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Patterns of Medication Exposure in Children on Extracorporeal Membrane Oxygenation: A Step in Prioritizing Future Pharmacologic Studies

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Objectives: To identify medications administered to pediatric patients on extracorporeal membrane oxygenation and to review the available pharmacokinetics and pharmacodynamics literature for the most commonly administered medications.

Design: Retrospective single-center study.

Setting: ICUs at Children's Hospital of Philadelphia.

Patients: Pediatric patients supported by extracorporeal membrane oxygenation between October 1, 2014, and September 30, 2018.

Interventions: None.

Measurements and Main Results: Drug exposure was described according to age group (< 1 mo, 1 mo to < 2 yr, 2 to < 12 yr, and > 12 yr) and ICU (cardiac, neonatal, pediatric). The association of drug exposure with patient's characteristics was examined using one-way analysis of variance for categorical variables and linear regression for continuous variables. All pharmacokinetics and pharmacodynamics literature for the 50 most commonly administered medications on extracorporeal membrane oxygenation was reviewed, with inclusion of studies that reported dosing regimens in conjunction with pharmacokinetics or pharmacodynamics data. A total of 179 different medications were administered to 254 children. Cumulative drug exposure increased with the duration of extracorporeal membrane oxygenation from a median (interquartile) of 10 drugs (6–14) at 1 week to 31 drugs (21–45) at 5 weeks following cannulation. There were significant differences in total drug exposure between age groups and ICUs. With exclusion of in vitro studies, published literature was available to support the use of 40% (20/50) of the most commonly administered medications. Dosing guidance was available for 20% (10/50) of medications and was primarily based on simulations and retrospective studies focusing on neonates and infants.

Conclusions: This study highlights specific needs for future pharmacokinetics and pharmacodynamics studies. Dosing guidelines are essential to optimize the care of critically ill children supported by extracorporeal membrane oxygenation.

Key Words: critical care; drug utilization; extracorporeal life support; pediatrics; pharmacokinetics; review literature

Extracorporeal membrane oxygenation (ECMO) is an advanced life support technique which provides temporary cardiopulmonary support for children and adults with severe cardiac or respiratory failure. Venovenous ECMO supports the lung, whereas venoarterial ECMO supports both the heart and the lungs. ECMO affects pharmacokinetics by a variety of mechanisms including increased volume of distribution (Vd), sequestration of drug in the circuit, and decreased clearance. However, the extent of these pharmacokinetics changes remains poorly characterized and vary between drugs (1, 2). The increase in the Vd is relatively more important for hydrophilic drugs as they have smaller Vd. The impact of drug sequestration correlates with

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specific drug physicochemical properties, occurring mostly with highly protein-bound and lipophilic molecules, and the age of the circuit, with older circuits sequestering less due to presumed saturation (3–5). Contemporary ECMO circuits are smaller and use polyvinyl chloride heparin-coated tubing and polymethylpentene oxygenator instead of noncoated tubing and a silicone oxygenator. Although drug sequestration in these newer circuits may not be as significant as previous versions, adsorption remains an important consideration. Recent in vitro studies using contemporary circuits demonstrate that less than 30% of lipophilic drugs such as fentanyl and midazolam remain in the circuit after 24 hours (4, 6). Drug clearance is also decreased in children on ECMO (7–12). However, this effect is not well characterized and is most likely multifactorial.

Children on ECMO are critically ill and often have multiple organ dysfunction and critical illness also impacts drug disposition (13, 14). Critical illness often promotes an inflammatory response, which is further promoted by the ECMO circuit (15). Inflammation has the potential to impact pharmacokinetics/pharmacodynamics by down-regulation of drug-metabolizing enzymes, transporters, and receptors (16, 17).

