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Anticoagulation practices associated with bleeding and thrombosis in pediatric extracorporeal membrane oxygenation; a multi-center secondary analysis

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Abstract

To determine associations between anticoagulation practices and bleeding and thrombosis during pediatric extracorporeal membrane oxygenation (ECMO), we performed a secondary analysis of prospectively collected data which included 481 children (<19 years), between January 2012 and September 2014. The primary outcome was bleeding or thrombotic events. Bleeding events included a blood product transfusion >80 ml/kg on any day, pulmonary hemorrhage, or intracranial bleeding, Thrombotic events included pulmonary emboli, intracranial clot,

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limb ischemia, cardiac clot, and arterial cannula or entire circuit change. Bleeding occurred in 42% of patients. Five percent of subjects thrombosed, of which 89% also bled. Daily bleeding odds were independently associated with day prior activated clotting time (ACT) (OR 1.03, 95% CI= 1.00, 1.05, p=0.047) and fibrinogen levels (OR 0.90, 95% CI 0.84, 0.96, p <0.001). Thrombosis odds decreased with increased day prior heparin dose (OR 0.88, 95% CI 0.81, 0.97, p=0.006). Lower ACT values and increased fibrinogen levels may be considered to decrease the odds of bleeding. Use of this single measure, however, may not be sufficient alone to guide optimal anticoagulation practice during ECMO.

Keywords
extracorporeal membrane oxygenation, bleeding, thrombosis, pediatric, anticoagulation

INTRODUCTION

Despite decades of extracorporeal membrane oxygenation (ECMO) experience, and support from the Extracorporeal Life Support Organization, the optimal anticoagulation and assay lab monitoring strategy which would decrease risk of thrombosis and simultaneously not induce bleeding, is not yet established[1–8]. In 2013, 99% of surveyed centers used a continuous infusion of unfractionated heparin as the mainstay for anticoagulation[9]. A recent survey shows practice has not significantly changed with only 6% of respondents using the direct thrombin inhibitor bivalirudin; however, 41% of respondent sites have added viscoelastic variables in daily anticoagulation monitoring[10].

The multisite Bleeding and Thrombosis on Extracorporeal Membrane Oxygenation (BATE) study, served as the first step towards optimizing anticoagulation practices in the pediatric sub-population[1]. Our aim is to use the BATE dataset to determine independent associations of anticoagulation assay results and transfusion practices with clinically important bleeding and thrombotic events on ECMO and the association of these events with mortality and functional status at hospital discharge. We hypothesize that after adjusting for patient factors, we will delineate which lab monitoring strategies, anticoagulation assay results, and transfusion practices are associated with decreased bleeding and thrombotic events.

METHODS

Setting and subjects

The study was a secondary analysis of data collected for the BATE study which investigated predictors of bleeding and thrombosis in patients less than 19 years treated with ECMO in a neonatal intensive care unit (ICU), pediatric ICU, or cardiothoracic ICU, at eight participating centers within the CPCCRN between December 2012 and September 2014[1]. The study was approved with a waiver of informed consent (Institutional Review Board # 00058707) by the Institutional Review Boards at each of the participating hospitals and the Data Coordination Center at the University of Utah.

Bleeding events were defined as transfusion >80 ml/kg of blood products on a study day or a transfusion related to a pulmonary or intracranial hemorrhage as determined by the treating physician, and the bedside ECMO specialist, who recorded reasons for each transfusion[11].

Thrombotic events included pulmonary, intracranial, or cardiac emboli and limb ischemia as determined by the treating clinician or circuit related thrombosis resulting in an entire circuit change or thrombosis of the arterial cannula.

Data on efforts to control bleeding were not specifically obtained. The decision to transfuse hemostatic blood products was at the discretion of the clinician and no algorithms were applied across institutions or mandated by the study protocol. Clinician driven daily hemostatic and transfusion goals have been previously reported [8,12].

In order to reduce the influence of early postoperative bleeding secondary to intra-operative anticoagulation techniques on post cardiotomy subjects, and to allow sufficient time for routine anticoagulation management to influence bleeding and thrombosis, bleeding, and thrombosis events that occurred during the first day on ECMO were excluded from the analysis.

We also analyzed the influence of day prior monitoring of prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, activated clotting time (ACT), and antifactor Xa (anti-Xa) on bleeding and thrombotic events.

