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The Influence of the Extracorporeal Membrane Oxygenation Circuit and Components on Anticoagulation Management: The Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE Consensus Conference

OBJECTIVES: To derive systematic-review informed, modified Delphi consensus regarding the influence of extracorporeal membrane oxygenation (ECMO) circuit components on anticoagulation practices for pediatric ECMO for the Pediatric ECMO Anticoagulation CollaborativE.

DATA SOURCES: A structured literature search was performed using PubMed, EMBASE, and Cochrane Library (CENTRAL) databases from January 1988 to May 2021.

STUDY SELECTION: Management of ECMO anticoagulation in the setting of different ECMO circuit components.

DATA EXTRACTION: Two authors reviewed all citations independently, with a third independent reviewer resolving conflicts. Twenty-nine references were used for data extraction and informed recommendations, evidence-based consensus statements, and good practice statements. Evidence tables were constructed using a standardized data extraction form.

DATA SYNTHESIS: Risk of bias was assessed using the Quality in Prognosis Studies tool. The evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation system. Forty-eight experts met over 2 years to develop evidence-based recommendations and, when evidence was lacking, expert-based consensus statements or good practice statements for the influence of ECMO circuit and components on anticoagulation management. A web-based modified Delphi process was used to build consensus via the Research And Development/University of California Appropriateness Method. Consensus was defined as greater than 80% agreement. One good practice statement, 2 weak recommendations, and 2 consensus statements are presented.

CONCLUSIONS: The incorporation of new component technologies into clinical practice has outpaced clinical investigations of anticoagulation strategies for pediatric ECMO. Future investigations should leverage academic and industrial collaborations, translational platforms, and modern biostatistical methods to improve patient outcomes.

KEYWORDS: anticoagulation; extracorporeal membrane oxygenation; hemolysis; oxygenators; pediatrics

Adam S. Himebauch, MD[1]
John R. Priest, BSRT, RRT-NPS[2]
Gail M. Annich, MD, MS[3]
D. Michael McMullan, MD[4]
David A. Turner, MD[5,6]
Jennifer A. Muszynski, MD, MPH[7]
Peta M.A. Alexander, MBBS[8,9]
Matthew L. Paden, MD[10]
Alison Gehred, MLIS[11]
Elizabeth Lyman, MLIS, AHIP[11]
Ahmed S. Said, MD, PhD[12]
for the Pediatric Extracorporeal Membrane Oxygenation (ECMO) Anticoagulation CollaborativE (PEACE), in collaboration with the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, the Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric ECMO subgroup of PALISI and the Extracorporeal Life Support Organization (PediECMO)

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Over the past three decades, the increased use of pediatric extracorporeal membrane oxygenation (ECMO) has been paralleled with ongoing evolution in ECMO circuit components, configuration, and

technology. ECMO cannula structure and dimensions, pump type (centrifugal or roller), tubing characteristics (size, connectors, biocompatible coating), membrane oxygenator characteristics (design, composition, material), and adjuvant devices (ultrafiltration, dialysis, plasmapheresis, etc.) may influence anticoagulation management. However, studies describing differences in anticoagulation management or hemorrhagic or thrombotic complications with the use of specific ECMO circuit components or configurations are limited (1). The objective of this subgroup of the Pediatric ECMO Anticoagulation CollaborativE (PEACE) was to derive systematic-review informed, modified Delphi consensus regarding the influence of circuit components on anticoagulation management during pediatric ECMO support intended to help guide bedside clinicians.

MATERIALS AND METHODS

Detailed methods and definitions of clinically relevant bleeding are described in the PEACE executive summary (2). Briefly, a structured literature search was performed using PubMed, EMBASE, and Cochrane Library (CENTRAL) databases from January 1988 to May 2020, with an update in May 2021, using a combination of medical subject heading terms and text words to investigate in pediatric patients supported on ECMO (population), does use of alternate circuit components (intervention/comparator) influence anticoagulation practice or outcomes (**Supplemental Methods 1**, http://links.lww.com/PCC/C492). Two authors reviewed all citations independently, with a third independent reviewer resolving any conflicts. Evidence tables were constructed using a standardized data extraction form (2). Risk of bias (RoB) was assessed using the Quality in Prognosis Studies (QUIPS) tool or the revised Cochrane RoB for randomized controlled trials, as appropriate (3–5), and the evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (6, 7). A panel of 48 experts met over the course of 2 years to develop evidence-based recommendations and, when evidence was lacking, expert-based consensus statements or good practice statements for the influence of ECMO circuit and components on anticoagulation management. The supporting literature was reviewed and statements were developed using the evidence-to-decision framework, emphasizing the panel's assessment of risks versus benefits of each proposed statement and a prioritized list of patient outcomes that had been created by a web-based survey of expert panel members (8–10). A web-based modified Delphi process was used to build consensus via the Research And Development/University of California Appropriateness Method. Consensus was defined as greater than 80% agreement (11, 12). Additional references, not included in the structured literature search, were included in rationale statements to provide context but were not used to derive recommendations, consensus statements, or good practice statements.

