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Priorities for Clinical Research in Pediatric Extracorporeal Membrane Oxygenation Anticoagulation From the Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE Consensus Conference

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OBJECTIVES: To identify and prioritize research questions for anticoagulation and hemostasis management of neonates and children supported with extracorporeal membrane oxygenation (ECMO) from the Pediatric ECMO Anticoagulation CollaborativE (PEACE) consensus.

DATA SOURCES: Systematic review was performed using PubMed, EMBASE, and Cochrane Library (CENTRAL) databases from January 1988 to May 2021, followed by serial consensus conferences of international, interprofessional experts in the management of ECMO for critically ill neonates and children.

STUDY SELECTION: The management of ECMO anticoagulation for critically ill neonates and children.

DATA EXTRACTION: Within each of the eight subgroups, two authors reviewed all citations independently, with a third independent reviewer resolving any conflicts.

DATA SYNTHESIS: Following the systematic review of MEDLINE, EMBASE, and Cochrane Library databases from January 1988 to May 2021, and the consensus process for clinical recommendations and consensus statements, PEACE panel experts constructed research priorities using the Child Health and Nutrition Research Initiative methodology. Twenty research topics were prioritized, falling within five domains (definitions and outcomes, therapeutics, anticoagulant monitoring, protocolized management, and impact of the ECMO circuit and its components on hemostasis).

CONCLUSIONS: We present the research priorities identified by the PEACE expert panel after a systematic review of existing evidence informing clinical care of neonates and children managed with ECMO. More research is required within the five identified domains to ultimately inform and improve the care of this vulnerable population.

KEYWORDS: anticoagulation; blood transfusion; extracorporeal membrane oxygenation; hemolysis; pediatrics

Critically ill children on extracorporeal membrane oxygenation (ECMO) support are at high risk for bleeding and thrombotic complications (1, 2). Although professional societies have published clinical practice guidelines for the management of anticoagulation and hemostatic transfusions in critically ill children on ECMO (3), these are based on clinical expertise stemming almost exclusively from observational data. After completion of a systematic review of the literature on anticoagulation management and hemostasis in neonates

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and children supported on ECMO, the Pediatric ECMO Anticoagulation CollaborativE (PEACE) Consensus Conference concluded that high-quality or even moderate-quality evidence is sorely missing on this topic (4). Anticipating a lack of high-quality evidence, the identification and rating of research priorities was a preplanned component of the PEACE Consensus Conference (5). The objective of this process was to identify and prioritize targeted areas for further clinical research to inform the management of anticoagulation and hemostasis for infants, children, and adolescents receiving ECMO support.

MATERIALS AND METHODS

The identification of research priorities was undertaken as part of the PEACE Consensus Conference. Gaps in the existing literature related to anticoagulation and hemostasis management of pediatric ECMO patients were identified through a systematic literature review conducted by the PEACE expert panel. Descriptions of the selection and organization of PEACE expert panel members, member characteristics, and methods of the literature search and modified Delphi process can be found in the PEACE executive summary and the accompanying supplement (4, 6–13). PEACE expert panel members were not paid or reimbursed for their participation.

Informed by the systematic literature review, research priorities were constructed using the Child Health and Nutrition Research Initiative (CHNRI) methodology (14, 15). A virtual expert panel meeting was held to finalize the research priority-setting methodology. During this meeting expert panelists defined the intended context and scope for research priorities as follows. The population of interest and intended beneficiaries were defined as neonates, infants, children, and adolescents receiving ECMO support for any indication. The focus of the research priorities was defined as anticoagulation and/or hemostasis management. The geographic scope is intended to include any areas where pediatric ECMO is provided. The research area of focus is clinical research, with questions of diagnosis, prevention, treatment, prognosis, and implementation considered. The target audience for these priorities includes clinicians, researchers, funders (both governmental and private), and industry partners.

At this initial meeting, criteria for setting research priorities were reviewed, defined, and selected. An anonymous web-based survey (Qualtrics) was used to determine the relative importance of each research priority-setting criterion among expert panel members. A sliding scale was used to assign points to each criterion (with higher points indicating higher priority) out of a total of 100 points across all criteria. Weights were assigned to each criterion based on the median value of points assigned in the survey (**Table 1**).

Each of the eight subgroups of the PEACE expert panel was charged with drafting three to five research topics. To ensure a similar depth of each research topic, the panel reviewed the CHNRI framework which lists the depth of research topics from very broad ("research avenue") to specific ("research option") to very specific ("research question"). Research topics were constructed to fall within the "research option" depth, which we defined as a program of research around a specific topic that would include several specific questions using different research modalities or instruments (15). Research topics were compiled and discussed at a subsequent virtual expert panel meeting, where panelists reviewed language, ensured a similar scope and depth across topics, collapsed topics where appropriate to minimize redundancy, and added new topics. Revisions were made by subgroups as necessary.

In a second web-based survey (Qualtrics), experts were asked to rate each research topic on a scale of 1–9 for each priority-setting criterion based on how favorably one would view the research topic in the context of the criterion. Median values of the expert panels' scores were used to calculate an overall weighted score for each research topic. Weighted scores were calculated by multiplying the median score for each criterion by the weight for that criterion to create a criterion subscore and then adding the criterion subscores together and multiplying by 10 (**Supplemental Digital Content**, http://links.lww.com/PCC/C500). Research topics were ordered based on their weighted scores. The top 20 of 24 total research topics, representing the top 85th percentile of weighted scores, were retained in the final priority list.

