REVIEW ARTICLE

blood VTH
vessels, thrombosis & hemostasis

ECMO-induced coagulopathy: strategic initiatives for research and clinical practice (a workshop report of the NHLBI)

Jerrold H. Levy,[1] Peta M. A. Alexander,[2] Alisa S. Wolberg,[3] Owen J. T. McCarty,[4] Anthony E. Pusateri,[5,6] Raquel R. Bartz,[7] Wolfgang Bergmeier,[8] Mitchell J. Cohen,[9] Jean M. Connors,[10] James H. Morrissey,[11] Matthew D. Neal,[12] Elisabeth T. Tracy,[13] Keith McCrae,[14-16] and Bruce A. Sullenger[17]

[1]Department of Anesthesiology, Critical Care, and Surgery (Cardiothoracic), Duke University School of Medicine, Durham, NC; [2]Department of Cardiology, Boston Children's Hospital and Department of Pediatrics, Harvard Medical School, Boston, MA; [3]Department of Pathology and Laboratory Medicine and University of North Carolina Blood Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC; [4]Department of Biomedical Engineering, Oregon Health & Science University, Portland, OR; [5]Naval Medical Research Unit San Antonio, Joint Base San Antonio-Fort Sam Houston, Houston, TX; [6]Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD; [7]Department of Anesthesia, Wake Forest School of Medicine, Winston Salem, NC; [8]Department of Biochemistry and Biophysics and UNC Blood Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC; [9]Department of Surgery, University of Colorado School of Medicine, Aurora, CO; [10]Hematology Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [11]Department of Biological Chemistry, University of Michigan Medical School, Ann Arbor, MI; [12]Department of Surgery, Trauma and Transfusion Medicine Research Center, University of Pittsburgh, Pittsburgh, PA; [13]Department of Surgery, UNC Children's, University of North Carolina School of Medicine, Chapel Hill, NC; [14]Benign Hematology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; [15]Department of Vascular Medicine, Miller Family Heart and Vascular Institute, Cleveland Clinic, Cleveland, OH; [16]Department of Cardiovascular and Metabolic Sciences, Cleveland Clinic Lerner College of Medicine, Cleveland, OH; and [17]Department of Surgery, Duke University School of Medicine, Durham, NC

In May 2024, the Division of Blood Diseases and Resources of the National Heart, Lung, and Blood Institute (NHLBI) hosted a hybrid workshop on "Extracorporeal membrane oxygenation (ECMO)-induced coagulopathy: strategic initiatives for research and clinical practice." The event brought together clinicians, scientists, bioengineers, and policymakers to address the challenges of ECMO-associated coagulopathy and explore novel therapeutic approaches. Through expert presentations and collaborative discussions, the workshop focused on innovative anticoagulation strategies, precision medicine, and advanced diagnostics to enhance patient care. The discussions also identified critical research gaps and opportunities for future interdisciplinary collaboration. This summary reviews the current state of knowledge and outlines future research directions for improving ECMO-induced coagulopathy management.

Introduction

In May 2024, the Division of Blood Diseases and Resources of the National Heart, Lung, and Blood Institute of the National Institutes of Health hosted a 2-day hybrid workshop titled "Extracorporeal membrane oxygenation (ECMO)-induced coagulopathy: strategic initiatives for research and clinical practice." Contributing clinicians, scientists, technology developers, and government agency representatives were included in the planning and orchestration of the workshop (supplemental Table 1), which brought together a multidisciplinary group of experts, including hematologists, critical care physicians, surgeons (trauma, thoracic, and pediatric), basic and translational scientists, and bioengineers whose clinical and research interests included the management of ECMO and associated coagulation and hemostasis. The meeting focused on the complex challenges associated with coagulopathy in ECMO, novel therapeutic approaches, and the potential impact of collaborative research

Submitted 18 September 2024; accepted 30 January 2025; prepublished online 25 February 2025; final version published online 30 April 2025. https://doi.org/10.1016/j.bvth.2025.100064.

The full-text version of this article contains a data supplement.

for improving patient outcomes. Through expert presentations, panel discussions, and interactive sessions, attendees explored innovative anticoagulation strategies, the role of precision medicine, and the use of advanced diagnostic and modeling tools to improve the care of patients receiving ECMO support. Attendees also identified critical research gaps and opportunities for future interdisciplinary collaborations. This workshop summary reviews current knowledge in ECMO-induced coagulopathy, examines current and future research opportunities, and identifies key gaps discussed during the workshop.

Background

ECMO is a potentially lifesaving intervention for patients with severe cardiac and/or respiratory failure that is refractory to less invasive therapies. Briefly, the use of this resource-intensive therapy has increased over the past decades.[1] Although first established for neonatal and pediatric care, more recently, the H1N1 influenza and then COVID-19 pandemics greatly expanded the use of ECMO, which is now predominantly used in adult patients with respiratory failure or cardiogenic shock, or as a rescue therapy for cardiopulmonary arrest in selected populations.[1,2] The combination of critical illness of the supported patient populations, circuit surface-blood interactions, and the use of systemic anticoagulants to mitigate circuit thrombosis results in coagulopathies that pose challenges to patient management, with patients suffering the consequences of this care.[3] Common ECMO-related hemorrhage events include cannulation and surgical site bleeding, gastrointestinal tract, pulmonary, and intracranial hemorrhage. Thrombotic events include circuit tubing or component clotting, deep vein thrombosis, pulmonary embolism, and ischemic stroke.[1,4,5] In addition to coagulopathic complications, ECMO is associated with an innate immune and inflammatory response, complicating the patient's underlying disease and management.[6,7] Importantly, neonates and children who receive ECMO are disproportionately affected by hemostatic adverse events.[1,8,9] Overall, these complications make understanding and managing anticoagulation critical to advancing the use of ECMO technologies across the lifespan. The increasing use of ECMO, especially during the COVID-19 pandemic, underscores the urgency for refined research and enhanced clinical protocols to improve outcomes for the vulnerable patient population who receive this care. Recent advancements in understanding the pathophysiology of ECMO-induced coagulopathies have highlighted the roles of contact pathway activation, platelet dysfunction, fibrinolysis, and inflammatory responses.[3-11] Despite these insights, significant gaps remain in our ability to effectively predict, diagnose, and manage ECMO-associated complications.

