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Bleeding and Thrombosis With Pediatric Extracorporeal Life Support: A Roadmap for Management, Research, and the Future From the Pediatric Cardiac Intensive Care Society: Part 2*

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Abstract

Objectives: To make recommendations on improving understanding of bleeding and thrombosis with pediatric extracorporeal life support including future research directions.

Data Sources: Evaluation of literature and consensus conferences of pediatric critical care and extracorporeal life support experts.

Study Selection: A team of 10 experts with pediatric cardiac and extracorporeal membrane oxygenation experience and expertise met through the Pediatric Cardiac Intensive Care Society to review current knowledge and make recommendations for future research to establish "best practice" for anticoagulation management related to extracorporeal life support.

Data Extraction/Data Synthesis: This white paper focuses on clinical understanding and limitations of current strategies to monitor anticoagulation. For each test of anticoagulation, limitations of current knowledge are addressed and future research directions suggested.

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*See also p. 1089.

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Conclusions: No consensus on best practice for anticoagulation monitoring exists. Structured scientific evaluation to answer questions regarding anticoagulation monitoring and bleeding and thrombotic events should occur in multicenter studies using standardized approaches and well-defined endpoints. Outcomes related to need for component change, blood product administration, healthcare outcome, and economic assessment should be incorporated into studies. All centers should report data on patient receiving extracorporeal life support to a registry.

Keywords

anticoagulation; extracorporeal membrane oxygenation; hemorrhage; monitoring; pediatrics; thrombosis

Despite decades of clinical experience using extracorporeal membrane oxygenation (ECMO), advances in understanding of pediatric hemostasis, and advances in circuit design, rates of bleeding and thrombosis in pediatric ECMO remain unacceptably high (1). Part 1 of this series reviewed anticoagulation strategies, with proposals for future research. In part 2, we focus on monitoring of anticoagulation. Given the complexity of coagulation, the ideal strategy to monitor anticoagulation should reflect the effect of the anticoagulant medication, and in addition identify coexisting coagulopathy. Such a strategy does not currently exist which has led to variability in testing practices (2). Monitoring commonly uses multiple tests, with each giving limited information about different aspects of the coagulation system, often with conflicting results.

The variability in anticoagulation management is not surprising in view of the absence of high-level evidence to guide management, reflected in guidelines that tend to be general in nature (3). The variation in practice between centers makes extrapolation of data from single-center reports difficult. Conclusions from database mining are also limited as they are retrospective and have missing data.

As cell-based models of hemostasis have continued to evolve over the last decade, there has been interest in investigating the role of RBC, platelet, WBC, and endothelial cell activation during pediatric ECMO (4). Platelet activation and adhesion have been described during ECMO as drivers of procoagulant tendencies (4, 5). Pilot data suggest that platelet aggregation is impaired in a majority of pediatric ECMO patients (6).

The goal of part two of this article is to describe current knowledge and research on anticoagulation monitoring for children supported with ECMO. We also propose a research approach to evaluate optimal anticoagulation monitoring strategies.

MATERIALS AND METHODS

The Pediatric Cardiac Intensive Care Society (PCICS) research subcommittee on scientific statements and white papers is comprised of 10 international members. All subcommittee members meet on a monthly basis by means of conference calls and also meetings at the annual PCICS scientific meeting. Details of the methods used to create this work are described in part one (7).

RESULTS

Section 3: Anticoagulation Monitoring

General Monitoring.—Unfractionated heparin (UFH) effect is variable and therefore requires close monitoring. Many monitoring strategies described below are in vitro plasma tests and as such they do not provide information about platelet function and endothelial function that affect in vivo risk of thrombosis or bleeding. Furthermore, commonly used tests measure different parts of the coagulation system and therefore will not always correlate. These results add to the conundrum that clinicians face when designing and implementing anticoagulation algorithms. Furthermore, anticoagulation testing values can vary depending on how they are performed in each local laboratory. Last, developmental differences in hemostasis will require that age be considered in any monitoring strategy. We recommend that algorithms for anticoagulation at individual centers be tailored to laboratory testing methods and ECMO circuitry used at those centers.

Activated Partial Thromboplastin Time.—Activated partial thromboplastin time (aPTT) measures the integrity of the intrinsic and common pathways of the clotting cascade. It has historically been the primary test for monitoring the effect of UFH and is also used with direct thrombin inhibitors. Its use in monitoring heparin was based largely on one study of adults with venous thromboembolism, where titration of heparin to obtain a goal aPTT of 1.5–2.5 times normal was associated with lower risk of recurrent thromboembolism (8). This became the reference standard for therapeutic heparinization; it has not been validated in pediatrics.