RESULTS

The survey response rate was 41 of 48 (85%). Final research topics and their weighted scores based on survey results are in **Table 2** and **Supplemental Table 1** (http://links.lww.com/PCC/C500). After reviewing the final

TABLE 1.
Criteria Used to Prioritize Research Topics for Anticoagulation and Hemostasis Management in Neonates and Children on Extracorporeal Membrane Oxygenation Support

Criterion	Weight
Cost (how much would the research cost?)	0.2
Maximum impact on the burden of disease (what is the theoretical potential of the research to lessen disease burden?)	0.15
Deliverability (how well would research result in interventions that can be delivered to the target population?)	0.15
Effectiveness (how likely is it that research would result in effective intervention(s)?)	0.1
Answerability (how likely is it that the research question(s) are answerable?)	0.1
Equity (will the research result in interventions that would be preferentially available to privileged individuals, thus increasing health inequity?)	0.1
Ethical aspects (will the research raise ethical concerns?)	0.1
Fundability (what is the likelihood that the research will be funded?)	0.1
Criteria and definitions are derived from the Child Health and Nutrition Research Initiative framework. Weights represent the relative importance of each criterion toward prioritizing research topics based on a web-based survey of expert panel members	

list, research priorities were categorized into one of five domains: 1) definitions and outcomes, 2) therapeutics (medications or blood products), 3) anticoagulant monitoring, 4) protocolized management of anticoagulation and hemostasis, and 5) impact of the ECMO circuit and its components on hemostasis. In addition to research priorities, three overarching good practice statements were generated to help guide research in the field (4).

Good Practice Statements

1. Clinical research studies of ECMO should include the ECMO circuit components and configurations that were used. 96% Agreement (n = 47), median 9, interquartile range (IQR) 8–9.
2. Clinical research studies of ECMO anticoagulation should report details on pump and membrane lung technology, circuit type and coating, connectors, and cannulation techniques. 95% Agreement (n = 44), median 9, IQR 8–9.
3. Research studies of ECMO anticoagulation should document anticoagulation monitoring details, including assay methodology (reagent and analyzer/coagulometer used) and reference ranges used, to compare results across studies. 98% Agreement (n = 44), median 9, IQR 7.25–9.

DISCUSSION

Definitions and Outcomes

A total of five research topics fell under the domain of "definitions and outcomes." The overall highest-ranked research topic was the development, validation, and implementation of standardized bleeding and thrombosis risk assessment tools and definitions for bleeding and thrombosis outcomes. These tools are foundational to consistency of reporting across clinical studies of pediatric ECMO anticoagulation and hemostasis (9, 11, 13 16). Challenges of ECMO research unique to pediatric patients include a small number of patients in each individual center and a high degree of patient heterogeneity (2, 17). These challenges necessitate multicenter studies, the design of which is currently hindered by the lack of standardized risk assessment tools and definitions of bleeding and clotting outcomes. Because of developmental changes in hemostasis over the pediatric age range and smaller intravascular volumes relative to circuit surface area and circuit blood volumes compared with adults, risks of bleeding and clotting are different for pediatric ECMO patients, and data cannot be confidently extrapolated from adult studies. At the same time, a greater array of diagnoses and indications for ECMO in pediatric patients leads to multiple sub-populations that likely have differential bleeding and thrombosis risk and may demonstrate differential treatment effects. Pursuit of evidence from randomized controlled trials will be limited by cost and feasibility given the small sample sizes in individual centers and the larger sample sizes required to account

TABLE 2.

Pediatric Extracorporeal Membrane Oxygenation Anticoagulation Collaborative Consensus Conference Research Priorities

Research Topic	Domain	Weighted Score
The development, validation, and implementation of standardized bleeding and thrombosis risk assessment tools and definitions for bleeding and thrombotic complications incorporating variability introduced by developmental hemostasis	Definitions and outcomes	82
Studies comparing unfractionated heparin to: 1) direct thrombin inhibitors and 2) unfractionated heparin plus adjunctive agents to determine the optimal anticoagulation strategy in the pediatric ECMO population. Algorithms should use standardized practice protocols and uniform definitions relating to management, monitoring, and outcomes and incorporate variability expected from developmental hemostasis	Therapeutics (medications or blood products)	81
Studies to determine whether multi-assay monitoring strategies are superior to single-assay monitoring for the prevention of bleeding and thrombosis in pediatric ECMO patients anticoagulated with either heparin or direct thrombin inhibitors	Anticoagulant monitoring	79.75
Studies to evaluate the clinical utility of the available monitoring assays for predicting bleeding and thrombosis in pediatric ECMO patients anticoagulated with either heparin or direct thrombin inhibitors, including evaluation of substances that may interfere with chromogenic and/or optical laboratory assays	Anticoagulant monitoring	77.5
Studies to examine thresholds for RBC, plasma, platelet, and cryoprecipitate transfusions in children supported by ECMO. Specific questions may include: the benefit of patient-specific thresholds that account for patient age, diagnosis, and the trajectory of their illness; whether thresholds incorporating physiologic indications such as measures of oxygen delivery, platelet function, and/or viscoelastic testing are superior to thresholds based on single numbers such as platelet count or hemoglobin alone	Therapeutics (medications or blood products)	77
Studies to determine whether a protocolized approach (anticoagulation management, fibrinolytics) to the management of thrombotic complications during ECMO support improves outcomes in pediatric ECMO patients	Protocolized management	77
Pharmacologic studies, including pharmacokinetic and pharmacodynamic studies, of anticoagulant, antifibrinolytic, and hemostatic medications to ensure efficacy and safety in the pediatric ECMO population	Therapeutics (medications or blood products)	76.5
Implementation studies to determine strategies to improve the capture of procedures, complications, and utilization of periprocedural protocols in data registries	Definitions and outcomes	75.5
Studies to identify the temporal relationships between days on ECMO and intracranial hemorrhage and/or thrombosis/ischemia in neonates, infants, and children and to determine optimum neuromonitoring/screening approaches (including but not limited to electroencephalogram, near infra-red spectroscopy, head ultrasound, head CT) to improve clinical outcomes	Definitions and outcomes	74
Studies to identify optimal strategies for monitoring and replacement of: 1) antithrombin and 2) fibrinogen in pediatric ECMO patients	Therapeutics (medications or blood products)	73.5
The development, validation, and implementation of protocols for procedural bleeding control in synergy with bleeding management algorithms for pediatric ECMO patients	Protocolized management	73.5
Studies comparing different hemostatic agents and bleeding management algorithms, including indications to reduce anticoagulant medications, blood product transfusion, and adjunct hemostatic agents (including topical agents, antifibrinolytics, factor VIIa, prothrombin complex concentrates as well as novel therapies). This requires data comparing different agents/algorithms/protocols using standardized practice protocols, pharmacologic data to guide dosing, and uniform definitions for indications, management, monitoring, and outcomes	Protocolized management	72

