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

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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,[1,2] 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.[3,4]

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 (V_d) 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 V_d, 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..[7] 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).[8–10] 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.[8,9,11–25] Of those that reported the type of ECMO used, 10 studies (24%) employed both veno-venous (VV) and venous-arterial (VA) ECMO,[26–32,32,33] 10 studies (24%) used VA ECMO only,[10,34–42] and the remaining 4 studies (10%) used VV ECMO only.[43–46] Only 7 studies (17%) were conducted with intra-study comparisons to non-ECMO controls.[12,18,25,28,31,39,46]

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%),[8,11,12,17,18,20,22–36,38–40,42,43,45–48] with the remaining 7 other drugs having only clearance values reported without V_d values.[9,10,13,14,19,21,37,41,44] 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.[19,23,24,31–36] Decreased V_d was reported for 2 drugs: acyclovir and ribavirin (50 and 69%, respectively).[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-phentyoin, phenobarbital and bumetanide.[2,12,31,40]

Of note, vancomycin was studied in 6 separate studies, only one of which included a non-ECMO comparator group[12] while the remaining 5 did not.[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.[12] However, when the V_d values were compared against historical controls, increased V_d was observed compared to pediatric patients not on ECMO.[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).

Alterations in drug clearance in ECMO-supported patients

Out of the 23 drugs studied, drug clearance was reported for 17 drugs (74%),[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.[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).[19,39–41] Increased clearance was reported for caspofungin, micafungin, clonidine, midazolam, morphine and sildenafil (range: 25-455% increase relative to non-ECMO controls).[11,28,33,35,37,46] Changes in clearance were not observed for cefotaxime, meropenem, vancomycin, oseltamivir, fluconazole, voriconazole and levetiracetam.[10,12,14,25,29,45,46]

Similarly, for vancomycin, the study by Buck et al.[12], 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.[16,27,32,47] 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.[10,14,22,24,25,28,29,32,35–39] Seven studies had compliance rate of less than 50%.[8,9,11,15–17,42]

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, [2,3] 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[27,32,36,38,47] while others demonstrated decreased values or no change[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.[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 distrbution

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.

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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.

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Tables

Table 1. Characteristics of Included Studies and Study Populations

Drug	Total no. of patients, N	Study population[a]	Age, median (IQR) [range], days
Antibiotics			
Cefotaxime[29]	37	Neonates and infants	[1 – 199]
Gentamicin[18,20,23,30,39,48]	120	< 18 years	[2 – 399]
Meropenem[9,10,13]	3	< 18 years	[10 – 1460]
Piperacillin/tazobactam[17]	6	Neonates and infants	[8 – 210]
Ticarcillin-clavulanate[19]	2	Adolescents	[2190 – 2372.5]
Vancomycin[12,16,27,32,36,38]	188	<18 years	[0 – 5510]
Anti-virals			
Acyclovir[8]	1	Infant	Not specified
Oseltamivir[14]	1	Adolescent	2190
Ribavirin[34]	1	Neonate	14
Anti-fungals			
Caspofungin[44]	1	Infant	330
Fluconazole[24,25]	31	< 18 years	[1 – 6498]
Micafungin[33]	12	< 18 years	[0 – 574]
Voriconazole[43,46]	2	<18 years	3056 [1825 – 6205]
Anti-convulsants			
Fos-phenytoin[31]	6	< 18 years	Not specified
Levetiracetam[45]	1	Adolescent	5840
Phenobarbital[22,31,42]	28	<18 years	Not specified
Others			
Bumetanide[40]	11	Neonates	[1 – 7]
Clonidine[28]	22	Infants	30 (192)
Heparin[15]	12	< 18 years	[0 – 5910]
Midazolam[26,35]	40	Neonates	[0.17 – 18]
Morphine[21,37]	25	Neonates	[0 – 9]
Ranitidine[41]	13	Neonates	[0 – 4]
Sildenafil[11]	11	Neonates and infants	20 [2 – 121]

