hydrophilic drugs with low V_d (e.g. fluconazole) are more affected by haemodilution than lipophilic drugs with a larger apparent V_d (e.g. posaconazole) with the effect being more significant in neonates and infants, as this volume of fluid required to be added to the circuit equates to a greater proportion of their circulating blood volume [38].

3.2 Altered Drug CL

While renal dysfunction is common in critically ill patients on ECMO support, the reasons are multifactorial but likely in part to be secondary to reduced renal perfusion and hypoxia prior to ECMO insertion. A recent meta-analysis showed no significant difference in the risk of developing AKI or severe AKI between those critically ill patients on VV and VA ECMO [23]. Additionally, the SIRS response can decrease the expression and function of drug metabolising enzymes, such as the cytochrome P450 (CYP450) enzymes [39, 40], and in combination with reduced hepatic perfusion and hypoxia, these phenomena can lead to decreased hepatic elimination of drugs.

4 Specific Antifungal Classes

Most of the reviewed data originated from ex vivo experiments, case reports and observational studies. Figure 1 summarises the interplay between antifungal drug, patient and fungi factors and their impact on antifungal PK and dosing in critical illness and ECMO.

4.1 Azoles

Azoles inhibit ergosterol synthesis, which is a major component of fungal cell membrane, affecting fungal cell growth and proliferation. All except fluconazole have antifungal activity against yeasts and moulds, with fluconazole being limited to yeasts. There is variability in PK amongst the azoles (Table 1) which in turn may influence both the choice of drug and dosing in critically ill patients. All are available

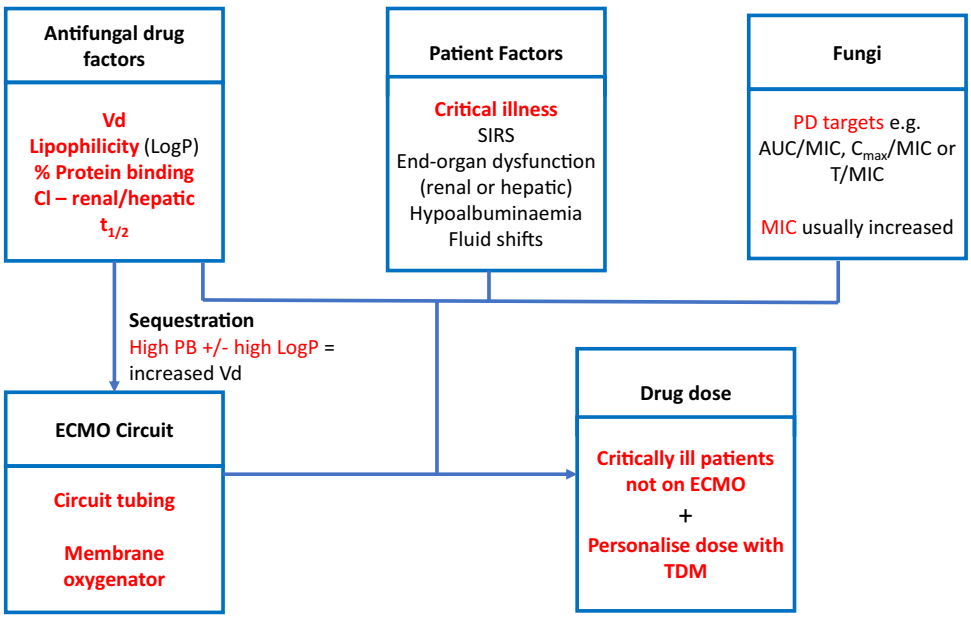

Fig. 1 Pharmacokinetic changes in critically ill patients receiving ECMO and alternative dosing strategies

as oral and intravenous (IV) formulations. Azole agents exhibit both concentration- and time-dependent anti-fungal activity with a prolonged post-antifungal effect (PAFE). As such, the ratio of the area under the concentration–time curve during a 24-h period to minimum inhibitory concentration ($AUC_{0–24}$/MIC) is considered the predictive PK/PD index associated with maximal antifungal activity. Common adverse effects include liver toxicity and QT-prolongation (except with isavuconazole), and they all exhibit to different degrees drug–drug interactions via the cytochrome P450 enzyme system and/or P-glycoprotein transporters. Fluconazole [41, 42], isavuconazole [43, 44], posaconazole [45] and voriconazole [46, 47] PK have been studied in critically ill patients on ECMO support.

