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Population pharmacokinetics in critically ill neonates and infants undergoing extracorporeal membrane oxygenation: a literature review

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ABSTRACT

Extracorporeal membrane oxygenation (ECMO) increases circulating blood volume, causes capillary leak and temporarily alters kidney function. Consequently, pharmacokinetics (PK) can be affected. When applied to neonates and infants, additional dose adjustments are a major concern, as the volume of distribution (Vd) is already generally greater for water-soluble drugs and the clearance (Cl) of drugs eliminated by glomerular filtration is reduced. A systematic search was performed on MEDLINE (1994–2022) using a combination of the following search terms: "pharmacokinetics", "extracorporeal membrane oxygenation" and "infant, newborn" using Medical Subject Headings search strategy. Nine out of 18 studies on 11 different drugs (vancomycin, meropenem, fluconazole, gentamicin, midazolam, phenobarbital, theophylline, clonidine, morphine, cefotaxime and cefepime) recommended dose increase/decrease by determining PK parameters. In other studies, it has been suggested to adjust the dose intervals. While the elimination half-life ($t_{1/2}$) and Vd mostly increased for all drugs, the Cl of the drugs has been shown to have variability except for midazolam and morphine. There are a limited number of population PK studies in neonates and infants undergoing ECMO circuits. Despite some divergences, the general pattern suggests an increase in Vd and $t_{1/2}$, an increased, stable or decreased Cl, and an increase in variability. Consequently, and if possible, therapeutic drug monitoring and target concentration intervention are strongly recommended to determine appropriate exposure and doses for neonates and infants undergoing ECMO support.

KEY MESSAGES

- ⇒ An increase in volume of distribution of many drugs in extracorporeal membrane oxygenation (ECMO) cohorts is observed.
- ⇒ Variable effects on clearance due to ECMO.
- ⇒ Therapeutic drug monitoring and target concentration intervention are strongly recommended to determine appropriate exposure and doses for neonates and infants undergoing ECMO.
- ⇒ There have been very few studies of the effect of ECMO on population pharmacokinetics data in neonates and infants.
- ⇒ We identified 11 drugs (vancomycin, meropenem, fluconazole, gentamicin, midazolam, phenobarbital, theophylline, clonidine, morphine, cefotaxime and cefepime).

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass procedure used to provide temporary respiratory or cardiac support to critically ill patients, including neonates and infants.[1 2] ECMO has two cannulation techniques: veno-venous (VV) and veno-arterial (VA). VV ECMO is mainly used for patients with respiratory failure, while VA ECMO support is used in patients with cardiac failure.[3 4]

While polypharmacy is well recognised in hospitalised adults, it is also quite common in hospitalised neonates and infants in intensive care units. Because survival and overall outcome rely on medicines, effective drug therapy is essential to improve care and minimise adverse effects.[5 6] This includes targeted dosing and exposure, but necessitates understanding and data on pharmacokinetic (PK) changes related to ECMO use in this specific population of neonates.

Volume of distribution (Vd), which specifies the dosage necessary to generate the desired peak concentration, and clearance (Cl), which is the volume of fluid cleared of drug from the body per unit of time, are the fundamental drivers of drug PK. Vd and Cl are also important drivers of elimination half-life ($t_{1/2}$). The $t_{1/2}$ can be calculated with the following simple formula:

$$t_{1/2} = 0.693 \times Vd/Cl$$

Although an approximate, from a clinical point of view, this formula relates $t_{½}$ to Vd, Cl and steady state, which represent the basic PK parameters.[7]

Understanding the parameters impacting medication PK and pharmacodynamics (PD) in the complicated setting of patient immaturity, severe illness, (multi)organ failure, and the necessity for supportive extracorporeal circuits are crucial for safe and successful prescription in neonates and infants undergoing ECMO.[8] Many medications' PK can be impacted by ECMO since it raises circulating blood volume, causes capillary leak and temporarily affects renal function.

The underlying mechanisms related to the additional (non)-maturational changes in PK during ECMO are diverse, and in part related to the ECMO equipment, the impact of the technique, and the medical condition of the neonates and infants.[9] The ECMO equipment alters drug exposure through adsorption by circuit components. This is to a certain extent drug specific, and is more pronounced for drugs with high lipophilicity.[10] The need for ECMO will result in shift in fluid balance, capillary leak and also in renal impairment. Acute kidney injury is common in ECMO or cardiac bypass cases.[8 11 12] Finally, the medical condition like sepsis or cardiac failure in itself will affect PK.[13] These non-maturational factors add to the maturational PK of many drugs in neonates, different from those in adults.

All of these PK parameters (absorption, distribution, metabolism and elimination (ADME)) exhibit maturation (age or weight-dependent alterations), but they are also influenced by non-maturational variables (disease, treatment, co-medications, environment or genetic background).[13] The Vd in neonates is usually larger for water-soluble drugs. Therefore, the Vd is generally increased, whereas Cl is decreased in neonates undergoing ECMO, especially for drugs cleared by renal route.[10–12] There are some variations in the Vd due to body composition, blood flow, protein binding and membrane permeability.[14] Because renal clearance of metabolites is decreased in preterm and term infants, active metabolites may accumulate.[15]

According to the current literature, we are aware that many pharmacological treatments in neonates and infants undergoing ECMO have not been fully studied and the risk–benefit ratios are not clearly defined. The aim of this literature review is therefore to provide an overview of the effects of ECMO on drug PK parameters in neonates (postnatal age (PNA) 0–28 days) and infants (birth–1 year old), specifically Cl, Vd and $t_{1/2}$ with recommended doses.

METHODS

A systematic literature search was performed on MEDLINE (National Library of Medicine PubMed) of all literature between January 1994 and February 2022 in the PubMed database in September 2022. The search was made using the following keywords: "pharmacokinetics", "extracorporeal membrane oxygenation", "infant, newborn". In MEDLINE, the corresponding Medical Subject Headings (MeSH) search strategy for these search terms as the main heading (descriptor) was used.[16] 'AND' was used to separate the main search terms. Papers meeting the following criteria were accepted for the study:

- Full text written in English.
- Concerned the human species.
- Research articles (clinical study, comparative study, multicentre study, observational study, etc).
- The reporting of a PK parameter for at least one of the ADME process.
- Full text is available.
- The references and citations of the retained papers were checked (backward snowball method).
- If necessary, additional paper added by the authors.

