Pharmacokinetics Alterations in Critically Ill Pediatric Patients on Extracorporeal Membrane Oxygenation: A Systematic Review

CURRENT STATUS: UNDER REVIEW

Natalia Sutiman  
Duke-NUS Medical School  
ORCiD: 0000-0001-5861-7079

Janine Cynthia Koh  
KK Women's and Children's Hospital

Kevin Watt  
Duke Clinical Research Institute

Christoph Hornik  
Duke Clinical Research Institute

Beverly Murphy  
Duke University School of Medicine

Yoke Hwee Chan  
KK Women's and Children's Hospital

Jan Hau Lee  lee.jan.hau@singhealth.com.sg  
Duke-NUS Medical School  
Corresponding Author

DOI: 10.21203/rs.2.19089/v1

SUBJECT AREAS  Critical Care & Emergency Medicine

KEYWORDS  ECMO, extracorporeal, pharmacokinetics, disposition, pediatrics,
critically ill
Abstract

BACKGROUND

To identify alterations in pharmacokinetics in children on extracorporeal membrane oxygenation (ECMO), identify knowledge gaps and inform future clinical pharmacology studies.

METHODS

We systematically searched the following databases from earliest publication until November 2018: MEDLINE, CINAHL and EMBASE, using a controlled vocabulary and keywords related to: “ECMO”, and “pharmacokinetics”, “pharmacology”, “drug disposition”, “dosing” and “pediatrics”. Inclusion criteria were: study population aged <18 years, supported on ECMO for any indications, receiving any medications while on ECMO and reported pharmacokinetics data. Clearance and/or volume of distribution (V_d) values were extracted from the included studies.

RESULTS

41 studies (total patients=574) evaluating 23 drugs met the inclusion criteria. The most common drugs studied were anti-microbials (n=13), and anticonvulsants (n=3). 28 studies (68%) were conducted in children < 1 year of age. 33 studies (80%) were conducted without intra-study comparisons to non-ECMO controls. Increase in V_d attributable to ECMO was demonstrated for 9 (56%) drugs: cefotaxime, gentamicin, piperacillin/tazobactam, fluconazole, micafungin, levetiracetam, clonidine, midazolam and sildenafil (range: 23-345% increase relative to non-ECMO controls), which may suggest the need for higher initial dosing. Decreased V_d was reported for 2 drugs: acyclovir and ribavirin (50 and 69%, respectively). Decreased clearance was reported for gentamicin,
ticarcillin/clavulanate, bumetanide and ranitidine (range: 26-95% decrease relative to non-ECMO controls). Increased clearance was reported for caspofungin, micafungin, clonidine, midazolam, morphine and sildenafil (range: 25-455% increase relative to non-ECMO controls).

**CONCLUSIONS**

There were substantial pharmacokinetic alterations in 70% of drugs studied in children on ECMO. However, studies evaluating pharmacokinetic changes of many drug classes, and those that allow direct comparisons between ECMO and non-ECMO patients, are still lacking. Systematic evaluation of pharmacokinetic alterations of drugs on ECMO that incorporate multi-drug opportunistic trials, physiologically based pharmacokinetic modeling, ex-vivo studies and other methods are necessary for definitive dose recommendations.

**Background**

Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass support system used to temporarily sustain cardiac and/or respiratory function in critically ill patients. ECMO been established as an effective modality in neonates and children who have failed conventional intensive care management. However, the ECMO circuit has been shown to sequester drug molecules in a highly unpredictable manner,

particularly with highly lipophilic and protein bound drugs, as shown in a series of ex vivo experiments in which drugs were administered into isolated ECMO circuits.

Pharmacokinetic studies conducted in critically ill neonates supported on ECMO have demonstrated marked alterations in drug pharmacokinetics and disposition. Specifically, the use of ECMO has been shown to increase the volume of distribution.
(Vₐ) of drugs and alter the clearance of certain drugs.⁵,⁶ Given the high variability in drug pharmacokinetics and disposition in patients on ECMO, a thorough understanding of the pharmacokinetics alterations that occur during ECMO is critical in guiding clinicians in determining dose adjustments.

To date, most studies involving pediatric ECMO clinical pharmacology have been conducted with anti-infective agents, but data have started to emerge for other classes of commonly used drugs in this patient population. However, there is currently no systematic review of the current evidence base of the alterations in drug pharmacokinetics and disposition in children supported on ECMO. We therefore performed this systematic review to assess and summarize the current literature up for alterations in drug pharmacokinetics, specifically clearance and Vₐ, in critically ill pediatric patients supported on ECMO.

Methods

This systematic review was registered in PROSPERO with the registration number CRD42019114881.

Search strategy

A systematic, computerized search of the literature in MEDLINE (via PubMed), CINAHL, and Embase was conducted by a medical research librarian (B.M.) using a controlled vocabulary and keywords related to extracorporeal membrane oxygenation (ECMO) and pharmacokinetics, pharmacology, drug disposition, or dosing in the pediatric population (birth to 18 years). Our search time frame was from database inception to November 1, 2018. The search strategies are shown in the Appendix. The reference lists of all selected publications were checked to retrieve relevant publications that were not identified in the computerized search.
Study selection and Risk of Bias Assessment

The final search results were compiled and imported into Covidence (Veritas Health Innovation, Melbourne, Australia). Two reviewers (N.S. and J.K.) independently screened and reviewed titles and abstracts to assess their eligibility. Full-text articles were retrieved if the abstract provided insufficient information to establish eligibility or if the article passed the first eligibility screening. Disagreements on study eligibility were resolved by consensus or by arbitration from a third independent reviewer (J.H.L).

