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Executive Summary: The Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE (PEACE) Consensus Conference*

OBJECTIVES: To present recommendations and consensus statements with supporting literature for the clinical management of neonates and children supported with extracorporeal membrane oxygenation (ECMO) from the Pediatric ECMO Anticoagulation CollaborativE (PEACE) consensus conference.

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

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

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

DATA SYNTHESIS: A systematic review was conducted using MEDLINE, Embase, and Cochrane Library databases, from January 1988 to May 2021. Each panel developed evidence-based and, when evidence was insufficient, expert-based statements for the clinical management of anticoagulation for children supported with ECMO. These statements were reviewed and ratified by 48 PEACE experts. Consensus was obtained using the Research and Development/UCLA Appropriateness Method. Results were summarized using the Grading of Recommendations Assessment, Development, and Evaluation method. We developed 23 recommendations, 52 expert consensus statements, and 16 good practice statements covering the management of ECMO anticoagulation in three broad categories: general care and monitoring; perioperative care; and nonprocedural bleeding or thrombosis. Gaps in knowledge and research priorities were identified, along with three research focused good practice statements.

CONCLUSIONS: The 91 statements focused on clinical care will form the basis for standardization and future clinical trials.

KEYWORDS: anticoagulants; bleeding; extracorporeal membrane oxygenation; hematologic tests; pediatrics; thrombosis

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Extracorporeal membrane oxygenation (ECMO) is an accepted, invasive form of cardiorespiratory support that is used to facilitate organ recovery in the most critically ill infants and children (1, 2). Complications associated with mechanical support are common, and mortality before hospital discharge following ECMO remains between 33% and 57% depending on etiology of cardiopulmonary failure (1, 2). Despite increasing utilization over the past decades (2), variability in all aspects of ECMO support, including anticoagulation and transfusion management, limit evidence generation from multicenter observational studies and existing registry analyses and challenge multicenter interventional trial design (1–5).

The objective of the Pediatric ECMO Anticoagulation CollaborativE (PEACE) Consensus is to provide expert opinion on the management of anticoagulation and hemostasis for neonates, infants, children, and adolescents receiving ECMO.

METHODS

Definitions

As technology evolves, variability in equipment and the configuration of extracorporeal life support (ECLS) components required standardization of the definition of ECMO. In 2018, the Nomenclature Task Force of the Extracorporeal Life Support Organization (ELSO) published a consensus-based position article to standardize definitions for ECLS modalities (6). For the purposes of the PEACE consensus statements, we defined ECMO, using this consensus-based document, as any combination of extracorporeal circuit, pump, and oxygenator.

The definition of clinically significant bleeding in children on ECMO has been approached previously, as summarized in **Table S1** (http://links.lww.com/PCC/C494). For the purposes of clinical consensus statements presented, "Clinically Significant Bleeding" is defined as meeting any of the criteria listed for moderate or severe bleeding (4, 7, 8).

Scope of Patients

The PEACE consensus statements apply to neonates, infants, children, and adolescents (i.e., patients 0 d to 21 yr old) supported by ECMO for any indication. For brevity, the term "pediatric ECMO patients" is used throughout this executive summary to indicate neonates, infants, children, and adolescents supported with ECMO. The upper age of 21 years is based on the American Academy of Pediatrics definition of the pediatric age limit (9). Neonatal patients were included because in many centers neonatal and pediatric ECMO patients are cared for by the same team using common protocols. Premature neonates were not specifically excluded because the included literature did not differentiate this age group.

At the time of the PEACE consensus conference, the use of ECMO support for pediatric patients with COVID-19 was not well known. We did not have access to the 2023 meta-analysis data about 110 pediatric cases in the worldwide literature (10), nor did we have information about 108 U.S.-based cases managed 2020–2021 (11). For this reason, we are unable to comment with confidence on whether our consensus statements apply to this patient population. That said, while adult studies suggest that COVID-19 is a risk factor for thrombosis, whether this risk is greater than the risks associated with sepsis due to other viral or bacterial causes or whether COVID-19-related thrombotic risk in pediatric patients supported by ECMO would be higher than for other pediatric ECMO

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patients remains unclear. Until further information is available, the expert panel decided that it was reasonable to apply the consensus statements contained herein to the care of pediatric ECMO patients with COVID-19 and/or multisystem inflammatory syndrome in children.

Literature Search, Evidence Synthesis, and Statement Development

Detailed methods are in the **Supplemental Methods** (http://links.lww.com/PCC/C494). Briefly, a multidisciplinary panel of experts (**Table S2**, http://links.lww.com/PCC/C494) in ECMO anticoagulation, hemostasis, and transfusion medicine convened in a series of in-person and online meetings (**Table S3**, http://links.lww.com/PCC/C494) to conduct a structured literature search; to synthesize and rate the quality of evidence using Grading of Recommendations Assessment, Development, and Evaluation methodology (12); and to develop and achieve consensus around recommendations, good practice statements, and expert opinion consensus statements for ECMO anticoagulation and transfusion management using a modified Delphi process (13, 14). Statements were developed using the Evidence to Decision framework with emphasis on balancing benefit vs. harm for each statement, guided by a prioritized list of clinical outcomes (**Table S4**, http://links.lww.com/PCC/C494) (15). The strength of each recommendation was assigned based on a combination of level of agreement, quality of supporting pediatric evidence, and the panel's assessment of the relative benefits/risks of following the recommendation. Consensus statements were ungraded, with the strength of agreement listed for each statement. **Table 1** summarizes the hierarchy of language used to indicate degree of certainty and uncertainty. Additional references, not included in the structured literature search (**Supplement References**, http://links.lww.com/PCC/C494), were included in rationale statements to provide context.

As a part of the PEACE process, knowledge gaps were identified, and research priorities were developed using the Child Health and Nutrition Research Initiative (CHNRI) methodology (16). The methods for drafting and prioritizing research questions are outlined in the Research Priorities Summary article in the accompanying supplement (17).

RESULTS

Clinical Recommendations, Consensus Statements, and Good Practice Statements

We present 23 recommendations, 52 expert consensus statements, and 16 good practice statements (summarized in **Table S5**, http://links.lww.com/PCC/C494). The rationale and supporting evidence are presented in the accompanying supplement (18–25).

Recommendations and Consensus Statements are displayed according to the categories: *General Care and Monitoring* (**Table 2**), *Perioperative Care* (**Table 3**), and *Nonprocedural Bleeding and Thrombosis* (**Table 4**). Sixteen good practice statements are listed by category in **Table 5**. Overall, four recommendations, 12 consensus statements, and 12 good practice statements suggest the development of institutional multidisciplinary teams and/or protocols to guide ECMO anticoagulation in individual centers. The general and periprocedural clinical recommendations for anticoagulation management are presented in **Figure 1**, with blood product, coagulation factor, and antifibrinolytic management presented in **Figure 2**. General management of nonprocedural bleeding and thrombosis is summarized in **Figure 3**, and organ-specific bleeding and thrombosis management is presented in **Figure 4**. An example pediatric ECMO anticoagulation and transfusion management algorithm is shown in **Figure 5**. Gaps in knowledge and research priorities are presented in the research priorities article in the PEACE Supplement, with the top research priorities listed in **Table 6** (17).

General Good Practice Statements.

During ECMO, each patient's unique clinical condition contributing to bleeding or thrombotic risk should be considered when balancing hemostasis including blood product transfusions, pharmacologic adjuncts, developmental hemostasis, and acquired bleeding/clotting risk including surgical considerations. *89% agreement (n = 44), median 8 (interquartile range [IQR] 7–9).*

During ECMO, the presence of a known hemostatic disorder, such as factor deficiency, platelet dysfunction, or thrombophilia, should be considered when balancing hemostasis. *93% agreement (n = 46), median 8 (IQR 7–9).*

Bleeding and thrombotic risks during ECMO should be assessed frequently and discussed in

TABLE 1.
Hierarchy Used in Statements and Recommendations for the Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE (PEACE) Consensus

Recommendations		Uncertainty ⇒ Certainty	Good Practice and Consensus Statements	
Against	**For**		**Against**	**For**
				Adopt and use; Use; Understand; Investigate; Measure and evaluate; Evaluate and address; Monitor (GPS)
			…should be discontinued (GPS)	…should be …/… should prompt … (GPS)
	We consider/consider (weak recommendation, low-quality pediatric evidence)		We advise against (CS-S)	We consider/consider (CS-S)
	It is reasonable to consider (weak recommendation, very low-quality pediatric evidence)		We do not suggest/ we suggest against (CS-W)	It is reasonable to consider/ … may be considered (CS-W)
Insufficient evidence to	Insufficient evidence to			

CS-S = consensus statement with strong agreement, CS-W = consensus statement with weak agreement, GPS = good practice statement.
Strong agreement defined as ≥ 95% agreement. Weak agreement defined as 80–94% agreement.

a multidisciplinary team setting. *91% agreement (n = 44), median 8.5 (IQR 7.25–9).*

Bleeding and thrombotic complications during pediatric ECMO are common and result in substantial morbidity and mortality (4, 26–28). These outcomes can arise from complicated alterations in hemostasis due to underlying patient coagulopathy and/or circuit-patient interactions including coagulation factor consumption, thrombocytopenia, platelet dysfunction, hyperfibrinolysis, acquired von Willebrand syndrome, and hemolysis (27). Due to the complexity of these interactions, management includes a thorough assessment of bleeding and thrombotic risks in individual patients by a team of clinicians with expertise across hemostasis and ECMO, with frequent reassessments as clinical status evolves (29, 30).

Influence of the ECMO Circuit and Components on Anticoagulation Management

Good Practice Statement.

1.1 Utilize policies informed by national and international guidelines to maintain local multidisciplinary groups of ECMO practitioners with expertise in up-to-date circuit technologies and good practices to optimize patient outcomes. *98% agreement (n = 47), median 9, IQR 8–9.*

Recommendations.

1.2 There is insufficient evidence to recommend a specific pump technology, circuit configuration or cannulation technique to improve mortality or morbidity for pediatric ECMO. *Weak Recommendation, very low-quality pediatric evidence, 93% agreement (n = 47), median 8 (IQR 7–8).*

1.3 There is insufficient evidence to recommend specific changes to anticoagulation strategy based on pump technology for pediatric ECMO. *Weak Recommendation, very low-quality pediatric evidence, 96% agreement (n = 47), median 8 (IQR 7–9).*

Evolution of ECMO circuit component technology has resulted in improvements in pump design, membrane lung function and biocompatibility of circuit tubing (18). Observational studies comparing centrifugal vs. roller pump incorporation into ECMO circuits have assessed mortality,

TABLE 2.

Recommendations and Expert Consensus Statements for General Care and Monitoring of Children Supported With Extracorporeal Membrane Oxygenation From the Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE (PEACE)

Topic	Category	Statement
Circuit and components	WR	There is insufficient evidence to recommend a specific pump technology, circuit configuration, or cannulation technique to improve mortality or morbidity for pediatric ECMO. (1.2)
		There is insufficient evidence to recommend specific changes to anticoagulation strategy based on pump technology for pediatric ECMO. (1.3)
	CS-S	Consider monitoring for hemolysis during ECMO as a marker of circuit related red cell damage with different circuit technologies, flow rates, and thrombosis. (1.5)
	CS-W	It is reasonable to consider minimizing the number of circuit connections for pediatric ECMO. (1.4)
Anticoagulant medications	WR	There is insufficient evidence to recommend bivalirudin as a first-line anticoagulant in pediatric ECMO. (2.2)
		There is insufficient evidence in pediatric ECMO to recommend for or against the addition of alternate or adjunct anticoagulant or antiplatelet agents to UFH or DTIs. (2.5)
	CS-S	None
	CS-W	It is reasonable to consider that anticoagulation be administered during pediatric ECMO, which may be reduced or held in specific cases when clinically significant bleeding exists, but the risks of circuit clotting (especially in low-flow conditions) must be weighed against potential benefit. (2.1)
		It is reasonable to consider bivalirudin as an alternative to UFH for select clinical scenarios and/or in centers with experience in use and monitoring. (2.3)
Anticoagulant monitoring and targets	WR	There is insufficient evidence to recommend a specific assay or therapeutic range for monitoring DTIs in pediatric ECMO. (3.6)
	CS-S	In each center, we consider that ECMO clinicians and their laboratory define thresholds of bilirubin, plasma free hemoglobin, and triglycerides above which chromogenic or optical clot detection-based anticoagulation monitoring assays should be considered unreliable. (3.5)
	CS-W	When monitoring unfractionated heparin-based anticoagulation, it is reasonable to consider a combination of anticoagulation monitoring assays including one or more "time to clot" assays (ACT, aPTT, and/or viscoelastic test) in combination with anti-factor Xa assay, where available. (3.1)
Indications for RBC transfusion	WR	In pediatric ECMO, there is insufficient evidence to make a recommendation regarding specific indications for RBC transfusion. (4.3)
		In ECMO, we consider that the decision to transfuse RBCs should be based on the clinical scenario and global assessment of the adequacy of oxygen delivery and oxygen consumption and not hemoglobin alone. (4.4)
		In ECMO, there is insufficient evidence to make a recommendation for or against the benefit of a specific storage duration of RBC units to either prime the circuit or transfuse to the patient. (4.5)
	CS-S	None
	CS-W	None