Articles were excluded if the study population did not include neonates/infants, or if only ECMO (for example, concomitant continuous renal replacement therapy (CRRT)) was not applied. Also, case reports, case series, reviews, commentaries and guidelines were excluded, as we only focused on population PK (popPK) studies. Physiologically based PK and therapeutic drug monitoring (TDM) studies were excluded. Full texts for all papers were retrieved through various research databases.

First, the titles of all articles were screened. If the relevance was unsure, the abstract was subsequently read. Finally, the resulting selected articles were thoroughly studied, and the references were screened for secondary inclusion after both authors (NS and NY) reach a consensus. All references and citations of the included articles were verified, and no additional studies were identified to be included. Furthermore, an additional search was performed by the authors using the keywords "pharmacokinetics", "extracorporeal membrane oxygenation" and "paediatrics" from MeSH search terms to identify studies with the paediatric population that included newborn and/or infant patients undergoing ECMO circuit.

Patient and public involvement

This study was done without the participation of patients or parents. Patients or parents were not invited to comment on the trial design, nor were they contacted to define patient-relevant outcomes or interpret the findings. Patients or parents were not asked to help write or revise this text for readability or accuracy.

RESULTS

In this search, a total of 16 papers were retained with the keywords "pharmacokinetics", "extracorporeal membrane oxygenation", "infant, newborn". One article related to morphine metabolite was excluded because it was a follow-up to another article with the same study protocol and population.[17] There are also three additional papers from 135 results added by the authors from children's studies including newborns and/or infants' data. In this manner, the literature review was completed with a total of 18 papers. The articles were published in the MEDLINE database starting in 1994 (one report before 2000, four between 2000 and 2009, seven between 2010 and 2019, and six reports from 2020 onwards), with a variety of nations participating (depending on the

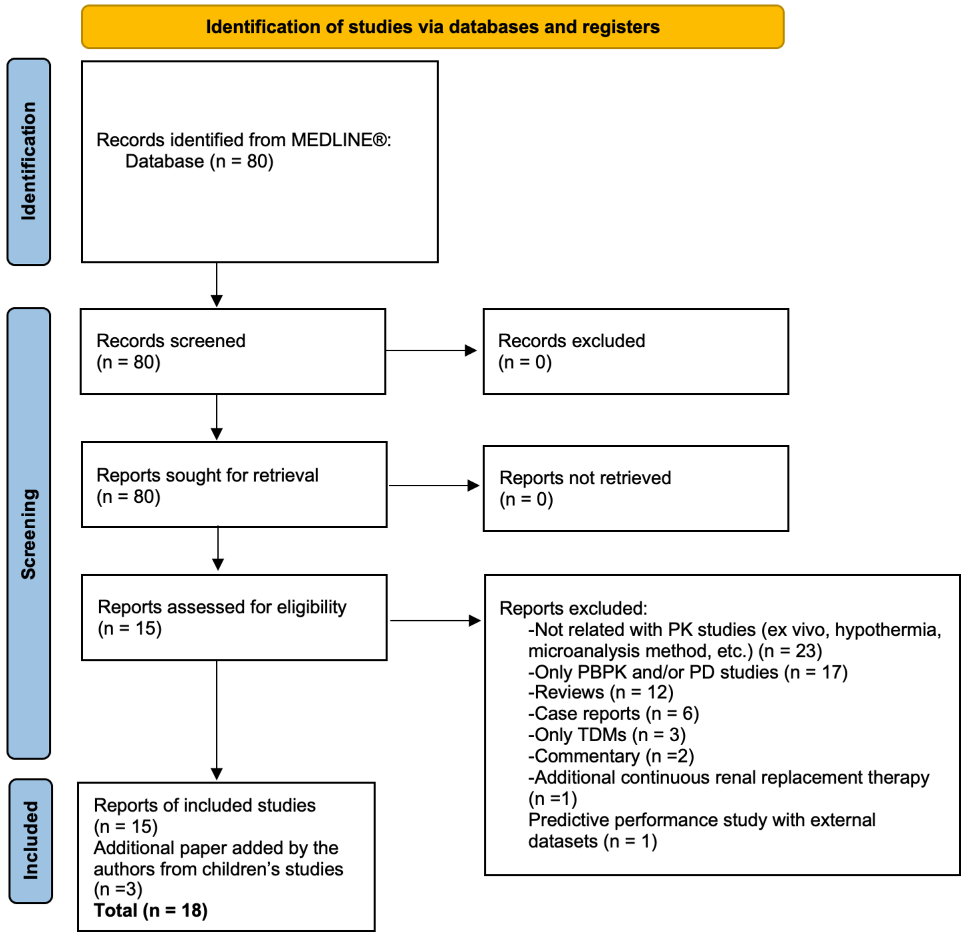

Figure 1 PRISMA flow diagram of data selection and subsequent results. MEDLINE, Medical Literature Analysis and Retrieval System Online; PBPK, physiologically based pharmacokinetic modelling; PD, pharmacodynamics; PK, pharmacokinetics; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TDM, therapeutic drug monitoring.

corresponding author). There were no additional articles found matching the inclusion criteria with the backward snowball method. A flow diagram of data selection, reasons for exclusion and subsequent results is provided in figure 1.

Characteristics of included studies (n=18) are provided in table 1. One of the included studies was both prospective and retrospective. Most of the drugs studied are antibiotics (vancomycin, meropenem, fluconazole and gentamicin), followed by midazolam and phenobarbital. The route of administration was intravenous in all studies. Therefore, enteral absorption was not evaluated. Studies were limited to the mother compounds, except for data on the PK parameters of midazolam and morphine metabolites. Vd and Cl parameters were reported in all studies. The clinical characteristics reflect the population of interest (late preterm, term neonates and infants), with a diversity of pathologies, but without sufficient details to further explore this.