Epidemiology

The risk of ECMO-related coagulopathy is influenced by several factors, including the patient's underlying conditions, such as sepsis, trauma, and postcardiotomy status, as well as the mode of ECMO used. According to analyses of the Extracorporeal Life Support Organization (ELSO) registry, reported bleeding rates range from 60% to 70% depending on the cohort.[1] Thrombotic events occur in 30% to 40% of patients and vary depending on the study, type of ECMO, or population analyzed.[1] For example, compared with venovenous (VV) ECMO used for respiratory support, venoarterial (VA) ECMO, used for cardiac support, is associated with higher risks of thrombotic complications such as ischemic strokes and circuit clots.[1] Increased clotting with VA ECMO is thought to be due to multiple factors that may be related to low cardiac pulsatility, shock liver/hepatic dysfunction, postcardiotomy status, more turbulent flow, higher shear stress, and return flow delivered directly to the systemic arterial system. Other factors, such as fibrinolytic activity, which potentiate bleeding risk, arise in both VA and VV ECMO. Thus, risks of bleeding and thrombosis are associated with ECMO use in general but are also highly associated with the type of ECMO support. In this context, however, it is important to note that the indications for VV and VA ECMO are different, and, as such, the underlying indication may also contribute to differences in the coagulopathy observed. Furthermore, anticoagulation strategies often differ for VV and VA ECMO, with therapeutic anticoagulation being a larger focus in VA ECMO because of the increased risk of clinically relevant thrombosis, whereas patients receiving VV ECMO can often be managed safely off anticoagulation for intervals.[10]

Current standards of care

Managing ECMO-related hemostatic derangement requires anticoagulation to prevent thrombosis and coagulopathy. Unfractionated heparin (UFH) is the most common anticoagulant used.[11-15] UFH is monitored routinely with anti–factor Xa (anti-FXa) levels or activated partial thromboplastin time (aPTT), and less commonly in the modern era with activated clotting time.[11,16] Direct thrombin inhibitors (DTIs) are increasingly used in patients receiving ECMO who have heparin-induced thrombocytopenia (HIT), those at increased risk of HIT, or to avoid antithrombin repletion.[11,14] The most commonly used DTI, bivalirudin, is a polypeptide with a half-life of ~30 minutes in individuals with normal renal function. Argatroban, a synthetic molecule, is used often in patients with renal failure and has a longer half-life (~2 hours). Both DTIs provide predictable pharmacokinetics, require aPTT or alternate monitoring at a higher cost than UFH, and lack a reversal agent. Standard coagulation testing includes platelet counts, fibrinogen levels, and clotting assays for bleeding management. Viscoelastic tests (eg, rotational thromboelastometry or thromboelastography) are increasingly used in association with coagulation management algorithms for anticoagulation and bleeding management.[16] When patients on ECMO support are recognized to have bleeding; therapy may include transfusion of platelets; fresh frozen plasma; fibrinogen repletion with cryoprecipitate or concentrates; and reduction of, or stopping, the anticoagulation.[17] Thrombotic complications may be recognized as changes in the circuit, membrane lung, or clinical examination. When present in the ECMO circuit, thromboses disrupt laminar flow causing local turbulence, which damages red blood cells and leads to hemolysis. Clinically, hemolysis is evaluated by serial measurements of free hemoglobin and lactate dehydrogenase levels and managed by increasing anticoagulation therapy. Affected patients may require circuit and/or oxygenator replacement because of hemolysis, which is both a result of circuit thrombosis and an important contributor to coagulopathy.

Definitive guidelines for anticoagulation management during ECMO are variably implemented, bleeding complications pose major challenges, and most data are based on retrospective observational studies. Additionally, definitions for bleeding and anticoagulation complications have only recently been

proposed.[18-21] The recent PROTECMO study (Prospective Observational Study on Transfusion Practice in Patients Receiving VV ECMO) was a prospective, observational, 41-center study that analyzed blood product use and transfusion thresholds by examining coagulation management and patient outcomes of 652 adult patients receiving 8471 ECMO days.[22] In 77% of patients, UFH was initially used and was continued for 73% of patients (6221 days), monitored by aPTT on 86% of days, with a median result of 52 seconds. After an initial bleeding event, the median aPTT decreased by 5.3 seconds. Bleeding occurred on 1202 days (16.5%), and 52.5% of patients developed ≥1 bleeding event, which resulted in death in 1.6% (10 patients). Cannulation site bleeding was the most frequent cause, but this varied over time and risk was increased based on the length of support. Bleeding during ECMO was associated with increasing intensive care unit–related mortality risk. Although prolonged aPTTs were associated with bleeding risk, doses of heparin administered did not correlate with aPTTs. Moreover, aPTT targets ranged between 40 and 60 seconds and monitoring frequency changed during anticoagulation therapy, demonstrating a lack of consistent anticoagulant management in patients receiving ECMO.[23]

COVID-19 and coagulopathy

ECMO deployment for COVID-19–associated refractory respiratory failure and/or cardiogenic shock dysfunction was an important therapeutic rescue for patients in intensive care units, failing conventional respiratory or other support.[24] ELSO data noted ECMO outcomes in patients with COVID-19 varied based on institutional experience, patient selection, and timing of institution.[25] As widely reported, the admission coagulopathy in patients with COVID-19 is consistent with hypercoagulability as evidenced by increased levels of fibrinogen, D-dimers, von Willebrand factor (VWF), and multiple biomarkers of thromboinflammation and coagulation activation.[26] However, the coagulopathy of patients on ECMO is associated with an increased risk of both thrombotic and bleeding events, depending on underlying disease severity and duration of ECMO support. A recent registry report of 1248 patients with COVID-19 on ECMO reported that 38% developed coagulopathy, 54% experienced hemorrhagic complications, 35% thrombotic complications, and 11% of patients were reported to experience both bleeding and thrombotic complications. The intensive care unit hazard ratio for mortality was higher in those with hemorrhagic-only complications (49.4%) than 42% in patients with multiorgan failure, 21% with respiratory failure, and 8.9% who developed subsequent septic shock.[27]

