JPPT | Survey

Antimicrobial Prophylaxis and Anticoagulation Therapy in Pediatric ECMO: A Survey Study

Cierra A. Frazier, PharmD; Brittany M. Scott, PharmD; Peter N. Johnson, PharmD; and Joseph M. LaRochelle, PharmD

OBJECTIVE The purpose was to characterize antimicrobial and anticoagulation therapies used in health systems with children receiving extracorporeal membrane oxygenation (ECMO).

METHODS An anonymous electronic survey assessing health system demographics and antimicrobial and anticoagulation therapies during ECMO was distributed to the American College of Clinical Pharmacy Pediatric Practice and Research Network and the Pediatric Pharmacy Association Critical Care Special Interest Group. The primary objective was to identify the number of respondents using antimicrobial prophylaxis for ECMO cannulation and ECMO runs. Secondary objectives included the first- and second-line anticoagulants and anticoagulation laboratory parameters. Additionally, the antimicrobial regimens and the dosing and administration of antithrombin III (AT III) with systemic anticoagulation were collected. Descriptive statistics were employed.

RESULTS The questionnaire was completed by 38 respondents from 33 health systems; respondents practiced in the pediatric ICU (n = 20; 52.6%), cardiovascular ICU (n = 14; 36.8%), and neonatal ICU (n = 4; 10.5%). Twenty-eight (73.6%) respondents use antimicrobial prophylaxis during ECMO cannulation or ECMO runs, with most units using cefazolin monotherapy. Thirty-five (92.1%) respondents use heparin as the first-line anticoagulant and used a variety of laboratory tests including anti-factor Xa, activated clotting time, and activated partial thromboplastin time. The most common second-line anticoagulant was bivalirudin (n = 24; 63.2%). Thirty-six (94.7%) respondents use AT III with heparin, with most patients receiving AT III dosing calculated based on a formula for the desired AT III concentration.

CONCLUSIONS The majority of respondents use antimicrobial prophylaxis, but variations in the regimens were noted. Heparin was the most common anticoagulant, but variations in laboratory monitoring and concomitant use of AT III were found.

ABBREVIATIONS ACT, activated clotting time; anti-Xa, anti-factor Xa; aPTT, activated partial thromboplastin time; AT III, antithrombin III; AUC/MIC, area under the curve over 24 hours to minimum inhibitory concentration; CVICU, cardiovascular intensive care unit; DTIs, direct thrombin inhibitors; ECMO, extracorporeal membrane oxygenation; ELSO, Extracorporeal Life Support Organization; ICU, intensive care unit; IV, intravenous; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; TEG, thromboelastogram

KEYWORDS antimicrobials; antithrombin III; child; extracorporeal membrane oxygenation; heparin; pediatrics

J Pediatr Pharmacol Ther 2022;27(1):72–79

DOI: 10.5863/1551-6776-27.1.72

Introduction

Extracorporeal membrane oxygenation (ECMO) is an advanced life support technique that is designed to support cardiac and/or pulmonary function for critically ill patients.[1] Since its development in the early 1970s, ECMO has been used in a variety of disease states including congenital diaphragmatic hernia, congenital cardiac defects, and severe pneumonia among others; however, it is associated with a number of complications including a risk of infection and thromboembolism.[1] Studies have noted that ECMO-associated nosocomial infections have occurred in 6% to 30% of infants and children.[2] The Extracorporeal Life Support Organization (ELSO) Infectious Disease Task Force does not recommend the use of antimicrobial prophylaxis beyond general surgical procedure prophylaxis.[3] Despite this, many providers may consider antimicrobial prophylaxis prior to surgical cannulation of arteries or veins or at various points during their ECMO run due to other comorbid conditions in ECMO patients. Thromboembolism has been reported in 12.8% of patients undergoing ECMO.[1] Due to this risk of thromboembolism, systemic anticoagulation is required during ECMO runs, but previous studies have demonstrated variations in anticoagulation practices and thromboembolic and bleeding complications.[1,4]

There are limited published studies that investigate antimicrobial prophylaxis, and anticoagulant drug therapy

best practices in pediatric patients on ECMO.[4–6] Because there is limited guidance in the literature, practices can differ widely between institutions and sometimes within different ICUs in the same health system. The purpose of this study was to characterize antibiotic and anticoagulation therapies used in health systems that have pediatric patients receiving ECMO.