The tremendous variability caused by the additive effect of patient-, disease-, and ECMO-related factors makes drug dosing during ECMO challenging. There is a paucity of dosing guidance in the literature describing the impact of patient-disease-ECMO on drug disposition, and few data on which medications are commonly used in the care of the children on ECMO. An understanding of the drugs that are used most frequently yet lack dosing guidance in this vulnerable population will inform future clinical research on those drugs, ultimately improving therapeutic efficacy and minimizing toxicity of these medications in the ECMO population. Studies such as this have been previously published to align drug utilization in critically ill children (18) and children receiving dialysis (19) and help target future studies for maximal impact. This study aimed to characterize the patterns of medication exposure in children supported with ECMO and align utilization data with reported guidance in the pharmacokinetics/pharmacodynamics literature. Our hypothesis was that more than 50% of the commonly used medications in children on ECMO were administered in the absence of any pharmacokinetics/pharmacodynamics data guiding their use.

METHODS

This was a single-center retrospective study conducted at Children's Hospital of Philadelphia (CHOP). After Institutional Review Board approval, all children who were supported with ECMO between October 1, 2014, and September 30, 2018, were included. Subjects were identified by querying the electronic medical record system (Epic, Epic Systems Corporation Software, Verona, WI) and the institutional ECMO database. Collected data included the following: 1) patient demographics (age and weight at the time of ECMO cannulation, race, sex, in-hospital length of stay); 2) principal diagnosis; 3) ECMO-related data (date and time of ECMO cannulation and decannulation, type of ECMO); 4) date and time of each medication administered during each ECMO day; and 5) ICU (neonatal ICU [NICU], PICU, and cardiac ICU [CICU]). Medication-related data were pulled from the patient's medication administration record (MAR; Epic, Epic Systems Corporation Software). Topical and ocular agents, glycerin suppositories, IV maintenance fluids, electrolytes replacements, and parenteral nutrition were excluded from analysis. Drugs were classified using the U.S. Pharmacopeia Therapeutic Categories Model Guidelines suggested by the U.S. Food and Drug Administration (FDA) (20). Each hospital admission was considered as a single patient encounter and patients who were placed on ECMO during different admissions were included for each separate encounter. However, multiple ECMO courses during a single admission were included only once for a specific hospitalization.

Statistical Analysis

Because prescription practices, as well as pharmacokinetics, vary based on age, patients were stratified into the following age groups based on the FDA pediatric age criteria, less than 1 month old (neonates), 1 month to less than 2 years old (infants), 2 to less than 12 years old (children), and more than 12 years old (adolescents) (21). Due to variability in drug prescription practices among ICUs, patients were also classified according to location (CICU, NICU, and PICU). For each drug, exposure was defined as the percent of total patients in each group with a drug exposure at any time during the ECMO course. Drug exposure was reported both for the specific generic drugs and their corresponding therapeutic drug categories. Cumulative drug exposure was defined as the additive number of unique drug exposures during an ECMO course, regardless of duration; multiple administrations of a single drug counting as one exposure. Cumulative drug exposure was reported as median and interquartile range (IQR). The association of drug exposure with patient's characteristics was examined using one-way analysis of variance for categorical variables and linear regression for continuous variables. The association of exposure to different therapeutic drug categories with age groups was analyzed using a chi-square or a Fisher exact test where appropriate.

Dosing Guidance

For each of the 50 most commonly administered medications across the entire cohort, the literature was reviewed for the evidence supporting pediatric dosing regimens used during ECMO. The literature search was performed in July 2019 using two databases (PubMed and Ovid EMBASE). Reference lists of relevant publications were cross-referenced. The search was limited to studies published in English. Search terms included the generic name of the drug, "pharmacokinetics, pharmacodynamics, ECMO, extracorporeal membrane oxygenation, extracorporeal life support, children, infants, neonates, and pediatrics." Two independent reviewers performed the literature search. All studies that reported dosing regimens in conjunction with either pharmacokinetics or pharmacodynamics data were included. Although pharmacodynamics typically refers to the relationship between drug concentrations and the resulting effect, studies that explored the relationship between administered drug dosage and the effect (efficacy and adverse effects) were also included. This was done to be inclusive because many studies did not include plasma drug concentrations or pharmacokinetics analyses.