Challenges and lessons learned from COVID-19

The COVID-19 pandemic provided challenges in ECMO management because of the large number of patients with acute lung injury and the variability of resources available for their treatment. Further, ECMO outcomes for patients with COVID-19 have been similar to those with other severe respiratory diseases, indicating that acute lung injury and underlying respiratory pathology present consistent challenges, especially with initially limited immunity and therapeutic agents for the severe acute respiratory syndrome coronavirus 2. Heterogeneity in practice patterns and resources suggested the utility of optimizing protocols to improve patient outcomes. However, the lack of high-quality, randomized, controlled trial data on ECMO use in patients with COVID-19 limits the ability to develop evidence-based guidelines. Institutional experience plays a crucial role, with higher volume centers generally achieving better results, underscoring the necessity for ongoing data collection and analysis to continually refine ECMO practices.[25]

The pandemic also highlighted the critical role of interdisciplinary collaboration in managing complex ECMO cases. Integrating insights from various specialties, including critical care, infectious disease, hematology, cardiology, and surgery has been essential for optimizing patient care. Adaptive trial designs and Bayesian statistical methods have been suggested to better handle the uncertainties and integrate prior knowledge into study analyses, offering a more flexible approach to research in rapidly evolving situations like a pandemic.[28] These approaches could significantly enhance the ability to develop robust clinical guidelines and improve patient outcomes in future pandemics and other critical care scenarios.

Pathophysiology

The pathophysiology of ECMO-related coagulopathy involves complex interactions between the underlying injury and/or issue requiring cardiopulmonary support, associated multiorgan dysfunction (eg, shock, or liver or hepatic dysfunction), and the interface between the ECMO circuit and the patient's blood.[6] The interaction of blood with the nonendothelial surface of the ECMO circuit initiates contact activation, leading to thrombin generation, consumptive coagulopathy, and thromboinflammation.[29-31] In particular, VWF undergoes shear-induced changes, altering its activity and amplifying the effects of endothelial activation and damage.[3,32] Platelets also become activated because of mechanical injury from extracorporeal support, which may contribute to bleeding and/or thrombosis. Platelet activation, hemolysis, and thromboinflammation promote thrombotic and inflammatory responses. Systemic inflammatory responses contribute to coagulopathy and are associated with complement activation and neutrophil extracellular trap (NET) formation, contributing to a perturbed inflammatory milieu and poor outcomes including thrombotic and bleeding complications.[33]

Role of platelets, endothelium, and mechanical forces

Platelets, the endothelium, and mechanical forces are important in understanding ECMO-related bleeding and thrombosis. These components interact with the ECMO circuit, contributing to the complex hemostatic imbalances observed in patients, which are discussed hereafter.

Platelet dynamics

Platelets are a critical component of hemostasis. Centrifugal ECMO pumps, particularly at low flow rates used to support children on ECMO, increase shear stress that causes hemolysis, and alters VWF.[34,35] Shear stress leads to conformational changes in VWF, which can cause loss of high-molecular-weight (HMW) VWF multimers due to proteolysis by ADAMTS-13. This phenotype resembles that of acquired von Willebrand disease type 2A and prophylactic treatment with desmopressin of patients on ECMO to increase VWF release from endothelial cells has been used with some effect.[36] Often coinciding with the loss of HMW VWF is a reduction in the peripheral platelet count and platelet dysfunction. Interestingly, measured changes occur and resolve within hours of

ECMO onset and discontinuation, respectively.[37] ECMO-associated thrombocytopenia was shown to be related to proteolytic degradation of the platelet receptor for VWF glycoprotein-Ibα (GPIbα), and inhibiting this event could be a novel approach to reducing thrombocytopenia during ECMO. However, it is currently unclear how shear forces induce GPIbα shedding, because it occurs independently of VWF-GPIbα interaction, platelet activation, or coagulation.[38] In addition to platelet receptor shedding, a prior study demonstrated a reduced ability to activate GPIIb-IIIa in the blood from patients supported with ECMO, which could contribute to ECMO-induced coagulopathy. Platelet hypofunction is observed in almost all patients on ECMO.[39] In addition to the shedding of important surface receptors such as GPIbα and GPV, the observed changes include impaired aggregation response to various agonists and defective granule secretion.[40,41] Whether these functional changes contribute to clinical complications, such as bleeding, remains to be established. It is also not clear what causes these defects. Platelet hypofunction could be platelet "exhaustion" due to previous platelet stimulation, resulting from continuous exposure to abnormal flow conditions, exposure to heme, or abnormal coagulation activity and thrombin generation. Platelet changes may also be influenced by methods of procurement, processing, pathogen reduction, and storage.

Platelets are implicated in thrombotic complications associated with ECMO. The ECMO circuit is a procoagulant surface that triggers thrombin formation and coagulation. Platelets are activated by shear stress and thrombin, and they likely contribute to circuit thrombosis by binding to fibrin(ogen) and contracting the clot. Platelets can also serve as a procoagulant surface,[42] but this has not been investigated in the context of ECMO. Moreover, platelets are important drivers of immunothrombosis,[43] a complication frequently seen in patients on ECMO. However, very little information on platelet-leukocyte aggregate formation and platelet-dependent leukocyte activation in patients on ECMO is available.