Patient outcomes were recorded at hospital discharge and included survival status, Functional Status Scale, and the Pediatric Overall Performance Category (POPC)[13–15].

Data collection

Questions related to identification of bleeding and thrombotic events were directed first to on-site research coordinators and then centrally to the project manager (S. Bisping) and the principal investigator (H.D.) who made the final adjudication.

Data related to bleeding and thrombosis events and blood products administered were collected daily. The anticoagulation assay results closest to 07:00a.m. were collected. Daily heparin dose (IU/kg/h) was calculated as the cumulative daily dose excluding any heparin used to prime the circuit or to keep lines open.

Additional data included demographics, primary ECMO indication(s), type of pump, mode of ECMO, duration of ECMO, ICU and hospital length of stay, number of failed organs, cardiopulmonary bypass in 24 h prior to ECMO, location of care, clinical site, acute diagnosis, and chronic diagnosis as previously described[1]. ECMO indication classifications were respiratory, cardiac, or extracorporeal cardiopulmonary resuscitation.

Statistical analysis

The incidence of bleeding and thrombotic events was calculated as the proportion of total subjects and separately as the proportion of total ECMO study days on which an event occurred. Subjects were divided into four groups; bleeding, thrombosis, both, and neither. Reported statistics are counts and percentages for categorical variables and median, first quartile, and third quartile for continuous variables.

Univariable logistic regression models were created to assess relationships with daily bleeding. Generalized estimating equations with an autoregressive correlation structure of order 1, were used to account for clustering of daily events within a subject. Bleeding was assessed on a daily basis but the time of day of the event was not

Table 1. Patient and circuit characteristics by event type.

	Bleeding (*N* = 200)	Thrombosis (*N* = 24)	Both (*N* = 88)	None (*N* = 169)	Overall (*N* = 481)
Age	—	—	—	—	—
Pre-term neonate	21 (47.7%)	3 (6.8%)	15 (34.1%)	5 (11.4%)	44
Full-term neonate	91 (44.8%)	3 (1.5%)	39 (19.2%)	70 (34.5%)	203
Infant	46 (40.4%)	8 (7.0%)	19 (16.7%)	41 (36.0%)	114
Child (1- <19 years)	42 (35.0%)	10 (8.3%)	15 (12.5%)	53 (44.2%)	120
Male	118 (41.7%)	13 (4.6%)	52 (18.4%)	100 (35.3%)	283
Primary ECMO indication	—	—	—	—	—
Respiratory	84 (36.7%)	12 (5.2%)	53 (23.1%)	80 (34.9%)	229
Cardiac	84 (45.7%)	7 (3.8%)	27 (14.7%)	66 (35.9%)	184
ECPR	32 (47.1%)	5 (7.4%)	8 (11.8%)	23 (33.8%)	68
Type of pump	—	—	—	—	—
Roller head	58 (34.9%)	12 (7.2%)	29 (17.5%)	67 (40.4%)	166
Centrifugal	142 (45.1%)	12 (3.8%)	59 (18.7%)	102 (32.4%)	315
Mode of ECMO	—	—	—	—	—
VA	172 (43.0%)	23 (5.8%)	77 (19.3%)	128 (32.0%)	400
VV	28 (34.6%)	1 (1.2%)	11 (13.6%)	41 (50.6%)	81
Duration of ECMO (days)	5.0 [2.8, 8.9]	6.8 [4.0, 13.9]	10.4 [6.1, 16.7]	4.6 [2.7, 7.1]	5.4 [3.0, 9.8]
Length of hospital stay (days)	37.2 [14.1, 72.8]	38.0 [19.1, 76.4]	43.7 [17.4, 66.5]	37.5 [19.2, 69.1]	37.6 [17.5, 69.9]
Length of ICU stay (days)	29.0 [12.6, 50.5]	25.0 [17.1, 61.1]	35.6 [17.0, 57.0]	27.6 [15.5, 49.4]	29.2 [15.3, 53.4]
Clinical site	—	—	—	—	—
A	31 (47.7%)	0 (0.0%)	16 (24.6%)	18 (27.7%)	65
B	32 (32.0%)	5 (5.0%)	17 (17.0%)	46 (46.0%)	100
C	13 (37.1%)	2 (5.7%)	3 (8.6%)	17 (48.6%)	35
D	20 (31.7%)	4 (6.3%)	22 (34.9%)	17 (27.0%)	63
E	21 (41.2%)	5 (9.8%)	6 (11.8%)	19 (37.3%)	51
F	31 (47.7%)	3 (4.6%)	6 (9.2%)	25 (38.5%)	65
G	9 (36.0%)	5 (20.0%)	5 (20.0%)	6 (24.0%)	25
H	43 (55.8%)	0 (0.0%)	13 (16.9%)	21 (27.3%)	77