Studies evaluating aPTT in children on ECMO suggest that it does not correlate well with heparin dose (9, 10). In part, this is because multiple factors affect aPTT, including abnormal activity of clotting factors, acute phase reactants, plasma free hemoglobin, and hyperbilirubinemia (Table 1). Age-dependent developmental differences in coagulation affect aPTT as baseline aPTTs are higher in neonates than in adults. The aPTT response to heparin is also likely age-dependent (11). Use of aPTT assumes that the patients baseline values are normal, which is not often true during critical illness. There is a high amount of variability between intra-and interpatient aPTT interpretation, which may require multiple blood tests as heparin doses are adjusted. Further limiting its utility in monitoring anticoagulation on ECMO is that as a plasma test of the clotting cascade, aPTT gives only a partial picture of overall bleeding or clotting risk.

Clinicians should also be aware of the significant variability between different aPTT assays. There are over 300 laboratory methods for measuring aPTT. Different thromboplastin reagents and coagulometers give dramatically different aPTT results for the same level of heparin. Each individual assay should be calibrated against a standard for heparin concentration (e.g., protamine titration) to develop a goal range for that specific assay (12).

Given the limitations of aPTT in children, we recommend against using it as the sole monitor of anticoagulation on ECMO. We recommend that if aPTT is used, each assay should be correlated with a standard for heparin effect (e.g., protamine titration). Goal aPTT levels for that individual assay should be determined from this correlation, and based on this,

a nomogram should be developed for heparin dosing and adjustment. This nomogram should be adjusted with changes in laboratory reagents or equipment. Further, if heparin dosing is escalating without observed effects, we recommend anti-thrombin activity monitoring.

Activated Clotting Time.—Activated clotting time (ACT) has been used since the 1960s in cardiac surgery, and it has been one of the widest used monitoring tests in pediatric ECMO as it adds the ease of point of care testing. It measures the time for whole blood to form fibrin clot, reflecting the integrity of the clotting cascade as well as platelet number and function.

The utility of ACT lies in its ability to identify a global impairment in coagulation. Its major limitation is that it lacks specificity as it does not allow identification of what part of the coagulation system is abnormal. Measurement is affected by multiple factors, including but not limited to abnormal levels of clotting factors, thrombocytopenia or platelet dysfunction, antithrombin level, fibrin degradation products, hemodilution, and temperature (13, 14). Multiple reports evaluating anticoagulation strategies that combine ACT with aPTT, anti-factor Xa (anti-Xa) activity, and/or thromboelastography, or that replace ACT all together (9, 10, 15–19), have shown poor correlation between anti-Xa, aPTT and ACT in neonatal and pediatric ECMO (9, 10, 15) (level B-NR). Additionally, monitoring ACT alone in pediatric ECMO when utilizing UFH may lead to insufficient anticoagulation (4, 5,20) (level B-NR).

We recommend against using ACT as the sole method of monitoring heparin anticoagulation for pediatric ECMO due to its poor correlation with heparin dose and measures whole blood hemostasis rather than heparin effect. If ACT is used, it should be in conjunction with other testing to assess heparin activity, coagulation, and platelet function. If heparin dosing is escalating without observed effects, we recommend anti-thrombin level monitoring.

Anti-Xa.—The anti-Xa activity quantifies the degree of inhibition of factor Xa and is used to monitor the effect of UFH and low molecular weight heparin. Current data suggest 1) anti-Xa activity correlates with heparin dose better than aPTT or ACT (9, 15, 21) (level B-NR); 2) anti-Xa levels maybe preferable to ACT as a marker for the degree of anticoagulation (9) (level B-NR); and 3) combined monitoring with anti-Xa, thromboelastography and anti thrombin activity measurements, may be associated with reductions in blood product transfusions and bleeding, improved circuit life and less laboratory sampling (18) (level B-NR). This is especially significant as 50% of RBC transfusions in children are related to replacement for laboratory sampling (22). The benefits and target ranges of anti-Xa guided protocols may vary by age as infants have been shown to require higher doses of UFH to achieve anti-Xa targets developed for adults (23) (level B-NR). Factors identified that affect anti-Xa activity include elevated levels of plasma free hemoglobin and bilirubin (17) (Table 1).

Given the clinical data above, we support the measurement of anti-Xa activity to monitor heparin anticoagulation in ECMO. We recommend a multicenter comparison of the efficacy of anticoagulation monitoring and titration protocols based primarily on anti-Xa versus based primarily, or in combination with other coagulation tests, on whole blood coagulation assays such as ACT or aPTT in reducing bleeding and clotting complications on ECMO. We

recommend that these studies be conducted with specific endpoints related to bleeding and thrombosis. In addition, the amount of blood required for testing, blood products administered, and costs related to testing should be compared.