Endothelial activation and injury

Multiple inflammatory mediators, including anaphylatoxins (C3a, C5a), thrombin, bradykinin, and cytokines (tumor necrosis factor α and interleukin-1β) are generated by the primary disease process and blood interfacing with the ECMO circuit, and these induce a complex response with profound impact on the endothelium.[6] The endothelial response is characterized by a biphasic activation pattern in which complement-driven endothelial activation results in transient P-selectin expression from Weibel-Palade bodies (early phase), and then cytokine-mediated endothelial activation leads to sustained upregulation of adhesion molecules (E-selectin) and chemokines, facilitating leukocyte adhesion and transmigration (late phase). Other patterns of insult demonstrated early after VA ECMO cannulation in adults include an increase in systemic inflammation (tumor necrosis factor α), endothelial injury (soluble thrombomodulin) or activation (soluble E-selectin, angiopoietin-2), glycocalyx shedding (syndecan-1), and platelet activation (sCD40L, soluble P-selectin).[44] Endothelial injury and apoptosis contribute to the systemic prothrombotic state, especially in patients with COVID-19 but also in other scenarios of acute injury, and these events increase the risk of thrombotic and/or bleeding complications. Mechanical stress from the ECMO circuit can also directly damage endothelial cells, further promoting thromboinflammation and coagulopathy.

Fibrinolysis in ECMO

Fibrinolysis is important in maintaining vascular patency by controlling hemostasis to limit clot formation and mediate clot resolution. Dysregulation may result in either bleeding or thrombosis. The fibrinolytic system is activated after ECMO initiation because of activation of FXII (contact activation).[45,46] In a recent study, higher levels of fibrinolytic activation occurred in patients who experienced hemorrhagic events, and plasma markers of fibrinolytic activity were increased before severe bleeding.[46] Other factors contributing to hyperfibrinolysis during ECMO include neutrophil elastase, which is elevated in the blood after ECMO.[47]

Impaired clot structure appears to be another contributor to hyperfibrinolytic bleeding in patients on ECMO. Activated FXIII cross-links fibrin monomers and links α_2-antiplasmin to fibrin, making the clot stronger and more resistant to lysis.[48] Acquired FXIII deficiency occurred in 69% of patients on ECMO and was independently associated with bleeding severity ($P = .03$).[49] Platelets contain most of the circulating plasminogen activator inhibitor 1, which they release when activated within the clot to protect it from premature lysis. Patients undergoing ECMO with anticoagulation may have the additional risk of impaired clot structure, because clots formed in the presence of various therapeutic anticoagulants are more susceptible to degradation by plasmin.[3]

Hypofibrinolysis may contribute to thrombotic complications. As observed in ECMO and COVID-19, it is possible to have an initially high level of activation or a sustained elevated level of D-dimer while exhibiting an overall hypofibrinolytic state. Hypofibrinolysis may result from a higher molar ratio of plasminogen activator inhibitor 1 to tissue plasminogen activator,[50] but the production of more resistant clots may also contribute. NETs, histones, and DNA also affect clot structure, slowing lysis.[51] NETs are present in patient blood and thrombi collected from the ECMO circuit.[52,53] Plasmin also has systemic effects that may contribute to a thrombotic phenotype, including thrombin generation, syndecan-1 cleavage, and matrix metalloproteinase activation, contributing to glycocalyx degradation and endothelial damage.[54] Additionally, plasmin influences acute inflammatory responses and is a potent C1 esterase activator.[55] The specific mechanisms underlying fibrinolytic dysfunction and the potential interactions with the inflammatory response, endothelium, or other systems during ECMO have not yet been well characterized. Additionally, the impact of the underlying disease process and other patient-specific factors requires further study.

Lysine analog antifibrinolytic agents have been used to treat ECMO-associated hyperfibrinolytic bleeding.[56-58] More recently, tranexamic acid has been used, with topical, IV, and intrabronchial routes of administration reported.[59,60] The use of catheter-directed thrombolysis in conjunction with ECMO for severe pulmonary embolism has been successful, whereas systemic thrombolysis with ECMO was associated with poor outcomes.[61] Currently, diagnostic and therapeutic options for managing fibrinolytic dysfunction during ECMO are limited.

Effects of artificial (nonendothelial) surfaces within the pump

The interaction between the ECMO circuit's blood and nonendothelial surfaces initiates the surface-dependent activation of

FXII and the contact pathway, contributing to consumptive coagulopathy.[62] Circuit components, such as connectors and branch circulatory networks, are a nidus for thrombus formation.[63-65] Research on modifying ECMO circuit surfaces to reduce their procoagulant activity, such as using biocompatible nitric oxide–releasing coatings, is ongoing to minimize protein adsorption and platelet adhesion to reduce clot formation within the circuit.[66] The primary focus is on the oxygenator, tubing, and connectors. Innovative approaches to mitigate these effects include adjusting the mechanical aspects of the circuit tubing, pump, and other agents are under investigation.[67,68]

Anticoagulation in ECMO

Effective anticoagulation strategies are a critical component of ECMO therapy because of the need to maintain circuit patency and prevent thrombotic complications; however, anticoagulation is especially challenging given the need to also avoid bleeding.[13,69]

UFH

UFH is the mainstay anticoagulant in ECMO because of its titratability, short half-life, ability to inhibit thrombin and FXa, and ability to be used with renal dysfunction.[14,69-71] Monitoring UFH includes anti-FXa/heparin levels, aPTT, or often both.[13,16,69] UFH is titrated to balance the risk of thrombosis against bleeding. Disadvantages of UFH include the need for antithrombin as a cofactor, the potential for heparin resistance, and the potential of HIT, necessitating alternative anticoagulants that include DTIs. Finally, the supply chain for producing the world's supply of UFH requires more than a billion pigs each year; the tremendous amount of greenhouse gases released because of this process has led to calls for the development of environmentally sustainable anticoagulants to help combat the climate crisis and limit its negative effects on global health.[72]

Coagulation monitoring

Anticoagulation management requires monitoring the anticoagulant effects.[16,69] In addition to aPTT and anti-FXa levels, activated clotting time is also less commonly used. Other tests of hemostatic function include platelet counts. In patients with bleeding, viscoelastic testing is frequently used to examine whole blood coagulation function in patients on ECMO and guide potential therapies. Hemolysis and the membrane lung pressure gradient are evaluated as part of this monitoring. The choice of monitoring tools and testing frequency can significantly affect patient outcomes, necessitating a tailored approach based on individual patient needs and institutional protocols.