Percentages are based on row totals presented in the "Overall" column. ECMO = extracorporeal membrane oxygenation, ECPR = extracorporeal cardiopulmonary resuscitation, VA = veno-arterial, VV = venovenous

identified. In order to ensure that predictors of daily bleeding were assessed prior to the occurrence of the bleeding event, lab values from the prior calendar day were used as predictors (e.g., Day 3 bleeding was predicted by lab values from Day 2, and Day 4 bleeding was predicted by lab. values from Day 3). This approach was also used for products administered, and the occurrence of lab monitoring. Odds ratios (OR) were reported for meaningful changes in the predictors. Variables from univariable modeling that were available for at least 90% of study days and were at least modestly associated with bleeding in univariable modeling ($p < 0.10$) were considered candidate variables for a bi-directional stepwise selection process with a criterion of $p < 0.10$ to enter the model and $p < 0.05$ to stay in the final model. Clinical site was forced into the multivariable model as a covariate because site factors may affect both clinical practice and bleeding, confounding the relationships with bleeding. Daily thrombosis was modeled analogously. Risk of bleeding as a function of ACT and fibrinogen was further explored using natural cubic splines while adjusting for other variables in the final multivariable model. The splines internal knots were placed at the 5th, 25th, 50th, 75th, and 95th percentiles of ACT and fibrinogen.

In-hospital mortality, Functional Status Scale, and POPC were summarized for each of the four bleeding/thrombosis subject groups. Differences in outcomes among these four subject groups were evaluated with logistic regression or ordinary linear regression, controlling for the pre-ECMO probability of mortality estimated by the Pediatric ECMO Prediction score; a pre-ECMO mortality prediction model derived from the BATE dataset[16].

RESULTS

A total of 481 subjects were eligible after excluding 33 subjects (21 of 33 died) who received less than 24h of ECMO. Patient and circuit characteristics by event type are shown in Table 1 and Supplemental Table 1. Median duration of ECMO was 5.4 days (IQR 3.0, 9.8). Eighty three percent of subjects were cannulated to venoarterial ECMO and 51% were ≤ 30 days of age at the time of cannulation. Cannulation occurred most frequently in the CICU (48%) followed by the NICU (31%).

Bleeding accounted for 42% of all events, and massive transfusion was the most common type of bleeding event (Table 2). Thrombotic events were rare (5%), but of those 89% (n=81) also had a bleeding event. Circuit related thrombosis (n= 83) were more common than patient thrombi (n=42). Thirty-five % of patients had no events. Of the 3767 ECMO days analyzed, bleeding events accounted for 36% (1353°days), thrombosis 7% (247 days), both 31% (1165 days), and none 27% (1002 days).

Table 2. Frequency of bleeding and thrombosis subtypes.

	Overall (N = 481)
Bleeding[1]	288 (59.9%)
Pulmonary	54 (11.2%)
Intracranial	80 (16.6%)
Massive transfusion[1]	244 (50.7%)
Thrombosis	112 (23.3%)
Patient	42 (8.7%)
Pulmonary	1 (0.2%)
Intracranial	19 (4.0%)
Limb ischemia	16 (3.3%)
Cardiac	7 (1.5%)
Circuit	83 (17.3%)
Entire circuit change	78 (16.2%)
Arterial cannula	17 (3.5%)

[a]>80 ml/kg/day.

Bleeding and thrombotic events across sites ranged between 32% and 56% and 0%–20%, respectively.

Anticoagulation monitoring and dosing

Site level anticoagulation monitoring and dosing are shown in Supplemental Table 2. An ACT was obtained on 99% and all ECMO study days and ranged between 97 and 100% across all sites. Goals for ACT values ranged between 160 and 220 s across sites. An anti-Xa was obtained on 61% of ECMO study days and ranged between 0 and 99% across all sites, with a goal between 0.3 and 0.7 IU/mL across sites. Heparin was given on 99% of ECMO study days, median dose when given ranged between 21.8 and 34.0 IU/kg/hour. Platelets were administered on 73% of ECMO study days, fresh frozen plasma on 36%, cryoprecipitate on 14%, antithrombin on 12%, aminocaproic acid on 5%, and Factor VII on 1%.