RESULTS

A total of 255 children were supported with ECMO between October 1, 2014, and September 30, 2018. One neonate was excluded from analysis because no drug administration was recorded during the ECMO course in the CICU. That patient underwent a Norwood operation for hypoplastic left heart syndrome and was unable to separate from cardiopulmonary bypass following surgery. The patient had severe neo-aortic insufficiency on diagnostic catheterization and remained hemodynamically unstable on ECMO, therefore, was removed from technologic support in the CICU and died. Median (IQR) age and weight were 0.6 months (0.07–28.7) and 5.7 kg (4.04–12.6), respectively. The type of ECMO support provided was venoarterial in 84% (214/254) and venovenous in 16% (40/254). ECMO duration and in-hospital length of stay were 7 days (3–13) and 41 days (20–77), respectively. ECMO decannulation successfully occurred in 78% (197/254), whereas 62% (158/254) survived to hospital discharge. The most common diagnoses were congenital heart disease in

TABLE 1. Population Demographics Stratified by Hospitalization Units

Patient Characteristics	Neonatal ICU (*n* = 87)	Cardiac ICU (*n* = 130)	PICU (*n* = 37)	All (*n* = 254)
Age,[a] median (IQR)	1 d (1–2)	3.36 mo (0.33–29.84)	12.02 yr (3.33–15.44)	0.59 mo (0.07–28.69)
Male, *n* (%)	47 (54)	71 (55)	14 (38)	132 (52)
Weight (kg), median (IQR)	4.73 (3.8–5.73)	6.5 (4.18–13.4)	31.6 (13.6–54.9)	5.71 (4.04–12.6)
Height (cm), median (IQR)	55 (51.5–59)	60 (52.65–86.8)	135.8 (86–158)	58.5 (52.5–83)
Ethnicity, *n* (%)				
Black	20 (23)	23 (18)	13 (35)	56 (22)
Hispanic	6 (7)	21 (16)	2 (5)	29 (11)
White	41 (47)	60 (46)	15 (41)	116 (46)
Other	15 (17)	19 (15)	6 (16)	41 (16)
Missing	5 (6)	6 (5)	1 (3)	12 (5)
ECMO duration (d), median (IQR)	11.33 (6.58–19.25)	4.69 (2.63–8.5)	6.69 (3.38–12.83)	6.69 (3.38–12.83)
ECMO type, *n* (%)				
Venoarterial	69 (79)	127 (98)	18 (49)	214 (84)
Venovenous	18 (21)	3 (2)	19 (51)	40 (16)
Length of stay (d), median (IQR)	52.18 (23.12–116.38)	37.96 (18.72–62.18)	30.68 (15.14–58.50)	40.68 (19.50–77.35)
Survived ECMO, *n* (%)	78 (90)	96 (74)	23 (62)	197 (78)
Survived to discharge or transfer, *n* (%)	67 (77)	71 (55)	20 (54)	158 (62)
Primary diagnosis, *n* (%)				
Acquired heart disease	0 (0)	23 (18)	0 (0)	23 (9)
Acute respiratory distress syndrome	1 (1)	1 (1)	16 (43)	18 (5)
Congenital heart disease	0 (0)	104 (80)	0 (0)	104 (41)
Congenital diaphragmatic hernia	38 (44)	0 (0)	0 (0)	38 (15)
Congenital lung anomalies	8 (9)	0 (0)	0 (0)	8 (3)
Intoxication	0 (0)	0 (0)	5 (14)	5 (2)
Meconium aspiration	20 (23)	0 (0)	0 (0)	20 (8)
Pulmonary hypertension	16 (18)	0 (0)	2 (5)	18 (7)
Sepsis	4 (5)	0 (0)	7 (19)	11 (4)
Other	0 (0)	2 (2)	7 (19)	9 (4)

ECMO = extracorporeal membrane oxygenation, IQR = interquartile range.

[a]Unit varies according to hospitalization units.