Studies that fulfilled the following inclusion criteria were included: (1) study population aged 18 years and below, including neonates (0 – 28 days of age), infants (29 days – 1 year of age), children (>1 – 12 years of age) and adolescents (>12 – 18 years of age), (2) study population receiving ECMO for any clinical indications and durations, (3) study population receiving any medications or therapeutics while on ECMO, and (4) studies reporting pharmacokinetic parameters, specifically clearance and $V_d$, in patients supported on ECMO. Case reports, case series, abstracts and conference proceedings were all included. We only included studies published in the English language. Articles with only pharmacodynamics, response or safety data were not included. Other exclusion criteria included: (1) ex vivo studies, (2) animal studies, (3) predominantly adult population with no separate description of pediatric sub-group. Given the nature of pharmacokinetics studies, traditional risk of bias assessment with tools, such as the Newcastle-Ottawa scale, was not conducted. Instead, each article was evaluated for completeness of reporting based on the consensus-based ClinPK statement by Kanji et al.7

Data extraction and synthesis
A standardized data collection form was used to extract the relevant data from each eligible study. The following data were collected: key characteristics of the study (e.g., study year, study design, type of publication), characteristics of the study population (e.g., age, clinical indications of ECMO, modality of ECMO), interventions received by the study population (e.g., medications received while on ECMO, including their dosage form and dose regimen), as well as pharmacokinetic parameters measured or estimated. For the purpose of this review, we specifically focused on two pharmacokinetic parameters – clearance and $V_d$.

**Comparison of clearance and volume of distribution of drugs between the ECMO and non-ECMO groups**

We extracted clearance and/or $V_d$ values from the included studies and compared these pharmacokinetic parameters between children supported with ECMO and children not on ECMO. For studies with intra-study comparators, the pharmacokinetic parameters were compared between the ECMO and non-ECMO groups within each study. For studies that did not include non-ECMO control groups, we compared these pharmacokinetic parameters against historical controls in other pharmacokinetic studies conducted in pediatric patients not supported with ECMO. For each drug, a computerized search was conducted in MEDLINE (via Pubmed) using keywords related to the *drug* and *pharmacokinetics, pharmacology or dosing* in the *pediatric* population (birth to 18 years). The titles and abstracts of the articles were screened, and full-text articles were subsequently reviewed for pharmacokinetic parameters of the drug and its metabolites (where applicable) in non-ECMO pediatric patients. Wherever possible, the non-ECMO historical controls were age-matched against the ECMO group. In addition, to evaluate the association
between changes in $V_d$ or drug clearance and the drug’s physicochemical properties, we compared the log $P$ values between drugs with increased, decreased or no change in $V_d$ or drug clearance.

**Assessment of quality of reporting of pharmacokinetic studies**

We evaluated each study included in this systematic review for their compliance rates with each item in the ClinPK checklist, a 24-item checklist for transparent and consistent reporting of clinical pharmacokinetic studies developed by Kanji et al.. The checklist included criteria such as: study rationale, eligibility criteria of study participants, co-administration of study drugs with potentially interacting drugs, validation of quantitative bioanalytical methods, pharmacokinetic modeling methods and reporting of results with appropriate measures.

**Results**

**Characteristics of included studies and study populations**

Out of the 3,428 records retrieved by the systematic search and hand search of reference lists, 41 studies met the inclusion criteria and included a total of 574 pediatric patients (Figure 1). These 41 publications reported clearance and $V_d$ data for 23 drugs: 6 antibiotics (cefotaxime, gentamicin, meropenem, piperacillin/tazobactam, ticarcillin/clavulanate, vancomycin), 3 anti-viral agents (acyclovir, oseltamivir, ribavirin), 4 anti-fungal agents (caspofungin, fluconazole, micafungin, voriconazole), 3 anti-convulsants (fos-phenytoin, levetiracetam, phenobarbital), and others (bumetanide, clonidine, heparin, midazolam, morphine, ranitidine, sildenafil). Twenty-eight studies (68%) were conducted in children less than 1 year of age. The clinical and methodological characteristics of included
studies are summarized in Table 1 and Supplementary Table 1. The studies were published between 1989 and 2018. There was substantial heterogeneity in the pharmacokinetic sampling and treatment modalities used across studies. These variations included differences in route of administration (intravenous or oral), dosages of medications, administration method (bolus, intermittent dosing or continuous infusion) and usage of co-medications. Three of the 41 studies (7%) included patients on continuous renal replacement therapy (CRRT). Renal and liver functions were not consistently reported in majority of the studies. In addition, 17 studies (41%) did not report the type of ECMO used. Of those that reported the type of ECMO used, 10 studies (24%) employed both veno-venous (VV) and venous-arterial (VA) ECMO, 10 studies (24%) used VA ECMO only, and the remaining 4 studies (10%) used VV ECMO only. Only 7 studies (17%) were conducted with intra-study comparisons to non-ECMO controls.

Alterations in volume of distribution of drugs in ECMO-supported patients

Of the 23 drugs studied, $V_d$ values were reported for 16 drugs (70%), with the remaining 7 other drugs having only clearance values reported without $V_d$ values. Relative to non-ECMO controls, significant alterations in $V_d$ were observed in pediatric patients supported on ECMO for 11 of 16 studied drugs (Table 2). Increased $V_d$ attributable to ECMO was demonstrated for 9 drugs: cefotaxime, gentamicin, piperacillin/tazobactam, fluconazole, micafungin, levetiracetam, clonidine, midazolam and sildenafil (range: 23.8 – 345% increase relative to non-ECMO
controls), suggesting the need for higher initial dosing.\textsuperscript{19,23,24,31-36} Decreased $V_d$ was reported for 2 drugs: acyclovir and ribavirin (50 and 69\%, respectively).\textsuperscript{8,34} $V_d$ of the following drugs were not substantially altered in patients supported on ECMO relative to non-ECMO controls: vancomycin, voriconazole, fos-phenytoin, phenobarbital and bumetanide.\textsuperscript{2,12,31,40} Of note, vancomycin was studied in 6 separate studies, only one of which included a non-ECMO comparator group\textsuperscript{12} while the remaining 5 did not.\textsuperscript{27,32,36,38,47} Although a trend was observed towards smaller $V_d$ of vancomycin relative to non-ECMO controls, the difference did not reach statistical significance in the study by Buck et al.\textsuperscript{12} However, when the $V_d$ values were compared against historical controls, increased $V_d$ was observed compared to pediatric patients not on ECMO.\textsuperscript{27,32,36,38,47} In addition, we did not identify any significant correlation between lipophilicity (as measured by log $P$) of drugs and changes in $V_d$ attributable to ECMO (Supplementary Table 1).

