International Journal of Pharmacy and Pharmaceutical Sciences

Print ISSN: 2656-0097 | Online ISSN: 0975-1491 Vol 18, Issue 5, 2026

Review Article

DRUG DOSING AND PHARMACOLOGICAL EFFECTS IN ECMO: A COMPREHENSIVE REVIEW

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Received: 30 Jan 2026, Revised and Accepted: 16 Mar 2026

ABSTRACT

Extracorporeal membrane oxygenation (ECMO) serves as a critical life-support modality for patients with severe cardiac or respiratory failure, yet the large surface area of the circuit introduces significant variability in the pharmacokinetics (PK) and pharmacodynamics (PD) of essential medications. This systematic review evaluates clinical evidence from 2015 to 2025 regarding drug dosing alterations in adult ECMO patients, focusing on anticoagulants, antibacterials, antifungals, and antivirals. Our analysis identifies drug sequestration as a primary determinant of therapeutic failure, particularly for highly lipophilic agents like voriconazole and fentanyl, which exhibit circuit losses exceeding 70% within hours of administration. Conversely, hydrophilic antibiotics such as beta-lactams and glycopeptides are primarily impacted by an increased volume of distribution (Vd) and augmented renal clearance, often necessitating loading dose increases of 20–50% or the use of extended infusions to maintain therapeutic levels. Regarding anticoagulation, evidence supports the superiority of anti-Xa (target 0.3–0.7 IU/ml) and viscoelastic assays over activated clotting time (ACT) for minimizing hemorrhagic risks. Current dosing guidelines remain fragmented; thus, clinicians must adopt individualized strategies involving aggressive therapeutic drug monitoring (TDM) and multimodal anticoagulation assessment to ensure efficacy and safety in this high-risk population.

Keywords: Extracorporeal membrane oxygenation (ECMO), Pharmacokinetics, Therapeutic drug monitoring (TDM), Drug sequestration, Antimicrobials

DOI: https://dx.doi.org/10.22159/ijpps.2026v18i5.58333 Journal homepage: https://innovareacademics.in/journals/index.php/ijpps

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a critical life-saving intervention for patients with refractory cardiac or respiratory failure, first successfully applied in 1971 for post-traumatic acute respiratory distress syndrome (ARDS) [1]. Its adoption surged during the 2009 H1N1 pandemic and the COVID-19 crisis, driven by technological advancements and clinical demand [2]. ECMO typically comprises a centrifugal pump, polymethylpentene oxygenator, tubing, and cannulae, enabling temporary cardiorespiratory support [3] (fig. 1).

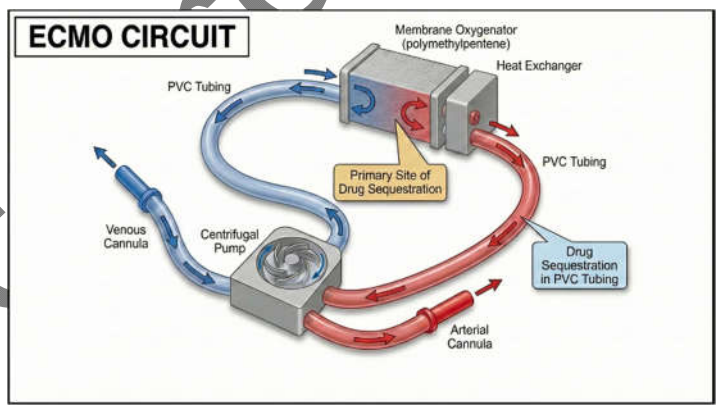

Fig. 1: Schematic of a typical venovenous ECMO circuit. The membrane oxygenator represents the primary site of drug sequestration, while PVC tubing acts as a secondary site. Blue indicates deoxygenated venous blood and red indicates oxygenated arterial blood; arrows show blood flow direction (Source: Created by the authors).

However, the circuit's large surface area and biomaterial interactions profoundly affect drug pharmacokinetics (PK) and pharmacodynamics (PD). This complicates dosing strategies for critical medications, including antibacterials, antifungals, anticoagulants, and antivirals. The Extracorporeal Life Support Organization (ELSO) registry reported supporting over 176, 000 ECMO cases globally by the end of 2022, making a significant milestone of 100, 000 survivors, with a high proportion of cases complicated by subsequent infections [4]. Adult ECMO use has grown, with median annual runs per centre rising from 4 to 15 between 2009 and 2022 [5]. Additionally, the application of ECMO has expanded to include extracorporeal cardiopulmonary resuscitation (ECPR), which demonstrates a significant survival benefit over conventional cardiopulmonary resuscitation (CPR) in select cardiac arrest patients [6]. During the COVID-19 pandemic, ECMO use for severe ARDS increased, with 38% mortality in 1, 035 patients across 213 centres in 2020 [7].

Regional trends highlight disparities: North America, led by the United States, accounts for 60% of global ECMO publications. Europe, particularly France and Germany, contributes significantly to research, while the Asia-Pacific region, notably China and Japan, shows a 216% increase in centers from 2010 to 2021 [8, 9]. Conversely, the South West Asia and Africa (SWAAC) chapter continues to face access limitations due to infrastructure and supply chain disruptions [10].