(*Continued*)

TABLE 2. (*Continued*)

Pediatric Extracorporeal Membrane Oxygenation Anticoagulation Collaborative Consensus Conference Research Priorities

Research Topic	Domain	Weighted Score
Studies to determine the impact of anticoagulation strategies on red cell damage and subsequent hemolysis with a focus on the specific threshold levels of hemolysis that correlate with morbidity or mortality in pediatric ECMO patients	Definitions and outcomes	71.5
Studies to determine the extent to which bleeding and thrombotic risks differ based on type(s) of invasive or operative procedures immediately preceding ECMO or while on ECMO support in pediatric patients	Definitions and outcomes	71.25
Studies to refine the appropriate volume and dosing of RBCs, plasma, platelets, cryoprecipitate, and/or whole blood transfused to children supported by ECMO that minimizes the associated risks and maximizes the efficacy	Therapeutics (medications or blood products)	71
Studies to determine the influence of specific pump and oxygenator technologies, circuit configurations, and/or cannulation techniques on patient outcomes related to anticoagulation strategies in pediatric ECMO patients	Impact of ECMO circuit and components on hemostasis	69.5
Studies to determine the effects of different types of biocompatible surface coatings and/or approaches to regional anticoagulation on patient outcomes in pediatric ECMO patients	Impact of ECMO circuit and components on hemostasis	69.5
Studies to evaluate: 1) indications for decreasing or temporarily ceasing anticoagulation around major procedures and 2) the efficacy of prophylactic antifibrinolytic medications around major procedures in pediatric ECMO patients	Therapeutics (medications or blood products)	69.5
Studies to determine whether individualized therapeutic laboratory ranges based on specific clinical conditions are superior to a single, "one-size-fits-all" range in preventing bleeding and thrombosis in pediatric ECMO patients anticoagulated with either heparin or direct thrombin inhibitors	Anticoagulant monitoring	68.5
Studies to determine the impact of adjuvant therapies and/or devices, including various renal replacement or fluid removal technologies, on outcomes related to anticoagulation strategies in pediatric ECMO patients	Impact of ECMO circuit and components on hemostasis	67.5

ECMO = extracorporeal membrane oxygenation.

for patient heterogeneity (17). Thus, it is likely that multicenter observational comparative effectiveness studies will inform clinical practice until randomized controlled trials can be performed. Validated risk adjustment tools are essential to mitigate confounding and estimate causal inference in observational studies, whereas objective definitions of bleeding and thrombosis are essential to evaluate outcomes attributable to hemostasis management across multiple centers.

Defining interventional procedures and identifying risks of bleeding or thrombosis associated with individual procedures represented two additional research priorities (12, 13). Descriptions of major procedure versus minor procedure are highly variable and there are currently no standardized definitions in this population (18–21). These definitions are necessary to identify differential bleeding risks among procedure categories, to interpret observational data across multiple centers, and to develop and evaluate risk-based hemostasis interventions for postoperative pediatric ECMO patients and those undergoing invasive procedures while on ECMO.

Two research priorities involved thresholds to predict the risk of adverse outcomes. Relationships between RBC hemolysis and resultant cell-free hemoglobin and clinical outcomes in pediatric ECMO patients remain uncertain (22–31). In multiple studies, hemolysis is associated with renal dysfunction and other adverse outcomes. However, current studies are limited by retrospective study designs that often lack

enough granularity to establish temporal relationships between measures of hemolysis and outcomes (24, 29, 30, 32). Because hemolysis could be a potential cause or result of renal dysfunction, establishing these temporal relationships is important. Likewise, because of differences in available assays and reporting across centers, establishing thresholds of cell-free hemoglobin applicable to multiple centers has not been possible and challenges multicenter clinical study design (24, 33).