\textit{Alterations in drug clearance in ECMO-supported patients}

Out of the 23 drugs studied, drug clearance was reported for 17 drugs (74\%),\textsuperscript{9-14,18-21,23-30,32,33,35-41,44,45,47,48} with the remaining 5 other drugs having only $V_d$ values reported.\textsuperscript{8,17,22,31,34,42} Compared to non-ECMO controls, significant changes in clearance were observed in pediatric patients supported on ECMO for 10 of 17 studied drugs (Table 2). Decreased clearance was reported for gentamicin, ticarcillin/clavulanate, bumetanide and ranitidine (range: 26-95\% decrease relative to non-ECMO controls).\textsuperscript{19,39-41} Increased clearance was reported for caspofungin, micafungin, clonidine, midazolam, morphine and sildenafil (range: 25-455\% increase.
relative to non-ECMO controls). Changes in clearance were not observed for cefotaxime, meropenem, vancomycin, oseltamivir, fluconazole, voriconazole and levetiracetam.

Similarly, for vancomycin, the study by Buck et al., which included a non-ECMO comparator group within the same study, did not report statistically significant difference in clearance. However, comparison of vancomycin clearance values in pediatric patients supported on ECMO against historical controls showed decreased clearance. No significant association was found between log $P$ values of drugs and changes in clearance attributable to ECMO (Supplementary Table 1).

**Quality of reporting of published pharmacokinetic studies of drugs in pediatric patients supported on ECMO**

The median compliance rate to the 24-item clinPK checklist among the 41 studies was 73.9% (IQR 63.2% to 81.8%). Only thirteen out of the 41 studies were deemed to be compliant, reporting >80% of the necessary items. Seven studies had compliance rate of less than 50%.

**Discussion**

To our best knowledge, this is the first systematic review that encompasses drugs across all therapeutic classes and specifically focuses on the available data in critically ill pediatric patients. Using a comprehensive systematic search strategy, we identified a total of 41 studies evaluating 23 drugs. In line with the results of ex vivo studies that demonstrated drug extraction by the ECMO circuit, particularly for highly lipophilic and protein-bound drugs, we found substantial pharmacokinetic alterations, either in drug clearance or $V_d$ or both, reported in 69.5% of drugs.
studied in pediatric patients supported on ECMO.

Most studies demonstrated increased $V_d$ and decreased clearance of drugs between ECMO and non-ECMO patients. The differences in pharmacokinetics for which we have the most confidence are those generated from studies that included the non-ECMO comparator groups. However, majority of the studies did not include the non-ECMO comparator groups and the comparisons were made based on pharmacokinetic parameters reported in different studies. The differences in $V_d$ and clearance of some of the studied drugs, such as vancomycin, between ECMO and non-ECMO controls showed marked intra-study variability, with some studies demonstrating increased values for the pharmacokinetic parameters\textsuperscript{27,32,36,38,47} while others demonstrated decreased values or no change\textsuperscript{12}.

Despite our best efforts to compare these values across studies with similar patient demographics, it is unclear whether the differences, or lack thereof, are confounded by differences in patient profiles, study designs and methodology. Notably, the lack of inclusion of non-ECMO controls within these studies may have contributed to such heterogeneity. For this reason, it is difficult to draw definite conclusions regarding the pharmacokinetic differences between the ECMO and non-ECMO groups and further highlights the need for future studies evaluating the impact of ECMO on drug pharmacokinetics and disposition to include the non-ECMO comparator groups.

Additionally, in contrast to the findings of ex vivo studies which showed the sequestration of drugs by the ECMO circuit to be particularly profound for more lipophilic drugs, we did not observe any correlation between log $P$ values of drugs and changes in both clearance as well as $V_d$ attributable to ECMO. However, this may be due in part to the limited number of drugs studied to date, which makes it
difficult to draw conclusive results.

There are several limitations to our systematic review. Firstly, most of the included studies had small sample sizes and were performed mainly in neonates and infants, with some studies including a mixed pediatric population. Given that the effect of ECMO on drug pharmacokinetics and disposition can vary by patient age, the extrapolation of these results to older children supported on ECMO cannot be robustly justified and requires dedicated pharmacokinetic trials to address.

Importantly, the ECMO setup has evolved considerably over time. Considering that most of the studies were conducted in the 1990’s, the differences in drug extraction between the older ECMO components and contemporary ECMO setup remain unclear and require further investigation.

The heterogeneity in pediatric patient populations contributes substantially to large pharmacokinetic variability. Such heterogeneity is further compounded by physiological derangements associated with critical illnesses, renal replacement therapy, drug-drug interactions, genetic polymorphisms and the use of ECMO.\textsuperscript{49–52}

Much deeper understanding of the interplay between these factors is critical in improving our ability to provide personalized dosing to pediatric patients on ECMO. Pediatric pharmacokinetic research presents specific challenges, some of which can be circumvented with the use of model-based approaches to study design and analysis, such as population pharmacokinetic modeling and physiologically based pharmacokinetic modeling. As such, identification of the most optimal study design and pharmacokinetic protocol would be crucial for future pharmacology studies in pediatric ECMO patients. Furthermore, the transparent and complete reporting of study data in clinical pharmacokinetics studies is essential for better assessment and evaluation of study information and its clinical translation. Although validated
tools for assessment of the quality and validity of pharmacokinetic studies have not yet been developed, the use of the ClinPK consensus in this systematic review has highlighted the poor compliance of most studies to the 24-item checklist considered to be necessary for the reporting of pharmacokinetic studies. We recommend more complete reporting of future pharmacokinetic studies that meet at least the minimum reporting criteria in this patient population. This may improve the utility and comparability of study findings and further circumvent the unique challenges associated with pediatric pharmacology studies.