Drug sequestration refers to the adsorption or absorption of medications onto ECMO circuit components, reducing their bioavailability in plasma [11]. Lipophilic drugs (e. g., voriconazole, linezolid, fentanyl) and highly protein-bound drugs (e. g., posaconazole, ceftriaxone) are particularly prone to sequestration. This is due to their affinity for hydrophobic circuit materials like polyvinyl chloride (PVC) tubing and polymethylpentene oxygenators [8, 9]. Sequestration is caused by the large surface area of the circuit (1–2 m^2), biomaterial interactions, and coating properties (e. g., heparin or albumin) that variably bind drugs [12]. For instance, ex vivo studies show 71% of voriconazole and 66% of fentanyl are lost within hours of circuit exposure [9]. The effects of sequestration include subtherapeutic plasma concentrations, potentially leading to treatment failure, or delayed release from binding sites, risking toxicity [8, 11].

ECMO alters PK through increased volume of distribution (Vd), reduced clearance, and drug sequestration [11]. Ex vivo studies report significant drug loss, with heparin-coated circuits reducing adsorption of hydrophilic drugs (e. g., vancomycin) but not lipophilic ones [12]. Protein binding complicates dosing, as drugs with>98% binding (e. g., posaconazole) are sequestered until saturation, risking subtherapeutic levels early or toxicity later [11]. Renal replacement therapy (RRT), used in ~50% of ECMO patients, enhances clearance of hydrophilic drugs (e. g., meropenem), necessitating dose adjustments [13]. Drug clearance is further altered by ECMO-related organ dysfunction and circuit flow rates (3–5 l/min), which affect drug exposure [14]. For example, oseltamivir clearance is unaffected by ECMO but impaired by renal dysfunction [15].

Therapeutic drug monitoring (TDM) is critical for drugs with narrow therapeutic windows (e. g., vancomycin, voriconazole), yet adoption is limited by assay availability and protocol standardization [5]. Standardized TDM protocols could improve dosing precision but require infrastructure investment. Immune dysregulation in ECMO patients, driven by systemic inflammation, may reduce drug efficacy, particularly for antimicrobials targeting minimum inhibitory concentrations (MIC). Beta-lactam antibiotics (e. g., meropenem) require extended infusions, while lipophilic agents like linezolid face sequestration [8]. Antifungals such as voriconazole exhibit significant circuit loss, necessitating TDM-guided dosing [9]. Anticoagulants, primarily heparin, require viscoelastic monitoring due to circuit-induced coagulopathy [6]. Antivirals like oseltamivir show stable PK but need renal function monitoring [15].

ECMO provides mechanical support but depends on pharmacological therapy to address underlying diseases and complications. Key drug classes such as anticoagulants, primarily heparin with varying doses, are used, though alternatives like argatroban may be employed in specific cases [6]. Antifungals, such as azoles, often require higher doses or therapeutic drug monitoring due to significant adsorption [9]. Antibacterials, including beta-lactams and glycopeptides, are essential, but dosing is complicated by circuit losses and renal replacement therapy [13]. Antivirals, like oseltamivir, follow non-ECMO dosing regimens but need renal function adjustments [15]. Consequently, strict adherence to standard dosing without adjustment often leads to therapeutic failure or delayed toxicity, necessitating the vigilant adverse event monitoring [16]. required to ensure patient safety.

Optimized drug therapy is vital for successful outcomes in ECMO patients, despite complex pharmacokinetic/pharmacodynamic changes. Limited evidence from case series and observational studies, with no specific guidelines, challenges dosing. This review summarizes recent clinical evidence for antibacterials, antifungals, anticoagulants, and antivirals in adult ECMO patients, offering evidence-based recommendations. Heterogeneous data preclude generalized dosing; thus, each drug requires individual evaluation, with summary statements provided. “Standard dosing” denotes antimicrobial doses for normal organ function and weight, tailored to the infection.

Research Gaps: Limited randomized controlled trials and small cohort sizes hinder robust dosing guidelines for ECMO patients. Variability in circuit designs and lack of standardized TDM protocols exacerbate dosing inconsistencies. Regional disparities in ECMO access limit generalizable data, particularly in low-resource settings. Novel circuit materials and real-time PK/PD monitoring systems remain underexplored, necessitating multicentre trials to establish evidence-based dosing strategies.

MATERIALS AND METHODS

This review synthesized evidence on drug therapy challenges in adult ECMO patients, focusing on antibacterials, antifungals, anticoagulants, and antivirals from 2015 to 2025. A systematic literature search was conducted using PubMed and Google Scholar, with terms including “ECMO, ” “pharmacokinetics, ” “pharmacodynamics, ” “antimicrobials, ” “anticoagulants, ” and specific drug names (e. g., “voriconazole, ” “heparin”). Studies were included if they reported PK/PD data, clinical outcomes, or dosing recommendations in adult ECMO patients, encompassing clinical trials, observational studies, case series, and ex vivo experiments. Paediatric studies were excluded due to differences in volume of distribution, as were non-English studies.