Materials and Methods

An electronic survey was developed and approved by the Xavier University of Louisiana and the University of Oklahoma Health Sciences Center. The survey consisted of 30 questions including health system demographic information (5 questions), antimicrobial prophylaxis (13 questions), and anticoagulation therapies (12 questions) during ECMO. The questions regarding antimicrobial prophylaxis focused on the types of agents used during cannulation and the entire ECMO run. If vancomycin was selected as an antibiotic choice, follow-up questions regarding pharmacokinetic monitoring were asked. For anticoagulation therapies, the questions focused on the initial anticoagulant used, alternative agents, primary monitoring parameters, and antithrombin III (AT III) dosage and administration for those using heparin infusions. The survey was administered via Google Forms (Google Technology Company, Mountain View, CA).

The survey was distributed via email to the 1005 Pediatric Pharmacy Association's Critical Care Special Interest Group members and 804 American College of Clinical Pharmacy's Pediatric Practice and Research Network members.[7,8] The target audience was pediatric clinical pharmacists with experience managing ECMO patients. The survey remained open from March to July 2020. Three reminder emails were sent over this time period. Survey participation was optional, and all responses were kept anonymous. Because the questionnaire included questions about ECMO practices in different units of each health system (PICU, cardiovascular ICU [CVICU], and NICU), the same or several clinical pharmacists could submit responses from the same institution. When filling out the survey, clinical pharmacists were asked to provide the first 2 letters of their health system's street name and the last 2 numbers of the health system's zip code. These data were used to account for multiple responses from pharmacists practicing in different units within the health system.

The primary objective was to identify the number of respondents that use antimicrobial prophylaxis for ECMO cannulation and ECMO runs. Secondary objectives included the first- and second-line anticoagulants and laboratory tests monitored during ECMO. Additionally, the antimicrobial regimen, the number of respondents using antifungal prophylaxis, and duration of antimicrobial prophylaxis was recorded. In addition, the dosing and administration of AT III with systemic anticoagulation was collected.

To ensure face validity of the survey instrument, the questionnaire was developed and reviewed by all investigators. In addition, informal feedback was obtained from 2 pediatric clinical pharmacists with experience in ECMO who did not participate in the survey. Data were analyzed and summarized using Excel 2019 (Microsoft, Redmond, WA). Descriptive statistics were used to report survey results.

Table 1. Baseline Demographics of Health Systems for Respondents

Variable	Value
Number of pediatric beds (n = 33), n (%)*	
50–100	2 (6.1)
100–150	8 (24.2)
150–200	8 (24.2)
>200	15 (45.5)
Intensive care units (n = 38), n (%)	
CVICU	14 (36.8)
NICU	4 (10.5)
PICU	20 (52.6)
ECMO patients per year, median (IQR)	
CVICU	30 (20–50)
NICU	20 (13.8–31.3)
PICU	13.5 (10–25.5)
Primary indication for ECMO, median % (IQR)	
Pulmonary etiology	40 (30–70)
Cardiac etiology	50 (20–61.3)

CVICU, cardiovascular intensive care unit; ECMO, extracorporeal membrane oxygenation

* Respondents who completed the questionnaire were from 33 different health systems, representing 38 total intensive care units.

Results

The questionnaire was accessed 41 times. Three entries were excluded for incomplete or duplicate data. Of the remaining 38 entries, 33 health systems were represented. A single respondent was identified from 29 different health systems, 2 respondents in 2 different units from 3 different health systems, and 3 respondents from 3 different units in 1 health system. An overall response rate was calculated as 25.3% based on the reported number of 150 ECMO centers affiliated with the ELSO.[9] Due to the small population size, aggregate data are commonly reported.