Univariable analysis

On univariable analysis, adjusting management according to results of hemostasis monitoring with PT, aPTT, ACT anti-Xa or platelet count was associated with lower odds of experiencing a bleeding event the following day (Supplemental Table 3). On univariable analyses, higher PT, lower fibrinogen, higher ACT, and lower platelet count were associated with higher odds of a bleeding event on the next day.

Univariable analyses of daily thrombotic events are shown in Supplemental Table 4. On univariable analyses, no associations were found between the act of monitoring any particular laboratory test and thrombotic event on the following day. Higher PTT, higher

fibrinogen, higher antithrombin, higher platelet count, receipt of cryoprecipitate, and higher heparin dose were associated with lower odds of thrombotic event on the next day.

Multivariable analysis

Multivariable analysis of bleeding and thrombotic events is shown in Table 3. Daily bleeding odds were independently associated with activated clotting time (ACT) (OR 1.03, 95% CI= 1.00, 1.05, p=0.047) and fibrinogen levels (OR 0.90, 95% CI 0.84, 0.96, p <0.001) on the prior day. Daily thrombosis odds decreased by 12% for every 10 IU/kg/h of heparin greater than 28.5 IU/kg/h (OR 0.88, 95% CI 0.81, 0.97, p=0.006) on the day prior to the event. Spline curves showing association of daily odds of bleeding and thrombosis with day prior ACT values, fibrinogen levels, and heparin dose are shown in Figure 1.

Additional variables associated with bleeding events on multivariable analysis were lower hematocrit, higher red blood cell and platelet transfusion, clinical site, arrhythmias, and gastrointestinal disorders (Table 3).

Additional variables associated with thrombotic events on multivariable analysis were receipt of platelet transfusion on the day prior, clinical site, venovenous ECMO,

Table 3. Multivariable model of daily bleeding and thrombosis events.

	OR (95% CI)	p-value
Bleeding event	—	—
Clinical site	—	<0.001
A	3.00 (1.80, 5.01)	—
B	Reference[a]	—
C	0.59 (0.23, 1.52)	—
D	2.47 (1.56, 3.92)	—
E	1.11 (0.60, 2.07)	—
F	2.25 (1.29, 3.93)	—
G	1.38 (0.64, 2.94)	—
H	2.52 (1.62, 3.94)	—
Cardiovascular disease (arrhythmia)	2.70 (1.67, 4.37)	0.011
Gastrointestinal disorder	3.03 (1.59, 5.78)	0.034
Fibrinogen (mg/dL) on previous day (OR is for a 50 mg/dL incr.)	0.90 (0.84, 0.96)	<0.001
ACT (seconds) on previous day (OR is for a 20 s incr.)	1.03 (1.00, 1.05)	0.047
Hematocrit (%) on previous day	0.96 (0.94, 0.98)	<0.001
PRBC (mL/kg) given previous day (OR is for a 20 mL/kg incr)	1.05 (1.00, 1.09)	0.020
Platelets (mL/kg) given previous day (OR is for a 20 mL/kg incr)	1.27 (1.12, 1.45)	0.010
Thrombotic event	—	—
Mode of ECMO	—	0.005
VA	Reference	—
VV	0.46 (0.26, 0.84)	—
Clinical site	—	0.004
A	1.13 (0.65, 1.96)	—
B	Reference[a]	—
C	1.40 (0.56, 3.50)	—
D	2.87 (1.72, 4.80)	—
E	1.33 (0.65, 2.71)	—
F	2.17 (0.82, 5.74)	—
G	1.71 (0.92, 3.17)	—
H	0.53 (0.28, 0.99)	—
Hypoxic/anoxic injury	0.24 (0.04, 1.60)	0.040
Acute or chronic neurologic condition	0.53 (0.28, 0.98)	0.026
Platelets (mL/kg) given previous day (OR is for a 20 mL/kg incr.)	1.29 (1.13, 1.47)	0.003
Heparin (IU/kg/hour) given previous day (OR is for a 10 IU/kg/hour incr.)	0.88 (0.81, 0.97)	0.006

[a]Reference was site with highest number of ECMO subjects, ECMO = extracorporeal membrane oxygenation, OR = odds ratio, VA = veno-arterial, VV = veno-venous.

hypoxic/anoxic injury, and acute or chronic neurologic condition (Table 3).