Three reviewers independently screened titles and abstracts, with full-text review for eligible studies. Data were extracted on study design, patient characteristics, ECMO type (venovenous or venoarterial), drug class, PK/PD parameters, and dosing recommendations. Discrepancies were resolved through discussion. Consensus on dosing recommendations was reached by reviewing extracted data and discussing clinical applicability, prioritizing studies with TDM data or comparator arms. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to classify evidence quality, ranging from high (randomized trials) to very low (case reports). Limitations, such as small sample sizes and lack of non-ECMO controls, were noted to guide future research.

Literature strength classification

The GRADE framework classifies literature strength for ECMO studies as follows: High quality stems from randomized controlled trials, which are rare in ECMO literature. Moderate quality includes observational studies with non-ECMO controls, such as piperacillin-tazobactam pharmacokinetic studies [8]. Low quality encompasses case series or ex vivo studies, like those on voriconazole adsorption [9]. Very low quality consists of expert opinions or anecdotal reports. Most ECMO pharmacokinetic and pharmacodynamic studies are of low to moderate quality due to small cohorts, heterogeneous circuits, and limited controls, highlighting the need for more robust trials.

Anticoagulants

Antithrombotic management during mechanical circulatory support remains a major clinical challenge [17]. Effective anticoagulation is critical in ECMO to prevent thromboembolic complications. These complications arise when blood contacts artificial circuit surfaces, promoting coagulation activation and platelet dysfunction [18-27, 28]. This prothrombotic environment necessitates a delicate balance between preventing thrombosis and avoiding bleeding, as highlighted by Vajter *et al* [21]. Traditional monitoring tools, such as activated partial thromboplastin time (aPTT) and activated clotting time (ACT), are increasingly supplemented or replaced by more precise methods. These include anti-Xa assays and viscoelastic

assays (VEA) like thromboelastography (TEG) and rotational thromboelastometry (ROTEM), which provide real-time assessments of clot dynamics [18-27] (table 1).

Table 1: Laboratory levels during anticoagulation with UFH for ECMO Anticoagulation VEA: viscoelastic assays, ISTH: international society on thrombosis and hemostasis, ELSO: extracorporeal life support organisation, EACTS: European association for cardiac-thoracic surgery, ISHLT: international society for heart and lung transplantation, SCA: society of cardiovascular anesthesiologists, STS society of thoracic surgeons, AATS: American association of thoracic surgery, ROTEM/TEG: rotational thromboelastometry/thromboelastography, N/A: not available

Parameters	ISTH [18]	ELSO [18, 22]	EACTS/ELSO/ STS/AATS [18]	AATS [18]	ISHLT [18]	SCA [22]
ACT	180–220 s	180–220 s	160–220 s	180–220 s	180–220 s	180–220 s
aPTT (seconds)	50–70	60–90	50–80	N/A	50–70	60–80
Anti-Xa activity	0.3–0.5 IU/ml	0.3–0.7 IU/ml	N/A	0.3–0.7 IU/ml	0.3–0.7 IU/ml	0.3–0.7 IU/ml
aPTT ratio	2–2.5	1.5–2.5	–	–	–	–
VEA (ROTEM/TEG)	N/A	Monitor clot stability	TEG-guided algorithm should be considered	N/A	Concurrent TEG and aPTT may cause excess anticoagulation	N/A
AT III Monitoring	Monitor and supplement if thrombosis	More evidence needed	Monitor to detect heparin resistance	N/A	Monitoring recommended; loading dose 45 IU/kg	N/A

VEAs, including newer systems such as TEG 6+, ROTEM sigma, and Quantra, offer superior insight and are particularly valuable in complex scenarios like heparin resistance or heparin-induced thrombocytopenia (HIT), although inter-device variability warrants careful interpretation [23]. Recent guidelines from the Society of Cardiovascular Anesthesiologists (2021), International Society on Thrombosis and Hemostasis (2023), and the Extracorporeal Life Support Organization (2021) support these advancements. They emphasize individualized anticoagulation strategies to reduce hemorrhagic risks associated with long-term therapy and minimize complications like stroke [22, 29]. While precise monitoring is essential, clinicians must also account for physiological changes. ECMO-induced shear stress impairs platelet aggregation, contributing to a natural anti-aggregation effect. This supports the use of lower-dose anticoagulation in scenarios such as extracorporeal cardiopulmonary resuscitation (ECPR) or post-percutaneous coronary intervention (PCI) [28]. With limited reliability of ACT alone—due to confounding factors like thrombocytopenia—its use alongside anti-Xa or aPTT is advised. Emerging trends favour lower initial doses of unfractionated heparin (UFH), low molecular weight heparin (LMWH), or direct thrombin inhibitors (DTIs). Furthermore, incorporating machine learning and advanced hemostasis monitoring helps personalize and optimize anticoagulation therapy [18-27]. Notably, LMWHs like enoxaparin show lower circuit sequestration compared to UFH, though some loss of activity still occurs, necessitating anti-Xa monitoring [26] (table 2).

Antimicrobials

Antifungal, antibacterials, and antiviral therapy during ECMO is highly complex due to profound alterations in pharmacokinetics and pharmacodynamics stemming from drug sequestration in ECMO circuit components and physiological changes of critical illness. The rising prevalence of antimicrobial resistance further complicates empiric therapy, underscoring the need for precise dosing and stewardship [30]. Detailed recommendations, monitoring parameters, and ECMO-specific considerations for these drugs are summarized in (table 2).