(*Continued*)

TABLE 2. (*Continued*)

Recommendations and Expert Consensus Statements for General Care and Monitoring of Children Supported With Extracorporeal Membrane Oxygenation From the Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE (PEACE)

Topic	Category	Statement
Indications for prophylactic platelet or plasma transfusion	WR	In ECMO there is insufficient evidence to recommend specific thresholds for prophylactic plasma and/or platelet transfusions. (4.6)
	CS-S	In ECMO, we consider that prophylactic platelet transfusions administered when the platelet count is > 100 × 10^9 cells/L are unlikely to benefit the patient and may cause harm. (4.7)
		In ECMO, we consider that prophylactic plasma transfusions administered to correct an INR when the INR is < 1.5 are unlikely to benefit the patient and may cause harm. (4.8)
	CS-W	In pediatric ECMO, in patients with low fibrinogen levels, to prevent bleeding, fibrinogen concentrate or cryoprecipitate, when available, may be considered instead of plasma transfusion. (4.9)
Monitoring and replacement of antithrombin, fibrinogen, and von Willebrand factor	WR	There is insufficient evidence to recommend routine monitoring or replacement of antithrombin for pediatric ECMO. (5.1)
	CS-S	During ECMO when antithrombin is administered either as a concentrate or plasma infusion, as an adjunct to heparin therapy, we consider that close monitoring be used, including: 1) hemostatic parameters (such as ACT, aPTT, or anti-Xa, where available) for assessment of heparin effect and 2) patient clinical condition for signs of bleeding, thrombosis, and/or neurologic changes. (5.2)
	CS-W	In the nonbleeding pediatric ECMO patient it is reasonable to consider monitoring fibrinogen level and supplementing if low; however, the optimal frequency of monitoring and threshold for supplementation are not evident. (5.3)
		In ECMO patients with bleeding, it is reasonable to consider monitoring fibrinogen level and supplementing to a minimum level of at least 150 mg/dL, but the optimal frequency for monitoring and threshold for supplementation are not evident. (5.4)
		In the nonbleeding ECMO patient, we suggest against routine monitoring or replacement of von Willebrand factor or specific coagulation factors. (5.5)
Antifibrinolytics and adjunct hemostatic agents	WR	In ECMO, consider prophylactic application of nonbovine derived topical hemostatic agents at the time of cannulation to decrease cannulation site bleeding as part of a multimodality blood management strategy. (6.3)
	CS-S	In the ECMO patient–because of the risk of thrombotic complications, we advise against the use of recombinant factor VIIa except in the case of life-threatening bleeding refractory to multimodality blood management and resuscitation that addresses factors contributing to bleeding. (6.2)
	CS-W	In ECMO patients with bleeding or anticipated to be at high-risk of bleeding, use of lysine analog antifibrinolytic agents (epsilon aminocaproic acid, tranexamic acid) may be considered to decrease bleeding as part of a multimodality blood management strategy. (6.1)
		During ECMO, it is reasonable to consider the application of nonbovine derived topical hemostatic agents in response to active cannulation site bleeding as part of a multimodality blood management strategy including surgical hemostasis. (6.4)

ACT = activated clotting time, aPTT = activated partial thromboplastin time, CS-S = consensus statement with strong agreement, CS-W = consensus statement with weak agreement, DTI = direct thrombin inhibitor, ECMO = extracorporeal membrane oxygenation, INR = international normalized ratio, UFH = unfractionated heparin, WR = weak recommendation.
Strong agreement defined as ≥ 95% agreement. Weak agreement defined as 80–94% agreement.

TABLE 3.

Recommendations and Expert Consensus Statements for Perioperative and Periprocedural Care of Children Supported With Extracorporeal Membrane Oxygenation From the Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE (PEACE)

Topic	Category	Statement
Low-bleeding risk procedures	WR	None
	CS-S	In ECMO patients undergoing a minor and/or low-bleeding risk procedure, we advise against the routine use of lysine analog antifibrinolytic agents (e.g., EACA, TXA) but they could be considered in patients with concerns for increased risk of bleeding. (7.7)
	CS-W	In ECMO patients undergoing a minor and/or low-bleeding risk procedure, it is reasonable to consider using an institutional protocol or guideline for the management of systemic anticoagulation and transfusion therapy. (7.4)
		In ECMO patients undergoing a minor and/or low-bleeding risk procedure, it is reasonable to consider that the decision to decrease or hold systemic anticoagulation be evaluated case-by-case based on the risk of bleeding and thrombosis in the context of the proposed procedure to be performed, the anatomical location of the invasive procedure, and the risk of clotting of the circuit. (7.5)
		In ECMO patients undergoing a minor and/or low-bleeding risk procedure, it is reasonable to consider the application of nonbovine derived topical hemostatic agents. (7.6)
		In ECMO patients undergoing a minor and/or low-bleeding risk procedure, we suggest against targeting predefined higher thresholds for platelet and fibrinogen transfusions. (7.8)
Postcardiotomy ECMO	WR	In pediatric ECMO patients, before and after CPB, consider using a predefined institutional protocol for the management of systemic anticoagulation and transfusion. (7.9)
		Before starting ECMO during cardiac surgery, consider activated clotting time targeted protamine reversal before ECMO initiation and delaying systemic anticoagulation until after the procedure and until surgical hemostasis is achieved and bleeding is controlled. (7.10)
		In ECMO post-CPB, consider maintaining platelets above 100 × 10^9 cells/L and fibrinogen levels above 150 mg/dL in the periprocedural period. (7.11)
	CS-S	In post-CPB ECMO patients—because of the risk of thrombotic complications, we advise against the use of rFVIIa except in the event of life-threatening bleeding refractory to multimodality blood management and resuscitation that addresses factors contributing to bleeding. (7.15)
	CS-W	In post-CPB ECMO patients, we cannot suggest for or against the routine use of prophylactic lysine analog antifibrinolytic agents (EACA, TXA). (7.12)
		In pediatric ECMO patients post-CPB, lysine analog antifibrinolytic agents (EACA, TXA) may be considered if there is bleeding. (7.13)
		In post-CPB ECMO patients, it is reasonable to consider using nonbovine topical hemostatic agents at the surgical site in response to active bleeding as part of a multimodal blood management strategy including surgical hemostasis. (7.14)

(*Continued*)

TABLE 3. (*Continued*)

Recommendations and Expert Consensus Statements for Perioperative and Periprocedural Care of Children Supported With Extracorporeal Membrane Oxygenation From the Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE (PEACE)

Topic	Category	Statement
High-bleeding risk procedures (noncardiac)	WR	It is reasonable to consider the use of lysine analog antifibrinolytic agents (EACA, TXA). If administered, we suggest antifibrinolytics be started before the procedure, continue during the procedure, and for at least 24 hr after the procedure based on frequent reassessment of bleeding and thrombosis, and clotting of the circuit. (7.16)
		It is reasonable to consider maintaining platelet thresholds above 100 × 10^9 cells/L and fibrinogen levels above 150 mg/dL in the periprocedural period. (7.17)
	CS-S	Because of the risk of thrombotic complications, we advise against the use of rFVIIa except in the event of life-threatening bleeding refractory to multimodal blood management and resuscitation that addresses factors contributing to bleeding. (7.19)
	CS-W	It is reasonable to consider prophylactic application of nonbovine derived topical hemostatic agents at the surgical site. (7.18)
		It is reasonable to consider utilizing a predefined institutional protocol or guideline for the management of systemic anticoagulation and transfusion therapy in pediatric ECMO during major and/or high-bleeding risk invasive procedures. (7.20)
		It is reasonable to consider decreasing or stopping systemic anticoagulation temporarily before the procedure, depending on: the procedure itself; the ability to achieve surgical hemostasis; the patient's condition; and the state of the ECMO circuit. (7.21)
Periprocedural bleeding	WR	Consider decreasing or stopping systemic anticoagulation temporarily until bleeding ceases or decreases to minimal/moderate grade or rate of bleeding. (7.23)
		It is reasonable to consider targeting higher transfusion thresholds by maintaining platelets thresholds above 100 × 10^9 cells/L and fibrinogen levels above 150 mg/dL until the bleeding ceases or decreases to minimal/moderate grade or rate of bleeding. (7.24)
	CS-S	Consider adoption and use of an institutional protocol for multimodal blood management strategy for periprocedural bleeding which takes into account: 1) the severity of bleeding and/or a bleeding score; 2) close monitoring of the amount of blood losses and the clinical consequences of the bleeding; 3) the need to change the target for systemic anticoagulation and indications for temporarily stopping systemic anticoagulation; 4) indications for the use of antifibrinolytics and/or hemostatic therapies; and 5) the targeting higher concentrations of platelet and fibrinogen levels. (7.25)
		In patients with periprocedural bleeding–because of the risk of thrombotic complications, we advise against the use of rFVIIa except in the event of life-threatening bleeding refractory to multimodal blood management and resuscitation that addresses factors contributing to bleeding. (7.28)
		In ECMO patients with bleeding associated with an invasive procedure, consider application of nonbovine derived topical hemostatic agents at the surgical site. (7.29)
	CS-W	In ECMO patients with refractory or severe bleeding associated with a procedure that persists after surgical hemostasis is achieved, it is reasonable to consider consultation with an expert in hemostasis (e.g., intensivist with expertise in ECMO, hematologist, transfusion medicine specialist, hematopathologist, etc.) depending on institutional expertise. (7.26)
		It is reasonable to consider the use of lysine analog antifibrinolytic agents (e.g., EACA, TXA) to decrease bleeding as part of a multimodality blood management strategy. (7.27)

CPB = cardiopulmonary bypass, CS-S = consensus statement with strong agreement, CS-W = consensus statement with weak agreement, EACA = epsilon aminocaproic acid, ECMO = extracorporeal membrane oxygenation, rFVIIa = recombinant factor VIIa, TXA = tranexamic acid, WR = weak recommendation.

Strong agreement defined as ≥ 95% agreement. Weak agreement defined as 80–94% agreement.

TABLE 4.

Recommendations and Expert Consensus Statements for Pediatric Extracorporeal Membrane Oxygenation Patients With Nonprocedural Bleeding or Thrombosis From the Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE (PEACE)

Topic	Category	Statement
General	WR	There is insufficient evidence to provide evidence-based recommendations for or against a specific protocol or guideline to manage bleeding or thrombotic complications in ECMO patients. (8.1)
		There is insufficient evidence to suggest for or against specific blood product transfusion thresholds to manage bleeding or thrombotic complications in ECMO patients. (8.2)
	CS-S	None
	CS-W	For clinically relevant bleeding in ECMO patients, it is reasonable to consider platelet transfusion to maintain a threshold of at least 100 × 10^9 cells/L. Higher thresholds may be considered for patients in whom platelet dysfunction is suspected. (8.3)
		For clinically relevant bleeding in ECMO patients, it is reasonable to consider an initial plasma transfusion for INR > 1.5. Repeated transfusions for the sole purpose of correcting the INR may not improve outcomes. (8.4)
		It is reasonable to consider the use of prothrombin complex concentrates when there is severe bleeding refractory to hemostatic blood product transfusion, antifibrinolytic therapy, decreased/discontinued anticoagulation, and/or consideration for surgical intervention as clinically applicable. (8.5)
		In ECMO patients with severe bleeding refractory to other measures, it is reasonable to consider reducing or withholding systemic anticoagulation with frequent reassessment of bleeding and clotting to guide resumption of full systemic anticoagulation. (8.6)
		In ECMO patients with life-threatening bleeding, it is reasonable to consider activating a massive transfusion protocol and utilizing balanced hemostatic resuscitation. (8.7)
CNS bleeding	WR	There is insufficient evidence to provide an evidence-based recommendation for intracerebral hemorrhage management for pediatric ECMO. (8.8)
	CS-S	None
	CS-W	It is reasonable to consider whether ECMO can be safely discontinued when intracranial hemorrhage is diagnosed. (8.9)
		In patients with intracranial hemorrhage for whom ECMO cannot be safely discontinued, it is reasonable to consider decreasing or stopping systemic anticoagulation with frequent reassessment of bleeding and clotting to guide the duration of decreased or no anticoagulation. (8.10)
		In patients with intracranial hemorrhage for whom ECMO cannot be safely discontinued, it is reasonable to consider transfusing platelets to at least a platelet count of 100 × 10^9 cells/L or higher in the setting of platelet dysfunction. (8.11)