RESULTS

The structured literature search identified 11,553 abstracts. Of these, 11,261 references were excluded based on the abstract. An additional 263 references were excluded based on full article review, leaving 29 references that were used for recommendation and consensus statement creation (**Fig. 1**). The included references are detailed in **Supplemental Table S1** (http://links.lww.com/PCC/C492). A summary of RoB assessments is in **Supplemental Figure S1** (http://links.lww.com/PCC/C492). Two recommendations, one good practice statement, and two consensus statements were developed and, in all, agreement greater than 80% was reached.

Good Practice Statement.

1.1 Use policies informed by national and international guidelines to maintain local multidisciplinary groups of ECMO practitioners with expertise in

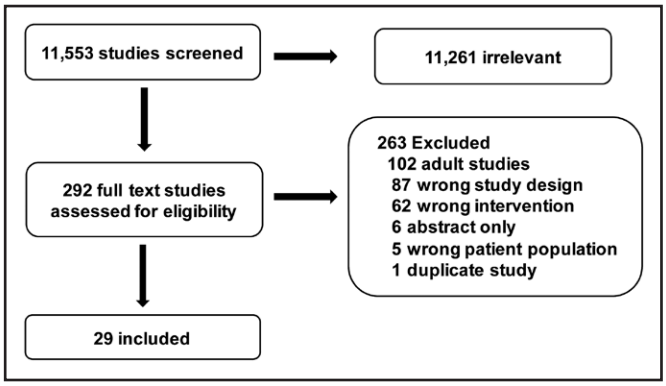

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of studies screened and included in the pediatric extracorporeal membrane oxygenation circuit components subgroup.

up-to-date circuit technologies and good practices to optimize patient outcomes. *98% agreement (n = 47), median 9, interquartile range (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.*

Summary of the Evidence: Fifteen of the 29 studies that met inclusion criteria for data extraction reported data on a mixture of centrifugal pump and roller pump use (13–23), with 11 studies focused on comparing centrifugal and roller pump technologies (14–17, 19, 20, 23–28). Study designs included case–control, prospective cohort, retrospective cohort, registry-based, and propensity-matched studies. There was heterogeneity in the reported patient outcomes in studies comparing centrifugal versus roller pumps including mortality, survival, thrombotic, and hemorrhagic complications. In multiple studies, associations were seen between the use of centrifugal pump technology and greater odds of hemolysis, although associations with patient-centered clinical outcomes were not reported (14–16, 24, 25, 27). There was an overall decrease in the prevalence of hemolysis in the recent era, regardless of pump technology (27). A single-center retrospective study showed decreased rate of hemolysis associated with transition from roller to centrifugal pump technology (26). In a propensity-matched retrospective cohort study of infants less than 10 kg from the Extracorporeal Life Support Organization (ELSO) Registry, centrifugal pump use was associated with a lower odds of survival to hospital discharge (odds ratio 0.91; 95% CI, 0.83–0.99), with mediation analysis supporting hemolysis as a mediator of the association (25). Another single-center, retrospective study found increased prevalence of hemorrhagic complications when using centrifugal pump compared with using roller pump, but this observation was not associated with a difference in intracranial hemorrhage, overall mortality, or mortality secondary to coagulopathy (28).

These findings are important to interpret in the context of two major limitations. First, there was an important change in ECMO technology in 2009, with subsequent increased centrifugal pump use; the widespread adoption of this technology cannot be delineated from the published studies. Second, the majority of the reviewed studies were single-center studies, mostly in the United States, where adoption of centrifugal pump technology was later than in other countries. Future research studies should account for the inter- and intra-institutional differences in circuit component and configuration practices (29). Additionally, new studies are needed that focus on practices and outcomes with the growing experience of using centrifugal pump technology.

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.*

Summary of the Evidence: There was a paucity of evidence from clinical research studies on the influence of circuit connectors on anticoagulation practices. Ex vivo studies support the concept of increased thrombogenicity at points of circuit connectors (19, 30).