Table 2: ECMO dosing for anticoagulants, antifungals, antibacterials, antivirals

Anticoagulants					
Drugs	**Effect of ECMO**	**Monitor-ing**	**Usual dose**	**ECMO dose**	**References**
Enoxaparin	Lower sequestration than UFH but reduced anti-Xa activity may still occur.	aPTT, anti-Xa	A bolus dose of IV 0.5 mg/kg before ECMO cannulation f/b continuous administration, with anti-Xa target levels of 0.4-0.6 IU/ml.	Initial: IV bolus: 0.5 mg/kg f/b Continuous infusion (anti-Xa 0.4-0.6 IU. ml) SC: Prophylactic: 0.5 mg/kg SC q12h Therapeutic: 1 mg/kg SC q12h Maintenance: Adjust based on anti-Xa levels (goal: 0.6–1.0 IU/ml for BID dosing)	[19-26]
Argatroban	Circuit adsorption, ↓hepatic clearance → ↑levels	Anti-Xa	5-10 ug/kg/hour, with a target aPTT range of 45-60 seconds.	Initial: 0.1–0.2 mcg/kg/min (lower than non-ECMO) Maintenance: Titrate to aPTT goal 1.5–3× baseline (max: 100 seconds)	[20]
UFH (unfractionated heparin)	Adsorption to circuit, ↑Vd, variable responsiveness	aPTT, ACT	10-20 IU/kg/hour or 8000-12, 000 IU/day based on patient weight.	Initial: 10–20 units/kg/hour based on patient weight.	[18, 26, 31]
Antifungals					
Anidulafungin	Low lipophilicity mitigates circuit adsorption despite high protein binding.	No routine TDM	Loading: 200 mg f/b 100 mg Every 24 hourly	200 mg IV loading → 100 mg IV daily (standard dosing)	[32]
Micafungin	Some circuit adsorption; possible ↓ exposure (noted especially in neonates)	Not routinely required	150 mg Every 24 Hourly	Consider increased dose (e. g., 150 mg/day in adults)	[33]
Caspofungin	Circuit loss reported; reduced	Not routinely	Loading: 75 mg f/b 50 mg	Consider higher loading	[34-36]

	levels especially in VV-ECMO	required	Every 24 Hourly	(100 mg) and maintenance (70 mg/day)[34]	
Fluconazole	Low protein binding and hydrophilicity avert circuit sequestration.	Optional TDM in severe infection; trough>12 mg/l	Loading: 800 mg f/b 400 mg Every 24 Hourly	No dose adjustment; use 400–800 mg/day IV	[37, 38]
Itraconazole	High lipophilicity and protein binding → significant ECMO loss	TDM essential; trough>0.5–1 mg/l	Loading: 200 mg Every 12 Hourly for 4 doses; Maintenance: 200 mg Every 24 Hourly	Use IV or oral solution; dose per TDM	[37, 38]
Voriconazole	Lipophilic+protein-bound → significant circuit adsorption and variability	TDM mandatory; trough 1–5.5 mg/l	Loading: 6 mg/kg Every 12 Hourly for 2 doses; Maintenance: 4 mg/kg Every 12 Hourly	6 mg/kg q12 h × 2 → 4 mg/kg q12 h IV; adjust per TDM	[39-45]
Posaconazole	High lipophilicity → circuit sequestration; delayed steady state	TDM essential; trough>1.0–1.25 mg/l	Loading: 300 mg Every 12 Hourly for 2 doses; Maintenance: 300 mg Every 24 Hourly	Use IV or DR tablets; adjust dose with TDM	[46]
Isavuconazole	Lipophilic and protein-bound → likely ECMO loss (limited data)	TDM recommended; target 2–4 mg/l	Loading: 372 mg Every 8 Hourly for 6 doses f/b 372 mg Every 24 Hourly	372 mg IV q8 h × 6 doses → 372 mg IV/day; adjust per TDM	[47-49]
Amphotericin B (liposomal)	Moderate-to-high loss due to lipophilicity and protein binding	No TDM; monitor renal/electrolytes	3-5 mg/kg/day	Use 3–5 mg/kg/day IV; monitor response/toxicity	[49, 50]
Amphotericin B (deoxycholate)	Hydrophilic nature prevents significant binding to hydrophobic circuit components.	No routine TDM	0.5-1.5 mg/kg/day	Use 0.5 mg/kg/day IV	
Antibacterials					
Amikacin	Hydrophilicity prevents circuit adsorption; primarily affected by ↑Vd.	Peak/trough levels (peak 20–30 mg/l; trough<1 mg/l gent)	15 mg/kg/day	Standard extended-interval dosing; TDM essential—check levels and adjust interval	[51]
Amoxicillin clavulanate	Low lipophilicity averts circuit adsorption; primarily affected by ↑Vd.	Renal function; TDM if available	1.2 gm Every 6-8 Hourly	Standard weight-based dosing; use extended infusions when feasible	[52, 53]
Ampicillin	Hydrophilicity prevents circuit adsorption; critical illness-induced ↑Vd reduces peak concentrations.	Renal function; consider β-lactam TDM if available (free concentration)	PO: 250-500 mg q6hr. IV/IM: 1-2 g q4-6hr or 50-250 mg/kg/day divided q4-6hr	Standard weight-based dosing; use extended infusions when feasible	[52, 53]
Azithromycin	Extensive tissue distribution limits free drug availability for circuit adsorption.	Liver function; clinical response	500 mg Every 24 Hourly	Standard dosing (500 mg IV daily); no ECMO adjustment	[51, 54]
Aztreonam	Low lipophilicity avoids circuit extraction; however, ↑Vd necessitates adequate dosing.	Renal function; consider TDM if available	2 gm Every 6-8 Hourly	Use standard dosing; consider extended infusion (e. g., 2 g over 3–4 h) for severe infections	[52, 53]
Cefazolin	Low lipophilicity and low protein binding prevent circuit adsorption; primarily affected by ↑Vd.	Renal function; TDM in unstable patients	1-2 gm Every 6-8 Hourly	Maintain usual dosing as extended infusion; consider higher end of interval if clinical response suboptimal	[55]
Cefepime	Low lipophilicity and low protein binding prevent circuit adsorption; primarily affected by ↑Vd.	Renal function; TDM in unstable patients	1-2 gm Every 8-12 Hourly	Maintain usual dosing as extended infusion; consider higher end of interval if clinical response suboptimal	[53, 56]
Ceftazidime	Moderate protein binding limits circuit adsorption; primarily affected by ↑Vd.	Renal function; TDM in unstable patients	2 gm Every 8 Hourly	Maintain usual dosing as extended infusion; consider higher end of interval if clinical response suboptimal	[57]
Ceftriaxone	Moderate protein binding → variable sequestration potential; ↑Vd	Renal function; TDM in unstable patients	2 gm Loading f/b 1 gm Every 12 hourly or 2 gm Every 24 Hourly. Meningitis: 2 gm Every 12 hourly	Maintain usual dosing as extended infusion; consider higher end of interval if clinical response suboptimal	[53, 56]
Ceftaroline	Moderate protein binding limits circuit adsorption; primarily affected by ↑Vd.	Renal function; TDM in unstable patients	600 mg Every 12 Hourly	Maintain usual dosing as extended infusion; consider higher end of interval if clinical response suboptimal	[58]
Ciprofloxacin	Low protein binding avoids	Renal function	200-400 mg Every 8-12	Standard dosing; no ECMO-	[51, 54]