Lastly, establishing temporal patterns of intracranial bleeding and thrombotic complications is necessary to employ risk-based neuromonitoring protocols to maximize clinical benefit. Although multiple neuromonitoring modalities are incorporated into clinical care, very little evidence exists to optimize neuromonitoring strategies in pediatric ECMO patients (13). This can be particularly problematic for neonatal patients who are at high risk for intracranial complications and often have less reliable neurologic exams due to the sedation required to maintain cannula position and circuit flow. Data to guide neuromonitoring strategies that incorporate differential risks of intracranial complications between different patients and within the same patients over time are needed.

Impact of the ECMO Circuit and Components on Hemostasis

Three research topics fell under the domain of the ECMO circuit and components. ECMO circuit technology continues to evolve in ways that are expected to impact anticoagulation and hemostasis management. Examples include biocompatible coatings on circuits designed to decrease immunogenicity and thrombogenicity; ECMO pumps designed for lower flow rates which decrease shear stress on blood cells; and decreases in or elimination of connection points that serve as areas of turbulent blood flow and niduses of clot formation (28). Given these changes, it is expected that optimal anticoagulation therapeutic targets could also change, but studies evaluating anticoagulation in the context of different circuit components are lacking (6). Importantly, one of the key limitations in the reviewed literature was a lack of description of ECMO circuit components and configurations in most studies of ECMO anticoagulation and hemostasis (6). Lacking these details, it is challenging to synthesize anticoagulation/hemostasis data from multiple studies, and it is impossible to estimate the influence of different circuit components and modifications on hemostasis and related outcomes in the clinical setting. Such data are essential for both clinical care and research protocols evaluating anticoagulation strategies.

An intriguing area of future development involves the provision of regional anticoagulation and/or the development of biocompatible surface coatings that would not require systemic anticoagulation. The ability to sustain ECMO circuits in pediatric patients in the absence of systemic anticoagulation without increasing the risk of patient or circuit thrombosis would be a great advance for the field. Lastly, pediatric ECMO patients often suffer organ dysfunction that requires additional support or devices to be added to the ECMO circuit. Examples include renal replacement therapy in the setting of renal dysfunction and plasmapheresis in the setting of thrombocytopenia-associated multiple organ failure. Optimal device combinations and configurations for these additional therapies, while children are on ECMO support, are unknown.

Therapeutics, Including Medications, and Blood Product Transfusion

Central to the provision of systemic anticoagulation for pediatric ECMO patients is the decision of which medication to use. Historically, unfractionated heparin has been the mainstay of ECMO anticoagulation (7). Recently, direct thrombin inhibitors have been used either in the setting of heparin resistance or as an alternate first-line agent (34–42). Prospective head-to-head comparisons between heparin and direct thrombin inhibitors are lacking and no randomized controlled trial data are available to guide anticoagulant medication choice in pediatric ECMO patients.

Nearly all pediatric ECMO patients receive blood product transfusions, with reported average RBC, platelet, and plasma transfusion volumes of 30 mL/kg, 17 mL/kg, and 16 mL/kg, respectively, for each day on ECMO support (43, 44). In multiple studies of critically ill children, including those on ECMO support, blood product transfusion is associated with adverse outcomes (1, 43, 45). Although some transfusion is likely beneficial, unnecessary transfusion is harmful. However, high-quality evidence to define necessary versus unnecessary transfusions is lacking. Observational studies are confounded by indication

bias, and it is difficult to estimate the true impact of different transfusion strategies on patient outcomes. Outside of the neonatal age group, there are no randomized control trial data available. Given the very high frequency of blood product transfusion in pediatric ECMO patients and associated adverse effects, interventional studies to define optimal transfusion indications in this population are needed (9).

Wide practice variation exists in monitoring for and replacing antithrombin (1, 46). Antithrombin is necessary for heparin to exert an anticoagulant effect. Pediatric ECMO patients, particularly neonates, often have low antithrombin levels and it is tempting to conclude that replacing antithrombin would lead to greater heparin efficacy and improved anticoagulation management. However, it is unknown whether optimal strategies would include routine monitoring and replacement of antithrombin, replacement only in the setting of heparin resistance, or no replacement at all. Results of observational studies are mixed, with some studies suggesting benefits associated with antithrombin replacement and others suggesting harm (47–55). No randomized controlled trial data exist for pediatric patients, and the risks versus benefits of antithrombin replacement in pediatric ECMO are largely unknown.

Pediatric ECMO patients are treated with multiple medications, with a recent single-center study documenting a median cumulative drug exposure of over 30 different medications at five weeks following ECMO cannulation (56). For many of these medications, there is insufficient data to understand pharmacokinetics, pharmacodynamics, and optimal drug dosing (57). Pharmacokinetics in pediatric ECMO patients can be highly variable due to drug binding to circuit components, fluid shifts and changes in the volume of distribution, blood loss and high volume of blood product transfusions, and changes in underlying organ function (58–62). For many drugs, therapeutic monitoring is not widely available. Even with the wider availability of therapeutic drug monitoring, serial blood draws to monitor multiple medications and to adapt dosing over time as changes in organ function, circuit saturation, and volume of distribution occur would be limited by small pediatric blood volumes. Innovative methods to estimate the pharmacokinetic and pharmacodynamic effects of the ECMO circuit and components and physiologic changes in ECMO patients over time are needed to guide optimal drug dosing (58, 62).