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TABLE 4. (*Continued*)

Recommendations and Expert Consensus Statements for Pediatric Extracorporeal Membrane Oxygenation Patients With Nonprocedural Bleeding or Thrombosis From the Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE (PEACE)

Topic	Category	Statement
Cardiorespiratory system bleeding	WR	There is insufficient evidence to provide an evidence-based recommendation for management of pulmonary hemorrhage for pediatric ECMO patients. (8.13)
	CS-S	In pediatric ECMO patients with hemodynamic compromise due to cardiac tamponade, consider surgical decompression or ultrasound-guided pericardiocentesis with or without placement of a pericardial drain, dependent on patient. (8.17)
	CS-W	In ECMO patients with pulmonary hemorrhage, it is reasonable to consider localized instillation of lysine analog antifibrinolytic agents as part of a multimodal approach to bleeding control. (8.14)
		In ECMO patients with thoracic hemorrhage/hemothorax, it is reasonable to consider a trial of conservative management with blood product replacement and/or withholding anticoagulation. (8.15)
		In ECMO patients with hemothorax, due to the risk of additional bleeding, we suggest against chest tube placement except in the setting of decreased pump flow and oxygenation, or if unable to wean from ECMO. It is reasonable to consider surgical intervention if no improvement with conservative measures. (8.16)
Gastrointestinal system bleeding	WR	There is insufficient evidence to provide an evidence-based recommendation for management of gastrointestinal hemorrhage for pediatric ECMO. (8.18)
	CS-S	None
	CS-W	It is reasonable to consider endoscopic cautery or vessel embolization to control bleeding for selected pediatric patients with gastrointestinal hemorrhage on ECMO. (8.19)
Patient thrombosis	WR	None
	CS-S	None
	CS-W	In ECMO patients with massive pulmonary emboli, intracardiac or intracoronary thrombi, or patient bladder thrombus, it is reasonable to consider direct thrombolysis. (8.20)
		In ECMO patients with intracardiac thrombus, it is reasonable to consider surgical removal of the thrombus. (8.21)
Circuit thrombosis	WR	None
	CS-S	None
	CS-W	In venoarterial ECMO patients with thrombus identified on the arterial side of the circuit, it is reasonable to consider urgent evaluation and consideration of options for clot removal or circuit change depending on cannulation site, thrombus size, and thrombus location. If the clot cannot be removed, careful neurologic monitoring should occur as patient is at high risk for systemic embolization, including stroke. (8.23)
		It is reasonable to consider component change rather than entire circuit change for localized thrombus in the bladder and/or oxygenator during ECMO. (8.24)
		In ECMO patients, it is reasonable to consider circuit change for diffuse clot and/or fibrin deposition with associated decrease in patient fibrinogen and platelet count and increase in D-dimer. (8.25)

CS-S = consensus statement with strong agreement, CS-W = consensus statement with weak agreement, ECMO = extracorporeal membrane oxygenation, INR = international normalized ratio, WR = weak recommendation.
Strong agreement defined as ≥ 95% agreement. Weak agreement defined as 80–94% agreement.

TABLE 5.
Good Practice Statements for Children Supported With Extracorporeal Membrane Oxygenation From the Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE (PEACE)

Clinical Context	Topic	Good Practice Statements
General	Overarching	During ECMO, each patient's unique clinical condition contributing to bleeding or thrombotic risk should be considered when balancing hemostasis including blood product transfusions, pharmacologic adjuncts, developmental hemostasis, acquired bleeding/clotting risk including surgical considerations.
		During ECMO, the presence of a known hemostatic disorder, such as factor deficiency, platelet dysfunction, or thrombophilia, should be considered when balancing hemostasis.
		Bleeding and thrombotic risks during ECMO should be assessed frequently and discussed in a multidisciplinary team setting.
	Circuit and components	Use policies informed by national and international guidelines to maintain local multidisciplinary groups of ECMO practitioners with expertise in up-to-date circuit technologies and good practices to optimize patient outcomes. (1.1)
	Anticoagulation medications	In ECMO patients who develop heparin-induced thrombocytopenia, all heparin should be discontinued, and direct thrombin inhibitors should be used for anticoagulation. (2.4)
	Anticoagulation monitoring and targets	A thorough understanding of anticoagulation assays is necessary for management of ECMO and includes: 1) obtaining manufacturer package insert information and 2) utilizing institutional experts in hemostasis to educate ECMO clinicians. (3.2)
		Use a multidisciplinary approach, which may include input from critical care, surgery, transfusion medicine, hematology, and pharmacy, to develop an institutional anticoagulation protocol; also consider consulting these experts in ECMO hemostasis in cases not easily managed with the institutional protocol. (3.3)
		Investigate promptly any discrepancies in results of anticoagulation assays in ECMO to identify underlying causes for the discrepancy. (3.4)
	Blood product transfusion	In ECMO, measures should be taken to minimize the overall transfusion volume. (4.1)
		When deciding to transfuse plasma or platelets during pediatric ECMO, not only monitor hemostasis (such as coagulation system dysfunction and the platelet count), but also consider the patient's perceived risk of bleeding and the benefits and alternatives to plasma and platelet transfusion. (4.2)
Perioperative	Timing	In ECMO, when a diagnostic or interventional procedure is considered, the benefits and risks, and alternatives of the procedure should be evaluated before deciding to perform an invasive procedure; however, do not postpone the procedure if it impacts diagnosis, treatment, and/or prognosis. (7.1)
	Major invasive/ high-bleeding risk	In the ECMO patient with a planned major invasive procedure and/or high-bleeding risk of the procedure, identify and optimize underlying coagulation status before the procedure. (7.2)
	Periprocedural bleeding	In the ECMO patient with any risk of bleeding, measure and evaluate blood loss during and after the invasive procedure for at least 24 hr and until the bleeding ceases or decreases to minimal/moderate grade or rate of bleeding. The severity of the bleeding should be determined by the quantity of blood lost, the site of the bleeding and the consequences of the bleeding on hemodynamics, hemoglobin, and organ dysfunction. (7.3)
		In ECMO patients who underwent an invasive procedure, early surgical consultation should be sought for procedure-associated bleeding. (7.22)

(*Continued*)

TABLE 5. (*Continued*)

Good Practice Statements for Children Supported With Extracorporeal Membrane Oxygenation From the Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE (PEACE)

Clinical Context	Topic	Good Practice Statements
Nonprocedural bleeding or thrombosis	General	In ECMO patients with significant bleeding and evidence of consumptive coagulopathy, evaluate and address all potential causes, including the circuit and components, patient thrombosis, and diagnoses associated with disseminated intravascular coagulopathy. (8.22)
	Pulmonary hemorrhage	In patients supported with ECMO for cardiogenic shock, the presence of pulmonary hemorrhage should prompt evaluation for left atrial hypertension and consideration of left heart decompression. (8.12)

ECMO = extracorporeal membrane oxygenation.

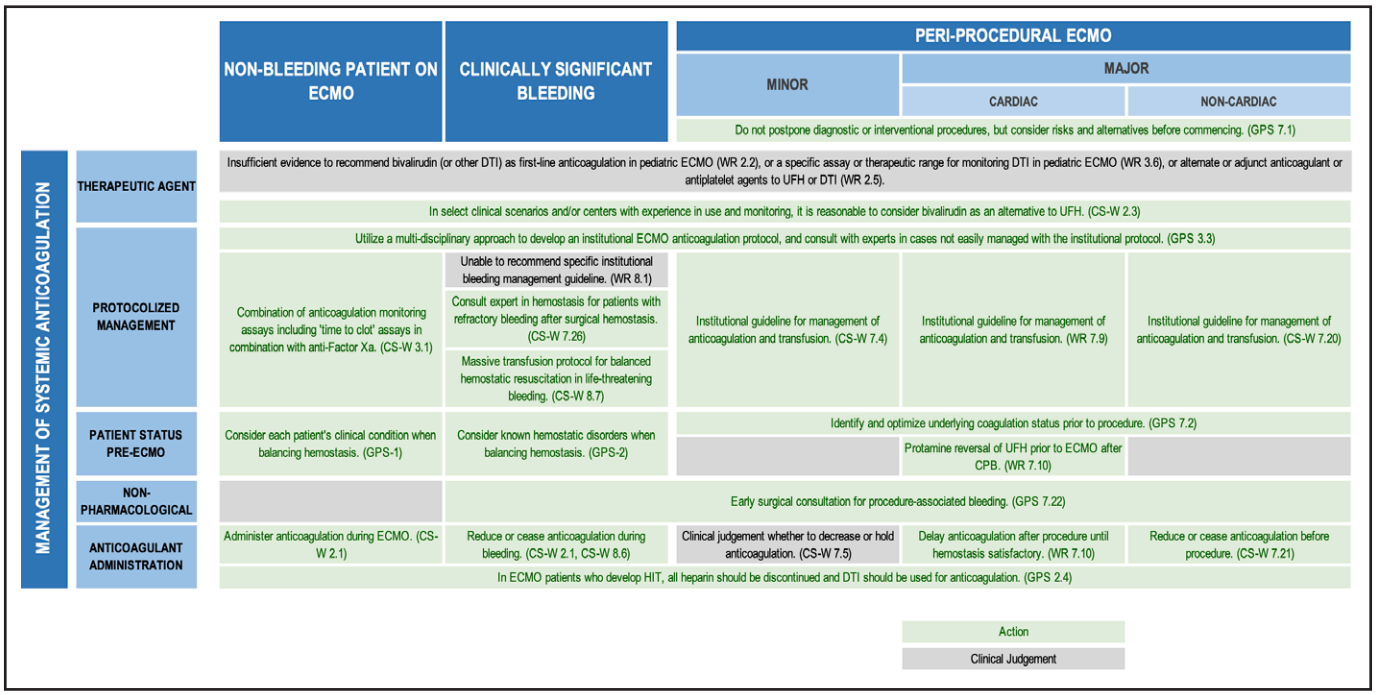

Figure 1. Clinical guidance for the anticoagulation management of children supported with extracorporeal membrane oxygenation (ECMO) from the Pediatric ECMO Anticoagulation CollaborativE (PEACE). Weak recommendations (WRs), consensus statement with weak agreement (CS-W), consensus statement with strong agreement (defined as > 95%), and good practice statements (GPSs) are presented. CPB = cardiopulmonary bypass, DTI = direct thrombin inhibitor, HIT = heparin-induced thrombocytopenia, UFH = unfractionated heparin.

thrombotic and hemorrhagic complications but have not routinely associated these outcomes with anticoagulation management.

Consensus Statement.

1.4 It is reasonable to consider minimizing the number of circuit connections for pediatric ECMO. *Consensus panel expertise with weak agreement, 93% agreement (n = 47), median 8 (IQR 7–9).*

Results of ex vivo studies support the concept of increased thrombogenicity at points of circuit connectors. Despite limited clinical correlation and no studies of patient-centered outcomes, we suggest weighing the benefits of each additional circuit connector with the potential risk of increased thrombotic burden.

Consensus Statement.