	circuit sequestration; primarily affected by ↑Vd.		Hourly	specific adjustment	
Cloxacillin	High protein binding/lipophilicity → potential circuit sequestration	Liver and renal function; no routine TDM	1-2 gm Every 6 hourly	May require higher end of usual range; maintain frequent dosing interval	[59, 60]
Colistin	High protein binding/lipophilicity → significant circuit loss	Colistin plasma levels (if available); renal	5 mg/kg stat f/b 3-5 mg/kg Every 12 hourly	Loading dose; consider higher end of dosing and close renal monitoring	[51]
Daptomycin	High protein binding/lipophilicity → significant sequestration	CPK levels; consider trough monitoring	6-10 mg/kg Every 24 Hourly	May require ↑dose (e. g., 8–10 mg/kg q48h); monitor CPK and adjust dosing interval based on clearance and circuit time	[33, 61]
Doxycycline	Lipophilic → potential for circuit adsorption; however, clinical data suggests stability	Clinical response (no routine TDM)	200 mg Every 12-24 Hourly on Day 1 f/b 100 mg Every 12 hourly	Consider unchanged dosing but monitor efficacy	[62]
Ertapenem	Hydrophilicity avoids circuit adsorption; primarily affected by ↑Vd.	Renal function; meropenem TDM if available	1 gm every 24 Hourly	Standard dosing; ensure adequate loading, consider continuous infusion for severe infections	[52, 53]
Flucloxacillin	High protein binding/lipophilicity → potential circuit sequestration	Liver and renal function; no routine TDM	1-2 gm Every 4-6 Hourly	May require higher end of usual range; maintain frequent dosing interval	[59, 60]
Fosfomycin	Hydrophilicity and negligible protein binding prevent circuit adsorption.	Renal function	12-24 gm/day divided to Every 6-8 Hourly.	Standard dosing (4 g q6–8h IV); no ECMO adjustment	[51]
Gentamicin	Hydrophilicity avoids circuit adsorption; primarily affected by ↑Vd.	Peak/trough levels (peak 20–30 mg/l; trough<1 mg/l gent)	Loading: 2 mg/kg f/b 1.7-2 mg/kg Every 8 Hourly	Standard extended-interval dosing; TDM essential—check levels and adjust interval	[51]
Imipenem/cilastatin	Hydrophilicity prevents circuit extraction; primarily affected by ↑Vd.	Renal function; meropenem TDM if available	500 mg Every 6 Hourly or 1 gm Every 8 Hourly	Standard dosing; ensure adequate loading, consider continuous infusion for severe infections	[63]
Levofloxacin	Hydrophilicity and low protein binding prevent circuit adsorption; primarily affected by ↑Vd.	Renal function	500-750 mg Every 24 Hourly	Standard dosing; no ECMO-specific adjustment	[51, 54]
Linezolid	Moderate lipophilicity results in negligible circuit adsorption over time.	Platelet count (thrombocytopenia risk); lactic acid; TDM optional (target>2 mg/l)	600 mg Every 12 hourly	No dose adjustment needed in ECMO; consider TDM in prolonged therapy or non-responders	[54, 64]
Meropenem	Hydrophilicity prevents circuit extraction; primarily affected by ↑Vd.	Renal function; meropenem TDM if available	Loading: 2 gm f/b 1 gm Every 8 Hourly Meningitis: 2 gm Every 8 hourly	Standard dosing; ensure adequate loading, consider continuous infusion for severe infections	[65]
Metronidazole	Hydrophilicity avoids circuit adsorption; primarily affected by ↑Vd.	Liver function	500 mg Every 6-8 Hourly	Standard dosing (500 mg q8h IV); no ECMO adjustment	[39, 51]
Oxacillin	High protein binding/lipophilicity → potential circuit sequestration	Liver and renal function; no routine TDM	2 gm Every 4 Hourly	May require higher end of usual range; maintain frequent dosing interval	[59, 60]
Penicillin G	Moderate protein binding allows partial sequestration, though ↑Vd is the primary kinetic driver.	Renal function; consider β-lactam TDM if available (free concentration)	6-1.3 mIU Every 24 Hourly	Standard dosing via prolonged/continuous infusion; ensure adequate loading dose	[53]
Piperacillin Tazobactam	Hydrophilicity prevents circuit extraction; PK driven by ↑Vd and critical illness-induced augmented renal clearance.	Renal function; consider β-lactam TDM if available (free concentration)	4.5 gm Every 6-8 Hourly	Standard dosing via prolonged/continuous infusion; ensure adequate loading dose	[66-69]
Polymyxin B	High protein binding/lipophilicity → significant circuit loss	Colistin plasma levels (if available); renal	Loading: 2.5 mg/kg stat; Maintenance: 1.5 mg/kg Every 12 Hourly	Loading dose; consider higher end of dosing and close renal monitoring	[51]
Tigecycline	Extensive tissue distribution outcompetes potential circuit adsorption.	Clinical response (no routine TDM)	Loading: 100 mg f/b 50 mg Every 12 Hourly.	Tigecycline standard (100 mg loading → 50 mg q12h); consider unchanged dosing	[70]