Anticoagulant Monitoring

Optimal approaches to anticoagulant monitoring are required for both clinical care and research. Which monitoring assays, alone or in combination, and optimal therapeutic targets to minimize bleeding and thrombotic complications to improve patient outcomes after ECMO support are unknown (8). No randomized controlled trial data are available to inform optimal anticoagulant monitoring strategies in pediatric ECMO patients. Observational studies are limited by insufficient details about monitoring assays used, limited data on preanalytic variables, different reference ranges and therapeutic targets, and different definitions of bleeding and clotting outcomes. The complexity of hemostasis in pediatric ECMO patients due to interaction with the ECMO circuit as well as coagulopathy associated with underlying diagnoses and critical illness lends credibility to multimodal monitoring strategies, incorporating measures of both anticoagulant effect and underlying patient hemostasis. However, the potential benefits of comprehensive laboratory monitoring must be balanced against the risks of high-volume blood draws in small pediatric patients and the contribution of blood sampling to acute blood loss and transfusion requirements in pediatric ECMO patients (1). Local availability of timely results of specialized assays may also be limited by the small number of patients at risk in most pediatric ECMO centers.

Therapeutic thresholds for anticoagulant monitoring assays are often derived from non-ECMO populations and extrapolated from adult data. Whether these thresholds are optimal for pediatric ECMO patients is unknown. Similarly, optimal strategies to adjust anticoagulant monitoring thresholds based on different patient ages, individualized risk of bleeding or thrombosis due to underlying pathophysiology, or different ECMO circuitry are unknown. Lastly, the exact effects of interfering substances, such as triglycerides, bilirubin, or plasma-free hemoglobin, and other preanalytic factors on anticoagulant monitoring assays are uncertain which further impedes the clinician's ability to optimally manage anticoagulation in pediatric ECMO patients.

Protocolized Management

Protocolized management is often employed for complex anticoagulation management including during

the management of critically ill children supported with ECMO (35, 55, 63–70). Advantages of protocolized management include consistency in clinical care; reduction in the cognitive load of frequent decisions for complex, high-risk patients; small total patient numbers in most centers such that institutional expertise is difficult to maintain across all providers; and the multidisciplinary nature of ECMO care (55, 63, 70). Although there has been some success in pediatric cardiac surgical protocolization of anticoagulation regimens (71), recent studies from adult ICUs suggest that the presence of protocols alone may not be beneficial (72, 73). Development and implementation of more successful protocols may benefit from nuanced approaches that combine learning healthcare systems with institutional experience resulting in "smarter protocols" that adapt over time as new information is learned.

CONCLUSIONS

We present the Research Priorities identified by the PEACE Expert Panel after a systematic review of existing evidence informing clinical care of neonates and children managed with ECMO. More research is required within the five identified domains (definitions and outcomes, therapeutics, anticoagulant monitoring, protocolized management, and impact of the ECMO circuit and its components on hemostasis) to ultimately inform and improve the care of this vulnerable population.

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Pediatric Extracorporeal Membrane Oxygenation Anticoagulation Collaborative (PEACE) members are listed in ***Appendix 1*** *(http://links.lww.com/PCC/C500).*

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REFERENCES

1. Dalton HJ, Reeder R, Garcia-Filion P, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network: Factors associated with bleeding and thrombosis in children receiving extracorporeal membrane oxygenation. *Am J Respir Crit Care Med* 2017; 196:762–771
2. Organization ELS: International Summary—ECLS Registry Report July 30, 2023. 2023. Available at: https://www.elso.org/registry/internationalsummaryandreports/international-summary.aspx
3. McMichael ABV, Ryerson LM, Ratano D, et al: 2021 ELSO adult and pediatric anticoagulation guidelines. *ASAIO J* 2022; 68:303–310
4. Alexander PMA, Bembea M, Cashen K, et al; Pediatric Extracorporeal Membrane Oxygenation (ECMO) Anticoagulation CollaborativE (PEACE), in collaboration with the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, the Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric ECMO subgroup of PALISI and the Extracorporeal Life Support Organization (PediECMO): Executive summary: Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE Consensus Conference. *Pediatr Crit Care Med* 2024; 25:643–675
5. Alexander PMA, Muszynski JA: Ongoing variability in pediatric extracorporeal membrane oxygenation anticoagulation practices—could consensus change the next survey results? *Pediatr Crit Care Med* 2021; 22:581–584
6. Himebauch AS, Priest JR, Annich GM, et al; Pediatric Extracorporeal Membrane Oxygenation (ECMO) Anticoagulation CollaborativE (PEACE), in collaboration with the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, the Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric ECMO subgroup of PALISI and the Extracorporeal Life Support Organization (PediECMO): The influence of the extracorporeal membrane oxygenation circuit and components on anticoagulation management: The Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE consensus conference. *Pediatr Crit Care Med* 2024; 25:e1–e6
7. Cashen K, Saini A, Brandão L, et al; Pediatric Extracorporeal Membrane Oxygenation (ECMO) Anticoagulation CollaborativE

(PEACE), in collaboration with the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, the Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric ECMO subgroup of PALISI and the Extracorporeal Life Support Organization (PediECMO): Anticoagulant medications: The Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE consensus conference. *Pediatr Crit Care Med* 2024; 25:e7–e13