4.1.1 Fluconazole

Fluconazole is hydrophilic, has low protein binding with a V_d of 0.7L/kg and high oral bioavailability of > 90% (Table 1). It is mainly excreted unchanged via the kidneys, thereby necessitating dose reduction in patients with renal impairment. However, fluconazole CL is increased in those patients on RRT with subsequent increased dosing recommended [48, 49]. Significant inter-individual variability was seen in a heterogeneous cohort of critically ill patients [50], with mean (± SD) $AUC_{0–24}$ of 359 ± 259 compared with 608 ± 118 reported in healthy volunteers [50], and 33% of patients not achieving the desired PK/PD index for maximal efficacy [51].

4.1.1.1 Ex Vivo In an ex vivo study, Watt et al. studied fluconazole in three closed-loop paediatric circuits isolating the influence of the oxygenator, haemofilter and tubing on circuit sequestration. This study showed that fluconazole was not sequestered into the ECMO circuits; the recovery of fluconazole in the complete circuit was 97.8% at 4 h and 100.2% in the controls. In the circuits which ran up to 24 h, the recovery was high in both the ECMO circuits and controls, 95.2 and 100.6%, respectively, at 24 h [27]. These were similar to the findings in the ex vivo study reported by Shekar et al. using adult circuits, where mean recovery was 91% in the ECMO circuit and 102% in the controls [22].

4.1.1.2 Clinical PK Studies/Case Reports Watt et al. studied the PK of fluconazole in children on ECMO using fluconazole samples from three prospective trials; a total of 40 children were included, of which 21 were on ECMO. The difference in fluconazole concentrations in ECMO compared with those without was related to the increased V_d secondary to blood volume needed to prime the ECMO circuits in addition to the increased V_d due to critical illness [42].

In the Antibiotic, Sedative and Analgesic Pharmacokinetics during ECMO (ASAP ECMO) study, Shekar et al. described the PK of fluconazole, given at 400–800 mg per day dosing, in 10 critically ill patients receiving ECMO, of whom 8 were on concomitant RRT support. Marked variability [coefficient of variation (CV) of ≥ 30%] in fluconazole PK parameters was reported. In this study, patients who received RRT demonstrated lower fluconazole minimum blood plasma concentration (C_{min}; 6.03 versus 20.15 mg/L), $AUC_{0–24}$ (206.70 versus 592.14 mg·h/L) and higher CL (3.46 versus 1.08 L/h) when compared with those not on RRT. Although patients receiving VV ECMO support demonstrated lower $AUC_{0–24}$ (95.45 versus 286.50 mg·h/L) when compared with VA ECMO patients, these observations could have also been influenced by concomitant RRT use, as all VV ECMO patients received continuous RRT during PK sampling. Only one patient did not achieve the PK/PD target in this analysis ($AUC_{0–24}$/MIC ≥ 100 against *C. albicans*) [52].

Dhanani et al. reported the PK of IV fluconazole in an adult patient on VV ECMO. At the administered dose of fluconazole 6 mg/kg daily, the trough concentration and $AUC_{0–24}$ met the PK/PD target for prophylaxis despite the 40% increase in V_d observed compared with critically ill adults not on ECMO [41].

Table 1 Potential PK changes in critically ill patients on ECMO for azole antifungal drug class

Drug	Log*P*	Protein binding (%)	Volume of distribution	Expected ECMO sequestration effect	General dosing guidance
Antifungals					
Fluconazole	0.56	12	0.7 L/kg	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
Posaconazole	5.5	> 98	1774 L	Moderate to significant circuit loss	TDM-guided dosing
Isavuconazole (active moiety)	3.6	> 98	450 L	Moderate to significant circuit loss	TDM-guided dosing

4.1.2 Isavuconazole

Isavuconazole is the newest agent in this class, having extended spectrum of activity with yeast and moulds, including the zygomycetes family. Isavuconazonium sulphate is a water-soluble prodrug which undergoes rapid hydrolysis to the active moiety isavuconazole, which is highly lipophilic [octanol–water partition coefficient (Log*P*) of 3.6], and protein bound (> 98%) with a large V_d of 450 L indicating wide distribution throughout the body (Table 1). It is available in both IV and capsule formulations, having high bioavailability (> 98%). As the prodrug is water soluble, there is no requirement of solubilisation by a cyclodextrin vehicle, in contrast to itraconazole, voriconazole and posaconazole. Also, of note, it is both a substrate and moderate inhibitor of the CYP enzymes and has linear PK, and oral absorption is not influenced by food.