Antimicrobials

Vancomycin

Similar results were observed for vancomycin Cl, while findings on Vd were consistent between the four studies retrieved (table 2). In all of these studies, it was observed that while Cl decreased, Vd increased for the patients undergoing ECMO circuits. In the study of Cies *et al*,[18] the vancomycin Cl increased in the presence of ECMO, so it was suggested to use a higher dose in these patients. The authors attributed this increased Cl to the specific ECMO circuit used. In all of these studies, the target range for vancomycin trough concentration was determined as greater than 10 mg/L,[18] less than 15 mg/L[19 20] or 5–15 mg/L.[21] In addition, in these four articles, the Vd of vancomycin increased in the presence of ECMO, be it not statistically significant in the individual studies.

In the Zylbersztajn *et al* study,[19] the PK/PD target was a ratio of >400 of the area under the curve to the minimum inhibitory concentration (AUC/MIC). Weight was also included as a covariate on both central Vd and Cl, and serum creatinine was also included on Cl for vancomycin. Furthermore, four vancomycin PK profiles met the lower PK/PD target, three of which corresponded to a dose of 15 mg/kg every 6 hours. A total of 63.6% of patients met the therapeutic achievement for sufficient exposure across all dosage intervals.

Moffett *et al*[22] described the PK of vancomycin in paediatric patients undergoing ECMO and provided dosing recommendations. Serum creatinine level and

Table 1 Study characteristics (N=18)

Characteristics	n
Type of study	
Prospective observational	11
Retrospective observational	6
Prospective and retrospective	1
Drug	
Vancomycin	4
Meropenem	2
Fluconazole	1
Gentamicin	2
Cefepime	2
Midazolam	2
Phenobarbital	2
Theophylline	1
Clonidine	1
Morphine	1
Cefotaxime	1
ECMO modality	
Veno-venous	–
Veno-arterial	2
Mixed	16
Pharmacokinetic parameters	
Absorption	–
Distribution	16
Metabolic clearance	2
Renal clearance	17

ECMO, extracorporeal membrane oxygenation.

postmenstrual age were significant factors for Cl, patient age for central Vd and albumin for peripheral Vd in this investigation. Furthermore, the simulation indicated a dosage of 25–30 mg/kg/dose every 12–24 hours as having the largest percentage of individuals with an AUC for 24 hours larger than 400 and trough values less than 15 mg/L. Serum vancomycin concentration monitoring is recommended in paediatric patients undergoing ECMO circuits.

Meropenem

Two studies looked at meropenem (table 3). Because of the low meropenem adsorption in the ECMO circuit and the high dialysate rate in CRRT, the effects of ECMO and CRRT vary. This is mostly due to meropenem's chemical characteristics. According to Wang *et al*'s study[23] about a popPK model of meropenem in children with sepsis receiving extracorporeal life support, the PK characteristics of meropenem were not affected by ECMO intervention. Furthermore, ECMO and CRRT can raise Vd due to the extracorporeal circuits, although this study indicated that the impact on meropenem concentration was smaller than previously documented haemofilters. In summary, there were no significant changes in PK parameters observed in children with sepsis who were receiving ECMO. However, this study harbours some conspicuous limitations due to limited data and sample size. For this reason, we need more data on meropenem for children with sepsis undergoing ECMO circuit.

Zylbersztajn *et al*[19] described primary PK/PD parameters of meropenem and vancomycin in paediatric patients undergoing ECMO. For meropenem, weight was added as a covariate on volume of the central compartment. To conclude, the authors suggested that maximal meropenem dose using a prolonged infusion and at least current vancomycin dosing with TDM are required to achieve adequate PK/PD targets in this patient population (table 3).

Fluconazole

The ECMO circuits can alter drug PK; therefore, standard fluconazole dosing may result in suboptimal drug exposures and efficacy. According to Watt *et al*'s study,[24] the fluconazole Vd was increased in neonates and infants supported by ECMO. Although the fluconazole Cl was not changed in neonates, it was increased in infants undergoing ECMO. As a result, children on ECMO who develop invasive candidiasis require a fluconazole loading dose of 35 mg/kg, followed by a daily maintenance dose of 12 mg/kg to achieve exposures comparable with those obtained in children who are not on ECMO and are loaded with 25 mg/kg and maintained on 12 mg/kg daily. However, children above the age of 2 years are under-represented in this study, and the findings should be generalised with caution to this demographic. As a result, confirmatory prospective clinical studies evaluating fluconazole exposure, safety and effectiveness in this group are required (table 4).

Gentamicin

Two articles examining the popPK of gentamicin in the presence of ECMO were reviewed. Dodge *et al*[25] show that while undergoing ECMO, neonates have a higher Vd for gentamicin, a lower Cl and a much longer $t_{1/2}$. Based on these findings, the required peak and trough plasma gentamicin concentrations for neonates receiving ECMO circuits (5–8 and 2 g/mL, respectively) were achieved. They recommended a loading dose of gentamicin (4.3 mg/kg) and a maintenance dose (3.7 mg/kg every 18–24 hours) followed by monitoring of serum concentrations and appropriate dose adjustments thereafter. Moffett *et al*[22] found that children had elevated trough concentrations when gentamicin dosed according to standard dosing procedures. Therefore, fat-free mass should be used to dose gentamicin in patients undergoing ECMO circuit. Serum creatinine is also a marker of gentamicin Cl and should be used to change gentamicin dose in paediatric patients (table 5). In all of these studies, the target range for gentamicin peak concentration was determined as approximately 6 mg/L.

Table 2 Characteristics of the studies, PK and dose recommendations related to vancomycin

Study	n	PNA	Weight	Type	Group	Model	Modality	Administered dose	Vd	CL	$t_{1/2}$ (hours)	Recommended dose
Mulla and Pooboni,[21] UK*	15	8.2	3.5	P and R	Children	2-compartment with WinNonMix	VV–VA	10–15 mg/kg every 6–24 hours	0.45±0.1 L/kg ↑	0.04±0.02 L/kg/hour ↓	10.40±6.67	—
Cies *et al*,[18] USA†‡	12	9.5	3.1	R	Neonates	1-compartment with Pmetrics	VV–VA	10–15 mg/kg every 8–24 hours	1.2±0.4 L/kg ↑	0.21±0.08 L/kg/hour ↑	14.1±6.9	—
Zylbersztajn *et al*,[19] Chile§‡		24 (2–132) months	10 (3.5–37)	P	Children	2-compartment with Pmetrics	VV–VA	10–15 mg/kg every 6–12 hours	0.42±0.28 L/kg ↑	0.06±0.05 L/kg/hour ↔	—	Across each dosing interval, 63.6% of patients achieved the PK/PD targets for adequate exposure.
Moffett *et al*,[20] USA§‡	N: 28 I: 28	0.64 (0.07–6.7) years	7.6 (3.7–21.9)	R	Children	2-compartment with NONMEM	VV–VA	25 mg/kg every 18 hours for neonates 30 mg/kg every 12 hours for infants	$Vd_{central}$: 0.36 L/kg $Vd_{peripheral}$: 0.46 L/kg ↑	0.06 L/kg/hour ↔	—	25–30 mg/kg/dose every 12–24 hours with serum concentration monitoring is a reasonable empirical dosing strategy to obtain an area under the curve for 24 hours greater than 400.