8. Ozment C, Alexander PMA, Chandler W, et al; Pediatric Extracorporeal Membrane Oxygenation (ECMO) Anticoagulation CollaborativE (PEACE), in collaboration with the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, the Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric ECMO subgroup of PALISI and the Extracorporeal Life Support Organization (PediECMO): Anticoagulation monitoring and targets: The Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE consensus conference. *Pediatr Crit Care Med* 2024; 25:e14–e24
9. Nellis ME, Moynihan KM, Sloan SR, et al; Pediatric Extracorporeal Membrane Oxygenation (ECMO) Anticoagulation CollaborativE (PEACE), in collaboration with the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, the Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric ECMO subgroup of PALISI and the Extracorporeal Life Support Organization (PediECMO): Prophylactic transfusions strategies in children supported by extracorporeal membrane oxygenation: The Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE consensus conference. *Pediatr Crit Care Med* 2024; 25:e25–e34
10. Zantek ND, Steiner ME, Teruya J, et al; Pediatric Extracorporeal Membrane Oxygenation (ECMO) Anticoagulation CollaborativE (PEACE), in collaboration with the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, the Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric ECMO subgroup of PALISI and the Extracorporeal Life Support Organization (PediECMO): Recommendations on monitoring and replacement of antithrombin, fibrinogen and von Willebrand factor in pediatric patients on extracorporeal membrane oxygenation: The Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE Consensus Conference. *Pediatr Crit Care Med* 2024; 25:e35–e43
11. Moynihan KM, Ryerson L, Le J, et al; Pediatric Extracorporeal Membrane Oxygenation (ECMO) Anticoagulation CollaborativE (PEACE), in collaboration with the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, the Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric ECMO subgroup of PALISI and the Extracorporeal Life Support Organization (PediECMO): Antifibrinolytic and adjunct hemostatic agents: The Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE Consensus Conference. *Pediatr Crit Care Med* 2024; 25:e44–e52
12. Willems A, Anders MM, Garcia A, et al; Pediatric Extracorporeal Membrane Oxygenation (ECMO) Anticoagulation CollaborativE (PEACE), in collaboration with the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, the Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric ECMO subgroup of PALISI and the Extracorporeal Life Support Organization (PediECMO): Management of extracorporeal membrane oxygenation anticoagulation in the perioperative period: The Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE Consensus Conference. *Pediatr Crit Care Med* 2024; 25:e53–e65
13. Rintoul NE, McMichael ABV, Bembea MM, et al; Pediatric Extracorporeal Membrane Oxygenation (ECMO) Anticoagulation CollaborativE (PEACE), in collaboration with the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, the Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric ECMO subgroup of PALISI and the Extracorporeal Life Support Organization (PediECMO): Management and bleeding and thrombotic complications during pediatric extracorporeal membrane oxygenation: The Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE Consensus Conference. *Pediatr Crit Care Med* 2024; 25:e66–e77
14. Rudan I, Chopra M, Kapiriri L, et al: Setting priorities in global child health research investments: Universal challenges and conceptual framework. *Croat Med J* 2008; 49:307–317
15. Rudan I, Yoshida S, Wazny K, et al: Setting health research priorities using the CHNRI method: V. Quantitative properties of human collective knowledge. *J Glob Health*. 2016; 6:010502
16. Alexander PMA, Habet V, Barbaro RP: Realizing potential: Pediatric extracorporeal membrane oxygenation needs common adverse event definitions to improve outcomes. *Pediatr Crit Care Med* 2023; 24:528–530
17. Bembea MM, Hoskote A, Guerguerian AM: Pediatric ECMO research: The case for collaboration. *Front Pediatr* 2018; 6:240
18. Nichols WL, Hultin MB, James AH, et al. The Diagnosis, Evaluation and Management of von Willebrand Disease. In: U.S. Department of Health and Human Services NIoH, National Heart, Lung and Blood Institute, editor.: NIH Publication No. 08-5832; 2007.
19. Malloy PC, Grassi CJ, Kundu S, et al; Standards of Practice Committee with Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Endorsement: Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. *J Vasc Interv Radiol* 2009; 20:S240–S249
20. Patel IJ, Rahim S, Davidson JC, et al: Society of Interventional Radiology Consensus guidelines for the periprocedural management of thrombotic and bleeding risk in patients undergoing percutaneous image-guided interventions—part ii: Recommendations: Endorsed by the Canadian Association for Interventional Radiology and the Cardiovascular and Interventional Radiological Society of Europe. *J Vasc Interv Radiol* 2019; 30:1168–1184.e1
21. Douketis JD, Spyropoulos AC, Duncan J, et al: Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant. *JAMA Intern Med*. 2019; 179:1469–1478
22. Betrus C, Remenapp R, Charpie J, et al: Enhanced hemolysis in pediatric patients requiring extracorporeal membrane oxygenation and continuous renal replacement therapy. *Ann Thorac Cardiovasc Surg* 2007; 13:378–383
23. Byrnes J, McKamie W, Swearingen C, et al: Hemolysis during cardiac extracorporeal membrane oxygenation: A case-control

comparison of roller pumps and centrifugal pumps in a pediatric population. *ASAIO J* 2011; 57:456–461