				but monitor efficacy	
Teicoplanin	Moderate protein binding → variable circuit loss; ↑Vd	TDM recommended; target trough>10–30 mg/l depending on infection severity	Loading: 400 mg Every 12 Hourly for First three doses f/b 400 mg every 24 Hourly	May need higher loading doses and TDM-guided maintenance to overcome sequestration	[71]
Trimethoprim-Sulfamethoxazole (TMP-SMX)	Moderate protein binding → potential sequestration; ↑Vd	Renal function; serum levels if available	10-15 mg/kg of Trimethoprim Component in 3-4 Divided doses Meningitis/Sepsis/PCP: 15-20 mg/kg/day	Standard dosing (TMP 15–20 mg/kg/day divided q6–8h); monitor renal/heme parameters	[51]
Tobramycin	Hydrophilicity prevents circuit adsorption; primarily affected by ↑Vd.	Peak/trough levels (peak 20–30 mg/l; trough<1 mg/l gent)	Loading: 2 mg/kg stat; Maintenance: 1.7-2 mg/kg Every 8 Hourly	Standard dosing to start, adjust based on TDM (may require ↑ dose or ↑ interval due to ECMO/renal effect)	[51]
Vancomycin	Hydrophilicity avoids circuit adsorption; PK driven by increased Vd and altered clearance.	Trough/MIC-based TDM (15–20 mg/l target)	30-45 mg/kg/day in 2-3 divided doses	Standard weight-based dosing (15–20 mg/kg q8–12h) with TDM; consider continuous infusion to maintain steady levels.	[71-75]
Antivirals					
Nucleoside/Nucleotide Analogues(e. g., acyclovir, ganciclovir, remdesivir)	Acyclovir/Ganciclovir: Hydrophilicity prevents circuit extraction; primarily affected by ↑Vd. Remdesivir: Lipophilic → potential circuit sequestration and ↑Vd.	Renal function (especially for acyclovir/ganciclovir); LFTs for remdesivir	Acyclovir: 5–10 mg/kg q8h, Ganciclovir: 5 mg/kg q12h, Remdesivir: 200 mg loading → 100 mg/day	Use standard dosing initially, but dose adjust in renal impairment; no robust ECMO data, monitor clinical response.	[45, 46]
Protease Inhibitors (e. g., lopinavir/ritonavir)	High lipophilicity and protein binding (>98%) → significant circuit sequestration and loss of drug.	LFTs, drug-drug interactions; TDM if available	Lopinavir/ritonavir: 400/100 mg PO/NG BID	Use standard dose; TDM if available; monitor clinical response closely.	[57, 62, 65]
Neuraminidase Inhibitors (e. g., oseltamivir, zanamivir)	-Oseltamivir: oral → not affected by ECMO circuit, but absorption may vary- Zanamivir (IV): Hydrophilicity averts circuit adsorption.	Renal function	Oseltamivir: 75 mg PO BID, Zanamivir: 600 mg IV BID	Standard dosing appropriate; adjust oseltamivir in renal impairment Consider IV form if enteral absorption is uncertain.	[15]
Monoclonal Antibodies (e. g., bamlanivimab, casirivimab/imdevimab, tocilizumab for COVID-19)	Large molecular size precludes sequestration into oxygenator micropores. Long half-life; not significantly affected.	LFTs, CRP/IL-6 for tocilizumab No routine TDM	Bamlanivimab: 700 mg IV once, Tocilizumab: 8 mg/kg (max 800 mg) IV once	No ECMO-specific dose adjustment needed; monitor clinical/lab response rather than serum drug levels.	[46]