Due to the absence of >10% of results for PT, aPTT, antithrombin, and anti-Xa, these assays were not included in the initial multivariable models. However, subgroup analysis using complete case selection of subjects with an anti-Xa result on the day prior to an event, we found no independent association with odds of bleeding events (OR=0.96, 95% CI 0.91, 1.02, p=0.198) or thrombotic events (OR=0.94, 95% CI 0.84, 1.06, p=0.269). Pump type was not associated with events.

Multivariable analysis stratified by neonates and non-neonates showed that day prior fibrinogen (for each increase in 50 mg/dL) levels decreased the odds of bleeding events in both groups (Supplementary Tables 5, 6). The small number of thrombotic events (n=24) precluded multivariable analysis (neonates n=6, non-neonates n=18).

Patient outcomes

Overall mortality was 45% and by event type was bleeding 50%, thrombosis 50%, both 60%, and neither 27% (Table 4). Bleeding and thrombotic events adversely influenced the POPC score secondary to higher rates of brain death/mortality in patients (Table 4). Subgroup analysis of Functional Status Scale limited to survivors showed that exposure to a bleeding or thrombotic event did not influence Functional Status Scale at hospital discharge (p=0.287).

DISCUSSION

Clinicians often rely on heparin assay results to understand the influence of heparin on the patient *and* the pediatric ECMO circuit[17–19]. By studying 481 pediatric ECMO patients across eight sites, we found that 89% of those who experienced thrombosis also bled. We found that while heparin dose decreased odds of thrombosis, neither ACT or anti-Xa results on the day prior (closest to 7a.m.) were informative of the associated odds of both bleeding and thrombotic events.

In this study, the only anticoagulation related variable independently associated with decreased odds of thrombosis was higher day prior cumulative heparin (IU/kg/hour) dose (OR=0.88, 95% CI 0.81, 0.97, p=0.006). Prior studies in pediatric venoarterial patients also demonstrate that heparin independently decreases odds of clinically important thrombosis[19,20]. However, the day prior heparin dose in our study was not associated with increased bleeding, suggesting that while heparin may prevent thrombosis, patient factors in addition to heparin dose influence bleeding.