Antithrombin Activity.—Antithrombin is the most important inhibitor of several factors in the coagulation pathway, particularly thrombin, and it is critical to the anticoagulant effect of heparin. Antithrombin activity. measurements vary based on age and illness severity. Although antithrombin repletion during pediatric ECMO is widely practiced (~80–85% of centers), neither the optimal goal level nor dose has been established, nor has its safety and efficacy in improving outcomes been proven (24–27) (level C-LD). As centers continue to use antithrombin replacement, we recommend collecting and reporting baseline antithrombin activity in critical illness prior to and during ECMO and also prior to starting antithrombin replacement in order to establish normal activity measurements stratified by age. Although there is not enough evidence to recommend or not recommend antithrombin replacement, we do recommend collecting data to determine normal levels in the setting of critical illness.

Von Willebrand Factor.

Acquired von Willebrand syndrome is characterized by the loss of high molecular weight von Willebrand factor (vWF) multimers in face of shear stress from extracorporeal devices (28–31). Acquired von Willebrand syndrome is increasingly described in pediatric ECMO as a risk factor for bleeding, with onset as early as the first 24 hours and quick resolution following decannulation (29, 32, 33) (level B-NR). Pilot data suggest that vWF administration maybe efficacious in controlling severe bleeding in children on ECMO with acquired von Willebrand syndrome confirmed by multimer analysis (32) (level C-LD). A more novel use of recombinant vWF found that administration of the A2 position of vWF in disseminated intravascular coagulation inhibited platelet adhesion, decreased microthrombi in brain, kidney, lung, and reduced death (34). Such data might have an important role in ECMO patients. However, the efficacy and safety of vWF concentrate administration in the ECMO population has not been proven and requires further investigation. Prior to any trial of vWF administration, we recommend a study of vWF levels at routine intervals during ECMO to determine if, and at what level, this correlates with bleeding complications.

Section 4: Novel Anticoagulation Monitoring

Thromboelastography.—Thromboelastography is a functional test of clotting assessing the interaction between soluble factors, platelets, and fibrinogen. Rotational thromboelastometry is another viscoelastic test that gives similar, although perhaps not the same results and this should be considered when evaluating results or designing a trial. Both have potential to be a useful adjunct to the assessment of coagulation status for patients on ECMO (for detailed description, see supplement, Supplemental Digital Content 1, http://links.lww.com/PCC/B61).

Thromboelastography and thromboelastography with platelet mapping are increasingly used to assess bleeding risk and guide transfusion strategy in cardiac surgery (35–38), trauma (39,40), and liver transplantation (41,42) and to guide anticoagulation management in

patients with ventricular assist devices (43). Individual studies have suggested benefits including mortality reduction and alteration in transfusion profiles (44–46). However, the quality of data was judged to be low due to risk of bias, substantial heterogeneity, and low event rate (level C-LD). Extrapolation of adult data should be undertaken with caution given developmental differences in hemostasis and baseline thromboelastography values for neonates (47). Thromboelastography variables on CPB vary based on age, with neonates demonstrating more abnormal values for MA,, and LY30.

The case for thromboelastography with platelet mapping to guide anticoagulation strategy is compelling. However, data regarding the use of thromboelastography during ECMO in pediatric patients are limited to retrospective reviews and small, prospective, observational studies (level C-LD). A 2013 survey of anticoagulation practices reported 43% of responding centers used thromboelastography with significant variability in frequency of testing, mode of testing (kaolin, heparinase, etc.), and variables used (2).

The appropriateness of thromboelastography to independently guide heparin dosing is limited in that 50% of patients heparinized on ECMO have “flat line” thromboelastography tracings (48, 49) representing indeterminately long initiation of clotting (R Times). Furthermore, data associating thromboelastography and clinical outcomes is limited, with only a retrospective study showing reduced bleeding events and a trend toward improved survival using historical controls (18).

Some centers use thromboelastography to understand bleeding risk and guide product replacement for patients on ECMO. A retrospective review of pediatric patients on ECMO demonstrated high rates of severe platelet dysfunction, defined as less than 50% of baseline platelet aggregation (6). Univariate analysis correlated thromboelastography/platelet mapping defined sub-sets of platelet dysfunction with mortality and bleeding events, however, on multivariate analysis only low platelet count was associated with mortality. These results were limited as it was a small retrospective study with potential for bias, as thromboelastography was performed by clinician discretion based on perceived risk of coagulation-related complication at nonstandardized time points.

Thromboelastography has also been used in adult ECMO to assess bleeding risk. Receiver operating characteristic curve analysis demonstrated a sensitivity of 85% for thromboelastography to predict freedom from clinically important bleeding following initiation of ECMO. The authors postulate that the cut-points to determine optimal sensitivity and specificity can be used to drive clinical decision, although data to support this assertion are not available (50).