Management of bleeding and thrombotic complications

Bleeding and thrombotic complications are prevalent among patients on ECMO, especially because they are critically ill, often have multiorgan dysfunction/injury, and have impaired responses to normal hemostatic function.[1] When patients bleed, UFH is frequently paused, or additional therapies are considered, including desmopressin, VWF repletion, and fibrinogen repletion, often as cryoprecipitate or factor concentrates to restore hemostatic balance.[17] Platelet transfusions may be given in patients with thrombocytopenia.[17,73,74] Thrombotic complications, including circuit clotting, deep vein thrombosis, and ischemic stroke, necessitate careful adjustments in anticoagulation therapy. Patients who will need surgical procedures while on ECMO, patients with polytrauma, and infants and children present additional challenges.[74-76] Balancing the selection of anticoagulants and dosing strategies is essential to prevent thrombosis without exacerbating bleeding risks. DTIs and FXa inhibitors are used in specific clinical scenarios to effectively manage thrombosis. Integrating these strategies is vital to optimizing patient outcomes in the ECMO setting. Unfortunately, very little controlled or comparative data suggest the superiority of specific approaches. Retrospective data suggest that, under some circumstances, the incidence of circuitry and patient thrombosis is comparable for patients whether they received continuous systemic anticoagulation or remain anticoagulant free while on ECMO.[77]

Clinical and research challenges

Challenges in ECMO management include the lack of standardized protocols and definitions for anticoagulation, bleeding, and thrombotic events, which complicate data interpretation and, potentially, best practices.[78] Additionally, the limited high-quality data and the scarcity of randomized controlled trials in patients on ECMO hinder the development of robust clinical guidelines because most of the current data are based on retrospective observational analysis, especially for anticoagulation. Prospective studies commonly examine the pharmacodynamics and pharmacokinetics of different anticoagulants for ECMO. One of the problems in developing clinical trials randomizing patients on ECMO is the heterogeneity of the many underlying disease processes that necessitate ECMO support, which is a major influence in determining meaningful outcomes.

A previous National Heart, Lung, and Blood Institute and US Department of Defense meeting developed consensus recommendations for primary outcomes in mechanical circulatory support, including ECMO.[18] The report recommended a primary ECMO outcome using a 5-point ordinal bleeding and thrombosis severity score adapted from the Common Terminology Criteria for Adverse Events, version 5.0. The authors suggested that their composite risk scores would be important for affecting clinical trial design and further facilitating investigation comparability. The report also suggested that disseminating management and global consensus definitions guidelines could reduce the heterogeneity of patients and help standardize primary outcomes for future ECMO research. Further work was undertaken to define a core outcome set for ECMO,[79,80] and, more recently, the ECMO-CENTRAL (ECMO Core Elements Needed for Clinical Trials, Regulatory Processes, and Quality of Life) academic research consortium leveraged an international panel of 165 stakeholders to define adverse events associated with ECMO.[19,21]

Challenges in biomarker identification

Identifying reliable biomarkers for ECMO-related coagulopathy is complex because of the multifactorial nature of the condition and the diverse patient populations involved. Several factors influence patient blood parameters, including age, nutrition, hereditary factors, and underlying pathologies such as sepsis and oncologic diseases. The use of anticoagulants and blood products further complicates biomarker interpretation. Sampling variability, including the timing and location of sample collection, can also affect baseline and the affect assessments of ECMO, making the

interpretation of these biomarkers challenging. Standard biomarkers such as D-dimer, which indicate both clot burden and bleeding, are often nonspecific, complicating the distinction between thrombotic and bleeding events.[81] Device-related biomarkers also present significant challenges. Biomarkers specific to ECMO circuit components, such as fibrin and platelet deposition, polymorphonuclear leukocytes, NETs, and VWF, must be accurately measured and interpreted.[53,82-84] Spatial analysis (3 dimensional) of these biomarkers is crucial to understanding their distribution and impact on the ECMO circuit, yet this area remains underdeveloped.[85,86] These biomarkers' accurate measurement and spatial analysis are critical for enhancing device design to reduce or create nonclotting surfaces. Compounding this is a lack of large "natural history" characterization cohorts. Indeed, the current data and total numbers of patients on whom sampling and assay have been performed are very small and largely heterogeneous, preventing an adequate view of the thromboinflammatory milieu of ECMO. Although problematic, this represents one of the best opportunities for advancement in this field.

To effectively integrate biomarkers into clinical practice, it is essential to prioritize which biomarkers and mechanistic markers to study, particularly in the context of limited sample volumes from pediatric patients.[84] Advanced multiomics approaches or targeted analyses are needed to effectively use these small sample volumes. This prioritization ensures that the most informative and clinically relevant biomarkers are identified and validated, thereby improving the management and outcomes of patients on ECMO.