Table 1 provides the baseline demographics from the health systems of the participants. Of the 33 institutions, there was heterogeneity in the health systems of the respondents. Fifteen of 33 (45.5%) respondents were from larger health systems with >200 pediatric beds. The majority of respondents practiced in PICUs (20/38; 52.6%) with the remaining 14 of 38 respondents (36.8%) in the CVICU and an additional 4 respondents (4/38; 10.5%) in the NICU. There was variability in the

Table 2. Antimicrobial Prophylaxis Among ICUs for Patients Receiving ECMO

Variable	Overall (N = 38)	CVICU (n = 14)	PICU (n = 20)	NICU (n = 4)
Prophylaxis not used during cannulation, n (%)	12 (31.6)	3 (21.4)	7 (35)	2 (50)
Combination of agents, n (%)	n = 26	n = 11	n = 13	n = 2
Cefazolin monotherapy	17 (65.4)	5 (45.4)	10 (76.9)	2 (50.0)
Cefepime/vancomycin	3 (11.5)	2 (18.2)	1 (7.7)	—
Cefazolin/vancomycin	2 (7.7)	1 (9.1)	1 (7.7)	—
Cefepime/vancomycin/cefazolin	2 (7.7)	2 (18.2)	—	—
Cefazolin/cefepime	1 (3.8)	1 (9.1)	—	—
Ceftazidime	1 (3.8)	—	1 (7.7)	—
Duration, n (%)	n = 26	n = 11	n = 13	n = 2
1 dose	15 (57.7)	4 (36.4)	9 (69.2)	2 (50.0)
First 24 hr after cannulation	6 (23.1)	2 (18.2)	4 (30.8)	—
First 48 hr after cannulation	1 (3.8)	1 (9.1)	—	—
Other	4 (15.4)	4 (36.4)	—	—
Prophylaxis during ECMO runs				
Antimicrobial prophylaxis not used during ECMO, n (%)	29 (76.3)	7 (50.0)	18 (90.0)	4 (100.0)
Combination of agents	n = 9	n = 7	n = 2	—
Cefazolin monotherapy	3 (33.3)	2 (28.6)	1 (50.0)	—
Cefepime/vancomycin	2 (22.2)	1 (14.3)	1 (50.0)	—
Cefazolin/vancomycin	2 (22.2)	2 (28.6)	—	—
Cefepime/vancomycin/cefazolin	2 (22.2)	2 (28.6)	—	—
Duration	n = 9	n = 7	n = 2	—
First 48 hr after cannulation	1 (11.1)	1 (14.3)	—	—
Duration of ECMO	6 (66.7)		2 (100.0)	—
Duration of open chest with ECMO	2 (22.2)		—	—
Antifungal prophylaxis not used, n (%)	31 (81.6)	9 (64.3)	18 (90.0)	—
Agent used	n = 7	n = 5	n = 2	—
Fluconazole	6 (85.7)	5 (100.0)	1 (50.0)	—
Caspofungin	1 (14.3)	—	1 (50.0)	—
Indications	n = 7	n = 5	n = 2	—
Broad spectrum antibiotics	1 (14.3)	—	1 (50.0)	—
All ECMO patients	2 (28.6)	2 (40.0)	—	—
Duration of open chest with ECMO	4 (57.1)	3 (60.0)	1 (50.0)	—

CVICU, cardiovascular intensive care unit; ECMO, extracorporeal membrane oxygenation

median number of ECMO runs in patients per year, with the highest number in those participants from the CVICU, median of 30 patients per year (IQR, 20–50). There was also variability in the primary indication for ECMO among the units with the cardiac etiology being the most common, median 50.0% (IQR, 20.0%–61.3%).

