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# Realizing potential: Pediatric Extracorporeal Membrane Oxygenation Needs Common Adverse Event Definitions to Improve Outcomes

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## Keywords

extracorporeal membrane oxygenation; ECMO; pediatrics; anticoagulants; hematologic tests; bleeding; thrombosis

Extracorporeal Membrane Oxygenation (ECMO) is an invasive life support technology delivered to critically ill children at relatively low volumes across centers around the world.(1) This type of support has been used for neonates and children refractory to conventional medical management for decades, but patient outcomes are largely unchanged with sustained in-hospital mortality near 40%.(2, 3) Despite this history, the field is characterized by extensive practice variability, including indications and perceived contraindications for support, timing of cannulation, cannulation strategies, anticoagulation management, blood product transfusion practice, sedation, and neuromonitoring routines. Further, ECMO circuits used for children are often assembled from component parts, unique to each institution. ECMO circuits include cannulas, blood pumps, oxygenators, tubing, connectors, access points and incorporated equipment such as renal replacement therapy circuits, which affect performance criteria of the composite devices and introduce risks for thrombosis, air entrainment or introduction of infection. Regulatory oversight of safety and efficacy of medical devices used for pediatric ECMO is limited, with only one cannula, but no blood pumps, oxygenators or complete circuits approved for pediatric ECMO use. Clinical studies to inform the field incorporate different definitions of adverse events and clinical outcomes,

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which impedes direct comparison or meta-analysis. These issues combine to confound progress toward improving pediatric ECMO management to achieve better patient outcomes.

Bleeding is a particularly common complication of ECMO support in children and has been consistently associated with increased mortality.(4–6) In this issue of the journal, Drs Rabinowitz, Said and colleagues present their institutional experience of pediatric ECMO outcomes for those children in whom circuit anticoagulation was either delayed or interrupted.(7) For the purposes of this study, clinical team concern of increased risk of bleeding prompted withholding anticoagulant infusions for short periods (median duration 18h) in the case series of 35 patients. The authors report survival to hospital discharge rates consistent with other mixed populations, and with only few patient- or circuit-related thrombotic complications. This may be the largest series reported of children managed with ECMO without continuous anticoagulation, and the results suggest that in well selected patients, this practice may be associated with acceptable patient outcomes. One of the most remarkable aspects of this report, to the authors' credit, is the thorough description of variability of standard patient care within the single institution. In order to depict their patient management protocol for other centers considering similar therapeutic strategies, Dr Rabinowitz and colleagues catalogue varied ECMO circuit components, dimensions and coatings, a change in primary anticoagulant during the course of the study, as well as variability in the use of blood-primed circuits, resuscitation strategy and surveillance for thrombosis. Their remarkable clarity includes reference, not just to the potential for difference in ECMO management between institutions, but indeed to intra-institutional management discrepancies which precluded pooling all neonates and children supported with ECMO at their institution for this analysis. Despite the limitations associated with the retrospective study, the practice of withholding anticoagulation to children supported with ECMO may be safe in selected populations for judicious periods. The authors note that multi-center collaborations are required to define categories of patients at high-risk of bleeding complications, to understand safety of withholding anticoagulants, and develop standards for better management of bleeding in children supported with ECMO.

It is increasingly recognized that accumulation of knowledge sufficient to change clinical practice will require assimilation of multi-center data across studies, including clinical trials and registries.(8, 9) One factor limiting such assimilation across pediatric ECMO studies is the lack of agreed upon definitions of adverse events and outcomes. As Rabinowitz and colleagues report, there are a number of different definitions of bleeding during pediatric ECMO which have been developed and used in clinical studies, with none widely adopted for use.(4, 10, 11) Further, in their study, the relative safety of withholding anticoagulation in the pediatric ECMO population was assessed using one of several existing definitions of thrombosis.(11–13) Unfortunately, death and adverse events are common in children supported with ECMO, but consistent cataloguing of complications requires agreed upon definitions articulated by families, clinicians, scientists and/or regulators.

There has been growth in ECMO utilization, science, and funding. In 2022, more than 3,000 children were reported as receiving ECMO support, and almost 1,000 pediatric ECMO studies were published in the last two years.(14) This resource-intensive support strategy is the focus of established device development initiatives, translational science projects, and

increasingly, competitively funded clinical trials. These investments highlight the growing interest and recognition of the importance of pediatric ECMO. At this opportune juncture, we believe that convergence of subspecialty fields which are required to optimize ECMO device development, utilization, safety and regulation would benefit from a shared mental model of adverse events and clinical outcomes associated with the use of ECMO in this population. Featuring input from key international stakeholders including clinicians, manufacturers, regulatory agencies, adjacent subspecialties, statisticians, established trialists, patients and families, we have convened ECMO-CENTRAL (*Core Elements Needed for Trials Regulation And quality of Life*) to address this imperative. Incorporating the established Academic Research Consortium (ARC) process with engagement with the U.S. Food and Drug Administration Center for Devices and Radiological Health,(15, 16) ECMO-CENTRAL ARC will leverage community engagement, ongoing clinical trials and evolving collaborative networks to define consensus adverse events associated with pediatric ECMO support to increase the value from future ECMO research. This process will be the foundation for the multi-center studies which Dr. Rabinowitz and colleagues and others recommend to inform improved pediatric ECMO clinical care and ultimately lead to better patient outcomes.

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