Overall, data on use of thromboelastography to guide anticoagulation are limited. Work in this area suffers from challenges related to developmental differences in hemostasis, inconsistent definitions related to bleeding and clotting, and lack of consistency regarding which thromboelastography variables are reported. Methodological questions remain regarding sample handling. Resolution of these challenges to gain understanding of how thromboelastography might aid in anticoagulation management on ECMO will require large,

multicenter, prospective studies with specifically defined endpoints for bleeding and thrombosis and requirement for blood component replacement.

DISCUSSION

Proposed Future Research Direction

There is now an improved understanding of the coagulation cascade and elements that control both bleeding and thrombosis. As new factors that affect the coagulation cascade in response to blood prosthetic surface and anticoagulation have been discovered, laboratory tests to measure them have become available. Despite these new tools, best practice recommendations remain elusive. In part one of this article, we describe practice and study variation that impedes progress in developing anticoagulation pathways that can be generalized across all centers. Many of these limitations encountered in studying anticoagulation are the same for anticoagulation monitoring. These include poorly standardized definitions of bleeding or thrombosis and how events are categorized. These difficulties extend to issues such as variable pumps, circuits, ECMO components, and how these variables interact with anticoagulation regimens and testing practices between sites. The solution to these difficulties in investigation for anticoagulation monitoring are similar to those proposed in part one. Primarily, greater granularity of data and standardization of terms paired with multicenter studies where uniform anticoagulation practices and testing regimens are used. Specifically, clear and standard definitions for bleeding and thrombosis should be used and these events should be documented to include timing of the events. Standardization of ECMO equipment and anticoagulation practices will allow comparison of testing regimens (including how tests are performed and how they are interpreted) between sites.

Given the continued frustration among clinicians in eliminating bleeding and thrombotic events during ECMO, and the adverse effects these events have on patient outcomes, the time is right to put aside personal preferences and work together to design and implement studies which will provide results that can be extrapolated to the field as “best practice.” Such efforts will require financing, collaboration, and careful analysis. Multidisciplinary investigators both within the field of extracorporeal life support as well as hematology, thrombosis, laboratory, statisticians, bedside providers, and likely industry partners should be incorporated. Although designing and completing such investigations will require adequate financial outlay to ensure scientifically viable results, given the heavy expense that bleeding and thrombotic events during ECMO add to our patients, investing in reduction of such complications seems ethically, clinically, and financially expedient.

CONCLUSIONS

Proposed Studies

1. A comparison of anti-Xa versus aPTT as the primary, although not only, laboratory value guiding anticoagulation monitoring protocols. There should be monitoring with endpoints such as need for circuit component change, patient bleeding and thrombotic events, amount of blood required for laboratory

sampling, amount of blood products administered, number of required heparin dosing changes to maintain anti coagulation in desired range and percent of time values in desired range, survival to ECMO decannulation and to hospital discharge. An economic assessment of costs for laboratory sampling between the two arms should also be provided.

2. Centers with reported low rates of bleeding and/or thrombotic complications should have anticoagulation algorithms evaluated and considered as a trial for "best practice." A comparison of identified "best practice" sites algorithms to other sites in a controlled fashion should be performed to see if similar results can be obtained.

3. A comparison trial of an anticoagulation monitoring strategy with and without thromboelastography as a supplement to evaluate anticoagulation efficacy should be conducted. The amount of blood products required and the degree of bleeding and thrombosis should be evaluated as important endpoints. As various forms of thromboelastography monitoring exist, comparing available devices for data obtained as well as cost and blood sampling volume is important.

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TABLE 1.

Anticoaugulation Monitoring

Test	Measures	Variables That Affect Results	How Results Are Affected
aPTT	Clotting via the intrinsic and common pathways	High levels of factor eight during acute phase reaction	aPTT remains shorter than expected with heparin infusion. More heparin is required to overcome “heparin resistance”
		Elevated plasma free hemoglobin	Shortens aPTT
		Hyperbilirubinemia	Prolongs aPTT
ACT	Entire clotting system in vitro	Thrombocytopenia or platelet dysfunction	Prolongs ACT. Thrombin formation with coagulation proteins may go on despite reassuring ACT
		Higher hematocrit	Shortens ACT
		Hypothermia	Prolongs ACT
Anti-Xa	Level of indirect and direct inhibition of factor Xa	Elevated plasma free hemoglobin (2 mg/mL)	Decreases anti-Xa levels
		Hyperbilirubinemia (1 0–20 mg/dL)	Decreases anti-Xa levels
		Hypertriglyceridemia (600–1,250 mg/dL)	Decreases anti-Xa levels
Thromboelastography	Activity of coagulation factors, platelets, and fibrinogen	Longer storage times	Thromboelastography appearance of hypercoagulable state
		Elevated plasma free hemoglobin	Increased R, MA, and K values

ACT = activated clotting time, aPTT = activated partial thromboplastin time.