Results regarding antibiotic prophylaxis are listed in Table 2. Twenty-eight (73.6%) respondents use antimicrobial prophylaxis during ECMO cannulation and/or the ECMO run. Twenty-six respondents (68.4%) noted their units use antimicrobial prophylaxis during initial ECMO cannulation, regardless of the mode of ECMO cannulation (i.e., veno-venous or veno-arterial). Most units (65.4%) use cefazolin monotherapy; however, a number of units also employ other regimens including use of vancomycin. The majority (57.7%) of patients receive just 1 dose prior to ECMO cannulation, but some units also use antimicrobial prophylaxis for the first 24 to 48 hours. Additionally, 9 units (23.7%) administer additional antimicrobial prophylaxis during the ECMO run. In particular, 2 of these units do not typically administer antimicrobials during ECMO cannulation but just during the ECMO run itself. For those units that administer prophylaxis during the ECMO run, a variety of different antimicrobials were noted to be used with the majority involving cefazolin in combination or as monotherapy and continued for the duration of ECMO. Respondents from 9 units (27.3%) use vancomycin for ECMO cannulation or use at some point during the ECMO runs. One respondent reported using area under the curve over 24 hours to minimum inhibitory concentration (AUC/MIC) monitoring. The remaining respondents use trough monitoring, with the most common goal being 10 to 15 mg/L, with 1 respondent reporting a goal of 15 to 20 mg/L.

Seven respondents (18.4%) noted that their units used antifungal prophylaxis. None of the respondents who practice in the NICU noted antifungal prophylaxis

Table 3. Anticoagulation Among ICUs for Patients Receiving ECMO

Variable	Overall (N = 38)	CVICU (n = 14)	PICU (n = 20)	NICU (n = 4)
Initial anticoagulant	n = 38	n = 14	n = 20	n = 4
Heparin	35 (92.1)	11 (78.6)	20 (100)	4 (100)
Bivalirudin	3 (7.9)	3 (21.4)	—	—
Alternative agent(s)	n = 38	n = 14	n = 20	n = 4
Argatroban	6 (15.8)	2 (14.3)	3 (15)	1 (25)
Bivalirudin	24 (63.2)	9 (64.3)	12 (60)	3 (75)
Argatroban or bivalirudin	1 (2.6)	—	1 (5)	—
Heparin	1 (2.6)	1 (7.1)	—	—
None listed	6 (15.8)	2 (14.3)	4 (20)	—
Monitoring for heparin as first-line agent	n = 35	n = 11	n = 20	n = 4
ACT	1 (2.9)	1 (9.1)	—	—
Anti-Xa	12 (34.3)	4 (36.3)	7 (35)	1 (25)
Anti-Xa, ACT	3 (8.6)	1 (9.1)	2 (10)	—
aPTT, ACT	3 (8.6)	—	3 (15)	—
aPTT, anti-Xa	6 (17.1)	3 (27.3)	1 (5)	2 (50)
aPTT, anti-Xa, ACT	10 (28.6)	2 (18.2)	7 (35)	1 (25)
Monitoring for bivalirudin as first-line agent	n = 3	n = 3	—	—
aPTT	2 (66.7)	2 (66.7)	—	—
aPTT, ACT	1 (33.3)	1 (33.3)	—	—
Rationale for switching to alternative agents	n = 38	n = 14	n = 20	n = 4
Adverse drug reactions	9 (23.7)	3 (21.4)	6 (30)	—
Heparin resistance	6 (15.8)	1 (7.1)	3 (15)	2 (50)
Adverse drug reactions and/or resistance	15 (39.5)	8 (57.1)	5 (25)	2 (50)
None listed	8 (21.0)	2 (14.3)	6 (30)	—

ACT, activated clotting time; anti-Xa, anti-factor Xa; aPTT, activated partial thromboplastin time; CVICU, cardiovascular intensive care unit; ECMO, extracorporeal membrane oxygenation

was used. The most common agent employed was fluconazole, and there were a variety of indications described including central ECMO cannulation through the open chest and use of broad-spectrum antibiotics.