41%, congenital diaphragmatic hernia in 15%, and acquired heart disease in 9%. ECMO occurred most commonly in the CICU in 51%, with 34% in the NICU, and 15% in the PICU. The most common diagnoses in the CICU, NICU, and PICU were congenital heart disease, congenital diaphragmatic hernia, and acute respiratory distress syndrome, respectively (**Table 1**).

A total of 179 different medications were administered to 254 children on ECMO. Cumulative drug exposure increased with the number of days on ECMO, with a median exposure to 10 drugs (6–14) at 1 week to 31 drugs (21–45) at 5 weeks following ECMO cannulation ($p < 0.05$). Total drug exposure was significantly different between age groups ($p < 0.05$) and ICUs ($p < 0.05$) (**Fig. 1**).

The most commonly administered therapeutic categories were cardiovascular agents (99%), antibiotics (98%), analgesics (97%), blood modifiers (93%), muscle relaxants (83%), and sedatives (83%). The proportions of children from each age groups exposed to different therapeutic categories are depicted in **Figure 2**. Infants had significantly higher exposures to antibiotics and analgesics, whereas older children and adolescents received more blood glucose regulators (insulin). There was also a significant difference in exposure to steroids and gastrointestinal agents between age groups.

Specific medications administered varied between age groups, as shown in **Table 2**. Although vancomycin, cefepime, and cefazolin were antibiotics administered in all age groups, ampicillin and gentamicin were frequently used only in infants less than 1 month old. Hydrocortisone and hydralazine were also preferentially administered in infants less than 1 month old. In contrast, nicardipine, hydromorphone, and insulin were more commonly administered drugs in children more than 12 years old but were not as frequently used in younger children. Medication use also differed between ICUs, as depicted in **Table 3**. In the NICU, commonly administered anti-infectives included antiviral (acyclovir) and antifungal (amphotericin) in addition to antibiotics. Treprostinil, alprostadil, and pentobarbital were also commonly used in the NICU. Levetiracetam was frequently administered only in the CICU. Several medications were preferentially used in the PICU, notably methylprednisolone, insulin, norepinephrine, and piperacillin-tazobactam.

A total of 78 pharmacokinetics or pharmacodynamics studies were reviewed including 31 prospective, 24 retrospective, 11 in vitro studies, 10 case report, and two studies combining retrospective and prospective data. Population pharmacokinetics modeling was used in 11 of the prospective studies, four of the retrospective studies, and one of the combined prospective and retrospective study. Twenty-two studies (six prospective and 16 retrospective) focused exclusively on pharmacodynamics and did not include any pharmacokinetics data. Published pharmacokinetics/pharmacodynamics studies on ECMO were found for 56% (28/50) of the most commonly administered medications (**Table S1**, Supplemental Digital Content 1, http://links.lww.com/CCX/A93). When excluding in vitro studies, relevant literature was available for 40% medications (20/50). Dosing guidance was available for 20% medications (10/50): amiodarone, fentanyl, fluconazole, gentamicin, meropenem, midazolam, nicardipine, phenobarbital, ranitidine, and vancomycin. Dosing recommendations were mainly issued from simulations and retrospective observations that were not prospectively validated and focused on neonates and infants.

DISCUSSION

This study highlights the current lack of pharmacokinetics/pharmacodynamics data on commonly administered drugs in children supported with ECMO. There were no data available for nearly half of the medications reviewed, and dosing guidance was available for only 20% of them.

The therapeutic categories that have been more extensively studied in children on ECMO are analgesics, sedatives, and antibiotics. Nonetheless, the pharmacokinetics and pharmacodynamics of these medications are not fully understood. For instance, vancomycin pharmacokinetics has been relatively well characterized. A decreased clearance and an increased Vd have been described in infants and children (10, 12, 22, 23), with recommendations to initiate treatment with a higher dose and a prolonged dosing interval. However, there are some data in infants and children recommending shorter dosing intervals, similar to those used in children not supported with ECMO (24, 25). These conflicting results support the fact that vancomycin kinetics are not entirely understood. Furthermore, standard dosing regimens are effective in adults on ECMO (26–29); therefore, it may be reasonable to extrapolate these data to older children and adolescents. However, the exact age and circumstances at which standard dosing regimens would be adequate in children remain unknown. Despite their different outcomes, all studies share the same message: a one-dose-fits-all approach does not apply to critically ill children, and therapeutic drug monitoring (TDM) is essential to achieve optimal efficacy. Significant variability in pharmacokinetics parameters potentially leading to treatment failure has been well described in critically ill patients (13), making it imperative for pharmacokinetics studies to better understand and predict this inherent variability in this vulnerable population. Characterizing interindividual variability is even more critical if