In addition, the majority of pharmacokinetics data in ECMO-supported pediatric populations to date have been from studies conducted in neonates and infants, with anti-microbial agents and anti-convulsants being the most commonly studied drugs. Notably, studies evaluating pharmacokinetic changes of many drugs such as dexmedetomidine as well as other drug classes, including analgesics, cardiovascular, sedative and anesthetic agents, which are commonly used in critically ill pediatric patients on ECMO are still lacking, and represent important areas of future studies. This highlights the urgent need for pharmacokinetic studies in these children for specific and clinically important drug classes, using contemporary ECMO setup and with appropriate study designs, including the inclusion of appropriate controls.

Conclusion

While the total number of drugs studied to date remains limited, we found substantial pharmacokinetic alterations in terms of $V_d$ and/or clearance in 69.5% of drugs studied in children on ECMO. We also identified major limitations of the existing evidence base, which explains at least partially our current inability to
readily predict pharmacokinetic changes and thus dose adjustments of drugs in critically ill children on ECMO. Systematic evaluation of pharmacokinetic alterations of drugs on ECMO that incorporate multi-drug opportunistic trials, physiologically based pharmacokinetic modeling, ex-vivo studies and other methods are necessary for definitive dose recommendations.

Abbreviations
ECMO: extra-corporeal membrane oxygenation; CL: clearance; Vd: volume of distribution

Declarations

**Ethics approval and consent to participate**
Not applicable

**Consent for publication**
Not applicable

**Availability of data and materials**
All data generated or analyzed during this study are included in this published article [and its supplementary information files].

**Competing interests**
The authors have no conflicts of interest to declare.

**Funding**
This work was supported by the SingHealth SMSTDA Award (FY2019 Cycle 1).

**Authors’ contributions**
NS conceptualized and designed the study, obtained funding, designed the data collection instruments, collected data, carried out analysis and interpretation of
data, drafted the manuscript and revised the manuscript. LJH conceptualized and
designed the study, obtained funding, collected data, carried out analysis and
interpretation of data, reviewed the manuscript and revised the manuscript. JCK
collected data, carried out analysis and interpretation of data and reviewed the
manuscript. KW and CH collected data, carried out analysis and interpretation of
data, drafted, reviewed and revised the manuscript. YHC collected data, carried out
analysis and interpretation of data, reviewed the manuscript and revised the
manuscript. BM provided technical support, collected data, and carried out analysis
and interpretation of data. All authors approved the final manuscript as submitted
and agree to be accountable for all aspects of the work.

References

1. Shekar K, Roberts JA, Mcdonald CI, et al. Sequestration of drugs in the circuit
may lead to therapeutic failure during extracorporeal membrane oxygenation.
Crit Care Lond Engl. 2012;16(5):R194. doi:10.1186/cc11679

2. Harthan AA, Buckley KW, Heger ML, Fortuna RS, Mays K. Medication adsorption
into contemporary extracorporeal membrane oxygenator circuits. J Pediatr
Pharmacol Ther J PPT Off J PPAG. 2014;19(4):288-295. doi:10.5863/1551-6776-
19.4.288

3. Shekar K, Roberts JA, Mcdonald CI, et al. Protein-bound drugs are prone to
sequestration in the extracorporeal membrane oxygenation circuit: results
from an ex vivo study. Crit Care Lond Engl. 2015;19:164. doi:10.1186/s13054-
015-0891-z

4. Mehta NM, Halwick DR, Dodson BL, Thompson JE, Arnold JH. Potential drug
sequestration during extracorporeal membrane oxygenation: results from an
ex vivo experiment. *Intensive Care Med.* 2007;33(6):1018-1024. doi:10.1007/s00134-007-0606-2

5. Anderson HL, Coran AG, Drongowski RA, Ha HJ, Bartlett RH. Extracellular fluid and total body water changes in neonates undergoing extracorporeal membrane oxygenation. *J Pediatr Surg.* 1992;27(8):1003-1007; discussion 1007-1008.

6. Noerr B. ECMO and pharmacotherapy. *Neonatal Netw NN.* 1996;15(6):23-31.

7. Kanji S, Hayes M, Ling A, et al. Reporting Guidelines for Clinical Pharmacokinetic Studies: The ClinPK Statement. *Clin Pharmacokinet.* 2015;54(7):783-795. doi:10.1007/s40262-015-0236-8

8. Chopra A, Miller K, Shea P, Conley S, Cies J. 1130: Continuous Acyclovir for Neonatal Disseminated HSV with Concurrent ECMO and CVVH Circuits. *Crit Care Med.* 2013;41(12).

https://journals.lww.com/ccmjournal/Fulltext/2013/12001/1130___Continuous_Acyclovir_f

9. Alqaqaa Y, Witcher R, Ramirez M, Fisher J, Malaga-Dieguez L, Chopra A. 1851: CONTINUOUS INFUSION OF MEROPENEM IN A PATIENT ON ECMO AND CRRT. *Crit Care Med.* 2016;44(12).

https://journals.lww.com/ccmjournal/Fulltext/2016/12001/1851___CONTINUOUS_INFUSION\n
10. Cies JJ, Moore WS, Conley SB, et al. Pharmacokinetics of Continuous Infusion Meropenem With Concurrent Extracorporeal Life Support and Continuous Renal Replacement Therapy: A Case Report. *J Pediatr Pharmacol Ther JPPT.* 2016;21(1):92-97. doi:10.5863/1551-6776-21.1.92

11. Ahsman MJ, Witjes BC, Wildschut ED, et al. Sildenafil exposure in neonates with pulmonary hypertension after administration via a nasogastric tube. *Arch Dis Child - Fetal Neonatal Ed.* 2010;95(2):F109-F114. doi:10.1136/adc.2009.168336
12. Buck ML. Vancomycin Pharmacokinetics in Neonates Receiving Extracorporeal Membrane Oxygenation. *Pharmacother J Hum Pharmacol Drug Ther.* 1998;18(5):1082-1086. doi:10.1002/j.1875-9114.1998.tb03938.x