Table 3 lists the results for anticoagulation use and monitoring. Thirty-five (92.1%) respondents use heparin as the initial choice of anticoagulation therapy. Respondents were asked about the laboratory monitoring used for heparin. Thirty-one (88.6%) respondents use anti-factor Xa (anti-Xa) alone or in combination with other laboratory parameters for monitoring heparin. However, other anticoagulation laboratory parameters were also performed at their centers including activated clotting time (ACT) and activated partial thromboplastin time (aPTT). Eleven (31.4%) of the 35 respondents that use heparin as a first-line agent use thromboelastogram (TEG) in monitoring anticoagulation. Three (7.9%) respondents, all in the CVICU, noted that their institutions use bivalirudin as a first-line agent and monitor using aPTT with or without the use of ACTs. A number of alternative agents were described with the majority of them being direct thrombin inhibitors (DTIs), including argatroban or bivalirudin (n = 31; 81.6%). One respondent (2.6%) that uses bivalirudin as a first-line agent mentioned that they use heparin as a second-line option. Six (15.8%) respondents did not mention any specific alternative used from their initial agent. Respondents noted that the main indication for switching to alternative agents was for adverse events or heparin resistance.

The majority of respondents (n = 36, 94.7%) use AT III in combination with heparin as a first-line or alternative agent. AT III concentrations were checked at varying frequencies, with the most institutions checking them every 24 hours (n = 16; 44.4%). Some of the respondents noted that they obtain AT III concentrations more frequently with patients on high heparin infusion rates ≥ 40 to 60 units/kg/hr. Respondents were asked for the method of determination of AT III dosing, including calculated based on formula and fixed dosing. Twenty-five of these respondents (69.4%) noted that they calculate based on formula, with the most common formula being:

AT III dose = (AT concentration % − baseline AT concentration %) – body wt (kg)/1.4

One respondent noted that their institution takes the calculated AT III dose generated from this equation and divides by 2 for children <5 kg. The remaining 11 respondents (30.6%) use fixed dosing. The goal AT III target noted by respondents was generally between 80% and 120%, though 1 respondent mentioned that the goal AT III for children <1 month was 50% to 80%. The majority (n = 32; 88.9%) received AT III via IV intermittent infusions, with only 3 (8.3%) indicating AT III was administered by a continuous infusion.

Discussion

A number of studies have described the use of antimicrobial and anticoagulant agents in children receiving ECMO.[4–6] However, to our knowledge, this is the first study describing different antimicrobial and anticoagulant practices in pediatric-specific health systems across the United States. Previous studies have surveyed respondents of ECMO centers regarding antimicrobial prophylaxis or anticoagulation therapy, but these studies varied on whether they included pediatric versus pediatric and adult patients.[4–6] In addition, many of these studies are over 10 years old, limiting the utility of the results considering advances in ECMO care. The respondents came from a range of health systems with a different number of pediatric beds, mix of ICU units, ECMO indications, and number of ECMO runs per year. Despite the small sample size, these findings may provide the pediatric pharmacy community with a glimpse at anticoagulant and antimicrobial practice trends in children receiving ECMO. These data may provide the impetus for future multicenter research projects among ECMO centers through pediatric pharmacy practice-based research networks.

Approximately 74% of respondents in this study received antimicrobial prophylaxis during ECMO cannulation and/or the ECMO run. As noted, the ELSO Infectious Disease Task Force does not routinely recommend antimicrobial prophylaxis.[3] However, in 2010, Kao et al[5] conducted a multicenter survey study of ESLO-registered ECMO centers in pediatric and adult health systems worldwide regarding antimicrobial and antifungal practices. Consistent with our study, they noted 74% of respondents receive antimicrobial prophylaxis and had an overall response rate of 41%. They noted the majority of respondents received antimicrobial prophylaxis during the entire ECMO run with a smaller number of respondents receiving antimicrobials with ECMO cannulation. In contrast, we noted 68% of respondents receiving prophylaxis during ECMO cannulation with approximately 24% of respondents receiving ECMO prophylaxis for the duration of the ECMO run. Kao et al[5] noted a larger variety of antimicrobials used compared with our findings including the use of aminoglycosides, penicillin derivatives, vancomycin, carbapenems, and various generations of cephalosporins, with the majority of centers noting these agents used in combination. We also noted some variety in antimicrobial usage, but the majority of patients received cefazolin monotherapy rather than combination antimicrobial agents. Because the study by Kao et al[5] included participants across the world and also adult centers, this may explain the wide array of antimicrobial options compared with our findings. Nine of the respondents (27.3%) in our study also received vancomycin, but only 1 respondent noted use of AUC/MIC versus trough monitoring. Recently, a committee representing the American Society of Health-System Pharmacists, Infectious Diseases Society of America, the Society of Infectious Diseases Pharmacists, and the Pediatric Infectious Diseases Society published guidelines regarding the therapeutic monitoring of vancomycin in adults and children; they recommended targeting an AUC/MIC ratio of 400 to 600 mg·hr/L to maximize efficacy and limit toxicity.[10] It is important to note that these guidelines were published during the dissemination of this survey. Because previous versions of these guidelines did not have widespread recommendations for AUC/MIC monitoring in children, it is likely that these institutions would not have time to implement AUC/MIC versus trough monitoring.