Biomarkers

Standard coagulation tests used to monitor coagulation status and guide anticoagulation have limitations, and improved analytical tools are needed for more accurate and timely data. Identifying and validating biomarkers for ECMO-related coagulopathy may improve the diagnosis, monitoring, and management of coagulopathic complications in patients on ECMO.[87] Biomarkers may provide insights into the underlying mechanisms of coagulopathy, guide anticoagulation therapy, and predict patient outcomes. Biomarkers should be considered for future clinical studies, and device-related biomarkers should be included to examine coagulopathic complications associated with ECMO circuits. Changes in platelet counts may indicate platelet adhesion and aggregation on circuit components.[88] Platelet activation can be assessed by evaluating integrin activation and α-granule secretion, which are influenced by ECMO surface interactions. Flow-based models that incorporate surface characteristics, such as microfluidics, are critical to studying platelet function above and beyond standard ex vivo platelet function assays.[63,89] Polymorphonuclear leukocytes indicate inflammatory responses and their role in thrombosis, whereas NETs may serve as a biomarker contributing to thrombosis and inflammation, highlighting their role in circuit clotting.[90] Changes in VWF levels with a reduction in HMW-VWF reflect increased shear rates and potentially circuit thrombosis. Thrombin generation assays would provide biomarker evaluation for thrombotic risks and bleeding management, in addition to D-dimer levels, which are important for fibrinolysis and potential clot formation.[91]

Biomarkers such as antithrombin, syndecans, and DNA markers are being explored for their potential to gauge endothelial health and predict coagulopathic complications.[45,92] Studies of endothelial injury, platelet dysfunction, and systemic inflammation in ECMO-related coagulopathy are ongoing.[78,93] Extracellular vesicles, predominantly derived from platelets and endothelial cells under high shear-stress conditions, can also be biomarkers of coagulation and inflammatory pathways.[94] However, their interpretation is complicated by their diverse origins and the lack of standardized measurement techniques. Moreover, accurately measuring these biomarkers and understanding their spatial distribution within the circuit remains challenging.

Novel anticoagulation strategies

Preclinical studies and clinical trials evaluating additional anticoagulants are in progress. These include studies evaluating the efficacy of FXI/FXIa inhibitors and FXII/FXIIa inhibitors, each of which has shown promise in reducing bleeding risks while preventing thrombosis for thromboembolic prophylaxis.[95-99] These novel agents aim to reduce the overall coagulopathic burden without increasing the risk of severe bleeding.[71,100] In particular, inhibiting FIX, FXI, or FXII may decrease or eliminate coagulation activation stemming from blood exposure to nonendothelial ECMO circuit surfaces.[101] This attenuation may reduce the need for potent anticoagulants such as UFH, although tissue factor–mediated coagulopathy in ECMO due to inflammation and innate immune system activation may still necessitate some level of conventional anticoagulation in addition to inhibiting contact activation. Therefore additional anticoagulant strategies that more effectively limit thrombin generation, coagulation factor consumption, and associated inflammation are also being explored. These include the development of potent, rapid-onset, yet rapidly reversible inhibitors of FX/FXa as well as combinations of such inhibitors.[102-104]

Preclinical animal models

Preclinical animal studies are pivotal in ECMO research, providing critical insights into the mechanisms of ECMO-related coagulopathy and evaluating the safety and efficacy of novel therapies before clinical application. Studies have used various animal models, each chosen for its specific advantages. Collectively, these studies are beginning to bridge the gap between basic research and clinical practice and ensure that new treatments and strategies will be both practical and safe for patients.

Current state of animal models

Animal models in ECMO research vary in size and type, addressing different research needs. Small animals, such as rats and rabbits, are commonly used for basic mechanistic studies because of their ease of handling, cost-effectiveness, and ability to provide detailed insights into fundamental biological processes.[105-107] Although primarily aimed at evaluating the benefit of ECMO for the underlying disease, these models have great potential for exploration of the fundamental biological mechanisms underlying ECMO-related coagulopathy, such as thromboinflammation and the activation of specific coagulation pathways. Although some limitations exist, including interspecies differences in systems such as complement and potentially platelet function, these models are suitable for exploitation to study thromboinflammation. In contrast, large animal models, mainly pigs and sheep, are used to achieve clinically relevant outcomes.[66,108-110] A nonhuman primate model of platelet deposition and fibrin formation within an extracorporeal membrane oxygenator has been used for preclinical studies of contact

Table 1. Strategic future directions

	Patient	Circuit and components	Anticoagulation	Monitoring
Preclinical roadmap	• Develop better ECMO animal models reflecting risks of bleeding and clotting, integrating patient data for accuracy. • Use technologies such as CRISPR to develop large animal models that are more human-like. • Create a translational roadmap for developing novel therapies that includes timing and integration with clinical studies, uses clinical trial tools, and ensures continuous improvement through data integration.	• Support the development of ECMO circuit component technology to reduce clinical burdens and improve patient care.	• Develop animal models of the hemostatic changes from prenatal, perinatal and infancy, as well as during other physiological changes, for example, pregnancy and older age. • Identify mechanisms underlying fibrinolytic dysfunction and factors contributing to hemorrhagic and thrombotic complications.	• Understand the role of DNA and nucleic acid–containing damage-associated molecular patterns in triggering immune responses and its complex interaction in ECMO-induced inflammation. • Understand the mechanisms of fibrinolytic (enzymatic) balance and clot structure in determining overall fibrinolytic dysfunction.
Technology		• Develop optimized circuits using flow dynamics principles, which reduce sheer stress, platelet and coagulation activation, absorb identified activators, use biofilm coatings, and incorporate smart circuit capabilities.		• Develop noninvasive sampling techniques to address concerns with obtaining postmortem samples. • Create tools to monitor the anticoagulation/clotting state, including detection/imaging tools, circulating probes, and assessment of circuit deposits. • Develop diagnostics to mitigate or prevent fibrinolytic dysfunction during ECMO.
Clinical definitions and protocols	• Develop and implement standardized definitions for bleeding and thrombotic events.	• Define and support technical standards for electronic data exchange of machine-interpretable data expressing ECMO-related data, for example, fast health care interoperability standards.	• Establish and implement clinical decision support tools for managing ECMO-related coagulation and coagulopathy.	
Patients and populations	• Focus on specific research needs of pediatric populations, developing ECMO technology and procedures that cater to their unique requirements. • Identify at-risk patient populations for developing hemorrhagic or thrombotic phenotypes related to fibrinolytic dysfunction.	• Support the development of ECMO circuit component technology to improve patient outcomes, especially in small children for whom devices optimized for low-flow states are lacking.		
Pathophysiology	• Develop advanced monitoring techniques using omics technologies to subphenotype patients on ECMO to better tailor therapeutic approaches. • Integrate precision medicine approaches through clinical practice and research to develop targeted therapies, ensuring treatments are optimized for specific patient populations.		• Identify a preclinical roadmap with reference to impact on coagulation requirements. • Use multiomics approaches to identify and validate biomarkers for better diagnosis, monitoring, and management of ECMO-related coagulopathies and thromboinflammation.	• Develop tools for rapid biomarker assessment to enable timely and tailored therapeutic interventions, facilitating precision medicine. • Improved understanding of coagulation factors, endothelial markers, and developing methods to identify platelet function changes. • Address thrombocytopenia, immune signaling pathways, and platelet adhesion issues observed in models.
Pharmacologic therapies	• Develop robust models to inform bleeding or clotting risk to risk stratify patient populations in which anticoagulation-free or low-dose anticoagulation for ECMO can be applied.		• Explore the development and clinical application of novel anticoagulants that target specific proteases within the coagulation pathways. • Explore the development and clinical translation of anticoagulation approaches that more effectively reduce thrombin generation, coagulation factor consumption, and thromboinflammation. • Investigate the use of combination anticoagulation therapies, drawing parallels with strategies used in cancer therapies and HIV to optimize patient outcomes. • Develop novel anticoagulants that reduce carbon cost compared with UFH to limit contribution to global warming/climate change.	• Develop diagnostics and drugs or other therapies to mitigate or prevent fibrinolytic dysfunction during ECMO.