13. Cies JJ, Moore WS, Dickerman MJ, et al. Pharmacokinetics of Continuous-Infusion Meropenem in a Pediatric Patient Receiving Extracorporeal Life Support. *Pharmacother J Hum Pharmacol Drug Ther.* 2014;34(10):e175-e179. doi:10.1002/phar.1476

14. Eyler RF, Klein KC, Mueller BA. The Pharmacokinetics of Oseltamivir and Oseltamivir Carboxylate in a Critically Ill Pediatric Patient Receiving Extracorporeal Membrane Oxygenation and Continuous Venovenous Hemodialysis. *J Pediatr Pharmacol Ther JPPT.* 2012;17(2):173-176. doi:10.5863/1551-6776-17.2.173

15. Grimaud M, Urien S, Borgel D, et al. Abstract P-114: PHARMACOKINETIC ANALYSIS OF UNFRACTIONATED HEPARIN IN CRITICALLY ILL CHILDREN DURING EXTRACORPOREAL MEMBRANE OXYGENATION DO WE ACHIEVE THE TARGET? *Pediatr Crit Care Med.* 2018;19(6S).

16. Cies JJ. Neonatal vancomycin dosing on extracorporeal membrane oxygenation. In: Vol 38. Critical Care Medicine; 2010:A215.

17. Cies J, Chopra A. 702: PIPERACILLIN/TAZOBACTAM (PTZ) PHARMACOKINETICS (PK) IN CRITICALLY ILL CHILDREN ON EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO). *Crit Care Med.* 2011;39(12).

18. Dodge WF, Jelliffe RW, Zwischenberger JB, Bellanger RA, Hokanson JA, Snodgrass WR. Population Pharmacokinetic Models: Effect of Explicit Versus
Assumed Constant Serum Concentration Assay Error Patterns upon Parameter Values of Gentamicin in Infants on and off Extracorporeal Membrane Oxygenation. *Ther Drug Monit.* 1994;16(6):552-559.

19. Lindsay CA, Bawdon R, Quigley R. Clearance of Ticarcillin-Clavulanic Acid by Continuous Venovenous Hemofiltration in Three Critically Ill Children, Two With and One Without Concomitant Extracorporeal Membrane Oxygenation. *Pharmacother J Hum Pharmacol Drug Ther.* 1996;16(3):458-462. doi:10.1002/j.1875-9114.1996.tb02978.x

20. MUNZENBERGER PJ, MASSOUD N. Pharmacokinetics of Gentamicin in Neonatal Patients Supported with Extracorporeal Membrane Oxygenation. *ASAIO J.* 1991;37(1). https://journals.lww.com/asaiojournal/Fulltext/1991/01000/Pharmacokinetics_of_Gentamicin_in_Neonatal_1.aspx

21. Peters JWB, Anderson BJ, Simons SHP, Uges DRA, Tibboel D. Morphine Metabolite Pharmacokinetics during Venoarterial Extra Corporeal Membrane Oxygenation in Neonates. *Clin Pharmacokinet.* 2006;45(7):705-714. doi:10.2165/00003088-200645070-00005

22. Pokorná P, Šíma M, Vobruba V, Tibboel D, Slanař O. Phenobarbital pharmacokinetics in neonates and infants during extracorporeal membrane oxygenation. *Perfusion.* 2018;33(1_suppl):80-86. doi:10.1177/0267659118766444

23. Southgate WM, DiPiro JT, Robertson AF. Pharmacokinetics of gentamicin in neonates on extracorporeal membrane oxygenation. *Antimicrob Agents Chemother.* 1989;33(6):817-819.

24. Watt KM, Benjamin DK, Cheifetz IM, et al. Pharmacokinetics and Safety of Fluconazole in Young Infants Supported with Extracorporeal Membrane
Oxygenation. *Pediatr Infect Dis J*. 2012;31(10):1042-1047. 
doi:10.1097/INF.0b013e31825d3091

25. Watt KM, Gonzalez D, Benjamin DK, et al. Fluconazole Population Pharmacokinetics and Dosing for Prevention and Treatment of Invasive Candidiasis in Children Supported with Extracorporeal Membrane Oxygenation. *Antimicrob Agents Chemother*. 2015;59(7):3935-3943. doi:10.1128/AAC.00102-15

26. Mulla H, Lawson G, Peek GJ, Firmin RK, Upton DR. Plasma Concentrations of Midazolam in Neonates Receiving Extracorporeal Membrane Oxygenation. *ASAIO J*. 2003;49(1).
https://journals.lww.com/asaiojournal/Fulltext/2003/01000/Plasma_Concentrations_of_Midazolam_in_Neonates_Receiving_Extracorporeal_Membrane_Oxygenation_49_1.aspx

27. Zylbersztajn BL, Izquierdo G, Santana RC, et al. Therapeutic Drug Monitoring of Vancomycin in Pediatric Patients With Extracorporeal Membrane Oxygenation Support. *J Pediatr Pharmacol Ther* JPPT. 2018;23(4):305-310. doi:10.5863/1551-6776-23.4.305

28. Kleiber N, Mathôt RAA, Ahsman MJ, Wildschut ED, Tibboel D, de Wildt SN. Population pharmacokinetics of intravenous clonidine for sedation during paediatric extracorporeal membrane oxygenation and continuous venovenous hemofiltration. *Br J Clin Pharmacol*. 2017;83(6):1227-1239. 
doi:10.1111/bcp.13235

29. Ahsman MJ, Wildschut ED, Tibboel D, Mathot RA. Pharmacokinetics of Cefotaxime and Desacetylcefotaxime in Infants during Extracorporeal Membrane Oxygenation. *Antimicrob Agents Chemother*. 2010;54(5):1734-1741. 
doi:10.1128/AAC.01696-09

30. Bhatt-Mehta V, Johnson CE, Schumacher RE. Gentamicin pharmacokinetics in
term neonates receiving extracorporeal membrane oxygenation.