[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[29,53,54]	↑ [f] (23.8)	↔ [f]
Gentamicin[18,20,23,30,39,48]	↑[a] (28.8 – 58.8)	↓[a] (26.3 – 31.7)
Meropenem[9,10,13,55,56]	N.A.	↔ [f]
Piperacillin/tazobactam[17,57]	↑ [f] (37.3)	N.A. [d]
Ticarcillin-clavulanate[19,58]	N.A. [c]	↓ [f] (46.8)
Vancomycin[12,16,27,32,36,38]	↔[a,b]	↔[a,b]
Anti-virals		
Acyclovir[8,59]	↓ [f] (50)	N.A. [d]
Oseltamivir[14,60]	N.A. [c]	↔ [f]
Ribavirin[34,61,62]	↓ [f] (69.3 – 82.2)	N.A. [d]
Anti-fungals		
Caspofungin[44,63]	N.A. [c]	↑ [f] (455)
Fluconazole[24,25]	↑[a] (39.8)	↔[a]
Micafungin[33,64]	↑ [f] (80.8)	↑ [f] (105)
Voriconazole[43,46]	↔[a]	↔[a]
Anti-convulsants		
Fos-phenytoin[31]	↔[a]	N.A. [d]
Levetiracetam[45,65,66]	↑ [f] (33.6 – 242)	↔
Phenobarbital[22,31,42]	↔[a]	N.A. [d]
Others		
Bumetanide[40,67,68]	↔ [f]	↓ [f] (42.7 – 83.8)
Clonidine[28]	↑[a] (55)	↑[a] (100)
Heparin[15]	N.A. [e]	N.A. [e]
Midazolam[26,35,69,70]	↑ [f] (188 – 345)	↑ [f] (192)
Morphine[21,37]	N.A. [c]	↑[b] (84.3)
Ranitidine[41,71]	N.A. [c]	↓ [f] (94.7)
Sildenafil[11,72]	↑ [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.

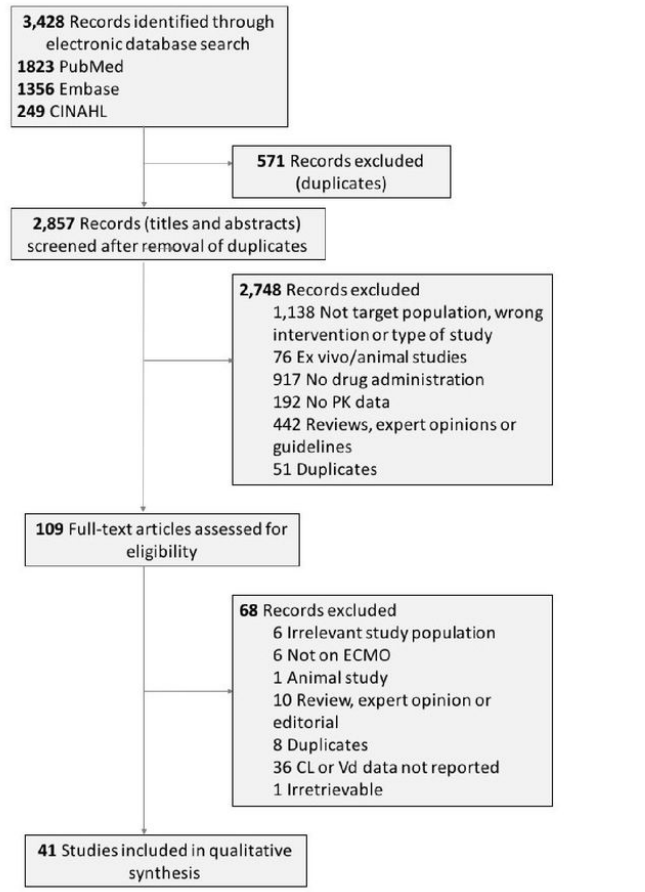
[c] Not available because volume of distribution was not measured and reported.

[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



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

Figure 1

PRISMA Diagram of Study Selection

Supplementary Files

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- SupplementaryTable1.docx
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