Boldfaced fonts represent comparisons with controls within the same study. In other studies, they represent comparisons with non-ECMO neonates from a different published study.
*The reference range for serum vancomycin concentrations was trough 5–15 mg/L.
†The reference range for serum vancomycin concentrations was trough >10 mg/L.
‡De Hoog *et al*'s neonatal PK data were used to compare Vd (0.57–0.69 L/kg) and Cl (0.04–0.09 L/kg/hour).[48]
§The reference range for serum vancomycin concentrations was trough <15 mg/L.
CL, clearance; ECMO, extracorporeal membrane oxygenation; I, infants; N, neonates; NONMEM, non-linear mixed-effects modelling; P, prospective; PD, pharmacodynamics; PK, pharmacokinetics; PNA, postnatal age; R, retrospective; $t_{1/2}$, elimination half-life; VA, veno-arterial; Vd, volume of distribution; VV, veno-venous.

Table 3 Characteristics of the studies, PK and dose recommendations related to meropenem

Study	n	PNA	Weight	Type	Group	Model	Modality	Administered dose	Vd	CL	$t_{1/2}$ (hours)	Recommended dose
Wang *et al*,[23] China	9*	2.00 (0.71–3.88) years	11.50 (9.50–36.30)	P	Children	2-compartment with first-order elimination with NONMEM	VV–VA	20–40 mg/kg every 8 hours	—	11.59 (5.92–20.19) vs 13.51 (3.71–20.80) L/hour **↓14.2% (compared with controls)** 11.59 (5.92–20.19) vs 7.9±5.9 L/hour ↑46.7% (compared with adults)	—	The authors recommended the optimised dosing regimens for children with sepsis receiving ECMO depending on the PTA of PK target 50% t>MIC and 100% t>MIC, for children with sepsis during ECMO with different body weight, estimated CI and MIC of bacteria.
Zylbersztajn *et al*,[19] Chile	9	48 (2–165) months	16 (3.5–45)	P	Children	2-compartment with Pmetrics	VV–VA	20–40 mg/kg every 8–12 hours	0.289±0.295 L/kg —	0.139±0.102 L/hour/kg —	—	Across each dosing interval, 91% of patients achieved the PK/PD targets for adequate exposure for meropenem. Higher dosing with extended infusion was needed in the meropenem administration.

Boldfaced fonts represent comparisons with controls within the same study. In other studies, they represent comparisons with non-ECMO neonates from a different published study.
*Number of patients undergoing only ECMO circuit.
CI, continuous infusion; CL, clearance; ECMO, extracorporeal membrane oxygenation; MIC, minimum inhibitor concentration; NONMEM, non-linear mixed-effects modelling; P, prospective; PD, pharmacodynamics; PK, pharmacokinetics; PNA, postnatal age; PTA, probability of target attainment; $t_{1/2}$, elimination half-life; VA, veno-arterial; Vd, volume of distribution; VV, veno-venous.

Table 4 Characteristics of the studies, pharmacokinetics and dose recommendations of isolated studies on fluconazole

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered dose	Vd	CL	$t_{1/2}$ (hours)	Recommended dose
Watt *et al*,[24] USA	40	22	3.4	P 2 groups	Infants	1-compartment with NONMEM	VV	25 mg/kg loading dose followed by 12 mg/kg/day maintenance therapy	For neonates (ECMO vs non-ECMO): 1.5 (1.3–1.8) vs 0.96 (0.55– 1.4) L/kg **↑56.2%** For infants (ECMO vs non-ECMO): 1.2 (0.91– 1.6) vs 0.83 (0.72–1.0) L/kg **↑44.6%**	For neonates (ECMO vs non-ECMO): 0.018 (0.013– 0.043) vs 0.018 (0.008– 0.042) L/hour/kg ↔ For infants (ECMO vs non-ECMO): 0.022 (0.011– 0.039) 0.017 (0.008–0.029) L/hour/kg **↑29.4%**	—	12 mg/kg for prophylaxis 35 mg/kg for invasive candidiasis treatment

Boldfaced fonts represent comparisons with controls within the same study. In other studies, they represent comparisons with non-ECMO neonates from a different published study.
CL, clearance; ECMO, extracorporeal membrane oxygenation; NONMEM, non-linear mixed-effects modelling; P, prospective; PNA, postnatal age; $t_{1/2}$, elimination half-life; Vd, volume of distribution; VV, veno-venous.

Table 5 Characteristics of the studies, pharmacokinetics and dose recommendations related to gentamicin

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered dose	Vd	CL	$t_{1/2}$ (hours)	Recommended dose
Dodge *et al*,[25] USA	11	37–42 PMA	2.67–5.10	P 1 group	Neonates and infants	1-compartment with NPEM	VV–VA	2.5 mg/kg loading dose and every 8–12 hours maintenance dose	From 0.748 L/kg to 0.471 L/kg after ECMO was discontinued ↑**58.8%**	From 0.239 L/hour to 0.350 L/hour after ECMO was discontinued ↓**31.7%**	From 9.24 hours to 3.87 hours after ECMO was discontinued ↑**138.7%**	4.3 mg/kg loading dose 3.7 mg/kg every 18–24 hours of maintenance dose.
Moffett *et al*,[22] USA	N: 28 I: 5	0.17 (0.12–0.82) months	3.1 (2.4–3.8)	R 1 group	Mostly neonates and infants	2-compartment with NONMEM	VV–VA	1.8 mg/kg/dose	0.60 L/kg –	0.03 L/kg/hour –	–	Children with elevated serum creatinine values should have extended dosing intervals (4–5 mg/kg/day).