4.1.2.1 Ex-Vivo There are no published ex vivo studies.

4.1.2.2 Clinical PK Studies/Case Reports Isavuconazole concentrations were studied in a mixed cohort of patients with invasive fungal conditions; 33 courses in 32 patients were included, and 11 patients were on renal replacement therapy, of which 4 patients were additionally on extracorporeal treatments (3 on ECMO and 1 Cytosorb® adsorber therapy) [44]. The authors found that isavuconazole concentrations were 3.05 mg/L [interquartile range (IQR) 1.93–4.35] in patients without RRT or ECMO but were significantly lower in those patients with RRT and 0.91 mg/L (IQR 0.9–1.36) and in those with RRT and additional ECMO± Cytosorb®, 0.88 mg/L (IQR 0.71–1.21). However, the sample size was small, and the authors proposed the use of therapeutic drug monitoring (TDM) to guide dosing in this patient population. Subsequently, a prospective observational PK study by Kriegl et al. included seven adult critically ill patients who received isavuconazole—six for prophylaxis while on VV ECMO and one for treatment of invasive aspergillosis while on VA ECMO. Isavuconazole blood concentrations were taken at a number of timepoints from 2 h up to 168 h after the first dose was administered, with additional samples from three patients taken from the inflow and outflow lines to determine whether there were any direct effects from the ECMO. Median isavuconazole concentrations were > 1 mg/L after the first dose and > 2 mg/L at 96 h, suggesting that the higher V_d secondary to critical illness and ECMO may have contributed to the lower early concentrations. The steady-state concentrations pre- and post-membrane oxygenator in addition to plasma concentrations all correlated well; hence, isavuconazole was not altered by the ECMO oxygenator [43].

There are two case reports of isavuconazole PK during ECMO, one in VV ECMO for invasive aspergillosis and the other in conjunction with liposomal amphotericin B in VA ECMO for blastomycosis, which required a two-fold increase in dose to achieve target concentration of 2–4 and > 3 mg/L, respectively [53, 54]. Mertens et al. reported their mixed experience in four VV ECMO patients receiving isavuconazole; two of the patients achieved the target concentration of > 1 mg/L and two did not using standard maintenance dosing regimen of 200 mg daily [55].

4.1.3 Posaconazole

Posaconazole, like isavuconazole, is very lipophilic (Log*P* 5.5) and highly protein bound (> 98%) with a very large V_d of 1774 L (Table 1). It was originally available as a suspension formulation only, although it is now available as delayed-release oral tablets and IV formulations with improved PK. Like voriconazole, the IV formulation contains sulfobutylether-beta-cyclodextrin (SBECD) to facilitate solubilisation of the lipophilic drug. It is excreted unchanged in the faeces; hence, no renal and liver dose adjustments are required. It is not a substrate of the CYP but is of the P-glycoprotein transporter system. It is a potent inhibitor of the CYP3A4 enzymes, and therefore is associated with many drug–drug interactions.

4.1.3.1 Ex-Vivo Lyster et al. conducted an ex vivo study investigating whether three antifungals were prone to circuit sequestration. The authors found that posaconazole exhibited significant sequestration in blood primed ECMO circuit of 63.6% compared with 11.4% ($p < 0.005$) in the controls at 24 h [56].

4.1.3.2 Clinical PK Studies/Case Reports A prospective multicentre study to determine the PK and PK/PD target attainment of six adult patients who were treated with IV posaconazole while on ECMO found all trough concentrations were ≥ 0.7 mg/L and 11 of the 16 were ≥ 1 mg/L. The probability of target attainment analysis supported the observed results of prophylaxis, although less than 90% of simulated patients achieved the lower treatment threshold of 1 mg/L. The authors observed that ECMO did not influence posaconazole PK as much as had been hypothesised [45, 57]. They did find a gradual increase in posaconazole concentrations after multiple administrations, suggesting that it could be due to saturation of the ECMO circuit concluding that an a priori dose adjustment was not needed, but the dose should be guided by TDM.