We also noted that 7 respondents (18.4%) used antifungal prophylaxis. In the study by Kao et al,[5] they noted 2% of respondents described routine use of antifungals, with most of the respondents noting their centers continued between 5 and 10 days. It is difficult to compare the findings from their study and the present study. One of the reasons for the differences may be related to the differences in the ECMO centers included between studies. Our study included respondents from the PICU, CVICU, and NICU, and some of these centers noted that patients do routinely receive antifungal prophylaxis in patients with central ECMO cannulation through the open chest by the cardiothoracic surgery team for cardiac indications. Because the study by Kao et al[5] did not include a breakdown of the different ICUs included in their study, it is difficult to determine how many respondents included centers from patients who may not have been managed by the cardiothoracic surgery team and had central ECMO cannulation.

Thirty-five (92.1%) respondents noted that heparin was the first-line anticoagulant, and the majority of respondents use anti-Xa monitoring alone or in combination with ACT and/or aPTT. From 2010–2011, Bembea et al[6] conducted a cross-sectional survey of 121 ELSO-registered ECMO centers regarding anticoagulation management. They noted heparin was used as the first-line anticoagulant. In addition, they found 97% of respondents used ACT as the main anticoagulation parameter to guide heparin titration and noted only 65% obtained anti-Xa concentrations on a routine or as needed basis. Compared with Bembea et al,[6] we

Table 4. Antithrombin III Supplementation With Heparin, Monitoring, Dosing, and Administration

Variable	Overall (N = 38)	CVICU (n = 14)	PICU (n = 20)	NICU (n = 4)
AT III with heparin infusions	36 (94.7)	12 (85.7)	20 (100)	4 (100)
Frequency of AT III concentration assessment	n = 36	n = 12	n = 20	n = 4
Every 2 hr	1 (2.8)	1 (8.3)	—	—
Every 6 hr	2 (5.5)	—	2 (10)	—
Every 8 hr	1 (2.8)	—	—	1 (25)
Every 12 hr	3 (8.3)	—	2 (10)	1 (25)
Every 24 hr	6 (44.4)	7 (58.3)	9 (45)	—
As needed/not routine	113 (36.1)	4 (33.3)	7 (35)	2 (50)
Determination of AT III dosing	n = 36	n = 12	n = 20	n = 4
Calculated based on formula	25 (69.4)	8 (66.7)	15 (75)	2 (50)
Fixed dosing	11 (30.6)	4 (33.3)	5 (25)	2 (50)
AT III goal concentration used for formula	n = 36	n = 12	n = 20	n = 4
60%–80%	1 (2.8)	—	1 (5)	—
80%	1 (2.8)	—	1 (5)	—
80%–100%	6 (16.7)	1 (8.3)	4 (20)	1 (25)
100%	2 (2.8)	1 (8.3)	—	1 (25)
80%–120%	6 (16.7)	3 (25)	2 (10)	1 (25)
100%–120%	1 (2.8)	—	1 (5)	—
120%	3 (8.3)	2 (16.7)	1 (5)	—
Not defined	16 (44.4)	5 (41.7)	10 (50)	1 (25)
AT III dosing administration	n = 36	n = 12	n = 20	n = 4
Intermittent IV infusion	32 (88.9)	10 (83.3)	19 (95)	3 (75)
Continuous IV infusion	3 (8.3)	1 (8.3)	1 (5)	1 (25)
Not defined	1 (2.8)	1 (8.3)	—	—