1.5 Consider monitoring for hemolysis during pediatric ECMO as a marker for circuit related

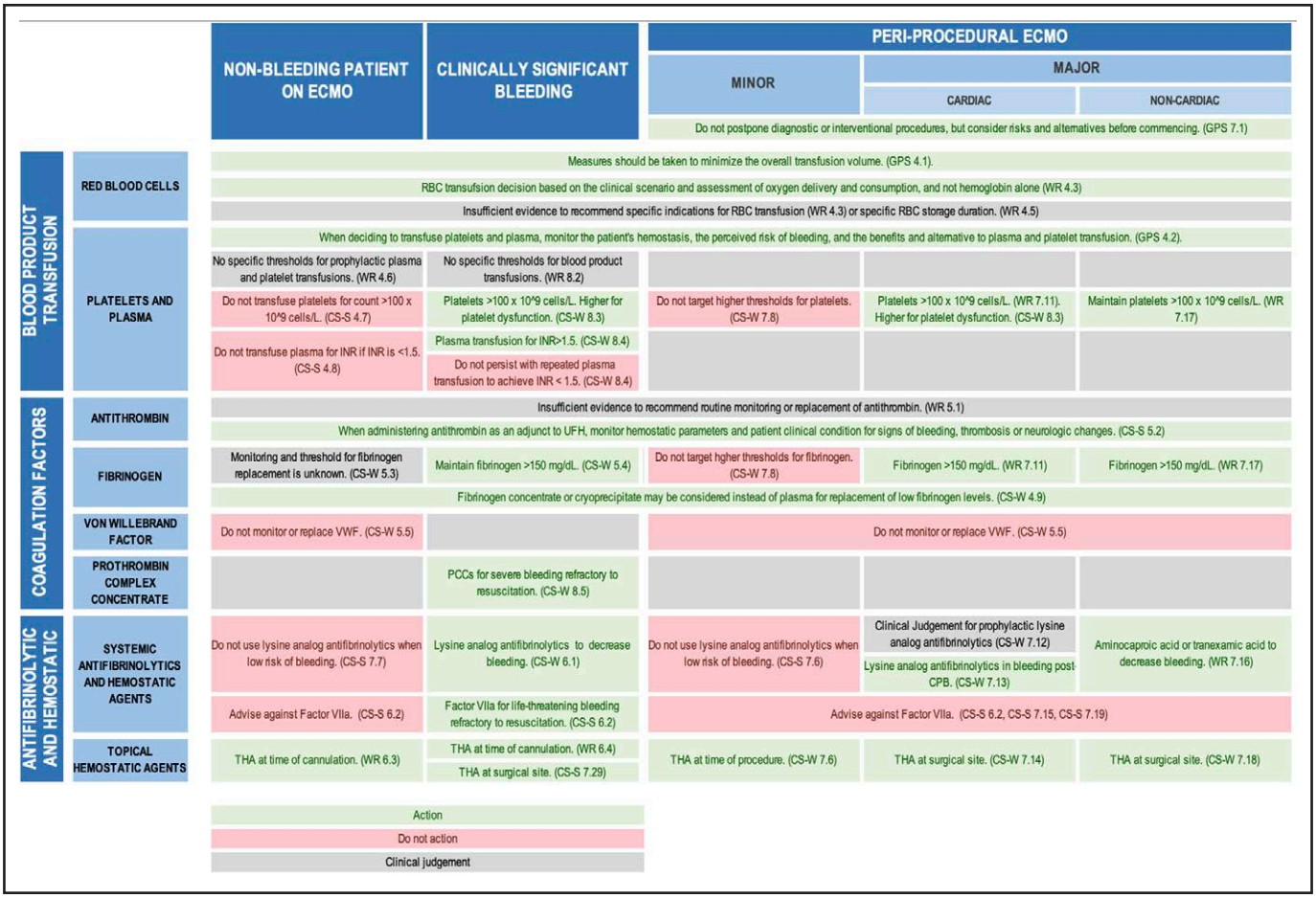

Figure 2. Clinical guidance for the transfusion, coagulation factor, and antifibrinolytic management of children supported with extracorporeal membrane oxygenation (ECMO) from the Pediatric ECMO Anticoagulation CollaborativE (PEACE). Weak recommendations (WRs), consensus statements with weak agreement (CS-W), consensus statements with strong agreement (CS-S, defined as > 95%), and good practice statements (GPSs) are presented. CPB = cardiopulmonary bypass, INR = international normalized ratio, PCC = prothrombin complex concentrate, THA = topical hemostatic agents, UFH = unfractionated heparin, VWF = von Willebrand factor.

red cell damage with different circuit technologies, flow rates, and thrombosis. *Consensus panel expertise with strong agreement, 95% agreement (n = 44), median 8 (IQR 7–9).*

The interpretation of plasma free hemoglobin should be considered primarily as a marker of RBC trauma and hemolysis that could be secondary to increased thrombotic load in addition to other patient and circuit factors. Although studies of different measures of hemolysis have not consistently associated free hemoglobin with patient-centered outcomes, standardizing collection of this biomarker and correlating with other markers of hemolysis was considered reasonable.

ANTICOAGULANT MEDICATIONS

Provision of Systemic Anticoagulation

Consensus Statement.

2.1 It is reasonable to consider that anticoagulation be administered during pediatric ECMO, which may be reduced or held in specific cases when clinically significant bleeding exists, but the risks of circuit clotting (especially in low flow conditions) must be weighed against potential benefit. *Consensus panel expertise with weak agreement, 91% agreement (n = 44), median 8 (IQR 7–9).*

There were no pediatric studies suggesting ECMO should be provided without systemic anticoagulation,

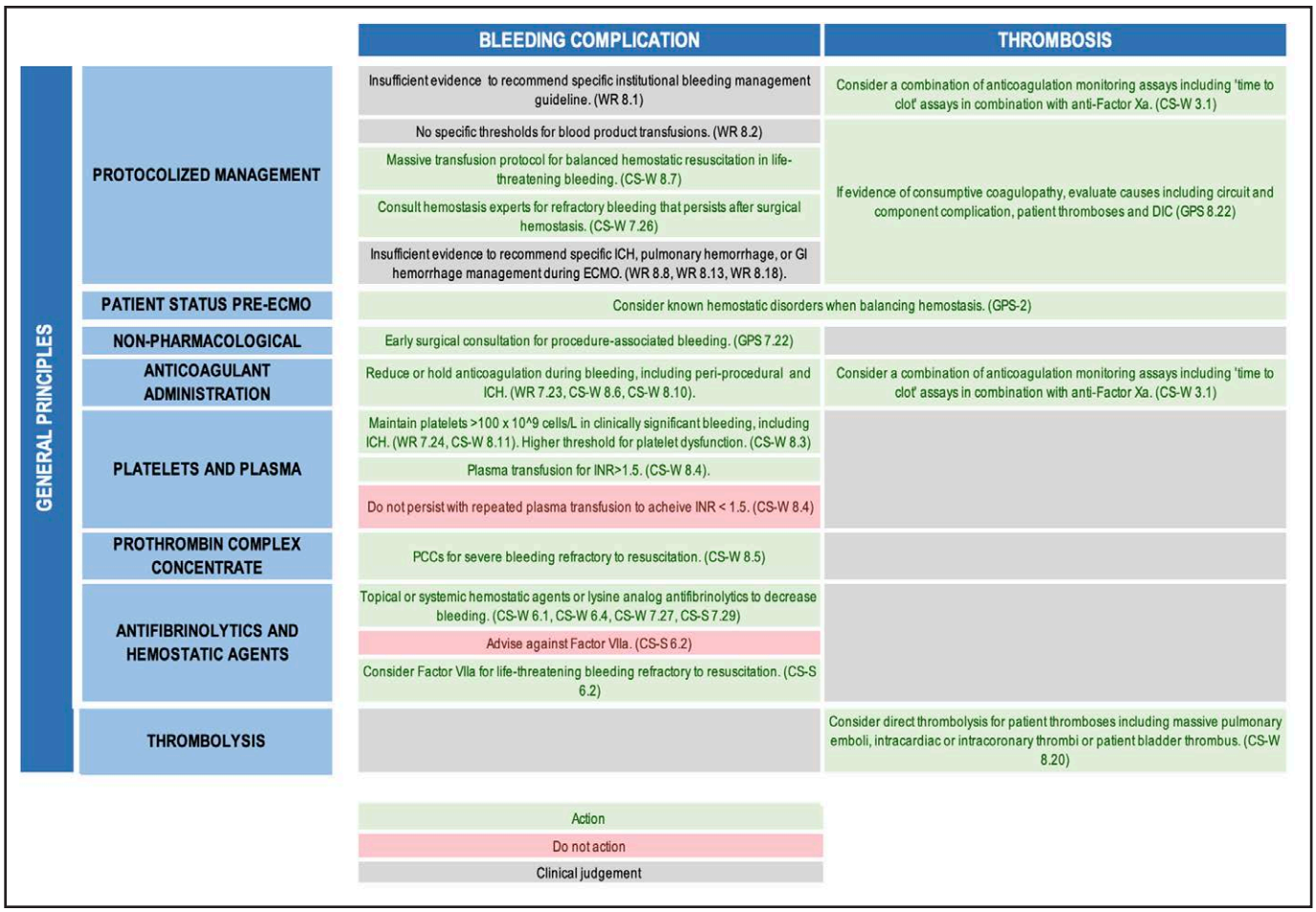

Figure 3. General clinical guidance for the anticoagulation and transfusion management of children with bleeding or thrombotic complications on extracorporeal membrane oxygenation (ECMO) from the Pediatric ECMO Anticoagulation CollaborativE (PEACE). Weak recommendations (WRs), consensus statement with weak agreement (CS-W), consensus statement with strong agreement (CS-S, defined as > 95%), and good practice statements (GPSs) are presented. DIC = disseminated intravascular coagulopathy, GI = gastrointestinal, ICH = intracranial hemorrhage, INR = international normalized ratio, PCC = prothrombin complex concentrate.

although small case series in patients with severe hemorrhage are documented (19).

Unfractionated Heparin and Direct Thrombin Inhibitors

Recommendation.

2.2 There is insufficient evidence to recommend bivalirudin as a first-line anticoagulant in pediatric ECMO. *Weak Recommendation, very low-quality pediatric evidence, 89% agreement (n = 44), median 8 (IQR 7–9).*

Consensus Statement.

2.3 It is reasonable to consider bivalirudin as an alternative to unfractionated heparin (UFH) for select clinical scenarios and/or in centers with experience in use and monitoring. *Consensus panel expertise with weak agreement, 89% agreement (n = 44), median 8 (IQR 7–9).*

Direct thrombin inhibitors (DTI) have been increasingly used in children receiving ventricular assist device (VAD) support, however, data informing the routine use in children on ECMO is limited to single-center reports. Small, observational studies suggest bivalirudin may be a reasonable alternative anticoagulant for patients with clinical indications including heparin-induced thrombocytopenia (HIT), heparin resistance, and continued circuit thrombosis despite UFH during ECMO.

Good Practice Statement.

2.4 In ECMO patients who develop HIT, all heparin should be discontinued, and DTI should be

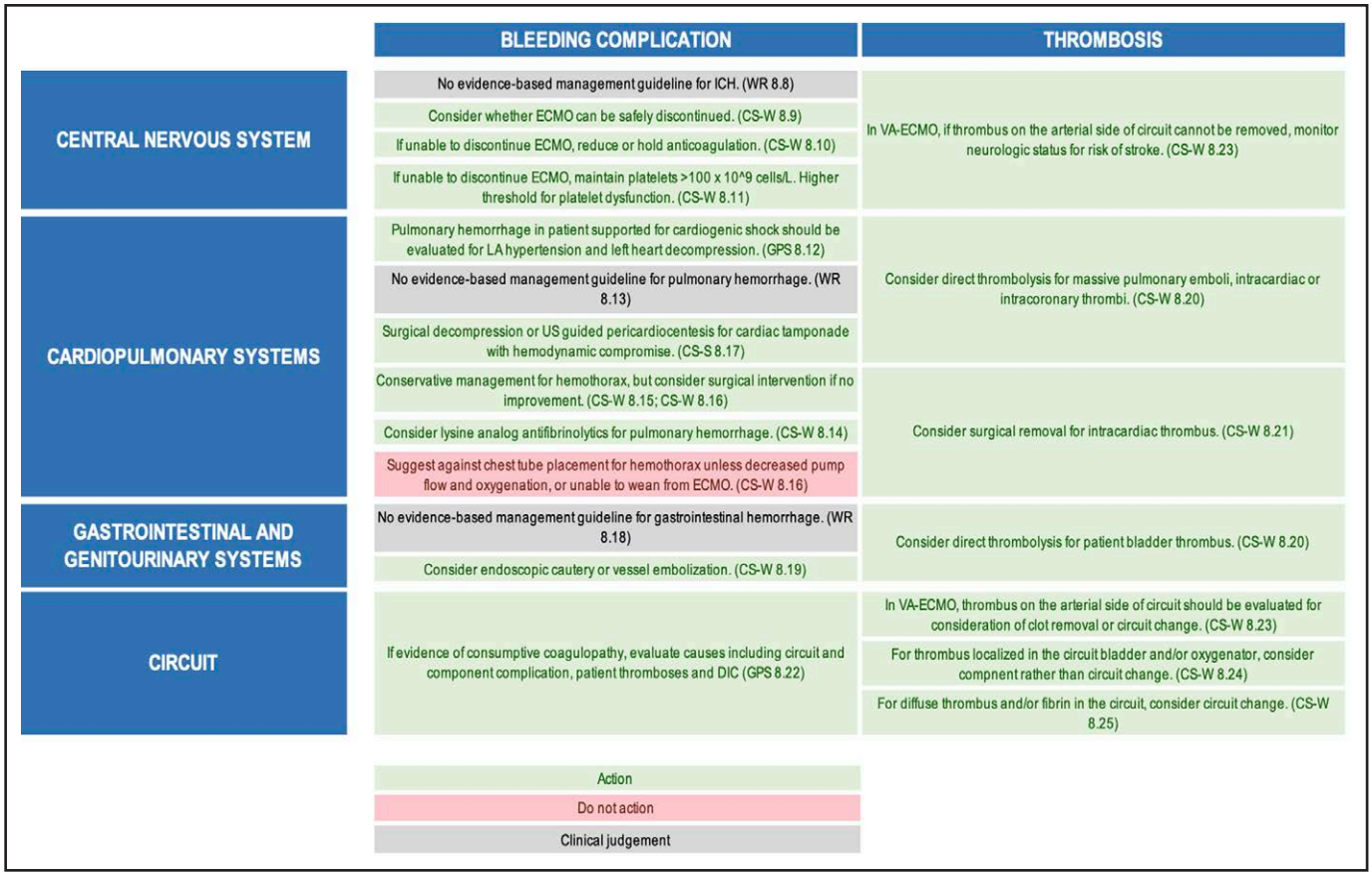

Figure 4. Organ-specific clinical guidance for the anticoagulation and transfusion management of children with bleeding or thrombotic complications on extracorporeal membrane oxygenation (ECMO) from the Pediatric ECMO Anticoagulation CollaborativE (PEACE). Weak recommendations (WRs), consensus statement with weak agreement (CS-W), consensus statement with strong agreement (CS-S, defined as > 95%), and good practice statements (GPSs) are presented. DIC = disseminated intravascular coagulopathy, ICH = intracranial hemorrhage, LA = left atrial, US = ultrasound, VA = venoarterial.

used for anticoagulation. *93% agreement (n = 44), median 9 (IQR 8–9).*

Cases of HIT in children have been increasingly reported; however, true prevalence is unclear as criteria for confirmation of HIT are not provided in every report. There were a few single-center reports of management of HIT with DTI (argatroban or bivalirudin) in children on ECMO though none included patient-centered outcomes.