4.1.4 Voriconazole

Voriconazole is lipophilic, (Log*P* 2.56) and moderately protein bound (58%), with a V_d of 4.6 L/kg (Table 1). It is available in both oral and IV formulations, with high

oral bioavailability (> 90%). It is extensively metabolised in the liver; hence, no dosage adjustments are required in patients with renal dysfunction or receiving RRT [58]. The IV formulation contains SBECD to facilitate solubilisation of voriconazole. Originally its use was considered contraindicated in those patients with a creatinine clearance (CrCL) < 50 mL/min or on RRT, due to concerns of SBECD accumulation and subsequent kidney damage; however, this has shown not to be clinically relevant in both an animal [59] and human studies [60, 61]. It is both a substrate and potent inhibitor of the CYP3A4 enzymes; hence, drug interactions may be challenging. In addition, voriconazole exposure is affected by genetic polymorphism of CYP2C19 and exhibits nonlinear PK and high intra- and interpatient variability, and therefore, there is a clear recommendation for TDM when it is used in critically ill patients [62].

4.1.4.1 Ex-Vivo There have been several ex vivo studies investigating potential voriconazole sequestration in ECMO circuits [33, 36, 56, 63, 64]. Mehta et al. reported a voriconazole loss of 71 versus 14.8% at 24 h using older style neonatal ECMO circuits with silicone and polyvinyl chloride materials involved [36]. Recently, Raffaeli et al. explored the extraction of voriconazole by the Xenios/Novalung ECMO circuits, finding the mean percentage recovery of 20% at 24 h, and Zhang et al. reported average recoveries of 60 and 101% [33]. Cies et al. demonstrated a significant loss of voriconazole in the ECMO circuits with an oxygenator in the circuit and no significant loss without one [63]. While Lyster et al. reported sequestration of 27% in the ECMO model versus 19.2% in controls [56], this is in contrast with previously published studies with results comparable to those reported by Cies et al. in the circuits without an oxygenator. The results suggest that differences may be attributable to differences in materials used for tubing and oxygenators.

4.1.4.2 Clinical PK Studies/Case Reports A large multicentre retrospective study by van Daele et al. assessed voriconazole exposure in 69 patients with ECMO [46]. Of the 337 samples taken, there was no significant difference in subtherapeutic voriconazole concentrations (< 2 mg/L) during (57% of samples) and before/after (39% of samples) ECMO therapy. There was significant inter- and intra-patient PK variability, and no independent effect of the ECMO was observed [46]. However, Ye et al. conducted a large single-centre retrospective observational cohort study of 132 patients, of which 66 were on ECMO support. In this study, ECMO patients demonstrated significantly lower median trough concentrations when compared with non-ECMO patients (1.9 versus 4.4 mg/L, $p < 0.001$). Additionally, the proportion of sub-therapeutic concentrations (< 2 mg/L) was significantly higher in the ECMO group when compared with the non-ECMO group (51.5 versus 7.6%, $p < 0.001$) [47].

In the ASAP ECMO study, Shekar et al. described the PK of voriconazole, 200 mg twice daily, in a single patient on VV ECMO support, where the PK/PD target of $C_{min} \geq 2$ mg/L was not achieved [52]. Reduced voriconazole exposure requiring dosing escalation in ECMO patients has been documented in several case reports [37, 65–69]. Spriet et al. pre-emptively increased the voriconazole dosing in their two patients when commencing ECMO, as they anticipated a loss to the circuit. Trough levels > 10 mg/L were observed 2 days later, suggesting possible saturation of the binding sites on the ECMO circuits [37]. Lin et al. described a case of a patient who received voriconazole and had two PK profiles taken before and after initiation of ECMO; while the trough concentrations were slightly lower while on ECMO, the voriconazole exposure as determined by area under the curve (AUC) were similar on and off ECMO [70]. Peterson et al. reported decreased dosing requirement in a patient following discontinuation of ECMO therapy, suggesting in addition to TDM consideration of empiric dose reduction of 40–50% of voriconazole dose when coming off ECMO [65].