Boldfaced fonts represent comparisons with controls within the same study. In other studies, they represent comparisons with non-ECMO neonates from a different published study.
CL, clearance; ECMO, extracorporeal membrane oxygenation; I, infants; N, neonates; NONMEM, non-linear mixed-effects modelling; NPEM, non-parametric expectation and maximisation; P, prospective; PMA, postmenstrual age; PNA, postnatal age; R, retrospective; $t_{1/2}$, elimination half-life; VA, veno-arterial; Vd, volume of distribution; VV, veno-venous.

Cefotaxime

Cefotaxime can be excreted unchanged or after hepatic conversion into its active metabolite via the renal system in adults. There may be an inverse correlation between renal function and $t_{1/2}$, notably for desacetylcefotaxime as an active metabolite. According to Ahsman *et al*'s study,[26] the standard cefotaxime dosing regimen produces a high enough t>MIC. The Vd was greater in ECMO patients than in non-ECMO patients (1.82 vs 0.68–1.14 L), while cefotaxime Cl levels were similar. To effectively treat neonates undergoing ECMO, a dosage regimen of 50 mg/kg every 12 hours (PNA 1 week), 50 mg/kg every 8 hours (PNA 1–4 weeks) or 37.5 mg/kg every 6 hours (PNA >4 weeks) can be used (table 6).

Cefepime

According to the current literature, the increase in peripheral Vd caused by blood transfusion is explained by the volume received more than by the kind of fluids obtained. Also, cefepime is a hydrophilic drug with minimal protein binding, and fluid administration may improve its Vd. In Thibault *et al*'s study,[27] in paediatric patients undergoing ECMO, renal function was a key driver of cefepime Cl. Based on simulations, dosing regimens of 50 mg/kg given every 8 hours resulted in optimum serum concentrations at an MIC of 8 mg/L. Indeed, with lower MICs and greater serum creatinine levels, longer dose intervals were adequate (table 7).

According to Zuppa *et al*'s study,[28] cefepime Cl was reduced compared with previously reported data in children not receiving ECMO.[29] Furthermore, the Vd of cefepime with the use of ECMO can increase about 2.5-fold compared with the volume without the use of ECMO; as a result, the total quantity of cefepime accessible for clearance is reduced. At the end of the study, it was concluded that only 74% of doses revealed an fT>MIC of 16 mg/L for more than 70% of the dosing interval. As a result, cefepime TDM should be evaluated in the clinical setting to improve the ability to achieve therapeutic targets while limiting possible toxicity.

Midazolam

Two articles reported on midazolam PK in patients undergoing ECMO. Mulla *et al*[30] reported that both the Vd and $t_{1/2}$ of midazolam increased. Cl was 1.4 (SD 0.15) mL/kg/min, so simulations with conventional doses resulted in excess levels. Altered PK may reflect sequestration of midazolam by components of the ECMO circuit. On the other hand, Ahsman *et al*[31] reported an increased Vd and $t_{1/2}$, as well as a threefold increase in midazolam and 1-Hydroxymidazolam Cl in the first 5 days following ECMO initiation. Interestingly, concomitant inotropic infusion during ECMO increased 1-Hydroxymidazolam glucuronide Cl by 23%. They also determined the 1-Hydroxymidazolam/midazolam metabolic ratio (MR), a surrogate measure of cytochrome P450(CYP)3A activity, as being higher than previous reports in (pre)

Table 6 Characteristics of the studies, pharmacokinetics and dose recommendations of isolated studies on cefotaxime

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered dose	Vd	CL	$t_{1/2}$ (hours)	Recommended dose
Ahsman *et al*,[26] the Netherlands	37	3.3 (0.67–199)	3.5 (2.0–6.2)	P 1 group	Neonates	1-compartment with NONMEM	VV–VA	50 mg/kg every 12 hours (PNA <1 week) 50 mg/kg every 8 hours (1<PNA<4 weeks) 37.5 mg/kg every 6 hours (PNA >4 weeks)	ECMO vs non-ECMO: 1.82 L vs 0.68–1.14 L ↑**59.6%–167.6%**	ECMO vs non-ECMO: 0.36 L/hour vs 0.20–0.55 L/hour ↔	3.5 hours	The standard cefotaxime dose regimen provides a sufficiently high t>MIC in infants undergoing ECMO.

Boldfaced fonts represent comparisons with controls within the same study. In other studies, they represent comparisons with non-ECMO neonates from a different published study.
CL, clearance; ECMO, extracorporeal membrane oxygenation; MIC, minimum inhibitor concentration; NONMEM, non-linear mixed-effects modelling; P, prospective; PNA, postnatal age; $t_{1/2}$, elimination half-life; VA, veno-arterial; Vd, volume of distribution; VV, veno-venous.

Table 7 Characteristics of the studies, pharmacokinetics and dose recommendations of isolated studies on cefepime

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered dose	Vd	CL	$t_{1/2}$ (hours)	Recommended dose
Thibault *et al*,[27] USA	9/17	0.5 (0.2–2.5) months	4.4 (3.5–4.6)	P 1 group	Children	2-compartment with NONMEM	VV–VA	50 mg/kg every 6–24 hours or 100–150 mg/kg/day continuous infusion	$Vd_{central}+Vd_{peripheral}$=0.6 L/kg	410 mL/hour/4.5 kg	–	Dosing regimens of 50 mg/kg every 8 hours reached optimal concentrations at an MIC of 8 mg/L based on simulations.
Zuppa *et al*,[28] USA	17	1.3–22 months	3.3–10	P 1 group	Infants	2-compartment with NONMEM	VV–VA	50 mg/kg every 8–24 hours	$Vd_{central}+Vd_{peripheral}$=0.4 L/kg ↑**250%**	7.1 mL/min/5.8 kg ↓**26.6%**	–	For free cefepime, only 14 of the 19 doses (74%) demonstrated an fT>MIC of 16 mg/L, an appropriate target for the treatment of pseudomonal infections, for greater than 70% of the dosing interval.