aPTT: activated partial thromboplastin time, Anti-Xa activity: anti-factor Xa activity, AATS: American association for thoracic surgery, ACT: activated clotting time, UFH: unfractionated heparin, SC: subcutaneous, VV: venovenous, IV: intravenous, DR: delayed release, Vd: volume of distribution, TMP-SMX: Trimethoprim-sulfamethoxazole, TDM: therapeutic drug monitoring, MIC: minimum inhibitory concentration, f/b: followed by, LFTs: Liver function test, PO: per oral, NG: nasogastric, BID: twice daily, IV: intravenous, CRP/IL-6:c-reactive protein/interleukin-6.

Antifungals

Lipophilic and highly protein-bound antifungals (e. g., azoles and echinocandins) are especially susceptible to adsorption by circuit components. This leads to an increased volume of distribution (Vd), reduced plasma concentrations, and delayed clearance [12, 76, 77]. Factors such as fluid shifts, hypoalbuminemia, organ dysfunction, and renal replacement therapy (RRT) exacerbate the risk of underexposure [51, 78-80]. Meanwhile, therapeutic drug monitoring (TDM) remains underutilized due to limited access and undefined PK/PD targets. [37, 81]. Echinocandins (e. g., anidulafungin, caspofungin, micafungin) exhibit variable sequestration and inter-patient PK variability, necessitating individualized dosing. [34, 38, 54, 82]. Azoles vary widely—fluconazole is hydrophilic and minimally affected by ECMO, whereas voriconazole and posaconazole are highly lipophilic and protein-bound, often requiring TDM to address circuit-related losses [38-40]. Liposomal amphotericin B may also be sequestered or contribute to circuit issues, though data on deoxycholate formulations are limited [49, 50].

Antibacterials

Beta-lactams (penicillins, cephalosporins, carbapenems) are variably sequestered depending on their physicochemical properties. Additionally, their PK is significantly altered by critical illness and RRT, which necessitates TDM and tailored dosing [37, 39-46, 51, 54, 60, 78-80]. Anti-staphylococcal penicillins like oxacillin may require high-end dosing due to hypoalbuminemia and circuit loss [59, 60]. Daptomycin and tetracyclines generally maintain stable PK with standard dosing sufficient [33, 55, 57, 58, 62, 70, 83]. Glycopeptides (vancomycin, teicoplanin) show increased Vd and altered clearance, requiring TDM and tailored dosing [71]. Conversely, linezolid experiences limited ECMO impact but may still require TDM during severe illness [54, 64]. Fluoroquinolones, azithromycin, and metronidazole are typically unaffected by ECMO. However, illness-

induced Vd increases may still reduce their plasma concentrations [39, 51, 54]. Aminoglycosides and polymyxins are hydrophilic and have minimal interaction with the ECMO circuit. Nevertheless, their PK is heavily influenced by renal clearance, making TDM essential. Sulfamethoxazole-trimethoprim and fosfomycin also appear ECMO-stable but are backed by limited data [51].

Antivirals

Antiviral agents vary in their susceptibility to ECMO. Hydrophilic agents (e. g., acyclovir) have minimal sequestration, whereas lipophilic drugs (e. g., remdesivir) require close monitoring and dose adjustment [45, 46]. Protease inhibitors (e. g., lopinavir/ritonavir) are highly lipophilic and protein-bound. This makes them prone to significant circuit loss and metabolic variability, necessitating TDM [57, 62, 65]. Neuraminidase inhibitors like oseltamivir are generally stable in ECMO circuits due to hydrophilicity, though ECMO-specific data are sparse. Monoclonal antibodies (e. g., sotrovimab, casirivimab/imdevimab) are unlikely to be affected by ECMO due to their large molecular size and long half-lives. They typically do not require dose modification, though timely administration remains essential [46].

DISCUSSION

This review's strength lies in its comprehensive analysis of recent literature, offering clinically relevant guidance for clinicians and pharmacists managing drug therapy in ECMO patients. A semi-quantitative approach, GRADE framework was used to evaluate evidence strength. Future research should address gaps in understanding antimicrobial exposure in ECMO, despite challenges posed by high mortality, inconsistent infection definitions, and diverse ECMO systems. Comparative studies between ECMO and non-ECMO cohorts could clarify a key issue. Specifically, they could determine whether PK alterations stem primarily from the circuit itself or from critical illness physiology. Furthermore, research must investigate the interplay between ECMO and continuous renal replacement therapy (CRRT). The impact of novel circuit designs and expanded access to rapid TDM assays are also urgently needed to optimize efficacy and minimize toxicity.