4.2 Echinocandins

Echinocandins exert their antifungal effect by inhibiting the synthesis of the polysaccharide 1,3 beta-D-glucan, causing fungal cell wall degradation and cell lysis. They have broad fungicidal activity against *Candida* spp. and fungistatic activity against most *Aspergillus* spp. While this antifungal class has varying lipophilicity characteristics, they all exhibit very high protein binding (Table 2), which raises concerns of circuit sequestration in patients receiving ECMO. They are available only as IV formulations. Their long half-life facilitates once-daily dosing, and they have very low excretion unchanged by the kidneys. They exhibit concentration-dependent fungicidal activity against *Candida* spp. and have prolonged PAFE, with both C_{max} and AUC_{0-24}/MIC associated with optimum activity.

4.2.1 Anidulafungin

4.2.1.1 Ex-Vivo There are no published ex vivo studies.

4.2.1.2 Clinical PK Studies/Case Reports Aguilar et al. reported the case of a single adult patient on ECMO and Novalung iLA Activve™ treated with anidulafungin at usual maintenance dose of 100 mg daily. All PK parameters were comparable to published data in critically ill patients without extracorporeal support [71] supporting that ECMO had minimal impact on the PK of anidulafungin [72].

Table 2 Potential PK changes in critically ill patients on ECMO for echinocandin antifungal drug class

Drug	Log*P*	Protein binding (%)	Volume of distribution	Expected ECMO sequestration effect	General dosing guidance
Echinocandins					
Anidulafungin	1.87	> 99	30–50 L	Moderate circuit loss V_d: increased	Insufficient adult data Dosing similar to critically ill not on ECMO
Caspofungin	− 2.8	97	NA	Moderate circuit loss V_d: increased	Moderate circuit loss Dosing similar to critically ill not on ECMO
Micafungin	0.4	> 99	0.39 ± 0.11 L/kg	Moderate circuit loss V_d: increased	Contradictory data Dosing similar to critically ill not on ECMO

4.2.2 Caspofungin

4.2.2.1 Ex-Vivo In an ex vivo study, Shekar et al. reported a lower average caspofungin recovery at 24 h in ECMO circuits compared with controls (56 versus 99%, $p = 0.001$) [22]. Another ex vivo study reported a similar loss from blood primed ECMO circuits and controls of 80 and 61%, respectively [56]. However, contrary to these findings, Zhang et al. found no significant sequestration with average drug recovery at 24 h of 80 and 85% in the ECMO circuit and control group, respectively [64].

4.2.2.2 Clinical PK Studies/Case Reports Wang et al. conducted a prospective single-centre study describing the PK of caspofungin in patients with or without ECMO during the postoperative period of lung transplantation [73]. Twelve ECMO and seven non-ECMO patients were enrolled. The PK of ECMO patients were compared with non-ECMO patients on the second dose of caspofungin. All 12 ECMO patients were weaned on the second day after surgery and became self-controls with PK data from the third dose. There were no significant differences in PK parameters between ECMO and non-ECMO groups [73].

In the ASAP ECMO study, Shekar et al. described the PK of caspofungin in nine critically ill patients receiving ECMO, of whom six were on concomitant RRT support. The authors found that caspofungin PK parameters were similar between VA and VV ECMO patients, and between those who received and did not receive RRT. Additionally, like the results with fluconazole, large variations (CV of ≥ 30%) in all PK parameters were observed. The authors reported that PK parameters were generally consistent with previously published data of critically ill patients without ECMO support. Only one patient did not achieve the PK/PD target in this analysis ($AUC_{0–24}$/MIC ≥ 865 against *C. albicans*) [52].

The PK of caspofungin has been described in three earlier case reports with contradictory results [37, 66, 74]. Koch et al. described subtherapeutic caspofungin AUC and increased CL in an 11-month-old receiving VV ECMO for the treatment of *Candida albicans* and *Candida tropicalis* despite receiving a higher dosage of 78 mg/m^2 daily compared with standard dosing of 50–70 mg/m^2 daily [74]. Meanwhile, Spriet et al. reported two adult cases on ECMO, one of whom received caspofungin for the treatment of *Candida albicans* and achieved adequate caspofungin concentrations [37]. However, another adult case reported undetectable caspofungin blood concentrations using standard dosing of 50 mg daily (patient weighed 50 kg) [66].