24. Dalton HJ, Cashen K, Reeder RW, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN): Hemolysis during pediatric extracorporeal membrane oxygenation: Associations with circuitry, complications, and mortality. *Pediatr Crit Care Med* 2018; 19:1067–1076
25. Gbadegesin R, Zhao S, Charpie J, et al: Significance of hemolysis on extracorporeal life support after cardiac surgery in children. *Pediatr Nephrol* 2009; 24:589–595
26. Guner YS, Delaplain PT, Schomberg J, et al; ELSO CDH Interest Group: Risk factors for hemolysis during extracorporeal life support for congenital diaphragmatic hernia. *J Surg Res* 2021; 263:14–23
27. Jenks CL, Zia A, Venkataraman R, et al: High hemoglobin is an independent risk factor for the development of hemolysis during pediatric extracorporeal life support. *J Intensive Care Med* 2019; 34:259–264
28. Maul TM, Aspenleiter M, Palmer D, et al: Impact of circuit size on coagulation and hemolysis complications in pediatric extracorporeal membrane oxygenation. *ASAIO J* 2020; 66:1048–1053
29. O'Halloran CP, Thiagarajan RR, Yarlagadda VV, et al: Outcomes of infants supported with extracorporeal membrane oxygenation using centrifugal versus roller pumps: An analysis from the extracorporeal life support organization registry. *Pediatr Crit Care Med* 2019; 20:1177–1184
30. Okochi S, Cheung EW, Barton S, et al: An analysis of risk factors for hemolysis in children on extracorporeal membrane oxygenation. *Pediatr Crit Care Med* 2018; 19:1059–1066
31. Santiago MJ, Gomez C, Magana I, et al: Hematological complications in children subjected to extracorporeal membrane oxygenation. *Med Intensiva (Engl Ed)* 2019; 43:281–289
32. Masalunga C, Cruz M, Porter B, et al: Increased hemolysis from saline pre-washing RBCs or centrifugal pumps in neonatal ECMO. *J Perinatol* 2007; 27:380–384
33. Almizraq RJ, Yi QL, Acker JP; Biomedical Excellence for Safer Transfusion (BEST) Collaborative: Impact of technical and assay variation on reporting of hemolysis in stored red blood cell products. *Clin Chim Acta* 2017; 468:90–97
34. Ryerson LM, Balutis KR, Granoski DA, et al: Prospective exploratory experience with bivalirudin anticoagulation in pediatric extracorporeal membrane oxygenation. *Pediatr Crit Care Med* 2020; 21:975–985
35. Bingham KR, Riley JB, Schears GJ: Anticoagulation management during first five days of infant-pediatric extracorporeal life support. *J Extra Corpor Technol* 2018; 50:30–37
36. Campbell CT, Diaz L, Kelly B: Description of bivalirudin use for anticoagulation in pediatric patients on mechanical circulatory support. *Ann Pharmacother* 2021; 55:59–64
37. Hamzah M, Jarden AM, Ezetendu C, et al: Evaluation of bivalirudin as an alternative to heparin for systemic anticoagulation in pediatric extracorporeal membrane oxygenation. *Pediatr Crit Care Med* 2020; 21:827–834
38. Machado DS, Garvan C, Philip J, et al: Bivalirudin may reduce the need for red blood cell transfusion in pediatric cardiac patients on extracorporeal membrane oxygenation. *ASAIO J* 2021; 67:688–696
39. Nagle EL, Dager WE, Duby JJ, et al: Bivalirudin in pediatric patients maintained on extracorporeal life support. *Pediatr Crit Care Med* 2013; 14:e182–e188
40. Schill MR, Douds MT, Burns EL, et al: Is anticoagulation with bivalirudin comparable to heparin for pediatric extracorporeal life support? Results from a high-volume center. *Artif Organs* 2021; 45:15–21
41. Seelhammer TG, Bohman JK, Schulte PJ, et al: Comparison of bivalirudin versus heparin for maintenance systemic anticoagulation during adult and pediatric extracorporeal membrane oxygenation. *Crit Care Med* 2021; 49:1481–1492
42. Snyder CW, Goldenberg NA, Nguyen ATH, et al: A perioperative bivalirudin anticoagulation protocol for neonates with congenital diaphragmatic hernia on extracorporeal membrane oxygenation. *Thromb Res* 2020; 193:198–203
43. Muszynski JA, Reeder RW, Hall MW, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN): RBC transfusion practice in pediatric extracorporeal membrane oxygenation support. *Crit Care Med* 2018; 46:e552–e559
44. Karam O, Goel R, Dalton H, et al: Epidemiology of hemostatic transfusions in children supported by extracorporeal membrane oxygenation. *Crit Care Med* 2020; 48:e698–e705
45. O'Halloran CP, Alexander PMA, Andren KG, et al: RBC exposure in pediatric extracorporeal membrane oxygenation: Epidemiology and factors associated with large blood transfusion volume. *Pediatr Crit Care Med* 2018; 19:767–774
46. Ozment CP, Scott BL, Bembea MM, et al; Pediatric ECMO (PediECMO) subgroup of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network and the Extracorporeal Life Support Organization (ELSO): Anticoagulation and transfusion management during neonatal and pediatric extracorporeal membrane oxygenation: A survey of medical directors in the United States. *Pediatr Crit Care Med* 2021; 22:530–541
47. Aiello SR, Flores S, Coughlin M, et al: Antithrombin use during pediatric cardiac extracorporeal membrane oxygenation admission: Insights from a national database. *Perfusion* 2021; 36:138–145
48. Gordon SE, Heath TS, McMichael ABV, et al: Evaluation of heparin anti-factor Xa levels following antithrombin supplementation in pediatric patients supported with extracorporeal membrane oxygenation. *J Pediatr Pharmacol Ther.* 2020; 25:717–722
49. Omecene NE, Kishk OA, Lardieri AB, et al: Comparison of antithrombin III products in pediatric patients receiving extracorporeal membrane oxygenation. *ASAIO J* 2020; 66:1042–1047
50. Stansfield BK, Wise L, Ham PB, 3rd, et al: Outcomes following routine antithrombin III replacement during neonatal extracorporeal membrane oxygenation. *J Pediatr Surg* 2017; 52:609–613
51. Todd Tzanetos DR, Myers J, Wells T, et al: The use of recombinant antithrombin III in pediatric and neonatal ECMO patients. *ASAIO J* 2017; 63:93–98
52. Wong TE, Nguyen T, Shah SS, et al: Antithrombin concentrate use in pediatric extracorporeal membrane oxygenation: A multicenter cohort study. *Pediatr Crit Care Med* 2016; 17:1170–1178