Boldfaced fonts represent comparisons with controls within the same study. In other studies, they represent comparisons with non-ECMO neonates from a different published study.
CL, clearance; ECMO, extracorporeal membrane oxygenation; MIC, minimum inhibitor concentration; NONMEM, non-linear mixed-effects modelling; P, prospective; PNA, postnatal age; $t_{1/2}$, elimination half-life; VA, veno-arterial; Vd, volume of distribution; VV, veno-venous.

term neonates and attribute the reduced renal elimination Cl of the metabolite (table 8).

Mulla *et al*[30] have analysed the PK of midazolam in neonates undergoing ECMO. Their midazolam model reveals a significantly altered Vd in ECMO patients, with a significant prolongation of the $t_{1/2}$ (from 6.8 to 33.3 hours). Mulla *et al*[30] did not report a correlation between Cl and duration of infusion or PNA. They also determined the MR, a surrogate measure of CYP3A activity, as being higher than previous reports in (pre) term neonates and attribute this to a reduced renal elimination Cl of the metabolite. Similarly, in the study of Ahsman *et al*,[31] it was shown that the Vd increased. But unlike Mulla *et al*,[30] they stated that Cl increased threefold within the first 5 days. It is estimated that this is due to the difference in the ECMO circuit construction (oxygenator). Ahsman *et al*[31] also reported that concomitant inotropic infusion increased hydroxymidazolam glucuronide Cl by 23% and midazolam dose could be increased starting from the fifth day.

Clonidine

Clonidine is used for sedation in the critically ill paediatric patients. However, clonidine during ECMO cannot be effectively titrated as PK parameters are lacking in neonates and infants. For this reason, Kleiber *et al*[32] aimed to describe clonidine PK in a particular ECMO system and propose dosing guidelines for children on this particular ECMO circuits. Clonidine Cl levels in children older than 1 month were double than those found in patients not on ECMO. Furthermore, Cl rose sharply with PNA, reaching 30%, 50%, and 70% of the adult Cl rate at days 6, 8, and 10, respectively. During ECMO assistance, Vd rose by 55%. As a consequence, the maximum suggested bolus dosage was 5 g/kg, and the authors simulated the number of 5 g/kg bolus doses required to attain the goal concentration of 2 ng/mL within 1 hour, and three repeated 5 g/kg bolus doses were required (table 9).

Morphine

Two articles on the same population evaluating the PK of morphine and its metabolites in neonates undergoing ECMO were retained by the same authors.[17,33] In the first study, morphine Cl was lower in neonates (PNA 7 days) at the start of ECMO (2.2 L/hour/70 kg) than in postoperative neonates (10.5 L/hour/70 kg), but rapidly increased (maturation $t_{1/2}$ 30 and 70 days, respectively) to equal that of the postoperative group after 14 days. The authors stated that Cl was affected by size and age only and that Vd increased with age and was 2.5 times higher in neonates undergoing ECMO than in postoperative cases. Similar to the findings on phenobarbital, the coefficient of variation was significantly higher in neonates on ECMO when compared with postoperative cases.[17,34] Morphine-3-glucuronide (M3G) was the primary metabolite. In the study evaluating the PK of M3G, elimination Cl of M3G was lower in the neonates

Table 8 Characteristics of the studies, pharmacokinetics and dose recommendations related to midazolam

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered dose	Vd	CL	$t_{1/2}$ (hours)	Recommended dose
Mulla *et al*,[30] UK	19	3.8	3.4	P Random 2 groups	Neonates	1-compartment with WinNonMix	VV–VA	50–250 µg/kg/hour	From 0.8±0.5 to 4.1±0.5 L/kg ↑**412.5%**	1.4±015 mL/kg –	From 6.8 (2.2–39.8) to 33.3 (7.4–178) ↑**389.7%**	LD: 350 µg/kg/hour for 6 hours MD: 50 µg/kg/hour
Ahsman *et al*,[31] the Netherlands	20	0.79	3.0	P 1 group	Neonates	A two-compartment model for midazolam and a one-compartment model for the metabolites with NONMEM	VA	LD: 0.2 mg/kg bolus MD: 0.1 mg/kg/hour CI	Midazolam: 14.6 L/3 kg 1-Hydroxymidazolam: 10.2 L/3 kg Hydroxymidazolam glucuronide: 1.21 L/3 kg ↑**240.3%**	Midazolam: 1.38 L/hour/3 kg 1-Hydroxymidazolam: 1.03 L/hour/3 kg Hydroxymidazolam glucuronide: 0.18 L/hour/3 kg ↑**300.0%**	1.85 –	LD: 300 µg/kg/hour for 6 hours MD: 150 µg/kg/hour

Boldfaced fonts represent comparisons with controls within the same study. In other studies, they represent comparisons with non-ECMO neonates from a different published study.
Cl, continuous infusion; CL, clearance; ECMO, extracorporeal membrane oxygenation; LD, loading dose; MD, maintenance dose; NONMEM, non-linear mixed-effects modelling; P, prospective; PNA, postnatal age; $t_{1/2}$, elimination half-life; VA, veno-arterial; Vd, volume of distribution; VV, veno-venous.

Table 9 Characteristics of the studies, pharmacokinetics and dose recommendations of isolated studies on clonidine

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered dose	Vd	CL	$t_{1/2}$ (hours)	Recommended dose
Kleiber *et al*,[32] the Netherlands	22	1 (IQR 6.4) month	4 (IQR 3.1)	P 2 groups	Children	1-compartment with NONMEM	VV–VA	0.24 (0.15) µg/kg/hour infusion	454 L/70 kg at ECMO start **↑55%**	29.9 L/hour/70 kg at ECMO start **↑200%**	–	The authors simulated the number of bolus doses of 5 µg/kg needed to reach the target concentration of 2 ng/mL within 1 hour: three repeated bolus doses of 5 µg/kg were needed.

Boldfaced fonts represent comparisons with controls within the same study. In other studies, they represent comparisons with non-ECMO neonates from a different published study.
CL, clearance; ECMO, extracorporeal membrane oxygenation; NONMEM, non-linear mixed-effects modelling; P, prospective; PNA, postnatal age; $t_{1/2}$, elimination half-life; VA, veno-arterial; VD, volume of distribution; VV, veno-venous.

on ECMO, attributed to reduced renal elimination Cl. These elimination clearances were correlated positively with ECMO flow and negatively correlated with dopamine dose.[17] However, Peters *et al* suggested that dopamine is very likely not causally associated with decreased Cl, but rather a reflection of poorer circulation[17] (table 10).