*Pharmacotherapy*. 1992;12(1):28-32.

31. Dillman NO, Messinger MM, Dinh KN, et al. Evaluation of the Effects of Extracorporeal Membrane Oxygenation on Antiepileptic Drug Serum Concentrations in Pediatric Patients. *J Pediatr Pharmacol Ther JPPT*. 2017;22(5):352-357. doi:10.5863/1551-6776-22.5.352

32. Moffett BS, Morris J, Galati M, Munoz F, Arikan AA. Population Pharmacokinetics of Vancomycin in Pediatric Extracorporeal Membrane Oxygenation*. *Pediatr Crit Care Med*. 2018;19(10).

https://journals.lww.com/pccmjournal/Fulltext/2018/10000/Population_Pharmacokinetics_.aspx

33. Autmizguine J, Hornik CP, Benjamin DK, et al. Pharmacokinetics and Safety of Micafungin in Infants Supported with Extracorporeal Membrane Oxygenation. *Pediatr Infect Dis J*. 2016;35(11):1204-1210.

doi:10.1097/INF.0000000000001268

34. Aebi C, Headrick CL, McCracken GH, Lindsay CA. Intravenous ribavirin therapy in a neonate with disseminated adenovirus infection undergoing extracorporeal membrane oxygenation: pharmacokinetics and clearance by hemofiltration. *J Pediatr*. 1997;130(4):612-615.

35. Ahsman MJ, Hanekamp M, Wildschut ED, Tibboel D, Mathot RAA. Population Pharmacokinetics of Midazolam and Its Metabolites during Venoarterial Extracorporeal Membrane Oxygenation in Neonates. *Clin Pharmacokinet*. 2010;49(6):407-419. doi:10.2165/11319970-000000000-00000

36. Amaker RD, DiPiro JT, Bhatia J. Pharmacokinetics of vancomycin in critically ill infants undergoing extracorporeal membrane oxygenation. *Antimicrob Agents Chemother*. 1996;40(5):1139-1142. doi:10.1128/AAC.40.5.1139
37. Geiduschek JM, Lynn AM, Bratton SL, et al. Morphine pharmacokinetics during continuous infusion of morphine sulfate for infants receiving extracorporeal membrane oxygenation. *Crit Care Med*. 1997;25(2):360.

38. Cies JJ, Moore WS, Nichols K, Knoderer CA, Carella DM, Chopra A. Population Pharmacokinetics and Pharmacodynamic Target Attainment of Vancomycin in Neonates on Extracorporeal Life Support. *Pediatr Crit Care Med*. 2017;18(10). https://journals.lww.com/pccmjournal/Fulltext/2017/10000/Population_Photokinetiics_.

39. Cohen P, Collart L, Prober CG, Fischer AF, Blaschke TF. Gentamicin pharmacokinetics in neonates undergoing extracorporeal membrane oxygenation. *Pediatr Infect Dis J*. 1990;9(8):562-566.

40. Wells TG, Fasules JW, Taylor BJ, Kearns GL. Pharmacokinetics and pharmacodynamics of bumetanide in neonates treated with extracorporeal membrane oxygenation. *J Pediatr*. 1992;121(6):974-980. doi:10.1016/S0022-3476(05)80355-5

41. Wells TG, Heulitt MJ, Taylor BJ, Fasules JW, Kearns GL. Pharmacokinetics and Pharmacodynamics of Ranitidine in Neonates Treated with Extracorporeal Membrane Oxygenation. *J Clin Pharmacol*. 1998;38(5):402-407. doi:10.1002/j.1552-4604.1998.tb04443.x

42. Elliott ES, Buck ML. Phenobarbital Dosing and Pharmacokinetics in a Neonate Receiving Extracorporeal Membrane Oxygenation. *Ann Pharmacother*. 1999;33(4):419-422. doi:10.1345/aph.18248

43. Brüggemann RJM, Antonius T, Heijst A van, Hoogerbrugge PM, Burger DM, Warris A. Therapeutic Drug Monitoring of Voriconazole in a Child With Invasive Aspergillosis Requiring Extracorporeal Membrane Oxygenation. *Ther Drug Monit*. 2008;30(6):643. doi:10.1097/FTD.0b013e3181898b0c
44. Koch BCP, Wildschut ED, Goede AL de, Hoog M de, Brüggemann RJM. Insufficient serum caspofungin levels in a paediatric patient on ECMO. *Med Mycol Case Rep.* 2012;2:23-24. doi:10.1016/j.mmcr.2012.12.006

45. Larochelle JM, Murvant MD, Creel AM, Tilton A. Levetiracetam use during extracorporeal membrane oxygenation in an adolescent patient. *Crit Care Shock.* 2016;19(2):41-43.

46. Spriet I, Annaert P, Meersseman P, et al. Pharmacokinetics of caspofungin and voriconazole in critically ill patients during extracorporeal membrane oxygenation. *J Antimicrob Chemother.* 2009;63(4):767-770. doi:10.1093/jac/dkp026

47. Donadello K, Roberts JA, Cristallini S, et al. Vancomycin population pharmacokinetics during extracorporeal membrane oxygenation therapy: a matched cohort study. *Crit Care Lond Engl.* 2014;18(6):632. doi:10.1186/s13054-014-0632-8

48. Moffett BS, Morris J, Galati M, Munoz FM, Arian AA. Population Pharmacokinetic Analysis of Gentamicin in Pediatric Extracorporeal Membrane Oxygenation. *Ther Drug Monit.* 2018;40(5). https://journals.lww.com/drug-monitoring/Fulltext/2018/10000/Population_Pharmacokinetic_Analysis_of_Gentamicin.7.a

49. Smith BS, Yogaratnam D, Levasseur-Franklin KE, Forni A, Fong J. Introduction to Drug Pharmacokinetics in the Critically Ill Patient. *Chest.* 2012;141(5):1327-1336. doi:10.1378/chest.11-1396