Adjunct Anticoagulant or Antiplatelet Medications

Recommendation.

2.5 There is insufficient evidence in pediatric ECMO to recommend for or against the addition of alternate or adjunct anticoagulant or antiplatelet agents to UFH or DTI. *Weak Recommendation, very low-quality pediatric evidence, 96% agreement (n = 46), median 8 (IQR 7–9).*

There were no prospective studies in pediatric ECMO comparing alternate or adjunct anticoagulant medication outside UFH or DTI. Although there are important differences between pediatric VAD and pediatric ECMO patients, children supported with durable VADs have lower stroke rate with the addition of antiplatelet drugs to anticoagulation. Additional studies focused on pediatric ECMO patients are needed.

ANTICOAGULATION MONITORING AND TARGETS

Assays to Monitor UFH Anticoagulation

Consensus Statement.

3.1 When monitoring UFH-based anticoagulation, it is reasonable to consider a combination

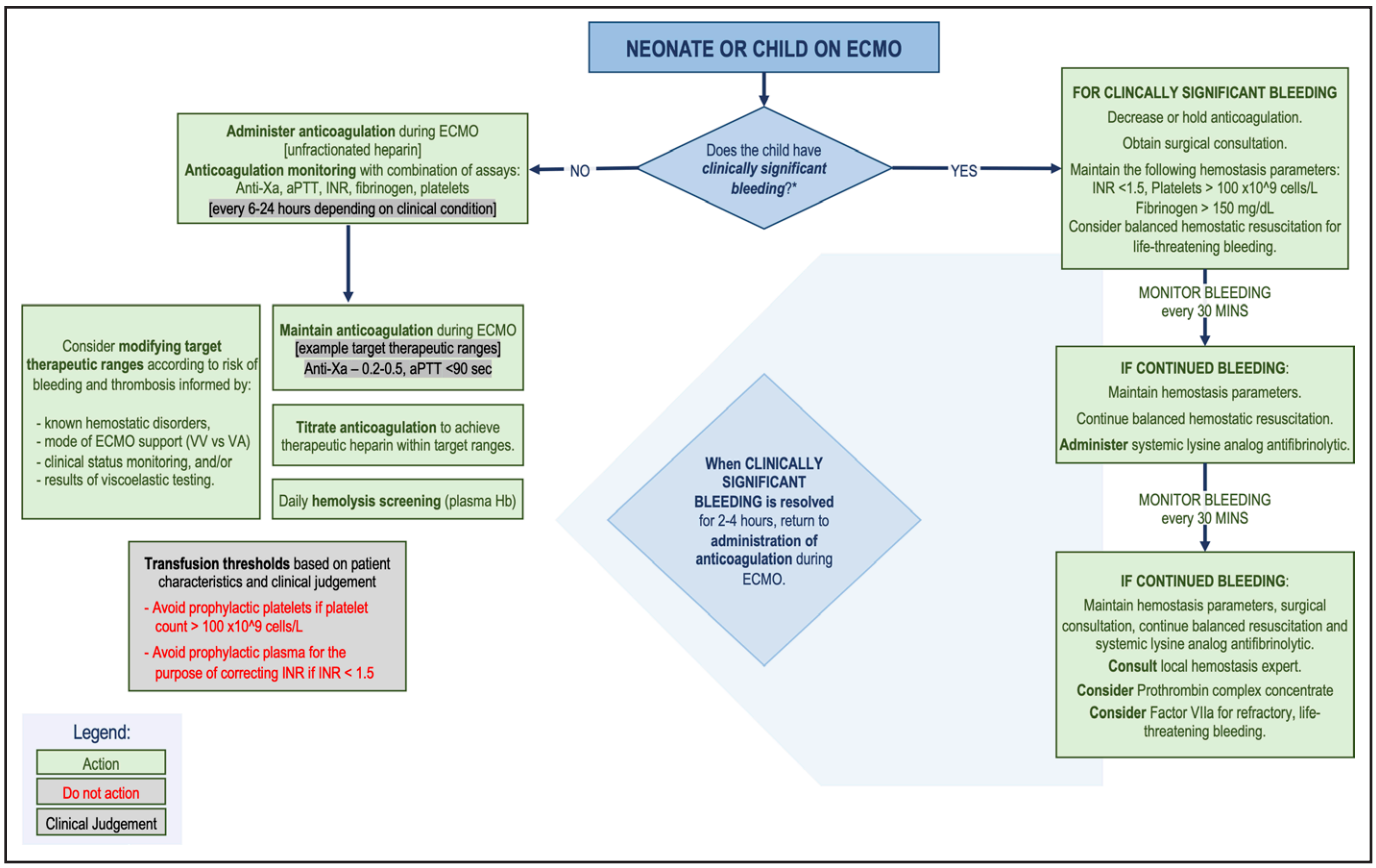

Figure 5. Anticoagulation and transfusion algorithm example for children supported with extracorporeal membrane oxygenation (ECMO) from the Pediatric ECMO Anticoagulation CollaborativE (PEACE). *Clinically significant bleeding is defined as meeting any of the criteria listed for moderate or severe bleeding according to published definitions (4, 7, 8). aPTT = activated partial thromboplastin time, Hb = hemoglobin, INR = international normalized ratio, VA = venoarterial, VV = venovenous.

of anticoagulation monitoring assays including one or more "time to clot" assays (activated clotting time [ACT], activated partial thromboplastin time [aPTT], and/or viscoelastic test) in combination with anti-factor Xa assay, where available. *Consensus panel expertise with weak agreement, 89% agreement (n = 44), median 8 (IQR 7–9).*

Good Practice Statements.

3.2 A thorough understanding of anticoagulation assays is necessary for management of ECMO and includes: 1) obtaining manufacturer package insert information and 2) utilizing institutional experts in hemostasis to educate ECMO clinicians. *98% agreement (n = 44), median 8 (IQR 7–9).*

3.3 Utilize a multidisciplinary approach, which may include input from critical care, surgery, transfusion medicine, hematology, and pharmacy, to develop an institutional anticoagulation protocol; also consider consulting these experts in ECMO hemostasis in cases not easily managed with the institutional protocol. *82% agreement (n = 44), median 8 (IQR 7–9).*

3.4 Investigate promptly any discrepancies in results of anticoagulation assays in ECMO to identify underlying causes for the discrepancy. " *85% agreement (n = 46), median 9 (IQR 7–9).*

There are single-center studies of anticoagulation monitoring of heparin therapy for ECMO patients associated with patient-centered outcomes (20). In some studies, monitoring of anticoagulation with aPTT, rather than ACT, was associated with decreased hemorrhagic complications. Similarly, increasing use of thromboelastography has been reported, associated with reduction of bleeding complications when used in association with a bleeding algorithm. Several studies have concluded that current laboratory assays may not be sufficient to predict bleeding and clotting complications in pediatric ECMO.

TABLE 6.
Top Research Priorities of the Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE (PEACE) Consensus Conference

Research Topic	Domain	Priority
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	1
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)	2
Studies to determine whether multiassay 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	3
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	4
Studies to examine thresholds for RBC, plasma, platelet, and cryoprecipitate transfusions in children supported by ECMO. Specific questions may include: benefit to 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)	5

ECMO = extracorporeal membrane oxygenation.

Interference in Anticoagulation Monitoring Assays

Consensus Statement.

3.5 In each center, we consider that ECMO clinicians and their laboratory define thresholds of bilirubin, plasma free hemoglobin, and triglycerides above which chromogenic or optical clot detection-based anticoagulation monitoring assays should be considered unreliable. Consensus panel expertise with strong agreement, 98% agreement ($n = 43$), median 8 (IQR 7–9).

Anticoagulation monitoring assays may be directly impacted by the presence of elevated plasma free hemoglobin and serum bilirubin. Heparin titration in response to assay results may be associated with increased risk of bleeding or clotting. No prospective studies have assessed this impact on patient-centered outcomes.

Monitoring Anticoagulation With DTI

Recommendation.

3.6 There is insufficient evidence to recommend a specific assay or therapeutic range for monitoring DTI in pediatric ECMO. *Weak Recommendation, very low-quality pediatric evidence, 83% agreement (n = 46), median 7 (IQR 7–9).*

The analytic response of aPTT, plasma diluted thrombin time, ecarin clotting time, and prothrombin time hemostasis assays have been evaluated for use in monitoring bivalirudin levels. Of these, only aPTT has been reported for monitoring bivalirudin in pediatric ECMO in single-center case series.

Prophylactic Transfusion Strategies

Good Practice Statements.

4.1 In ECMO, measures should be taken to minimize the overall transfusion volume. *93% agreement (n = 46), median 9 (IQR 7–9).*

4.2 When deciding to transfuse plasma or platelets during pediatric ECMO, not only monitor hemostasis (such as coagulation system dysfunction and the platelet count), but also consider the patient's perceived risk of bleeding and the benefits and alternatives to plasma and

platelet transfusion. *93% agreement (n = 46), median 8 (IQR 7–9).*

Evidence-based prophylactic transfusion targets remain undefined. Thoughtful decision-making weighing risks and benefits for each patient is recommended, including justification beyond a laboratory value (21).

RBC Transfusion

Recommendations.

4.3 In pediatric ECMO, there is insufficient evidence to make a recommendation regarding specific indications for RBC transfusion. *Weak Recommendation, very low-quality pediatric evidence, 91% agreement (n = 46), median 8 (IQR 7–9).*

4.4 In ECMO, we consider that the decision to transfuse RBCs should be based on the clinical scenario and global assessment of the adequacy of oxygen delivery and oxygen consumption, and not hemoglobin alone. *Weak recommendation, low-quality pediatric evidence, 100% agreement (n = 46), median 9 (IQR 8–9).*

In five observational studies, higher RBC transfusion volume was independently associated with adverse clinical outcomes, although studies were confounded by indication bias. A small interventional trial identified fewer thrombotic complications in neonates randomized to a threshold hematocrit of 35% vs. 45%; and in a pre/post study, a change in threshold hematocrit from 40% to 35% was associated with a lower RBC exposure without difference in clinical outcomes, suggesting that lower RBC transfusion thresholds in pediatric ECMO patients may be safe. Although hemoglobin alone is likely not the best indication for RBC transfusion, studies of physiologic indications for RBC transfusion are limited.

Recommendation.

4.5 In ECMO, there is insufficient evidence to make a recommendation for or against the benefit of a specific storage duration of RBC units to either prime the circuit or transfuse to the patient. *Weak Recommendation, very low-quality pediatric evidence, 84% agreement (n = 44), median 8 (IQR 7–9).*

Clinical trials of RBC storage duration have not included pediatric ECMO patients. Two small observational studies did not demonstrate associations between RBC storage duration and the adequacy of oxygen delivery post-transfusion in ECMO patients, although transfusions were given to patients with mild anemia and without evidence of oxygen debt.

Prophylactic Platelet and Plasma Transfusion

Recommendation.

4.6 In ECMO, there is insufficient evidence to recommend specific thresholds for prophylactic plasma and/or platelet transfusions. *Weak Recommendation, very low-quality pediatric evidence, 89% agreement (n = 46), median 8 (IQR 7–9).*

There have been no clinical trials of plasma and/or platelet transfusion strategies in pediatric ECMO patients. Three studies of platelet and/or plasma transfusion in pediatric ECMO patients demonstrated that low platelet count, coagulopathy, plasma, and/or platelet transfusion volumes were associated with adverse patient outcomes.

Consensus Statements.