AT III, antithrombin III; CVICU, cardiovascular intensive care unit

found a higher percentage of respondents that use anti-Xa versus other laboratory parameters including ACT. Over the last 10 years, there have been studies evaluating different anticoagulation monitoring parameters with heparin, and evidence suggests that anti-Xa is more specific for heparin activity and associated with less bleeding compared with ACT monitoring.[4,6] As a result, it is plausible that this is why we noted a higher percentage of respondents whose centers use anti-Xa more commonly than ACT. We also noted one-third of respondents using heparin as a first-line agent also employ the use of TEGs to assess anticoagulation; TEGs are an addition tool that a number of ECMO centers use to monitor anticoagulation and also detection of hypercoagulable states.[6] In our study, 3 respondents (7.9%) use bivalirudin as the first-line agent, and a majority of respondents identified use of DTIs including bivalirudin and argatroban as a second-line agent. Bembea et al[6] noted that only 8% of respondents had used an alternative anticoagulant within 6 months prior to completion of the study. Over the last few years, there have been an increased body of evidence supporting the use of DTIs, given the variability in anticoagulation monitoring and fluctuation in AT III concentrations in infants and children.[11,12]

In our study, we also found 95% of respondents monitor and administer AT III when heparin is used as a first- or second-line agent (Table 4). Protti et al[4] conducted a survey of 273 ECMO centers from 50 countries including pediatric and adult health systems regarding anticoagulation and AT III supplementation. They found only 38% of respondents whose centers supplemented AT III, with the majority of respondents who implemented this monitoring being in countries with a higher versus lower income levels and pediatric versus adult health systems. Previous research has noted that neonates and young children have lower AT III concentrations.[4] Because our study included respondents from children's hospitals, then it is understandable why the respondents noted a higher use of AT III supplementation than ECMO centers in adult health systems. Approximately 70% of respondents noted that they determine AT III dosing that they calculate based on a formula, with the most common goal being 80% to 120%. Protti et al[4] did not describe AT III dosing and goal AT III concentrations, so it is difficult to compare their findings with ours. However, they also noted one-third used a fixed dose of AT III. Some reports have described the use of fixed doses of AT III including full vial sizes to reduce waste and aid in cost savings.[13] The majority (88.9%) of respondents noted that AT III was administered via intermittent infusions versus 3 (8.3%)

respondents whose centers use AT III continuous infusions. Most reports in the literature describe the use of AT III supplementation via intermittent infusions.[14] However, some reports have described the use of continuous infusions of AT III to ensure more consistent AT III concentrations, and a greater time within the goal range of anticoagulation laboratory parameters.[14]

This study included several limitations. First, the study included a small sample size. Three reminder emails were sent out during March to July 2020. Given that the survey was distributed during the height of the coronovirus-19 pandemic, it is likely that this contributed to the small number of respondents. Despite this, our study included responses from a variety of health systems with small to large pediatric beds, mix of ICUs, ECMO indications, and number of ECMO runs per year. In addition, although previous studies have assessed antimicrobial and anticoagulation therapy practices in ECMO centers, our findings provide a more recent trend in these practices across the United States. Second, psychometric data for the survey are limited, and thus there is a potential that there could have been some confusion by respondents in completing responses on the questionnaire. However, face validity was addressed through the input from 2 pediatric clinical pharmacists with expertise in ECMO prior to survey dissemination.

This study found that the majority of respondents use antimicrobial prophylaxis, but variations in the regimens were noted. Heparin was the first-line anticoagulant but variations in laboratory monitoring and concomitant use of AT III were found. These findings may be employed to provide pediatric clinical pharmacists with a glimpse of antimicrobial and anticoagulation therapies in children undergoing ECMO and provide opportunities for quality improvement and a foundation for multicenter research through pediatric pharmacy practice-based research networks.

Article Information

Affiliations. Xavier University of Louisiana College of Pharmacy (BMS, CAF, JML), New Orleans, LA; University of Oklahoma College of Pharmacy (PNJ), Oklahoma City, OK.