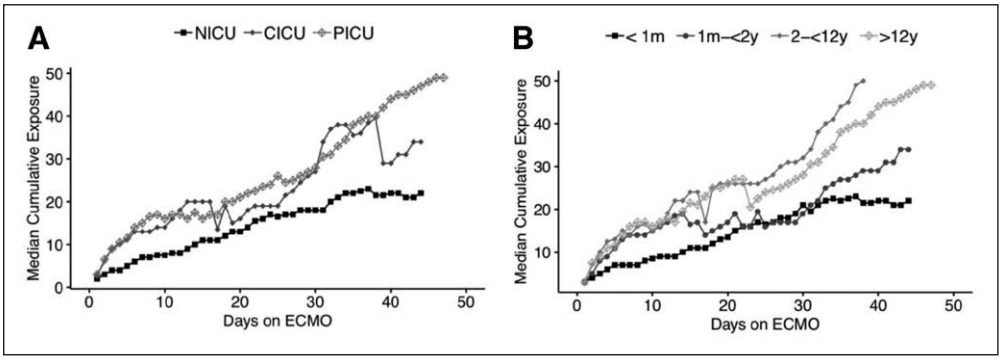

Figure 1. Median cumulative drug exposure versus days on extracorporeal membrane oxygenation (ECMO) stratified by hospitalization units (**A**) and age groups (**B**). CICU = cardiac ICU, NICU = neonatal ICU.