4.7 In ECMO, we consider that prophylactic platelet transfusions administered when the platelet count is greater than 100 × 10^9 cells/L are unlikely to benefit the patient and may cause harm. *Consensus panel expertise with strong agreement, 100% agreement (n = 44), median 8 (IQR 7–9).*

More bleeding events and increased mortality have been associated with coagulopathy and thrombocytopenia in multiple observational studies of pediatric ECMO. Other studies have also associated platelet transfusion volume with adverse outcomes. No clinical trials have been reported.

4.8 In pediatric ECMO, we consider that prophylactic plasma transfusions administered to correct an international normalized ratio (INR) when the INR is less than 1.5 are unlikely to benefit the patient and may cause harm. *Consensus panel expertise with strong agreement, 95% agreement (n = 44), median 8 (IQR 7.25–9).*

In a secondary analysis of an international point prevalence study, plasma transfusions given to pediatric

ECMO patients when the pre-transfusion INR was less than or equal to 2.0, resulted in a nonsignificant reduction in INR.

4.9 In pediatric ECMO, in patients with low fibrinogen levels, to prevent bleeding, fibrinogen concentrate or cryoprecipitate, when available, may be considered instead of plasma transfusion. *Consensus panel expertise with weak agreement, 87% agreement (n = 46), median 8 (IQR 7–9).*

No included studies evaluated plasma transfusion compared with cryoprecipitate or fibrinogen concentrate to correct hypofibrinogenemia. Despite this lack of data in pediatric ECMO, it seems reasonable to avoid low fibrinogen levels by transfusing either fibrinogen concentrate or cryoprecipitate to prevent bleeding complications.

MONITORING AND REPLACEMENT OF ANTITHROMBIN, FIBRINOGEN, AND VON WILLEBRAND FACTOR

Antithrombin Monitoring and Replacement

Recommendation.

5.1 There is insufficient evidence to recommend routine monitoring or replacement of antithrombin for pediatric ECMO. *Weak Recommendation, very low-quality pediatric evidence, 91% agreement (n = 46), median 8 (IQR 7–9).*

Consensus Statement.

5.2 During ECMO when antithrombin is administered either as a concentrate or plasma infusion, as an adjunct to heparin therapy, we consider that close monitoring be used, including: 1) hemostatic parameters (such as ACT, aPTT, or anti-Xa, where available) for assessment of heparin effect and 2) patient clinical condition for signs of bleeding, thrombosis, and/or neurologic changes. *Consensus panel expertise with strong agreement, 98% agreement (n = 43), median 8 (IQR 7–9).*

Many observational studies attempted to address the association between antithrombin on ECMO with the following findings: 1) antithrombin activities were low at initiation of ECMO; 2) antithrombin activity increased after administration but the dose-response was variable; 3) the association between antithrombin administration and UFH dose rate and coagulation monitoring parameters was variable and many showed no association; and 4) there was not a consistent association between antithrombin and clinical outcomes (22).

Fibrinogen Monitoring and Replacement

Consensus Statements.

5.3 In the nonbleeding pediatric ECMO patient it is reasonable to consider monitoring fibrinogen level and supplementing if low; however, the optimal frequency of monitoring and threshold for supplementation are not evident. *Consensus panel expertise with weak agreement, 83% agreement (n = 46), median 8 (IQR 7–9).*

5.4 In ECMO patients with bleeding, it is reasonable to consider monitoring fibrinogen level and supplementing to a minimum level of at least 150 mg/dL, but the optimal frequency for monitoring and threshold for supplementation are not evident. *Consensus panel expertise with weak agreement, 84% agreement (n = 44), median 7 (IQR 7–8).*

Although hypofibrinogenemia in pediatric ECMO patients is common and associated with bleeding risks, the quality of evidence to estimate benefits or harms of specific thresholds for fibrinogen replacement is weak and based on observational studies.

Von Willebrand Factor Monitoring and Replacement

Consensus Statement.

5.5 In the nonbleeding ECMO patient, we suggest against routine monitoring or replacement of von Willebrand factor or specific coagulation factors. *Consensus panel expertise with weak agreement, 91% agreement (n = 45), median 8 (IQR 7–9).*

Acquired von Willebrand syndrome occurs at a high frequency in patients on ECMO but has not been associated with patient-level outcomes of bleeding, blood product transfusion, or mortality. Until data exist to support routine replacement of deficient factor(s), it seems reasonable to not routinely measure individual coagulation factors in nonbleeding pediatric ECMO patients.

ANTIFIBRINOLYTIC AND ADJUNCT HEMOSTATIC AGENTS

Systemic Antifibrinolytic and Hemostatic Agents

Consensus Statements.

6.1 In ECMO patients with bleeding or anticipated to be at high risk of bleeding, use of lysine analog antifibrinolytic agents (epsilon aminocaproic acid [EACA], tranexamic acid [TXA]) may be considered to decrease bleeding as part of a multimodality blood management strategy. *Consensus panel expertise with weak agreement, 93% agreement (n = 46), median 8 (IQR 7–9).*

Several small observational studies and one clinical trial assessed protocolized use of antifibrinolytic agents in "high bleeding risk" children on ECMO and associate use of these agents with fewer bleeding events but there was an inconsistent association with increased patient and circuit thrombotic events (23).

6.2 In the ECMO patient—because of the risk of thrombotic complications, we advise against the use of recombinant factor VIIa (rFVIIa) except in the case of life-threatening bleeding refractory to multimodality blood management and resuscitation that addresses factors contributing to bleeding. *Consensus panel expertise with strong agreement, 96% agreement (n = 46), median 8 (IQR 7–9).*

In case reports and small, observational studies, the use of rFVIIa in neonates and children on ECMO may reduce bleeding volume and blood product use but with increased risk of clinically significant patient and circuit thrombotic events.

Topical Hemostatic Agents

Recommendation.

6.3 In ECMO, consider prophylactic application of nonbovine derived topical hemostatic agents at the time of cannulation to decrease cannulation site bleeding as part of a multimodality blood management strategy. *Weak recommendation, low-quality pediatric evidence, 83% agreement (n = 46), median 8 (IQR 7–9).*

Consensus Statement.

6.4 During ECMO, it is reasonable to consider the application of nonbovine derived topical hemostatic agents in response to active cannulation site bleeding as part of a multimodality blood management strategy including surgical hemostasis. Consensus panel expertise with weak agreement, 83% agreement (*n* = 46), median 8 (IQR 7–9).

The use of fibrin sealant with or without standard cauterization was assessed in a clinical trial of neonates on ECMO, with improved hemostatic control, less bleeding in the group who received fibrin sealant, but no difference in blood product administration. Extensive data reviews of topical hemostatic agents for bleeding or as prophylaxis exist in other populations, including adult ECMO and cardiac surgery.

MANAGEMENT OF ECMO ANTICOAGULATION IN THE PERIOPERATIVE PERIOD

Risk Categories for Periprocedural Bleeding

Informed by other professional guidelines addressing procedural bleeding risk (24), we derived four categories of periprocedural risk of bleeding complications as a framework for these decisions (31–34).

1) Low-bleeding risk procedures/interventions: Expected to rarely result in hemorrhagic complications, in anatomical regions where bleeding is readily diagnosed and readily controlled.
2) Postcardiotomy ECMO: Children cannulated to ECMO after cardiotomy or cardiac surgery with cardiopulmonary bypass (CPB) with a high risk of bleeding.
3) High-bleeding risk procedures (noncardiac): Are more likely to result in hemorrhagic complications and/or occur in anatomical regions where bleeding may be difficult to diagnose or treat (e.g., intra-abdominal cavity, lung parenchyma, retroperitoneum) and/or occur in anatomical regions where even minor amounts of bleeding may have devastating consequences (e.g., eye, spinal cord, brain),
4) Bleeding in the periprocedural period: Defined as the 24-hour period after the procedure.

Good Practice Statements.

7.1 In ECMO, when a diagnostic or interventional procedure is considered, the benefits and risks, and alternatives of the procedure should be evaluated before deciding to perform an invasive procedure; however, do not postpone the procedure if it impacts diagnosis, treatment, and/or prognosis. *89% agreement (n = 46), median 8 (IQR 7–9).*

7.2 In the ECMO patient with a planned major invasive procedure and/or high bleeding risk of

the procedure, identify and optimize underlying coagulation status before the procedure. *89% agreement (n = 44), median 9 (IQR 7–9).*

7.3 In the ECMO patient with any risk of bleeding, measure and evaluate blood loss during and after the invasive procedure for at least 24 hours and until the bleeding ceases or decreases to minimal/moderate grade or rate of bleeding. The severity of the bleeding should be determined by the quantity of blood lost, the site of the bleeding, and the consequences of the bleeding on hemodynamics, hemoglobin, and organ dysfunction. *93% agreement (n = 44), median 8 (IQR 7–9).*

Procedures during pediatric ECMO occur frequently in published reports. Despite associated bleeding risks, some children may benefit from invasive diagnostic or surgical management during ECMO support. Preemptive correction of coagulopathy and early evaluation and management of bleeding associated with procedures should be considered to prevent and treat complications.

Children Undergoing Low-Bleeding Risk Procedures or Interventions

Consensus Statements.

7.4 In ECMO patients undergoing a minor and/or low-bleeding risk procedure, it is reasonable to consider using an institutional protocol or guideline for the management of systemic anticoagulation and transfusion therapy. *Consensus panel expertise with weak agreement, 91% agreement (n = 46), median 8 (IQR 7–9).*

7.5 In ECMO patients undergoing a minor and/or low-bleeding risk procedure, it is reasonable to consider that the decision to decrease or hold systemic anticoagulation be evaluated case-by-case based on the risk of bleeding and thrombosis in the context of the proposed procedure to be performed, the anatomical location of the invasive procedure, and the risk of clotting of the circuit. *Consensus panel expertise with weak agreement, 93% (n = 43), median 8 (IQR 7–9).*

7.6 In ECMO patients undergoing a minor and/or low-bleeding risk procedure, it is reasonable to consider the application of nonbovine derived topical hemostatic agents. *Consensus panel expertise with weak agreement, 89% agreement (n = 44), median 8 (IQR 7–9).*

7.7 In ECMO patients undergoing a minor and/or low-bleeding risk procedure, we advise against the routine use of lysine analog antifibrinolytic agents (e.g., EACA, TXA) but they could be considered in patients with concerns for increased risk of bleeding. *Consensus panel expertise with strong agreement, 95% agreement (n = 43), median 8 (IQR 7–8).*

7.8 In ECMO patients undergoing a minor and/or low-bleeding risk procedure, we suggest against targeting predefined higher thresholds for platelet and fibrinogen transfusions. *Consensus panel expertise with weak agreement, 85% agreement (n = 46), median 7.5 (IQR 7–9).*

No data informed a specific protocol or guideline for the management of systemic anticoagulation, blood product transfusion, or use of antifibrinolytic medications in children undergoing minor or low-bleeding risk procedures on ECMO. A multicenter randomized controlled trial demonstrated that standard cauterization plus fibrin sealant as topical hemostatic agent resulted in decreased bleeding compared with standard cauterization.

Postcardiotomy ECMO

Recommendations.

7.9 In pediatric ECMO patients, before and after CPB, consider using a predefined institutional protocol for the management of systemic anticoagulation and transfusion. *Weak recommendation, low-quality pediatric evidence, 91% agreement (n = 43), median 8 (IQR 7–9).*

7.10 Before starting ECMO during cardiac surgery, consider ACT targeted protamine reversal before ECMO initiation and delaying systemic anticoagulation until after the procedure and until surgical hemostasis is achieved and bleeding is controlled. *Weak recommendation, low-quality pediatric evidence, 93% agreement (n = 42), median 7.5 (IQR 7–9).*

7.11 In ECMO post-CPB, consider maintaining platelets above 100 × 10^9 cells/L and fibrinogen levels above 150 mg/dL in the periprocedural period. *Weak recommendation, low-quality pediatric evidence, 88% agreement (n = 43), median 8 (IQR 7–8).*

Consensus Statements.

7.12 In post-CPB ECMO patients, we cannot suggest for or against the routine use of prophylactic

lysine analog antifibrinolytic agents (EACA, TXA). *Consensus panel expertise with weak agreement, 91% agreement (n = 43), median 8 (IQR 7–8).*

7.13 In pediatric ECMO patients post-CPB, lysine analog antifibrinolytic agents (EACA, TXA) may be considered if there is bleeding. *Consensus panel expertise with weak agreement, 91% agreement (n = 43), median 8 (IQR 7–8).*

7.14 In post-CPB ECMO patients, it is reasonable to consider using nonbovine topical hemostatic agents at the surgical site in response to active bleeding as part of a multimodal blood management strategy including surgical hemostasis. *Consensus panel expertise with weak agreement, 93% agreement (n = 42), median 8 (IQR 7–9).*

7.15 In post-CPB ECMO patients—because of the risk of thrombotic complications, we advise against the use of rFVIIa except in the event of life-threatening bleeding refractory to multimodality blood management and resuscitation that addresses factors contributing to bleeding. *Consensus panel expertise with strong agreement, 98% agreement (n = 42), median 8 (IQR 7–9).*

ECMO support after CPB in children is associated with high risk of bleeding and associated morbidity and mortality. Published retrospective case-control studies of protocolized use of protamine, maintenance of platelet count greater than or equal to 100 × 10^9 cells/L, delaying systemic UFH titration, and/or the use of EACA or TXA report less bleeding, although the protocols are highly variable and reported outcomes lack standardization. As such, understanding which protocols or specific elements of protocols may be most efficacious remains a challenge.