Table 1 (continued)

	Patient	Circuit and components	Anticoagulation	Monitoring
Collaboration and clinical trial design	• Foster collaborative interdisciplinary networks to support ECMO research and data sharing, and establish centralized networks and resource centers such as a common animal blood bank and biorepository. • Encourage interprofessional partnerships, including critical care, cardiology, hematology, and bioengineering, to effectively address complex challenges of ECMO treatment. • Define and support technical standards for electronic data exchange of machine-interpretable data expressing ECMO-related scientific knowledge, for example, fast health care interoperability standards. • Implement adaptive clinical trial designs that can respond to evolving clinical scenarios and emerging data, enhancing the flexibility and efficiency of research efforts; lessons can be learnt from the approaches used during the COVID-19 pandemic to develop robust research strategies for ECMO and other critical care scenarios. • Consider innovative clinical trial designs including implementation strategies to reduce the time between evidence generation and adoption of best practices into clinical care.			

pathway inhibitors.[95] These models are thought to reasonably closely mimic human physiological responses, making them ideal for evaluating ECMO's impact on coagulation, survival metrics, histological changes, and organ damage and repair biomarkers.[111] However, a significant limitation in using large animals is the restricted availability of blood resources to support the animals during ECMO experiments, because there are no established blood banks for these animals, complicating long-term and high-volume studies.

Challenges and gaps

One of the primary challenges in using animal models for ECMO research is accurately replicating human hemostasis, coagulopathies, and responses to ECMO. Although providing valuable mechanistic insights, small animal models often lack the physiological complexity seen in humans. Large animal models offer closer physiological parallels but face practical issues such as limited availability of blood products and resources. Additionally, the need for sophisticated and long-term monitoring systems to assess the chronic impacts of ECMO on coagulation remains a significant hurdle. The variability in how different animal species respond to ECMO complicates the translation of findings to human clinical practice. Researchers must carefully consider these differences and continuously refine their models to ensure they provide meaningful and translatable insights. Integrating multiple studies, including in vivo, in vitro, and computational approaches is essential to comprehensively understand ECMO-related coagulopathy.

Adult special populations

Against this background of complexity of basic and translational science complexity, ECMO is clinically deployed only when patients are perceived to be at risk of mortality without invasive support, so the entire ECMO population is a vulnerable group. However, several special populations should be considered as priorities for clinical and research advances. For example, gravid and early postpartum patients pose specific anatomic changes, increased cardiovascular demands, and significant potential for hemorrhagic and thrombotic complications, all complicated further when ECMO is considered a lifesaving therapy. Patients with hematologic disorders and oncologic diagnoses present unique challenges because of factors such as cytopenia and hypercoagulability,[112] and patients supported on ECMO after traumatic or burn injury may benefit from particular attention.[113] Those patients who receive extracorporeal cardiopulmonary resuscitation may present an additional population at risk of organ injury complication, ECMO-associated coagulopathy, and be at higher risk of neurologic consequences during ECMO support.

Neonatal and pediatric population

Pediatric and neonatal patients account for 40% of ECMO runs (https://www.elso.org/registry/internationalsummaryandreports/internationalsummary.aspx), making this group by far the largest special population. Children supported with ECMO continue to experience higher rates of adverse events associated with ECMO than equivalently supported adults.[1,19] This is likely multifactorial, including the challenges of miniaturization of the technology, availability of devices for optimal cannulation strategy, the heterogeneous populations supported, and the small numbers of patients supported with ECMO at any individual center.[1,34,35,114] Neonates and infants also have age-related changes in the coagulome, requiring nuanced and tailored approaches to anticoagulation.[75,115,116] There have been many initiatives to organize pediatric ECMO stakeholders through a collaborative research network, PediECMO, an organization between the Pediatric Acute Lung Injury and Sepsis Investigators and ELSO, and in association with other professional organizations and research groups. The Pediatric ECMO Anticoagulation Collaborative consensus conference brought together international stakeholders to assess available evidence and derive mainly expert consensus-based guidance for the clinical management of pediatric ECMO, including an algorithm for dosing and monitoring of UFH.[13] Recognizing the lack of evidence to inform practice, 20 Pediatric ECMO Anticoagulation Collaborative clinical research priorities were developed and prioritized.[78] Consensus adverse events for pediatric ECMO have been defined according to the ECMO-CENTRAL academic research consortium process for use in clinical trials and regulatory evaluation of ECMO device components.[19,21] The pediatric ECMO community is coming together for important studies of neurodevelopmental outcome after ECMO (ClinicalTrials.gov identifier: NCT05388708), to identify biomarkers of brain injury on ECMO (ClinicalTrials.gov identifier: NCT05041712), as well as clinical trials addressing blood product transfusion practices (ClinicalTrials.gov identifier: NCT05405426), optimal platelet thresholds on ECMO (ClinicalTrials.gov identifier: NCT05796557), and the use of hydrogen gas to reduce neurologic injury after extracorporeal cardiopulmonary resuscitation (ClinicalTrials.gov identifier: NCT05574296).[117]