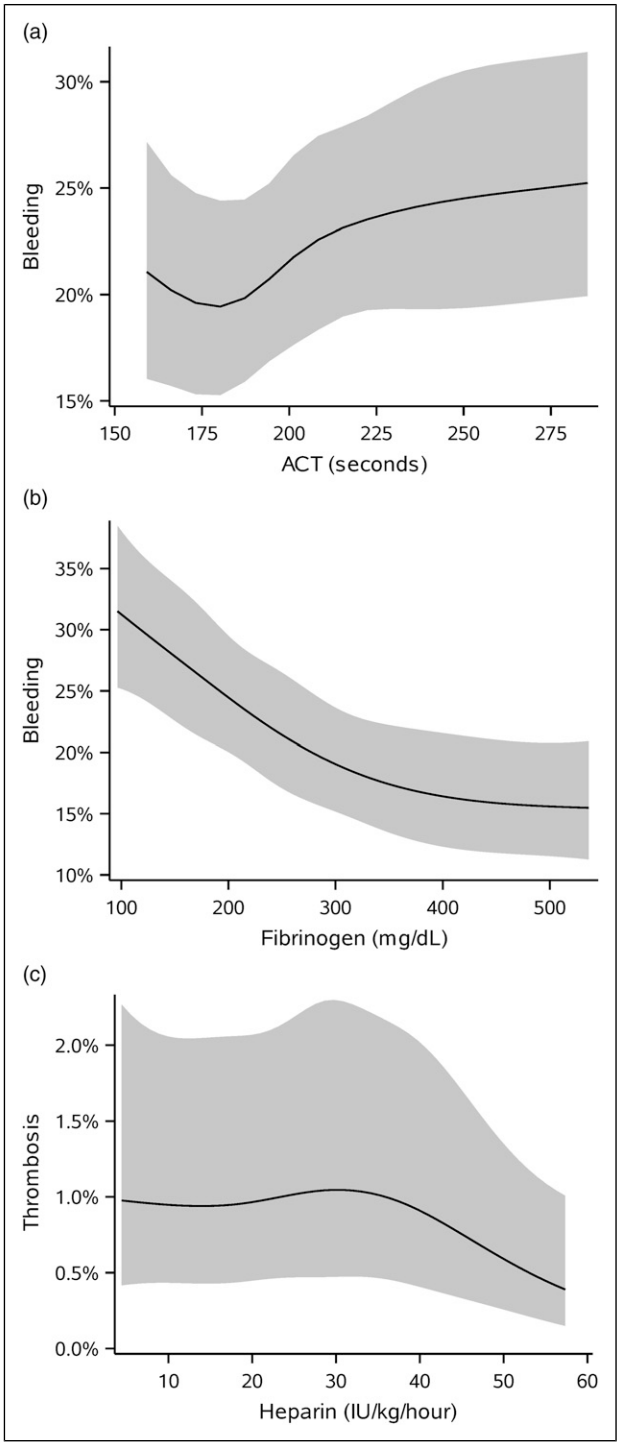

Figure 1. Spline curves showing probability of daily bleeding and thrombosis as predicted by day prior ACT values (A), fibrinogen levels (B), and heparin dose (C). The black curve represents the estimated probability, and the gray region represents the 95% pointwise confidence band for the probability. Lowest risk of bleeding occurred with prior day ACT values between 160 and 180 s (A) and when prior day fibrinogen levels were greater than 400 mg/dL (B). Risk of thrombosis was lowest when the prior day heparin dose was greater than 40 IU/kg/hour (C).

Table 4. Mortality and patient outcomes.

	Bleeding (*N* = 200)	Thrombosis (*N* = 24)	Both (*N* = 88)	None (*N* = 169)	*p*-value
In-hospital mortality	100 (50.0%)	12 (50.0%)	53 (60.2%)	46 (27.2%)	<.001[1]
POPC score at hospital discharge	—	—	—	—	<.001[1]
1—Good	15 (7.5%)	2 (8.3%)	4 (4.5%)	25 (14.8%)	—
2—Mild disability	45 (22.5%)	6 (25.0%)	17 (19.3%)	56 (33.1%)	—
3—Moderate disability	30 (15.0%)	3 (12.5%)	10 (11.4%)	33 (19.5%)	—
4—Severe disability	10 (5.0%)	1 (4.2%)	4 (4.5%)	9 (5.3%)	—
6—Brain death/death	100 (50.0%)	12 (50.0%)	53 (60.2%)	46 (27.2%)	—
Functional status at hospital discharge	—	—	—	—	0.740[1,2]
Good	26 (26.0%)	2 (16.7%)	9 (25.7%)	46 (37.4%)	—
Mildly abnormal	41 (41.0%)	6 (50.0%)	14 (40.0%)	46 (37.4%)	—
Moderately abnormal	28 (28.0%)	4 (33.3%)	10 (28.6%)	24 (19.5%)	—
Severely abnormal	5 (5.0%)	0 (0.0%)	2 (5.7%)	6 (4.9%)	—
Very severely abnormal	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	—

[a]*p*-values are based on regression models that control for estimated pre-ECMO probability of mortality (PEP). POPC = pediatric overall performance category.
[b]Sub analysis including only survivors; $p = 0.287$.

In a recent study of 70 United States academic centers, unfractionated heparin infusion remains the primary anticoagulant at 94% of sites. The most common assays used for heparin titration are ACT and anti-Xa, with goals similar to our sites, and 40% of sites still using a single assay (8, 12, 21).

Importantly, our study analyzed the association between ACT and anti-Xa results and the daily risk of both bleeding and thrombotic events. The median high daily ACT goal was between 200-220 (IQR 200,220) depending on bleeding status with a median low daily antithrombin goal between 75-80% (IQR 50–85) as previously reported [8]. We found that higher day prior ACT results (OR 1.03, 95% CI 1.00, 1.05, p=0.047) were associated with higher odds of bleeding, particularly when ACT values exceeded 200 s (Figure 1). However, the anticipated corollary that higher ACT would reduce odds of thrombosis was not found. Although the literature is inconsistent in regards to the correlation between anticoagulation test results, heparin dose and bleeding and thrombotic events,[17–23] our results suggest that heparin titration using ACT values is more likely to decrease the odds of bleeding than to decrease the odds of thrombosis. Furthermore, although 38% of the cohort were missing anti-Xa results, when using complete case analysis, we found no association between anti-Xa results on the day prior and odds of either bleeding or thrombotic events.