Balance of Benefits Versus Harms: We suggest weighing the benefits of each additional circuit connector with the potential risk of increased thrombotic burden. More clinical research is needed on the impact of the number and types of circuit connectors on bleeding, thrombosis, and morbidity of patients supported with ECMO.

Consensus Statement.

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

Summary of the Evidence: Of the 29 informing studies (Supplemental Table S1, http://links.lww.com/PCC/C492), 15 reported plasma-free hemoglobin as a measure of hemolysis (13, 15–18, 20, 21, 24, 25, 27, 31–35). There was heterogeneity in the methods

of measuring and reporting plasma-free hemoglobin. Cutoff values used for clinically significant hemolysis also varied with the most common being greater than 50 mg/dL, which is the definition used in the ELSO Registry (36). There was a lack of consistent association between reported plasma-free hemoglobin levels and patient outcomes. 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.

Balance of Benefits Versus Harms: We suggest using plasma-free hemoglobin as one of the screening tools for hemolysis because it is correlated with other markers of hemolysis (e.g., lactate dehydrogenase, haptoglobin, etc.). Because multiple modalities are used for monitoring hemolysis, it is reasonable to consider developing institutional standardized laboratory collection and processing practices of markers of hemolysis during pediatric ECMO. We suggest considering the potential influence of additional circuit components and partial or total circuit exchange when interpreting plasma-free hemoglobin values. There should be transparency of methods when reporting markers of hemolysis and prioritizing clinical research studies to investigate the impact of different circuit components on hemolysis, the association of hemolysis with different clinically significant outcomes, and the different cutoff levels of hemolysis associated with these outcomes (29).

Other Evidence to Decision Considerations: There was paucity of evidence on the impact of: 1) additional circuit components, such as in-line hemofilters or renal replacement therapy (31), 2) alternative cannulation strategies, 3) ventricular assist device technologies (31, 37–39), or 4) extracorporeal carbon dioxide removal technologies on bleeding and thrombosis in neonates, infants, children, and adolescents supported by ECMO. One retrospective, single-center cohort study included in the PEACE review showed higher peak and peak percent change in plasma-free hemoglobin in congenital heart disease patients managed with ECMO and continuous renal replacement therapy (31). However, a thorough evaluation of the impact of adjuvant devices on anticoagulation practices and on clinically relevant outcomes was beyond the scope of the PEACE systematic review and deserves future consideration.

CONCLUSIONS

The existing clinical research investigating the influence of ECMO circuit components on anticoagulation practices is limited, with only low-quality evidence to inform recommendations, good practice statements, and consensus statements. The evolution and incorporation of new circuit component technologies into clinical practice have outpaced clinical investigations with respect to the effect of these technologies on anticoagulation strategies for pediatric ECMO and consequent patient outcomes. Despite the challenges with the broad applicability of published clinical research data and institutional variability in practice, there is real opportunity to use translational platforms, multicenter collaborations, partnerships with industry, electronic data gathering methods, standardization of reporting transparency, and modern causal inference-focused biostatistical methods to increase the data quality for more successful bedside application to improve patient outcomes (29).

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1 *Division of Critical Care Medicine, The Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA.*

2 *Department of Respiratory Care, ECMO Program, Boston Children's Hospital, Boston, MA.*

3 *Department of Critical Care Medicine, The Hospital for Sick Children, Toronto, ON, Canada.*

4 *Department of Surgery, Seattle Children's Hospital, Seattle, WA.*

5 *American Board of Pediatrics, Chapel Hill, NC.*

6 *Division of Pediatric Critical Care, Department of Pediatrics, Duke Children's Hospital, Durham, NC.*

7 *Division of Critical Care Medicine, Department of Pediatrics, Nationwide Children's Hospital, Ohio State University College of Medicine, Columbus, OH.*

8 *Department of Cardiology, Boston Children's Hospital, Boston, MA.*

9 *Department of Pediatrics, Harvard Medical School, Boston, MA.*

10 *Division of Pediatric Critical Care, Emory University/ Children's Healthcare of Atlanta, Atlanta, GA.*

11 *Grant Morrow III MD Medical Library, Nationwide Children's Hospital Columbus, OH.*

12 *Division of Pediatric Critical Care, St. Louis Children's Hospital, Washington University in St. Louis, St. Louis, MO.*

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Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE (PEACE) members are listed in ***Appendix 1*** *(http://links.lww.com/PCC/C492).*

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For information regarding this article, E-mail: peta.alexander@childrens.harvard.edu

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