Managing pharmacotherapy in ECMO patients presents a formidable challenge. It requires navigating the intricate interplay of patient-specific factors, circuit dynamics, and drug-specific PK/PD alterations [12, 76]. The ECMO circuit can sequester drugs, particularly those with high lipophilicity and protein binding. This leads to an increased Vd, reduced clearance, and highly variable plasma concentrations [12, 51, 76]. These effects are compounded by critical illness factors like fluid overload, hypoalbuminemia, and organ dysfunction. Together, these universally disrupt PK/PD profiles across all therapeutic classes [51, 78-80]. Recent guidelines have improved dosing strategies, but significant gaps in clinical data persist. This underscores the need for robust prospective studies that evaluate patient outcomes beyond mere PK/PD parameters [37].

For anticoagulants, achieving optimal dosing is critical to balance thrombotic and bleeding risks. This is especially true since circuit interactions and critical illness severely exacerbate PK variability [46, 50]. Heparin and direct thrombin inhibitors require meticulous monitoring via anti-Xa or viscoelastic assays. This is necessary to navigate circuit-induced drug losses and patient-specific factors like renal dysfunction [51, 79]. Antifungals face similar challenges from circuit sequestration. Lipophilic agents, like voriconazole, demand strict vigilance and TDM to maintain therapeutic levels [37, 39, 77]. Echinocandins often require dose escalation (e. g., anidulafungin 200 mg daily) to overcome circuit losses. Meanwhile, fluconazole's hydrophilic nature allows for standard dosing [48, 52, 55]. Antibacterials exhibit diverse PK profiles during ECMO [12, 51]. Beta-lactams generally require aggressive dose escalation or extended infusions. This counters the increased Vd rather than just sequestration [63, 66]. In contrast, drugs like daptomycin, fluoroquinolones, and polymyxins are minimally affected by the circuits, allowing standard regimens with routine renal adjustments [33, 62, 75]. Agents like metronidazole and fosfomycin lack ECMO-specific data, so clinicians must rely on standard dosing [51, 73].

Antivirals remain underexplored. The lack of robust ECMO-specific data necessitates extrapolating from antibacterial and antifungal principles [12, 37]. Lipophilic antivirals (e. g., remdesivir) may require dose escalation and TDM due to potential sequestration. Conversely, hydrophilic agents and monoclonal antibodies likely maintain standard dosing. Critical illness universally increases Vd and complicates dosing across antiviral classes [61-63, 65]. Therapeutic drug monitoring (TDM) is pivotal across all classes to optimize therapeutic outcomes, particularly for drugs with high circuit sequestration risks (e. g., voriconazole, meropenem, remdesivir) [37, 39, 66]. However, TDM availability is limited, and consensus on optimal PK/PD targets remains elusive, particularly for antifungals and antivirals [37].

Currently, most evidence is derived from ex vivo studies, case reports, and small cohorts. This scarcity highlights a critical need for large-scale prospective trials to establish evidence-based guidelines and evaluate patient-centered outcomes, such as infection resolution and survival. Future research must prioritize standardized PK/PD protocols, circuit-specific drug interaction studies, and the impact of RRT integration [37, 51]. Until such data emerge, clinicians must rely on individualized, physiology-based dosing guided by TDM. This approach is essential to navigate the multifaceted challenges of pharmacotherapy and ensure optimal care in this high-risk setting [12, 37, 51].

CONCLUSION

Anticoagulant and antimicrobial management in ECMO patients is highly complex due to interactions between the patient, circuit, and drug properties. Critical illness alters pharmacokinetics/pharmacodynamics (PK/PD), and ECMO circuits can sequester drugs, especially beta-lactams like meropenem and piperacillin-tazobactam, which require high doses and TDM. Other antibiotics, including daptomycin, tetracyclines, and polymyxins, are less impacted and can follow standard regimens with renal adjustments. Data on drugs like metronidazole and fosfomycin are limited. Antiviral management lacks ECMO-specific studies, but lipophilic agents (e. g., remdesivir) may require dose adjustment and TDM, while hydrophilic antivirals (e. g., oseltamivir) are less affected. TDM, where feasible, is critical across all drug classes, but robust prospective studies are urgently needed to guide evidence-based dosing in this vulnerable population.

AI USE STATEMENT

During the preparation of this work, the authors used Gemini Pro to assist in organizing the initial outline of the review and for language editing. After using this tool, the authors reviewed and edited the content thoroughly and take full responsibility for the accuracy and integrity of the published work.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

Dr. Tushar Jha conceptualized the review, conducted the systematic literature search, synthesized the data, and drafted the original manuscript.

Dr. Dhanraj Shinde provided critical intellectual content, supervised the project, and extensively reviewed and edited the manuscript.

We have read and approved the final version of the manuscript for publication.

CONFLICTS OF INTERESTS

Declared none

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