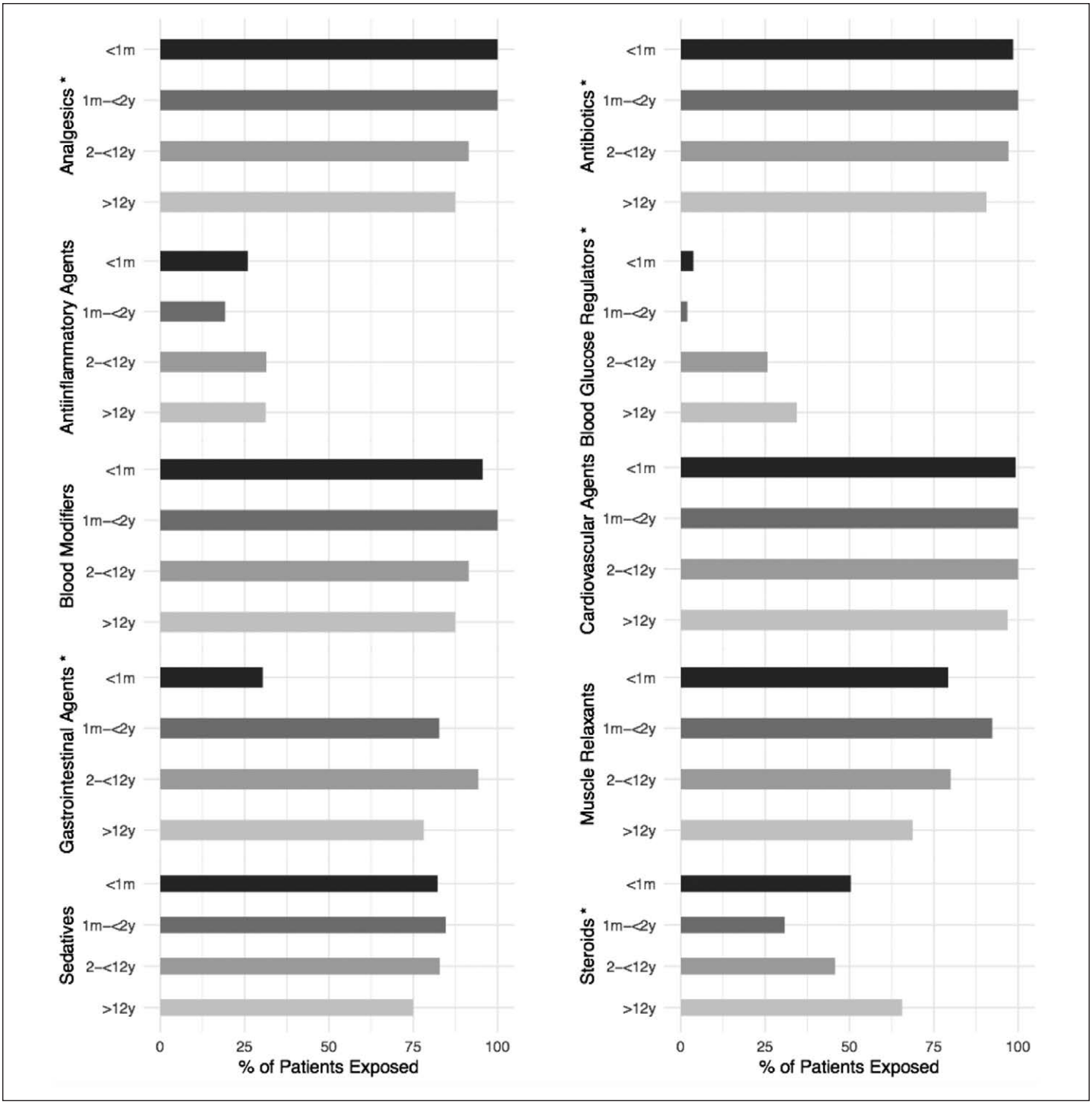

Figure 2. Proportion of children supported on extracorporeal membrane oxygenation exposed to different drug classes stratified by age groups (*$p < 0.05$).

1) the medication cannot be easily titrated to a desirable effect; 2) TDM is not routinely done; and 3) a narrow therapeutic range leads to an increased risk of toxicity.

This study also characterized medication exposures according to age and ICU where ECMO occurred and found significant differences in the exposition to individual and therapeutic drug categories between age groups and ICUs. This was done to highlight specific needs and help design future studies. First, there is an urgent need for pharmacologic studies focusing on drugs for which currently there are no data. Pantoprazole, vecuronium, and milrinone are examples of medications used across the pediatric age spectrum in the absence of pharmacokinetics/pharmacodynamics literature supporting their use on ECMO. Heparin is the most commonly used medication on ECMO, and more comprehensive understanding of heparin pharmacokinetics and pharmacodynamics is needed considering that thrombosis and

TABLE 2. Most Frequently Used Medications in Patients Supported by Extracorporeal Membrane Oxygenation Stratified by Age Groups