4.2.3 Micafungin

4.2.3.1 Ex-Vivo In an ex vivo study, Watt et al. separately studied micafungin in three closed-loop paediatric circuits isolating the influence of the oxygenator, haemofilter and tubing on circuit sequestration. This study showed that the loss was dependent on the time (4 and 24 h) as well as the circuit configuration, with 91% micafungin recovery at 4 h when there was no haemofilter compared with 46% with one in-line [27]. However, by 24 h micafungin recovery was 26–43% in all configurations and 57% recovery in the controls. In another ex vivo study, Zhang et al. demonstrated that the recovery of micafungin was higher, at 67% in the Sorin ECMO circuit and 99% in the control at 24 h [64].

4.2.3.2 Clinical PK Studies/Case Reports Micafungin use has been studied in neonates and children. Autmizguine et al. reported a PK study with micafungin in 12 infants, 11 of whom received a prophylactic dose of 4 mg/kg/day and a treatment dose of 8 mg/kg/day. In this infant cohort, the PK model demonstrated a 20–90% higher V_d and a CL in the upper range of historical controls of infants not on ECMO [75]. To match adult exposure proven effective against *Candida* spp., the group recommended dosing of 2.5 mg and 5 mg/kg/day for prophylaxis and treatment, respectively [75].

Lopez-Sanchez et al. reported the PK of micafungin in 12 adult patients on ECMO. The PK values on day 1 and day 4 showed no difference between the samples taken before the membrane and those taken after, including C_{max}, C_{min}, V_d and CL [76]. Additionally, there was no significant difference with the AUC in samples taken before and after membrane, and on days 1 and 4.

In contrast, a post hoc analysis of the Empiricus randomised control trial [77], comparing the PK of first dose micafungin between those patients on ECMO and those without, showed that the AUC of micafungin was reduced by 23% in ICU patients on ECMO, suggesting a dose increase in this patient population [78].

A case report of micafungin described the successful treatment of a *Candida glabrata* fungaemia in an adult critically ill patient receiving VV ECMO and continuous renal replacement using the higher dose of 150 mg every 24 h [79].

4.2.4 Amphotericin

Amphotericin is a polyene antifungal agent with a broad spectrum of activity against yeast and moulds. It binds to ergosterol in the fungal cell membrane leading to disruption of the membrane structure, ultimately causing cell death. The original amphotericin deoxycholate formulation is associated with common nephrotoxicity and infusion-related reactions which led to the development of less toxic formulations such as liposomal amphotericin B (LAmB), allowing for higher dosage. It is only available as an IV formulation for systemic therapy, and no dosing adjustment is required for liver or renal dysfunction. LAmB is a concentration-dependent antifungal where C_{max}/MIC > 40 has been linked to therapeutic effectiveness [80]. LAmB exhibits a nonlinear PK profile over the dosage range 7.5–15 mg/kg/day where the maximum serum concentration and AUC achieved an upper limit at 10 mg/kg/day. The AmBiLoad and AmbiZygo trials evaluated doses of 10 mg/kg/day; they observed no efficacy or mortality benefit but significantly increased incidence of nephrotoxicity [81, 82]. Amphotericin B deoxycholate is slightly lipophilic with a Log*P* 0.8, while lipid formulations such as LAmB are highly lipophilic; hence, there is potential for sequestration within ECMO circuit (Table 3).

4.2.4.1 Ex-Vivo An early in vitro study suggested that, in the first 10–14 h on an ECMO circuit, more than 10% loss in liposomal amphotericin concentration occurs [83].

An ex vivo study found no loss of amphotericin B deoxycholate at 4 or 12 h in the complete ECMO circuit configuration, with recovery of 98.9% (88.7, 109.1) and 99.2% (88.5, 110.1), respectively [84].