50. Belle DJ, Singh H. Genetic Factors in Drug Metabolism. 2008;77(11):8.

51. Pistolesi V, Morabito S, Di Mario F, Regolisti G, Cantarelli C, Fiaccadori E. A Guide to Understanding Antimicrobial Drug Dosing in Critically Ill Patients on Renal Replacement Therapy. *Antimicrob Agents Chemother.* 2019;63(8).
52. Churchwell MD, Mueller BA. THE CLINICAL APPLICATION OF CRRT—CURRENT STATUS: Drug Dosing During Continuous Renal Replacement Therapy. *Semin Dial.* 2009;22(2):185-188. doi:10.1111/j.1525-139X.2008.00541.x

53. Maksoud E, Koehl B, Facchin A, et al. Population Pharmacokinetics of Cefotaxime and Dosage Recommendations in Children with Sickle Cell Disease. *Antimicrob Agents Chemother.* 2018;62(4). doi:10.1128/AAC.00637-17

54. Gouyon JB, Pechinot A, Safran C, Chretien P, Sandre D, Kazmierczak A. Pharmacokinetics of cefotaxime in preterm infants. *Dev Pharmacol Ther.* 1990;14(1):29-34.

55. Pettit RS, Neu N, Cies JJ, et al. Population pharmacokinetics of meropenem administered as a prolonged infusion in children with cystic fibrosis. *J Antimicrob Chemother.* 2016;71(1):189-195. doi:10.1093/jac/dkv289

56. Cies JJ, Moore WS, Enache A, Chopra A. Population Pharmacokinetics and Pharmacodynamic Target Attainment of Meropenem in Critically Ill Young Children. *J Pediatr Pharmacol Ther JPPT.* 2017;22(4):276-285. doi:10.5863/1551-6776-22.4.276

57. Cies JJ, Shankar V, Schlichting C, Kuti JL. Population Pharmacokinetics of Piperacillin/Tazobactam in Critically Ill Young Children: *Pediatr Infect Dis J.* 2014;33(2):168-173. doi:10.1097/INF.0b013e3182a743c7

58. Watt KM, Hornik CP, Balevic SJ, et al. Pharmacokinetics of ticarcillin-clavulanate in premature infants. *Br J Clin Pharmacol.* 2019;85(5):1021-1027. doi:10.1111/bcp.13882

59. Sampson MR, Bloom BT, Lenfestey RW, et al. Population Pharmacokinetics of Intravenous Acyclovir in Preterm and Term Infants. *Pediatr Infect Dis J.*
60. Kimberlin DW, Acosta EP, Prichard MN, et al. Oseltamivir Pharmacokinetics, Dosing, and Resistance Among Children Aged <2 Years With Influenza. *J Infect Dis.* 2013;207(5):709-720. doi:10.1093/infdis/jis765

61. Connor E, Morrison S, Lane J, Oleske J, Sonke RL, Connor J. Safety, tolerance, and pharmacokinetics of systemic ribavirin in children with human immunodeficiency virus infection. *Antimicrob Agents Chemother.* 1993;37(3):532-539.

62. McJunkin JE, Nahata MC, De Los Reyes EC, et al. Safety and Pharmacokinetics of Ribavirin for the Treatment of La Crosse Encephalitis: *Pediatr Infect Dis J.* 2011;30(10):860-865. doi:10.1097/INF.0b013e31821c922c

63. Neely M, Jafri HS, Seibel N, et al. Pharmacokinetics and Safety of Caspofungin in Older Infants and Toddlers. *Antimicrob Agents Chemother.* 2009;53(4):1450-1456. doi:10.1128/AAC.01027-08

64. Leroux S, Jacqz-Aigrain E, Elie V, et al. Pharmacokinetics and safety of fluconazole and micafungin in neonates with systemic candidiasis: a randomized, open-label clinical trial. *Br J Clin Pharmacol.* 2018;84(9):1989-1999. doi:10.1111/bcp.13628

65. Shin JW, Jung YS, Park K, et al. Experience and pharmacokinetics of Levetiracetam in Korean neonates with neonatal seizures. *Korean J Pediatr.* 2017;60(2):50-54. doi:10.3345/kjp.2017.60.2.50

66. Chhun S, Jullien V, Rey E, Dulac O, Chiron C, Pons G. Population pharmacokinetics of levetiracetam and dosing recommendation in children with epilepsy. *Epilepsia.* 2009;50(5):1150-1157. doi:10.1111/j.1528-1167.2008.01974.x
67. Sullivan JE, Witte MK, Yamashita TS, Myers CM, Blumer JL. Pharmacokinetics of bumetanide in critically ill infants. *Clin Pharmacol Ther*. 1996;60(4):405-413. doi:10.1016/S0009-9236(96)90197-6

68. Marshall JD, Wells TG, Letzig L, Kearns GL. Pharmacokinetics and Pharmacodynamics of Bumetanide in Critically Ill Pediatric Patients. *J Clin Pharmacol*. 1998;38(11):994-1002. doi:10.1177/009127009803801102

69. de Wildt SN, de Hoog M, Vinks AA, van der Giesen E, van den Anker JN. Population pharmacokinetics and metabolism of midazolam in pediatric intensive care patients: *Crit Care Med*. 2003;31(7):1952-1958. doi:10.1097/01.ccm.0000084806.15352.da

70. Wildt SN de, Kearns GL, Hop WCJ, Murry DJ, Abdel-Rahman SM, Anker JN van den. Pharmacokinetics and metabolism of intravenous midazolam in preterm infants. *Clin Pharmacol Ther*. 2001;70(6):525-531. doi:10.1016/S0009-9236(01)15882-0

71. Asseff IL, Gaucin GB, Olguín HJ, et al. Pharmacokinetics of ranitidine in preterm and term neonates with gastroesophageal reflux. *BMC Pediatr*. 2016;16. doi:10.1186/s12887-016-0630-x

72. Olguín HJ, Martínez HO, Pérez CF, et al. Pharmacokinetics of sildenafil in children with pulmonary arterial hypertension. *World J Pediatr*. 2017;13(6):588-592. doi:10.1007/s12519-017-0043-4