< 1 mo (*n* = 135), *n* (%)		1 mo to < 2 yr (*n* = 52), *n* (%)		2 to < 12 yr (*n* = 35), *n* (%)		> 12 yr (*n* = 32), *n* (%)	
Heparin	134 (99)	Heparin	52 (100)	Heparin	32 (91)	Heparin	28 (88)
Morphine	132 (98)	Morphine	51 (98)	Midazolam	32 (91)	Midazolam	25 (78)
Furosemide	118 (87)	Vecuronium[a]	49 (94)	Morphine	30 (86)	Epinephrine	21 (66)
Midazolam	116 (86)	Furosemide	47 (90)	Pantoprazole[a]	30 (86)	Furosemide	20 (63)
Vecuronium[a]	110 (81)	Midazolam	45 (87)	Furosemide	26 (74)	Morphine	20 (63)
Dopamine	95 (70)	Milrinone[a]	43 (83)	Vecuronium[a]	25 (71)	Vancomycin	20 (63)
Vancomycin	85 (63)	Vancomycin	42 (81)	Milrinone[a]	24 (69)	Pantoprazole[a]	19 (59)
Cefazolin	82 (61)	Cefepime	37 (71)	Vancomycin	22 (63)	Vecuronium[a]	19 (59)
Fentanyl	78 (58)	Chlorothiazide[a]	37 (71)	Epinephrine	21 (60)	Methylprednisolone[a]	13 (41)
Ampicillin	77 (57)	Cefazolin	35 (67)	Cefazolin	20 (57)	Cefepime	12 (38)
Cefepime	73 (54)	Dopamine	34 (65)	Dopamine	20 (54)	Acetaminophen	11 (34)
Hydrocortisone	70 (52)	Pantoprazole[a]	29 (56)	Acetaminophen	19 (54)	Albuterol[a]	11 (34)
Gentamicin	55 (41)	Acetaminophen	25 (48)	Albuterol[a]	18 (51)	Hydromorphone	11 (34)
Milrinone[a]	40 (30)	Epinephrine	24 (46)	Cefepime	18 (51)	Insulin[a]	11 (34)
Hydralazine	36 (27)	Ranitidine	23 (44)	Dexmedetomidine	17 (49)	Nicardipine	11 (34)
						Ranitidine	11 (34)

[a]No data on pharmacokinetics and/or pharmacodynamics on extracorporeal membrane oxygenation.

bleeding remain the major complications associated with ECMO (30). Although several studies have tried to establish the optimal pharmacodynamics target correlating with its effects (activated clotting time, anti-factor Xa, or thromboelastogram), there are no recent data examining the complex interaction between drug disposition and effect. Second, future studies should extend their study population to better represent all pediatric age groups supported with ECMO. Most of the available literature concerns neonates and infants, for example, morphine pharmacokinetics has been described exclusively in infants less than 1 year old (31–35). Maturation of metabolic and elimination pathways, distinct diseases, and differences in the ECMO circuit prevent extrapolation of infants' pharmacokinetics parameters to older children. Third, larger studies are needed to characterize interindividual variability adequately. Given that ECMO use is uncommon with children's hospitals in the United States performing an average of 1–58 cases per year (36), multicenter collaborations represent a practical strategy to pursue greater impact studies.

Adult literature suggests that patient factors and critical illness may have a greater impact on pharmacokinetics than the ECMO circuit. Pharmacokinetics parameters on ECMO compared with critically ill adults not on ECMO were no different in patients receiving vancomycin (28, 29), piperacillin-tazobactam (37), and meropenem (37). However, these data are not generalizable to children as Hahn et al (38) reviewed literature on different antibiotics, antivirals, and antifungal in adults on ECMO and concluded that changes in pharmacokinetics vary among drugs and do not correlate with results from pediatric studies. As previously mentioned, there are unique physicochemical properties of a drug and patient characteristics that impact drug pharmacokinetics on ECMO.

Our study has several limitations. It is a single-center study and depicts patterns of medication exposure that may not correspond to other centers' prescription practices. Data collection was based on the MAR which prevented a description of daily medication exposure, for example, a bag or syringe of a continuous infusion may last 48–72 hours; therefore, administration is recorded in the MAR only when the bedside nurse performs an action potentially skipping a day or two in a child receiving a small volume of medication. Furthermore, data extraction rounded the date and time of ECMO initiation to the nearest hour preventing characterization of the first hour following ECMO initiation adequately. Finally, parenteral nutrition which sometimes includes medications such as ranitidine was excluded. Therefore, ranitidine exposure may have been underestimated, and the difference observed between age groups in the use of gastrointestinal agents may not be accurate.