Peters *et al*[33] found that morphine Cl on ECMO lags behind that in healthy postoperative neonates of the same age but matures rapidly and was similar to the cohort of postoperative surgical neonates within 2 weeks. After this study, on the contrary, the same authors found that formation Cl to M3G is reduced during the first 10 days of ECMO with the same study population.[17]

Others

Phenobarbital

Phenobarbital is an anticonvulsant still commonly used in neonates and infants undergoing ECMO to treat seizures (18%–20%) and withdrawal symptoms, with midazolam as a commonly used second-line drug to treat seizures or to sedate the newborn.[35] The distribution of phenobarbital, a lipophilic drug, was not affected by ECMO as the sodium salt formulation has good water solubility (log p=1.77). In contrast, it was shown in two studies that the distribution of midazolam increased. Pokorná *et al*[35] found similar high interindividual PK variability for Vd and Cl and no statistical differences in Vd or Cl. The authors assumed that the physicochemical characteristics of phenobarbital resulted in differences in the distribution in comparison with ECMO-induced changes for typical lipophilic drugs. Michaličková *et al*[34] found that the phenobarbital Cl increased in the time interval (days 1–12) studied within 12 days. Different loading and maintenance doses were used in both studies, and different Vd and Cl values were calculated. Because of the substantial unexplained variability, individual patients should consider regular and recurrent therapeutic drug monitoring and therapeutic concentration intervention, even with the model-derived regimen.[34]

Body weight was the main PK covariate of phenobarbital disposition.[35] In the study by Michaličková *et al*, the Vd of phenobarbital was not much affected by ECMO, while its Cl increased over time, especially in the first 12 days.[34] Both (body weight and PNA) rather reflect maturational covariates. Furthermore, there was still high unexplained variability.[34] In both studies, the suggested target range for phenobarbital therapeutic concentration was 10–40 mg/L.

Thibault *et al*[36] created a popPK model for intravenous phenobarbital in neonates following cardiac surgery and ran simulations to find the optimal dose regimens. Loading doses of 30 and 20 mg/kg reached target concentration with albumin levels less than or equal to 3 and 3.5 mg/dL, respectively, in neonates not on ECMO. Also, loading doses of 30 mg/kg were effective on ECMO independent of albumin levels. In addition, all neonates attained target concentrations with maintenance doses of 4–5 mg/kg/day. The purpose of this study was to assess

Table 10 Characteristics of the studies, pharmacokinetics and dose recommendations of isolated studies on morphine

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered dose	Vd	CL	$t_{1/2}$ (hours)	Recommended dose
Peters *et al*,[33] the Netherlands	14	82	4.2	P	Infants	1-compartment with NONMEM	VA	LD: 100 µg/kg MD: 40 µg/kg/hour	Day 1: 1.89 mL/kg/min Day 10: 3.33 mL/kg/min **↑76.2%**	Day 1: 1.1 mL/kg/min Day 10: 6.0 mL/kg/min **↑445.5%**	–	Serum concentrations decrease during the first 10 days of ECMO, and that dose adjustments should be carried out.

Boldfaced fonts represent comparisons with controls within the same study. In other studies, they represent comparisons with non-ECMO neonates from a different published study.
CL, clearance; ECMO, extracorporeal membrane oxygenation; LD, loading dose; MD, maintenance dose; P, prospective; PNA, postnatal age; $t_{1/2}$, elimination half-life; VA, veno-arterial; Vd, volume of distribution.

the effect of changed protein binding or, more likely, positive fluid balance in phenobarbital dosing (table 11).

Theophylline

According to Mulla *et al*'s study[37] that determined popPK for theophylline during ECMO from routine monitoring data, the estimated Cl is significantly lower and Vd higher than previously reported in non-ECMO patients of similar age. These variations are most likely due to the increased circulation volume during ECMO as well as decreased renal and hepatic function in this population. The high interindividual variability reflects the varied character of ECMO patients (table 12).

DISCUSSION

Most of the studies included in the review were on antimicrobials including vancomycin, meropenem, fluconazole, gentamicin, cefotaxime and cefepime. This confirms the pattern on drug utilisation described by Buck in 2003[9] that these drugs are hydrophilic, have a rather low Vd (L/kg) and a narrow therapeutic range. Vd relates the amount of drug in the body to the plasma concentration of the drugs, depending on the fluid in which concentration is measured.[38] Vd depends on substance characteristics and patient factors which can be different between neonates and adults.

In this literature review, because drug Cl is difficult to predict due to dynamic ontogenetic changes in renal function, ECMO received by neonates and infants without concomitant CRRT was included to avoid heterogeneity.[39] Therefore, target concentration intervention based on serum concentrations is indispensable to ensure therapeutic exposure in this population.

Most studies found that patients undergoing ECMO had higher Vd and lower Cl than non-ECMO patients. The PK differences in which we have the highest confidence are from trials that included non-ECMO comparison groups. However, the bulk of the studies did not include non-ECMO comparator groups, and the comparisons were based on PK data provided in other published data.[40] The differences in Vd and Cl of some of the studied drugs, such as vancomycin, between ECMO and non-ECMO controls demonstrated significant intrastudy variability, with some studies showing increased values for the PK parameters,[31 32 36] while others showed decreased values or no change.[23 24 41]

In this literature review, most studies evaluated both VV and VA modalities of ECMO together. According to Bhatt-Mehta *et al*'s study,[42] there was no statistically significant difference between VA and VV bypass type in terms of Vd (0.61±0.15 vs 0.74±0.23 L/kg), Cl (0.157±0.046 vs 0.199±0.085 L/hour) and $t_{1/2}$ (10.04±2.45 vs 10.75±3.43 hours) ($p>0.05$).[42] Therefore, it is estimated that none of the included studies analysed the VV–VA difference in terms of PK parameters.