Tables

Table 1. Characteristics of Included Studies and Study Populations
| Drug                          | Total no. of patients, N | Study population \( a \) | Age, median [range] |
|------------------------------|--------------------------|--------------------------|--------------------|
| **Antibiotics**              |                          |                          |                    |
| Cefotaxime\(^{29}\)         | 37                       | Neonates and infants     | 1 – 1              |
| Gentamicin\(^{18,20,23,30,39,48}\) | 120                      | < 18 years               | 2 – 3              |
| Meropenem\(^{9,10,13}\)     | 3                        | < 18 years               | 10 – 1             |
| Piperacillin/tazobactam\(^{17}\) | 6                        | Neonates and infants     | 8 – 2              |
| Ticarcillin-clavulanate\(^{19}\) | 2                        | Adolescents              | 2190 – 2           |
| Vancomycin\(^{12,16,27,32,36,38}\) | 188                      | < 18 years               | 0 – 5              |
| **Anti-virals**              |                          |                          |                    |
| Acyclovir\(^{8}\)           | 1                        | Infant                   | Not specified      |
| Oseltamivir\(^{14}\)        | 1                        | Adolescent               | 219                |
| Ribavirin\(^{34}\)          | 1                        | Neonate                  | 14                 |
| **Anti-fungals**             |                          |                          |                    |
| Caspofungin\(^{44}\)        | 1                        | Infant                   | 33                 |
| Fluconazole\(^{24,25}\)     | 31                       | < 18 years               | 1 – 6              |
| Micafungin\(^{33}\)         | 12                       | < 18 years               | 0 – 5              |
| Voriconazole\(^{43,46}\)    | 2                        | < 18 years               | 3056 [182]         |
| **Anti-convulsants**         |                          |                          |                    |
| Fos-phenytoin\(^{31}\)      | 6                        | < 18 years               | Not specified      |
| Levetiracetam\(^{45}\)      | 1                        | Adolescent               | 584                |
| **Others**                   |                          |                          |                    |
| Bumetanide\(^{40}\)         | 11                       | Neonates                 | 1 – 1              |
| Clonidine\(^{28}\)          | 22                       | Infants                  | 30 (1              |
| Heparin\(^{15}\)            | 12                       | < 18 years               | 0 – 5              |
| Midazolam\(^{26,35}\)       | 40                       | Neonates                 | 0.17 – 1           |
| Morphine\(^{21,37}\)        | 25                       | Neonates                 | 0 – 1              |
| Ranitidine\(^{41}\)         | 13                       | Neonates                 | 0 – 1              |
| Sildenafil\(^{11}\)          | 11                       | Neonates and infants     | 20 (2              |

\( a \) Neonates: 0 – 28 days of age), infants: 29 days – 1 year of age, children: >1 – 12 years of age and adolescents: >12 – 18 years of age

Table 2. Summary of pharmacokinetic changes (\(V_d\) and clearance) published in critically ill pediatric patients on ECMO
| Drug               | Volume of distribution (% change) | Clearance (% change) |
|--------------------|----------------------------------|---------------------|
| **Antibiotics**    |                                  |                     |
| Cefotaxime         | ⩾ (23.8)                         |                     |
| Gentamicin         | ⩾ a (28.8 – 58.8)                | ⩾ d (26.3 – 31.7)   |
| Meropenem          | N.A.                             |                     |
| Piperacillin/tazobactam | ⩾ f (37.3) | N.A. d |
| Ticarcillin-clavulanate | N.A. c |                     |
| Vancomycin         | ⩾ a,b                            |                     |
| **Anti-virals**    |                                  |                     |
| Acyclovir          | ⩾ f (50)                         | N.A. d |
| Oseltamivir        | N.A. c                           |                     |
| Ribavirin          | ⩾ f (69.3 – 82.2)                | N.A. d |
| **Anti-fungals**   |                                  |                     |
| Caspofungin        | N.A. c                           | ⩾ f (455)           |
| Fluconazole        | ⩾ a (39.8)                       |                     |
| Micafungin         | ⩾ f (80.8)                       | ⩾ f (105)           |
| Voriconazole       | ⩾ a                              |                     |
| **Anti-convulsants** |                                  |                     |
| Fos-phenytoin      | ⩾ a                              | N.A. d |
| Levetiracetam      | ⩾ f (33.6 – 242)                 |                     |
| Phenobarbital      | ⩾ a                              | N.A. d |
| **Others**         |                                  |                     |
| Bumetanide         | ⩾ f                              | ⩾ f (42.7 – 83.8)   |
| Clonidine          | ⩾ a (55)                         | ⩾ a (100)           |
| Heparin            | N.A. e                           | N.A. e |
| Midazolam          | ⩾ f (188 – 345)                  | ⩾ f (192)           |
| Morphine           | N.A. c                           | ⩾ b (84.3)          |
| Ranitidine         | N.A. c                           | ⩾ f (94.7)          |
| Sildenafil         | ⩾ f (68.9)                       | ⩾ f (24.7)          |

Abbreviations: NA, not available; ⩾, increased relative to non-ECMO controls; ⩾, decreased relative to non-ECMO controls, ⩾, equal to non-ECMO controls.

a Clearance and $V_d$ values between ECMO and non-ECMO groups were compared within the same studies.

b Clearance and $V_d$ have been shown to be altered compared to the non-ECMO group when comparisons are made with historical controls.

c Not available because volume of distribution was not measured and reported.

d Not available because clearance was not measured and reported.

e Not available because data on non-ECMO comparators were not available.

f Clearance and $V_d$ values between ECMO and non-ECMO groups were compared
against historical controls.

Figures
Figure 1

PRISMA Diagram of Study Selection

Abbreviations: PK, pharmacokinetics; ECMO, extracorporeal membrane oxygenation; CL, clearance; Vd, volume of distribution
Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.

Supplementary Table 1.docx
Supplementary Information 1.docx