53. Byrnes JW, Swearingen CJ, Prodhan P, et al: Antithrombin III supplementation on extracorporeal membrane oxygenation: Impact on heparin dose and circuit life. *ASAIO J* 2014; 60:57–62
54. Ryerson LM, Bruce AK, Lequier L, et al: Administration of antithrombin concentrate in infants and children on extracorporeal life support improves anticoagulation efficacy. *ASAIO J* 2014; 60:559–563
55. Agati S, Ciccarello G, Salvo D, et al: Use of a novel anticoagulation strategy during ECMO in a pediatric population: Single-center experience. *ASAIO J* 2006; 52:513–516
56. Thibault C, Collier H, Naim MY, et al: Patterns of medication exposure in children on extracorporeal membrane oxygenation: A step in prioritizing future pharmacologic studies. *Crit Care Explor*. 2019; 1:e0045
57. Bailly DK, Reeder RW, Muszynski JA, et al: Anticoagulation practices associated with bleeding and thrombosis in pediatric extracorporeal membrane oxygenation: A multi-center secondary analysis. *Perfusion* 2023; 38:363–372
58. Roberts JA, Bellomo R, Cotta MO, et al: Machines that help machines to help patients: Optimising antimicrobial dosing in patients receiving extracorporeal membrane oxygenation and renal replacement therapy using dosing software. *Intensive Care Med* 2022; 48:1338–1351
59. Autmizguine J, Hornik CP, Benjamin DK, Jr, et al: Pharmacokinetics and safety of micafungin in infants supported with extracorporeal membrane oxygenation. *Pediatr Infect Dis J* 2016; 35:1204–1210
60. McDaniel CG, Honeycutt CC, Watt KM: Amiodarone extraction by the extracorporeal membrane oxygenation circuit. *J Extra Corpor Technol* 2021; 53:68–74
61. Watt K, Li JS, Benjamin DK, Jr, et al: Pediatric cardiovascular drug dosing in critically ill children and extracorporeal membrane oxygenation. *J Cardiovasc Pharmacol* 2011; 58:126–132
62. Watt KM, Cohen-Wolkowiez M, Barrett JS, et al: Physiologically based pharmacokinetic approach to determine dosing on extracorporeal life support: Fluconazole in children on ECMO. *CPT Pharmacometrics Syst Pharmacol*. 2018; 7:629–637
63. Al-Jazairi A, Raslan S, Al-Mehizia R, et al: Performance assessment of a multifaceted unfractionated heparin dosing protocol in adult patients on extracorporeal membrane oxygenator. *Ann Pharmacother* 2021; 55:592–604
64. Figueroa Villalba CA, Brogan TV, McMullan DM, et al: Conversion from activated clotting time to anti-Xa heparin activity assay for heparin monitoring during extracorporeal membrane oxygenation. *Crit Care Med* 2020; 48:e1179–e1184
65. Jenks CL, Landry LM, Garrison CF, et al: Pediatric extracorporeal membrane oxygenation anticoagulation protocol associated with a decrease in complications. *ASAIO J* 2022; 68:275–280
66. Kessel AD, Kline M, Zinger M, et al: The impact and statistical analysis of a multifaceted anticoagulation strategy in children supported on ECMO: Performance and pitfalls. *J Intensive Care Med* 2017; 32:59–67
67. Mazzeffi MA, Tanaka K, Roberts A, et al: Bleeding, thrombosis, and transfusion with two heparin anticoagulation protocols in venoarterial ECMO patients. *J Cardiothorac Vasc Anesth* 2019; 33:1216–1220
68. Northrop MS, Sidonio RF, Phillips SE, et al: The use of an extracorporeal membrane oxygenation anticoagulation laboratory protocol is associated with decreased blood product use, decreased hemorrhagic complications, and increased circuit life. *Pediatr Crit Care Med* 2015; 16:66–74
69. O'Meara LC, Alten JA, Goldberg KG, et al: Anti-Xa directed protocol for anticoagulation management in children supported with extracorporeal membrane oxygenation. *ASAIO J* 2015; 61:339–344
70. Yu JS, Barbaro RP, Granoski DA, et al: Prospective side by side comparison of outcomes and complications with a simple versus intensive anticoagulation monitoring strategy in pediatric extracorporeal life support patients. *Pediatr Crit Care Med* 2017; 18:1055–1062
71. Nair AG, Oladunjoye OO, Trenor CC, 3rd, et al: An anticoagulation protocol for use after congenital cardiac surgery. *J Thorac Cardiovasc Surg* 2018; 156:343–352.e4
72. Michetti CP, Newcomb AB, Liu C: Protocol use in surgical intensive care units. *J Surg Res* 2021; 264:242–248
73. Kavanagh BP, Nurok M: Standardized intensive care. Protocol misalignment and impact misattribution. *Am J Respir Crit Care Med* 2016; 193:17–22