Despite these limitations, our study also has considerable strengths. CHOP is one of the most active ECMO centers in North America. The high volume of ECMO support provided at CHOP allowed review of cases over a relatively short time period, thereby limiting the effect of prescription variations over time. To our knowledge, this is the first study to describe medication use in infants and children on ECMO, and also the first to characterize drug exposure by age and hospitalization unit. Combined with our extensive review of literature which highlighted medications

TABLE 3. Most Frequently Used Medications in Patients Supported by Extracorporeal Membrane Oxygenation Stratified by Hospitalization Units

Neonatal ICU (*n* = 87), *n* (%)		Cardiac ICU (*n* = 130), *n* (%)		PICU (*n* = 37), *n* (%)	
Heparin	85 (98)	Heparin	125 (96)	Heparin	34 (92)
Morphine	84 (97)	Morphine	124 (95)	Midazolam	31 (84)
Midazolam	80 (92)	Furosemide	118 (91)	Vancomycin	30 (81)
Vecuronium[a]	73 (84)	Milrinone[a]	109 (84)	Epinephrine	30 (81)
Furosemide	71 (82)	Midazolam	106 (82)	Pantoprazole[a]	29 (78)
Fentanyl	68 (78)	Vecuronium[a]	104 (80)	Vecuronium[a]	25 (68)
Ampicillin	64 (74)	Cefazolin	96 (74)	Morphine	24 (65)
Dopamine	60 (69)	Dopamine	88 (68)	Furosemide	21 (57)
Vancomycin	60 (60)	Chlorothiazide[a]	82 (63)	Hydrocortisone	17 (46)
Cefepime	56 (64)	Vancomycin	78 (60)	Cefepime	16 (43)
Gentamicin	51 (59)	Acetaminophen	71 (55)	Insulin[a]	16 (43)
Cefazolin	45 (52)	Pantoprazole[a]	68 (52)	Methylprednisolone[a]	16 (43)
Hydrocortisone	43 (49)	Cefepime	67 (52)	Norepinephrine[a]	16 (43)
Hydralazine	36 (41)	Epinephrine	56 (43)	Hydromorphone	14 (38)
Dexamethasone[a]	34 (39)	Hydrocortisone	47 (36)	Albuterol[a]	13 (35)
Alprostadil	26 (30)	Ranitidine	44 (34)	Dexmedetomidine	13 (35)
Pentobarbital[a]	23 (26)	Dexmedetomidine	42 (32)	Docusate sodium[a]	13 (35)
Acyclovir	20 (23)	Albuterol[a]	41 (32)	Fentanyl	13 (35)
Hydromorphone	20 (23)	Ketamine[a]	38 (29)	Piperacillin-tazobactam[a]	13 (35)
Lorazepam	20 (23)	Fentanyl	31 (24)	Ketamine[a]	12 (32)
Aminocaproic acid	19 (22)	Nicardipine	28 (22)	Acetaminophen	11 (30)
Treprostinil[a]	18 (21)	Levetiracetam[a]	26 (20)	Nicardipine	11 (30)
Dexmedetomidine	16 (18)	Hydromorphone	25 (19)	Ranitidine	11 (30)
Amphotericin	12 (14)	Acetazolamide[a]	22 (17)	Rocuronium[a]	11 (30)
Phenobarbital	11 (13)	Vasopressin[a]	22 (17)	Sennosides[a]	11 (30)

[a]No data on pharmacokinetics and/or pharmacodynamics on extracorporeal membrane oxygenation.

for which there is a critical need for pharmacologic studies, this allowed us to identify areas for prioritization for future research in key populations who would benefit the most from further pharmacokinetics/pharmacodynamics data. For clinicians, we have provided a useful document summarizing the available dosing guidance for commonly used medications in infants and children on ECMO (Table S1). Furthermore, our results support the use of TDM in clinical practice. Indeed, the absence of dosing guidance for a given drug or significant variability between recommended dosing regimens supports using TDM whenever possible. As described by Di Nardo et al (39) with meropenem, this may represent an efficient way to palliate the lack of data and to optimize drug exposure on ECMO.

In conclusion, dosing guidance was available for only 20% of the most commonly used medications on ECMO. Dosing recommendations were mainly issued from simulations or retrospective observations and were not prospectively validated. Furthermore, they were primarily based on studies focusing on neonates and infants. Further pharmacokinetics/pharmacodynamics studies in a broader population are needed. Dosing guidelines are essential to optimize the care of critically ill children supported with ECMO.

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