Children Undergoing High-Bleeding Risk Procedures (Noncardiac Surgery)

Recommendations.

7.16 It is reasonable to consider the use of lysine analog antifibrinolytic agents (EACA, TXA). If administered, we suggest antifibrinolytics be started before the procedure, continue during the procedure, and for at least 24 hours after the procedure based on frequent reassessment of bleeding and thrombosis, and clotting of the circuit. *Weak recommendation, very low-quality pediatric evidence, 93% agreement (n = 42), median 7.5 (IQR 7–9).*

7.17 It is reasonable to consider maintaining platelet thresholds above 100 × 10^9 cells/L and fibrinogen levels above 150 mg/dL in the periprocedural period. *Weak recommendation, very low-quality pediatric evidence; 90% agreement (n = 42), median 7.5 (IQR 7–9).*

Consensus Statements.

7.18 It is reasonable to consider prophylactic application of nonbovine derived topical hemostatic agents at the surgical site. *Consensus panel expertise with weak agreement, 90% agreement (n = 42), median 8 (IQR 7–9).*

7.19 Because of the risk of thrombotic complications, we advise against the use of rFVIIa except in the event of life-threatening bleeding refractory to multimodal blood management and resuscitation that addresses factors contributing to bleeding. *Consensus panel expertise with strong agreement, 95% agreement (n = 42), median 8 (IQR 7–9).*

7.20 It is reasonable to consider utilizing a predefined institutional protocol or guideline for the management of systemic anticoagulation and transfusion therapy in pediatric ECMO during major and/or high bleeding risk invasive procedures. *Consensus panel expertise with weak agreement, 91% agreement (n = 46), median 8 (IQR 7–9).*

7.21 It is reasonable to consider decreasing or stopping systemic anticoagulation temporarily before the procedure, depending on: the procedure itself; the ability to achieve surgical hemostasis; the patient's condition; and the state of the ECMO circuit. *Consensus panel expertise with weak agreement, 93% agreement (n = 46), median 8 (IQR 7–9).*

Similar to postcardiotomy ECMO, institutional protocols on management of anticoagulation, hemostasis, and transfusion thresholds that balance bleeding risks with risks of circuit or patient thrombosis for pediatric ECMO patients around major invasive or high-bleeding risk procedures are likely beneficial. Due to wide variation in institutional protocols and limited evidence, however, identifying protocolized therapy that maximizes benefit while minimizing harm is challenging.

Periprocedural Bleeding

Good Practice Statement.

7.22 In ECMO patients who underwent an invasive procedure, early surgical consultation

should be sought for procedure-associated bleeding. *96% agreement (n = 46), median 9 (IQR 8–9).*

Recommendations.

7.23 Consider decreasing or stopping systemic anticoagulation temporarily until bleeding ceases or decreases to minimal/moderate grade or rate of bleeding. *Weak recommendation, low-quality pediatric evidence, 85% agreement (n = 46), median 8 (IQR 7–8.25).*

7.24 It is reasonable to consider targeting higher transfusion thresholds by maintaining platelets thresholds above 100 × 10^9 cells/L and fibrinogen levels above 150 mg/dL until the bleeding ceases or decreases to minimal/moderate grade or rate of bleeding. *Weak recommendation, very low-quality pediatric evidence, 93% agreement (n = 42), median 7.5 (IQR 7–9).*

Consensus Statements.

7.25 Consider adoption and use of an institutional protocol for multimodal blood management strategy for periprocedural bleeding which takes into account: 1) the severity of bleeding and/or a bleeding score; 2) close monitoring of the amount of blood losses and the clinical consequences of the bleeding; 3) the need to change the target for systemic anticoagulation and indications for temporarily stopping systemic anticoagulation; 4) indications for the use of antifibrinolytics and/or hemostatic therapies; and 5) the targeting higher concentrations of platelet and fibrinogen levels. *Consensus panel expertise with strong agreement, 96% agreement (n = 42), median 8 (IQR 7–9).*

7.26 In ECMO patients with refractory or severe bleeding associated with a procedure that persists after surgical hemostasis is achieved, it is reasonable to consider consultation with an expert in hemostasis (e.g., intensivist with expertise in ECMO, hematologist, transfusion medicine specialist, hematopathologist, etc.) depending on institutional expertise. *Consensus panel expertise with weak agreement, 93% agreement (n = 42), median 8 (IQR 7–9).*

7.27 It is reasonable to consider the use of lysine analog antifibrinolytic agents (e.g., EACA, TXA) to decrease bleeding as part of a multimodality blood management strategy. *Consensus panel expertise with weak agreement, 86% agreement (n = 42), median 7 (IQR 7–9).*

7.28 In patients with periprocedural bleeding—because of the risk of thrombotic complications, we advise against the use of rFVIIa except in the event of life-threatening bleeding refractory to multimodal blood management and resuscitation that addresses factors contributing to bleeding. *Consensus panel expertise with strong agreement, 95% (n = 42), median 8 (IQR 7–9).*

7.29 In ECMO patients with bleeding associated with an invasive procedure, consider application of nonbovine derived topical hemostatic agents at the surgical site. *Consensus panel expertise with strong agreement, 95% agreement (n = 43), median 8 (IQR 7–8).*

It is difficult to assess the balance of benefit vs. harm for individual interventions in the setting of limited informing evidence. Because bleeding and associated transfusion requirements carry significant risk, efforts to control bleeding are vital, including early consideration for surgical hemostasis. The presented consensus statements are informed by studies of protocolized management of children on ECMO postcardiotomy or congenital diaphragmatic surgery and are intended to balance the risks of prolonged bleeding with transfusion exposure or circuit or patient thrombosis that could arise from bleeding management.

MANAGEMENT OF BLEEDING AND THROMBOTIC COMPLICATIONS

The definition of clinically significant bleeding in children supported with ECMO has been summarized in Table S1 (http://links.lww.com/PCC/C494). For the purposes of consensus statements presented (25), "Clinically Significant Bleeding" is defined as meeting any of the criteria listed for moderate or severe bleeding (4, 7, 8).

Management of Bleeding and Thrombotic Complications

Recommendation.

8.1 There is insufficient evidence to provide evidence-based recommendations for or against a specific protocol or guideline to manage bleeding or thrombotic complications in ECMO patients. *Weak Recommendation, very low-quality pediatric evidence, 91% agreement (n = 46), median 8 (IQR 7–9).*

Limited data exist to inform a bleeding protocol despite the importance of bleeding and thrombotic complications of ECMO to patient outcomes.

Management of Bleeding

Recommendation.

8.2 There is insufficient evidence to suggest for or against specific blood product transfusion thresholds to manage bleeding or thrombotic complications in ECMO patients. *Weak Recommendation, very low-quality pediatric evidence, 83% agreement (n = 46), median 7.5 (IQR 7–9).*

Consensus Statements.

8.3 For clinically relevant bleeding in ECMO patients, it is reasonable to consider platelet transfusion to maintain a threshold of at least 100 × 10^9 cells/L. Higher thresholds may be considered for patients in whom platelet dysfunction is suspected. *Consensus panel expertise with weak agreement, 81% agreement (n = 43), median 8 (IQR 7–9).*

8.4 For clinically relevant bleeding in ECMO patients, it is reasonable to consider an initial plasma transfusion for INR greater than 1.5. Repeated transfusions for the sole purpose of correcting the INR may not improve outcomes. *Consensus statement with weak agreement, 88% agreement (n = 43), median 7 (IQR 7–9).*

Multiple studies associate platelet transfusion volume with adverse outcomes in bleeding and nonbleeding patients but studies to date are confounded by indication bias. The extent to which platelet dysfunction contributes to bleeding and the threshold of dysfunction that should prompt treatment are unknown. Limited data in children and adults suggest that plasma transfusion to target an INR value of less than 2.5 may not be efficacious. Potential benefits of platelet and plasma transfusion in clinically significant bleeding have been inferred from trauma studies that higher plasma or platelet to RBC ratios during resuscitation may benefit survival.

8.5 It is reasonable to consider the use of prothrombin complex concentrates (PCCs) when there is severe bleeding refractory to hemostatic blood product transfusion, antifibrinolytic therapy, decreased/discontinued anticoagulation, and/or consideration for surgical intervention as clinically applicable. *Consensus panel expertise with weak agreement, 93% agreement (n = 43), median 8 (IQR 7–9).*

No included studies evaluated the use of PCC in pediatric ECMO patients, and the potential benefit of PCC over plasma transfusion in bleeding ECMO patients remains unknown.

8.6 In ECMO patients with severe bleeding refractory to other measures, it is reasonable to consider reducing or withholding systemic anticoagulation with frequent reassessment of bleeding and clotting to guide resumption of full systemic anticoagulation. *Consensus panel expertise with weak agreement, 87% agreement (n = 46), median 8 (IQR 7–9).*

No included studies evaluated cessation of systemic anticoagulation for refractory bleeding in pediatric ECMO patients. There are case reports and some case series of pediatric ECMO with some portion of ECMO run managed without anticoagulation. Many of the expert panel reflected clinical experience with this practice and agreed that in the setting of life-threatening hemorrhage, the benefit of decreasing or withholding systemic anticoagulation likely outweighs the risk for most patients.

8.7 In ECMO patients with life threatening bleeding, it is reasonable to consider activating a massive transfusion protocol and utilizing balanced hemostatic resuscitation. *Consensus panel expertise with weak agreement, 90% agreement (n = 42), median 8 (IQR 7–9).*

No prospective studies have evaluated massive transfusion protocols in pediatric ECMO patients, but randomized controlled trials in adult trauma patients and observational studies from pediatric trauma patients support a balanced resuscitation strategy with RBC:plasma:platelet ratios of 1:1:1 to 1:1:2 for life-threatening bleeding.

CNS Bleeding

Recommendation.

8.8 There is insufficient evidence to provide an evidence-based recommendation for intracerebral hemorrhage management for pediatric ECMO. *Weak Recommendation, very low-quality*

pediatric evidence, 91% agreement (n = 46), median 7.5 (IQR 7–9).

Consensus Statements.

8.9 It is reasonable to consider whether ECMO can be safely discontinued when intracranial hemorrhage (ICH) is diagnosed. *Consensus panel expertise with weak agreement, 91% agreement (n = 46), median 8 (IQR 7–9).*

8.10 In patients with ICH for whom ECMO cannot be safely discontinued, it is reasonable to consider decreasing or stopping systemic anticoagulation with frequent reassessment of bleeding and clotting to guide the duration of decreased or no anticoagulation. *Consensus panel expertise with weak agreement, 87% agreement (n = 46), median 8 (IQR 7–9).*

8.11 In patients with ICH for whom ECMO cannot be safely discontinued, it is reasonable to consider transfusing platelets to at least a platelet count of 100 × 10^9 cells/L or higher in the setting of platelet dysfunction. *Consensus panel expertise with weak agreement, 88% agreement (n = 42), median 7.5 (IQR 7–9).*

For an individual patient supported with ECMO in whom ICH is diagnosed, the clinical care team must weigh the advantages and disadvantages of discontinuing ECMO support as well as the family's goals of care. Consideration must be given to the likelihood of ICH expansion (partially based on the degree of anticoagulation required) in comparison to the likelihood of survival if ECMO was discontinued. The duration for which systemic anticoagulation can be held for pediatric ECMO patients, who have lower flow rates compared with adults, remains unknown.

Cardiorespiratory System Bleeding

Good Practice Statement.

8.12 In patients supported with ECMO for cardiogenic shock, the presence of pulmonary hemorrhage should prompt evaluation for left atrial hypertension and consideration of left heart decompression. *100% agreement (n = 46), median 8 (IQR 8–9).*

Pulmonary hemorrhage is an established complication of left atrial hypertension in cardiogenic shock. The occurrence of pulmonary hemorrhage in a patient supported with ECMO for cardiogenic shock should promptly lead to diagnostic evaluation of left atrial hypertension and consideration of left heart decompression as indicated.

Recommendation.

8.13 There is insufficient evidence to provide an evidence-based recommendation for management of pulmonary hemorrhage for pediatric ECMO patients. *Weak Recommendation, very low-quality pediatric evidence, 91% agreement (n = 46), median 7 (IQR 7–8.25).*

Consensus Statements.