Correspondence. Joseph M. LaRochelle, PharmD; jlaroche@xula.edu

Disclosures. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including equipment, medications, employment, gifts, and honoraria. The project described is supported by the Health Resources and Services Administration, Grant D34HP00006. The views expressed in this presentation are solely the opinion of the author(s) and do not necessarily reflect the official policies of the US Department of Health and Human Services or the Health Resources and Services Administration, nor does mention of the department or agency names imply endorsement by the US Government. CAF, BMS, PNJ, and JML had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by our institution review board. Given the nature of this study, informed consent, assent, and parental permissions were not required.

Acknowledgments. Preliminary results for this study were presented virtually at the 2020 Pediatric Pharmacy Annual Meeting. The authors would like to thank Marcia L. Buck for her assistance with this project.

Submitted. March 23, 2021

Accepted. May 10, 2021

References

1. Dalton HJ, Reeder R, Garcia-Filion P, et al. Factors associated with bleeding and thrombosis in children receiving extracorporeal membrane oxygenation. *Am J Respir Crit Care Med*. 2017;196(6):762–771.
2. Butler DF, Lee B, Molitor-Kirsh E, Newland JG. Extracorporeal membrane oxygenation-associated bloodstream infections in children. *Pediatr Infect Dis J*. 2017;36(3):346–347.
3. The Extracorporeal Life Support Organization Infectious Disease Task Force Recommendation Summary. Accessed March 2, 2021. http://www.elso.org/Portals/0/Files/ELSO-ID-Task-Force-Recommendations-Summary.pdf
4. Protti A, Iapichino GE, Di Nardo M, et al. Anticoagulation management and antithrombin supplementation practice during veno-venous extracorporeal membrane oxygenation: a worldwide survey. *Anesthesiology*. 2020;132(3):562–570.
5. Kao LS, Fleming GM, Escamilla RJ, et al. Antimicrobial prophylaxis and infection surveillance in extracorporeal membrane oxygenation patients: a multi-institutional survey of practice patterns. *ASAIO J*. 2011;57(3):231–238.
6. Bembea MM, Annich G, Rycus P, et al. Variability in anticoagulation management of patients on extracorporeal membrane oxygenation: an international survey. *Pediatr Crit Care Med*. 2013;14(2):e77–e84.
7. American College of Clinical Pharmacy Pediatric Practice and Research Network. Accessed March 2, 2021. http://pediprn.accp.com/directory.aspx
8. Pediatric Pharmacy Association Critical Care Special Interest Group. Accessed March 2, 2021. https://www.ppag.org/?&pg=PPAGCriticalCare&commpg=PPAGCriticalCareMemberDirectory&seed=749096
9. Extracorporeal Life Support Organization Center Directory. Accessed March 2, 2021. https://www.elso.org/Membership/CenterDirectory.aspx

10. Ryback MJ, Le J, Lodise TP. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, The Infectious Disease Society of America, and the Pediatric Infectious Diseases Society, and the Society of the Infectious Diseases Pharmacists. *Am J Health-Syst Pharm*. 2020;77(11):835–863.
11. Hamzah M, Jarden AM, Ezetendu C, Stewart R. Evaluation of bivalirudin as an alternative to heparin for systemic anticoagulation in pediatric extracorporeal membrane oxygenation. *Pediatr Crit Care Med*. 2020;21(9):827–834.
12. Campbell CT, Diaz L, Kelly B. Description of bivalirudin use for anticoagulation in pediatric patients on mechanical circulatory support. *Ann Pharmacother*. 2021;55(1):59–64.
13. Stockton WM, Padilla-Tolentino E, Ragsdale CE. Antithrombin III doses rounded to available vial sizes in critically ill pediatric patients. *J Pediatr Pharmacol Ther*. 2017;22(1):15–21.
14. Nelson KM, Hansen LA, Steiner ME, et al. Continuous antithrombin III administration in pediatric veno-arterial extracorporeal membrane oxygenation. *J Pediatr Pharmacol Ther*. 2017;22(4):266–271.