In general, changes in tissue distribution caused by a severe illness are more likely to be clinically important

Table 11 Characteristics of the studies, pharmacokinetics and dose recommendations related to phenobarbital

Study	n	PNA	Weight	Type	Group	Model	Modality	Administered dose	Vd	CL	$t_{1/2}$ (hours)	Recommended dose
Michaličková *et al*,[34] Czech Republic	13	2	3.21	R	Neonates	1-compartment with NONMEM	VV–VA	LD: 7.5 mg/kg (8.5–16 mg/kg) MD: 6.9 mg/kg/day (4.5–8.5 mg/kg/day)	2.72 L	0.0096 L/hour	—	In the first 12 days of ECMO with a regimen of an LD of 20 mg/kg and an MD of 4 mg/kg/day divided in two doses with an increase of 0.25 mg/kg every 12 hours during ECMO.
Thibault *et al*,[36] USA	12/37*	5 (0–26)	3.2 (1.3–3.8)	R	Neonates	1-compartment with first-order elimination with NONMEM	VV–VA	LD: 15–20 mg/kg MD: 3–6 mg/kg/day	**↑22%** (normalisation of albumin values from 2.5 mg/dL to 3.5 mg/dL decreased the estimated volume by 13%)	**↑114%** (over the first 20 days of life)	—	LD of 30 mg/kg achieved goal peak concentration. MD of 4–5 mg/kg/day sustained goal trough concentration.

Boldfaced fonts represent comparisons with controls within the same study. In other studies, they represent comparisons with non-ECMO neonates from a different published study.
*Number of patients undergoing only ECMO circuit.
CL, clearance; ECMO, extracorporeal membrane oxygenation; LD, loading dose; MD, maintenance dose; NONMEM, non-linear mixed-effects modelling; PNA, postnatal age; R, retrospective; $t_{1/2}$, elimination half-life; VA, veno-arterial; Vd, volume of distribution; VV, veno-venous.

Table 12 Characteristics of the studies, pharmacokinetics and dose recommendations related to theophylline

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered dose	Vd	CL	$t_{1/2}$ (hours)	Recommended dose
Mulla *et al*,[37] UK	N: 38 I: 14	8.4±5.9 for neonates 122±107 for infants	3.3±0.5 for neonates 4.8±2.0 for infants	R 1 group compared with the literature	Children	1-compartment with first-order elimination with WinNonMix Professional	VV–VA	9.2±2.6 µg/kg/min infusion	The interindividual variability **↑40%**	The interindividual variability **↓38%**	—	Maintenance infusion rates following an initial loading dose (0.57×weight (kg)×10 mg/L). Maintenance infusion rate calculated from: average steady-state concentration=rate of infusion/clearance (using clearance parameters determined in the final model).

Boldfaced fonts represent comparisons with controls within the same study. In other studies, they represent comparisons with non-ECMO neonates from a different published study.
CL, clearance; ECMO, extracorporeal membrane oxygenation; I, infants; N, neonates; PNA, postnatal age; R, retrospective; $t_{1/2}$, elimination half-life; VA, veno-arterial; Vd, volume of distribution; VV, veno-venous.

for hydrophilic drugs that lack meaningful intracellular penetration and so have a low Vd.[43] Also, because neonates have a larger proportion of body water, the Vd per kg for water-soluble substances may be higher.[44] In addition to all these factors, it is reasonable to expect that the Vd of hydrophilic drugs will increase once the ECMO circulation is connected. This can be attributed to the circuit itself, as well as to the additional capillary leak commonly observed in these patients. To further illustrate this, all studies examining vancomycin and gentamicin consistently showed an increased Vd in neonates undergoing ECMO.[8 9]

Critical illness may significantly affect dexmedetomidine PK, mainly through decreased hepatic metabolism and elevated Vd induced by organ failure and inflammation, which may be modified further by the presence of ECMO. Increases in Cl result in higher dexmedetomidine concentrations, while increases in Vd result in lower concentrations. According to Thibault and Zuppa,[45] exploration of PK data using previously published models resulted in overprediction of observed values, which might have theoretically suggested higher Vd and Cl. Adding a component on Vd, on the other hand, did not enhance their goodness-of-fit plots, implying that increasing Vd does not explain their findings. This study found that popPK models that are relevant to a wide range of ages and diseases are more feasible in paediatric critical care settings but more difficult to design.

As a final reflection, we wanted to mention that we could not retrieve reports on any subsequent validation study for the adapted dosing regimens suggested. Furthermore, the reporting on toxicity and safety in these popPK studies is not present in these papers, so additional studies to validate the adapted dosing regimens on efficacy and toxicity are warranted.[41] From a methodological perspective, better descriptions on the pathophysiology over time can be very useful to feed (patho)physiology-based PK models as illustrated for fluconazole PK over the human age span, including neonates.[8 46] Previously, Hoie *et al*[47] had recommended a vancomycin dose of 20 mg/kg at an 18-hour interval for infants on ECMO with serum creatinine levels of <1.5 mg/dL. However, Amaker *et al*'s[41] data indicate that infants on ECMO with serum creatinine levels of <1.5 mg/dL should be given vancomycin no more frequently than every 24 hours. In comparison with previously published data, the neonates undergoing ECMO in this study demonstrated a much larger Vd, a lower Cl and a longer $t_{1/2}$ with an individual PK study.

This paper has its strengths and limitations. The predefined approach to focus on popPK studies has limitations, but these methods do provide the best approach to analyse trends over time, as well as covariates involved. Furthermore, the search strategy was structured, but not compliant with all guidelines (like number of databases searched) relevant for a meta-analysis.

CONCLUSION

The aim of this paper was to determine the effect of ECMO use on PK in neonates, based on a systematic assessment of popPK studies. At present, there are a limited number of popPK studies for a limited number of compounds reported in neonates undergoing ECMO. Despite some differences in results for the same drug, the general pattern suggests an increase in Vd and $t_{1/2}$, a stable to decreased Cl, and an increase in intrapatient and interpatient variability on ECMO. There were no relevant toxicity and safety parameters reported, including in those studies with more than 100% increased PK parameters. Therefore, we recommend more studies to address this toxicity and safety concern. Consequently, and if possible, TDM and target concentration intervention are strongly recommended to determine the appropriate exposure and doses for neonates undergoing ECMO.

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