8.14 In ECMO patients with pulmonary hemorrhage, it is reasonable to consider localized instillation of lysine analog antifibrinolytic agents as part of a multimodal approach to bleeding control. *Consensus panel expertise with weak agreement, 91% agreement (n = 46), median 7 (IQR 7–8.25).*

8.15 In ECMO patients with thoracic hemorrhage/hemothorax, it is reasonable to consider a trial of conservative management with blood product replacement and/or withholding anticoagulation. *Consensus panel expertise with weak agreement, 91% agreement (n = 46), median 7.5 (IQR 7–8.25).*

8.16 In ECMO patients with hemothorax, due to the risk of additional bleeding, we suggest against chest tube placement except in the setting of decreased pump flow and oxygenation, or if unable to wean from ECMO. It is reasonable to consider surgical intervention if no improvement with conservative measures. *Consensus panel expertise with weak agreement, 85% agreement (n = 46), median 7.5 (IQR 7–9).*

8.17 In pediatric ECMO patients with hemodynamic compromise due to cardiac tamponade, consider surgical decompression or ultrasound-guided pericardiocentesis with or without placement of a pericardial drain, dependent on patient. *Consensus panel expertise with strong agreement, 98% agreement (n = 42), median 8 (IQR 7–9).*

While bleeding from lung parenchyma and intercostal vessels is often difficult to control, aggressive interventional approaches may exacerbate hemorrhage rather than control it. Our approach is to trial a conservative management strategy before invasive

strategies to achieve hemostasis. The exception to this approach is cardiac tamponade with hemodynamic compromise which can be life-threatening even with full ECMO support. In this emergent situation, surgical or ultrasound-guided decompression is essential.

Gastrointestinal System Bleeding

Recommendation.

8.18 There is insufficient evidence to provide an evidence-based recommendation for management of gastrointestinal hemorrhage for pediatric ECMO. *Weak Recommendation, very low-quality pediatric evidence, 87% agreement (n = 46), median 7 (IQR 7–9).*

Consensus Statement.

8.19 It is reasonable to consider endoscopic cautery or vessel embolization to control bleeding for selected pediatric patients with gastrointestinal hemorrhage on ECMO. *Consensus panel expertise with weak agreement, 89% agreement (n = 46), median 7.5 (IQR 7–8).*

Endoscopic cautery or vessel embolization is reasonable for the pediatric ECMO patient with gastrointestinal bleeding originating from a focal source and refractory to conservative measures, balancing the severity of bleeding with the risks of bleeding from the procedure itself.

Patient Thrombosis

Consensus Statements.

8.20 In ECMO patients with massive pulmonary emboli, intracardiac or intracoronary thrombi, or patient bladder thrombus, it is reasonable to consider direct thrombolysis. *Consensus panel expertise with weak agreement, 82% agreement (n = 46), median 7 (IQR 7–8).*

8.21. In ECMO patients with intracardiac thrombus, it is reasonable to consider surgical removal of the thrombus. *Consensus panel expertise with weak agreement, 87% agreement (n = 46), median 8 (IQR 7–8).*

Relative risks vs. benefit of either direct thrombolysis or thrombectomy for thoracic thromboses in the pediatric ECMO population remain uncertain. For individual patients, decisions are best made by a multidisciplinary team considering the availability of required equipment, resources, and institutional expertise.

Circuit and Circuit Component Thrombosis

Good Practice Statement.

8.22 In ECMO patients with significant bleeding and evidence of consumptive coagulopathy, evaluate and address all potential causes, including the circuit and components, patient thrombosis, and diagnoses associated with disseminated intravascular coagulopathy (DIC). *100% agreement (n = 43), median 8 (IQR 7–9).*

Signs and symptoms of consumptive coagulopathy can arise from a variety of etiologies in pediatric ECMO patients, including patient thrombus, circuit thrombus, or DIC. Each of these etiologies requires a different set of diagnostic and management approaches.

Consensus Statements.

8.23 In venoarterial ECMO patients with thrombus identified on the arterial side of the circuit, it is reasonable to consider urgent evaluation and consideration of options for clot removal or circuit change depending on cannulation site, thrombus size, and thrombus location. If the clot cannot be removed, careful neurologic monitoring should occur as patient is at high risk for systemic embolization, including stroke. *Consensus panel expertise with weak agreement, 90% agreement (n = 42), median 8 (IQR 7–9).*

8.24 It is reasonable to consider component change rather than entire circuit change for localized thrombus in the bladder and/or oxygenator during ECMO. *Consensus panel expertise with weak agreement, 87% agreement (n = 46), median 8 (IQR 7–9).*

8.25 In ECMO patients, it is reasonable to consider circuit change for diffuse clot and/or fibrin deposition with associated decrease in patient fibrinogen and platelet count and increase in D-dimer. *Consensus panel expertise with weak agreement, 89% agreement (n = 46), median 7 (IQR 7–9).*

When thrombosis occurs in components of the ECMO system, the clinical team must decide whether to replace the affected components or change the entire pump system. While no definitive data exist to support

either approach, one must consider the multiple variables including institutional expertise, estimated time off pump to change the component/system, expense, component/system availability, possibility of the clot reforming at the same site, and anticipated risk to the patient.

Research Priorities

Good Practice Statements.

Clinical research studies of ECMO should include the ECMO circuit components and configuration that were utilized. *96% agreement (n = 47), median 9 (IQR 8–9).*

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).*

Research studies of ECMO anticoagulation should document anticoagulation monitoring details, including assay methodology (reagent and analyzer/coagulometer used) and reference ranges used, in order to compare results across studies. *98% Agreement (n = 44), median 9 (IQR 7.25–9).*

Available literature to guide evidence-based recommendations for anticoagulation and transfusion management in pediatric ECMO is sparse (17). Accordingly, the PEACE expert panel created consensus-based research priorities to guide future studies (17). Each subgroup developed three to five research priorities pertinent to their subgroup topic. We then used the CHNRI methodology to prioritize research topics based on a consensus-based weighted list of review criteria (16). Twenty research topics were prioritized and categorized into five domains: 1) definitions and outcomes; 2) therapeutics (including medications and blood product administration); 3) anticoagulation monitoring; 4) protocolized management; 5) impact of the ECMO circuit and its components on hemostasis. The top five research priorities are in Table 6. The full list of priorities are in the Research Priorities Summary article in the accompanying supplement (17).

DISCUSSION

After systematic literature review, the PEACE experts identified insufficient evidence to support evidence-based recommendations for most evaluated topics. Of 91 statements, only nine are weak recommendations based on low or very low-quality pediatric evidence. These evidence-based recommendations were limited to the subtopics of RBC transfusion (21), antifibrinolytic and adjunct hemostatic agents (23), and anticoagulation management perioperative procedures (24). The expert panel reached consensus on 52 literature-informed expert consensus statements and 16 good practice statements.

PEACE methodology was based on the Transfusion and Anemia EXpertise Initiative (TAXI) and TAXI-Control and Avoidance of Bleeding (CAB) Consensus recommendations for RBC, platelet, and plasma transfusion in critically ill children (35, 36). TAXI and TAXI-CAB included discussions of blood product transfusion for children supported with ECMO and there is some overlap with the statements presented here. Because TAXI-CAB and PEACE conferences were held concurrently, a PEACE representative (37) was included in the TAXI-CAB ECMO subgroup and a TAXI-CAB representative (36) was included in the PEACE blood product transfusion subgroup to ensure that recommendations developed by the two groups would not be in contradiction. With respect to RBC transfusion, the TAXI recommendations were published in 2018. Although the PEACE and TAXI statements regarding indications for RBC transfusion are similar, the PEACE literature review includes an additional six observational studies (total n = 867) relevant to RBC transfusion in pediatric ECMO (37–42). PEACE also includes a statement regarding RBC storage duration. This Population, Intervention, Comparator, and Outcome question was added because many centers use fresh RBCs for pediatric ECMO patients, although several randomized controlled trials in critically ill adults and children failed to demonstrate differences in clinical outcomes in patients transfused with fresh vs. standard issue RBCs (43–48). These studies, including the recent Age of Blood in PICUs trial, excluded patients supported with ECMO. Because it is unknown whether trial results would generalize to ECMO patients, the PEACE panel concluded that evidence was insufficient to provide a recommendation (48). Regarding prophylactic platelet and plasma transfusions, TAXI-CAB and PEACE statements are similar with the exception that PEACE adds a consensus statement suggesting

against prophylactic plasma transfusion if the INR is greater than 1.5. PEACE also includes statements about platelet or plasma transfusion for perioperative or bleeding children on ECMO, which were not addressed by TAXI-CAB (24, 25).

Previous anticoagulation guidelines for adult and pediatric ECMO patients have been published by ELSO (49). The ELSO guidelines offer an excellent narrative literature review with a stated objective to provide educational content rather than consensus recommendations. In contrast, PEACE is the first multidisciplinary consensus conference to provide consensus-based recommendations and expert consensus statements for anticoagulation and hemostasis management in pediatric ECMO patients guided by a systematic literature review. Important similarities between the two documents include suggestions for multimodal monitoring for heparin-based anticoagulation, with patient and circuit-specific factors considered in the clinical interpretation of monitoring assays; a call for more evidence before recommending routine antithrombin monitoring and replacement; and challenges due to lack of standardized monitoring or optimal therapeutic thresholds for DTI. Suggested indications for blood product transfusion are similar with the exception that both PEACE and TAXI-CAB experts were unable to provide consensus-based thresholds to prompt platelet or plasma transfusion in nonbleeding patients owing largely to a lack of informing evidence (21, 36, 50).

The intended population for the PEACE statements includes neonates and children supported with ECMO, as defined by the 2018 Nomenclature Task Force of the ELSO (6). While other forms of mechanical circulatory support, such as VADs pose similar challenges with respect to anticoagulation and hemostasis in pediatric patients, the PEACE experts deemed inclusion of VAD-supported patients beyond the scope of the PEACE process. Because our focus was on management strategies for pediatric patients, we chose to limit our systematic literature review to only studies that included greater than or equal to 50% pediatric patients or for which pediatric-specific data could be extracted. The PEACE experts considered that adult evidence should not be extrapolated to pediatric patients because of important differences in underlying etiologies prompting ECMO support, circuit size relative to patient size, and differences in ECMO flow. Even within the pediatric age range, it is likely that optimal anticoagulation and hemostasis strategies might differ by age due to age-related differences in normal hemostasis. While some evaluated studies included exclusively neonates or non-neonatal patients, many studies included patients across the neonatal/pediatric age range and analyses were often not stratified by age. As such, data to guide age-based considerations in pediatric ECMO anticoagulation are sparse.

Strengths of the PEACE consensus conference include a multidisciplinary expert panel representing key stakeholders in the care of ECMO patients and a rigorous methodology. There were limitations. There are no agreed upon standard definitions for clinically relevant bleeding in pediatric ECMO patients. Several definitions have been proposed for mild, moderate, severe, or life-threatening bleeding by groups that include PEACE expert panel members (4, 7, 8, 28, 51). Building consensus around a single definition of clinically relevant bleeding was deemed beyond the scope of this PEACE consensus process and for the purposes of the statements contained here clinically relevant bleeding was defined as bleeding that met any of the criteria for moderate or severe bleeding for any of the included definitions. Standardizing definitions for bleeding and thrombotic complications was identified as our top research priority and future directions include validating and implementing standardized bleeding definitions for pediatric ECMO patients.

The most important limitation of the PEACE process is the lack of high-quality evidence to guide management recommendations. To address knowledge gaps, the PEACE expert panel created consensus-based research priorities (17). Next steps of the PEACE process include collaborative efforts to address research priorities in future observational and interventional trials. Because of the complexity of ECMO patients, including patient heterogeneity and small numbers of patients in individual centers, innovative clinical trial methodologies employed across multiple centers will likely be necessary. Future PEACE meetings will convene clinicians and clinical researchers with methodologic experts in comparative effectiveness observational studies, learning healthcare system models, and innovative randomized clinical trials to catalyze future studies. Meetings will benefit from lessons learned from ongoing clinical trials, currently conducted by PEACE members (Trial of Indication-Based Transfusion of RBCs in ECMO, NCT05405426; ECMO Hemostatic Transfusions in

Children trial, NCT05796557). Such research efforts are necessary to determine optimal anticoagulation, hemostasis, and transfusion strategies for pediatric ECMO patients and to guide evidence-based recommendations in the future.

CONCLUSIONS

The PEACE consensus conference presents good practice statements, recommendations, and expert opinion consensus statements to help guide anticoagulation and transfusion management for pediatric ECMO patients. For all included statements, available pediatric evidence was either low quality, very-low quality, or of insufficient quality to provide evidence-based recommendations. Key knowledge gaps were identified, and research topics were prioritized to guide future clinical studies.

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