Another clinically important finding of this study is the association between higher day prior fibrinogen result and decreased odds of bleeding (OR 0.90, 95% CI 0.84, 0/96, p <0.001), particularly when fibrinogen levels were above 400 mg/dl (Figure 1). These findings persisted in multivariable analysis of neonates versus non-neonates. Notably, we found no association between higher day prior fibrinogen and increased odds of thrombosis. The association between decreased bleeding and higher fibrinogen is consistent with previous pediatric studies.[33,34] However, contrary to prior reports, despite the association we found between fibrinogen results and odds of bleeding, we found no association between day prior dose of FFP or antithrombin and odds of events.[19,23–26] Our findings suggest that higher fibrinogen levels may decrease the associated odds of bleeding without increasing the associated odds of thrombosis. This finding may be particularly impactful given that the average lower limit for fibrinogen was 150 s (IQR 100, 150) regardless of bleeding status, type of ECMO, or age (≤28 days vs > 28 days)[8].

In the absence of study mandated thresholds, previously reported, clinician driven platelet transfusion goals ranged between 80 and 100 (x 10^9/L) and average goal hematocrits varied between 28 and 41%[8,12]. In our cohort, platelets were transfused on 73% of ECMO study days. We found that the volume of transfused platelets was independently associated with increased bleeding *and* thrombosis. The association between platelet transfusions and odds of thrombosis is concerning, particularly given that prior studies demonstrate that the majority of platelet transfusions given to critically ill children and neonates are for prophylaxis and not for bleeding[26,27]. The role of platelets in preventing bleeding remains dubious and determining optimum platelet transfusion strategies for pediatric ECMO patients remains of the utmost importance[28–31].

Prior studies using the BATE dataset report that the bleeding status of the patient did not modify daily hemostatic goals by the medical team[32,33]. Yu et al. previously demonstrated no difference in clinical outcomes

between simple versus intensive monitoring across two centers,[34] Similarly, we found that more frequent lab monitoring did not decrease the odds of bleeding or thrombosis. The competing priorities of needing to maintain balanced hemostasis and the high volume of frequent laboratory blood draws in pediatric patients makes this a vitally important question[1].

Limitations

As an observational study, the associations observed do not infer causation and practice related to transfusion triggers, anticoagulation strategies, and ECMO equipment varied between sites. Anticoagulation management was driven by individual clinicians and not by study protocol. Because our multivariable models adjusted for clinical site, we are unable to detect many important factors of patient care that likely contribute to bleeding and thrombosis and our sample size was inadequate to permit multilevel modeling to account for center-level, ICU level, and patient-level factors or to allow for multivariable modeling comparing age groups by mode of ECMO. Although we adjusted for type of ECMO, Karam et al. demonstrated that in this cohort plasma and platelet doses were higher in those who received VA ECMO compared to VV which could influence our findings.[8] We excluded events in the first 24 h of receiving ECMO, but we did not adjust for intra- or peri-operative anticoagulation management or cardiac diagnosis. We did not account for left atrial hypertension as an etiology for pulmonary bleeding or for other potential causes of intracranial bleeding, and circuit related thrombosis may have been over-estimated if centers exchanged entire circuits at time of oxygenator change. Despite data abstraction training, the subjective nature of some definitions may influence the reported rates. Although anticoagulation is a dynamic process, lab results were only captured closest to 7a.m. regardless of time when the bleeding or thrombosis occurred and indication for lab draws or transfusions were not recorded. We did not control for different anticoagulation assay analyzers or different lots of heparin across sites and are falsely lowered by plasma free hemoglobin >50 mg/dl and hyperbilirubinemia which we did not adjust for in our analysis.[35] Heparin activity may also be altered by antithrombin levels which were not included in the multivariable models due to missingness.

Conclusions

Pediatric patients with clinically important thrombosis also have clinically important bleeding events. Lower ACT values and increased fibrinogen levels may be considered to decrease the odds of bleeding. Given the conflicting results of other studies which have found no association with laboratory monitoring tests for anticoagulation and bleeding and thrombosis during ECMO, more study is needed to refine practice for optimal outcomes.[7] In this report, ACT was associated with decreasing bleeding events.

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Declaration of conflicting interests

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Supplemental Material

Supplemental material for this article is available online.

Abbreviations

ACT; Activated clotting time; Antifactor Xa; anti-Xa; aPTT; activated partial thromboplastin time; BATE; Bleeding and thrombosis on extracorporeal membrane oxygenation; ICU; intensive care unit; PT; Prothrombin time.

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