4.2.4.2 Clinical PK Studies/Case Reports The use of LAmB in ECMO has been described in a few case reports with contradictory findings. Hertzog et al. reported the use of conventional amphotericin deoxycholate in a 15-year old patient receiving ECMO with acute respiratory distress syndrome secondary to pulmonary blastomycosis. Amphotericin concentrations were measured prior to dose and 1 h post-completion of IV infusion and when there was a circuit change. The authors found no significant changes in the PK of amphotericin secondary to the ECMO circuit, with concentrations remaining within the therapeutic range using standard dosing of 1 mg/kg daily [85].

Subsequent reports have used LAmB which has different properties and PK from conventional amphotericin B, in particular in that it is more lipophilic. Case reports of LAmB for the treatment of invasive aspergillus in patients on ECMO have suggested that the PK was not altered, with concentrations observed in the therapeutic range [66], and that PK parameters were like those in critically ill patients not on ECMO [86]. In contrast, other case reports have demonstrated significant loss of LAmB to the ECMO circuit, necessitating increased dosing to 10 mg/kg daily in one [54] and switching to conventional amphotericin B deoxycholate in another [87], both in the management of blastomycosis in adult patients on ECMO.

5 Therapeutic Drug Monitoring (TDM)

As most drug dosing studies are conducted in healthy volunteers, extrapolating these recommendations to other patient groups such as critically ill patients on ECMO does not take into consideration pathophysiological and PK differences. Another challenge seen is lower pathogen susceptibility in the critical care setting, with higher MICs influencing PK/PD target attainment. TDM was traditionally used to minimise drug adverse effects, e.g., when using anti-infective agents with narrow therapeutic windows, but its use has now expanded to optimise efficacy. Individualised dosing using TDM is a tool which can be used individually or together with dosing software. In a recent conference report and expert panel position paper, antifungal TDM in critically patients has been shown to be of clinical benefit in those where a therapeutic target has been established, such as voriconazole [62]. Although the panel's recommendation

Table 3 Potential PK changes in critically ill patients on ECMO for amphotericin

Drug	Log*P*	Protein binding (%)	Volume of distribution (L/kg)	Expected ECMO sequestration effect	General dosing guidance
Amphotericin	0.8	> 90	0.5–2 LAmB: 0.05–2.2	Deoxycholate—minimal Liposomal amphotericin—moderate	Conflicting data Consider deoxycholate formulation

is to "neither recommend or discourage" for several other antifungal drugs [62], due to significant PK/PD variability in this population, routine TDM would be advantageous, where available, to guide dosing to prevent sub-optimal exposure and to minimise the likelihood of adverse events during ECMO. The need for antifungal dose optimisation using TDM in critically ill patients is well described in a review by Baracaldo-Santamaria et al. [88].

6 Conclusions and Future Directions

There is still a lack of well-established guidelines for dosing antifungal drugs in critically ill adults who are on ECMO. This emphasises the need for a comprehensive approach that includes additional clinical pharmacokinetic studies to identify all the covariates contributing to the variability seen. Most observational studies are limited in that they do not include a non-ECMO comparator group, with comparison based on PK studies in other populations, not on ECMO support. Another limitation in the studies is total concentrations are measured; often unbound drug concentrations are not feasible, as protein binding can change over time in critically ill patients and between individuals, assuming a protein binding may translate into error. The PK studies did not report antifungal drug-related adverse effects; these are scarcely reported in and investigated in critically ill, including ECMO, patients, and should be included in future studies. The challenge of establishing appropriate dosing is exacerbated by the physiological changes that accompany critical illness, including inflammation and hepatic and renal dysfunction (including the use of RRT). It is crucial to understand the complex interactions between these factors.

The physicochemical properties of antifungal drugs can be used to anticipate PK changes: ex vivo studies have shown that drugs with high protein binding (e.g., > 70%) and that are highly lipophilic (e.g., Log $P > 2$) are likely to be sequestered on the circuit; hence, increased loading or maintenance dosing may be required [89]. In contrast, recent comprehensive reviews 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. The ASAP ECMO study, authors have shown that the high PK variability in this patient group (CV ± 30%) may result in patients receiving sub-therapeutic antifungal drug exposures, the clinical consequence of which is uncertain. Therefore, it is acceptable to use dosing approaches that are based on critically ill adult patients who are not receiving ECMO. However, it is important to include the organism variable PD susceptibility and optimise these approaches through TDM to avoid treatment failure, drug accumulation and potential toxicity.

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