Current and ongoing challenges

The complexity of ECMO-related coagulopathy presents several clinical and research challenges. Clinically, managing the hemostatic imbalances caused by these factors requires precise

Table 2. Key opportunities and future directions

Standardization and protocol development
Standardized definitions: develop and implement standardized definitions for bleeding and thrombotic events to improve consistency across institutions and enhance data interpretation.
Clinical protocols: establish and implement clinical decision support tools for managing ECMO-related coagulopathy, ensuring best practices are integrated and widely adopted.
Ethical and logistical considerations
Tailored research: focus on specific research needs of pediatric populations, developing ECMO technology and procedures that cater to their unique requirements.
Noninvasive sampling techniques: develop noninvasive sampling techniques or alternative methods to address ethical concerns and logistical challenges associated with obtaining postmortem samples.
VV vs VA ECMO: identify commonalities and differences between VV and VA ECMO to understand the impact on coagulation and treatment needs.
Collaboration and data sharing
Centralized networks: to support ECMO research and data sharing, foster interdisciplinary collaborations, and establish centralized networks and resource centers, such as a common animal blood bank and a biorepository.
Collaborative efforts: encourage interprofessional partnerships, including critical care, cardiology, hematology, and bioengineering, to tackle the complex challenges of ECMO treatment effectively.
Toward learning health care systems: define and support technical standards for electronic data exchange of machine-interpretable data expressing ECMO-related scientific knowledge, for example, fast health care interoperability standards.
Adaptive clinical trials and flexible research approaches
Adaptive trial designs: implement adaptive clinical trial designs that can respond to evolving clinical scenarios and emerging data, enhancing the flexibility and efficiency of research efforts.
COVID-19 lessons: apply lessons from the adaptive trial approaches used during the COVID-19 pandemic to develop robust research strategies for ECMO and other critical care scenarios.
Innovative trial design for implementation: consider clinical trial designs to include implementation strategies to reduce the time between evidence generation and adoption of best practices into clinical care.
Focused research on patient population heterogeneity
Subphenotyping: develop advanced monitoring techniques using omics technologies to subphenotype patients on ECMO, enhancing understanding diverse patient groups and tailoring therapeutic approaches accordingly.
Precision medicine: integrate precise patient data into clinical practice and research to develop targeted therapies, ensuring treatments are optimized for specific patient populations.
Enhanced biomarker research and validation
Reverse translation: use multiomics approaches (genomics, proteomics, etc) to identify and validate biomarkers for better diagnosis, monitoring, and management of ECMO-related coagulopathies and thromboinflammation.
Rapid assessment tools: develop tools for rapid biomarker assessment to enable timely and tailored therapeutic interventions, facilitating precision medicine.
Understanding ECMO-induced coagulopathies: focus on coagulation factors, endothelial markers, and developing methods to manage platelet function changes.
Innovative anticoagulation strategies
Novel anticoagulants: explore the development and clinical application of novel anticoagulants that target specific proteases within the coagulation pathways (eg, FIX, FXI, and FXII inhibitors) to minimize bleeding risks while effectively preventing thrombosis. Explore the development and clinical translation of anticoagulant approaches that more effectively reduce thrombin generation, coagulation factor consumption, and associated thromboinflammation. Develop novel anticoagulants that can support ECMO at significantly reduced carbon cost compared with UFH to limit climate change and combat its negative impact on planetary health.
Combination therapies: investigate the efficacy of combinatory anticoagulation therapies, drawing parallels with strategies used in HIV and cancer treatments to optimize patient outcomes.
Risk stratification directed therapy: develop robust models to inform individual bleeding or clotting risk to identify patient populations in whom anticoagulation-free, or low-dose anticoagulation for ECMO can safely be applied.
Targets for coagulopathy and platelet dynamics
Platelet dynamics: address thrombocytopenia, immune signaling pathways, and platelet adhesion issues observed in models.
DNA and immune response: understand the role of DNA and nucleic acid–containing damage-associated molecular patterns in triggering immune responses and its complex interaction in ECMO-induced inflammation.
Technological innovations in ECMO
Integrated circuits and smart technologies: develop circuits optimized using flow dynamics principles, which reduce sheer stress, platelet and coagulation activation, absorb identified activators, use biofilm coatings, and incorporate smart circuit capabilities.
Monitoring systems: create tools to monitor the anticoagulation/clotting state, including detection/imaging tools, circulating probes, and assessment of circuit deposits.
Engineering advancements: support the development of ECMO circuit component technology to reduce clinical burdens and improve patient care, especially in small children for whom devices optimized for low-flow states are lacking.
Advancement in animal model development
Representative animal models: develop better ECMO animal models reflecting risks of bleeding and clotting, integrating patient data for accuracy.
Developmental hemostasis models: develop animal models of the hemostatic changes from prenatal, perinatal and infancy, as well as during other physiological changes, for example, pregnancy and older age.
Preclinical roadmap: create a translational roadmap for developing novel therapies that includes timing and integration with clinical studies, uses clinical trial tools, and ensures continuous improvement through data integration.
Gene-editing technologies: use technologies such as CRISPR to develop large animal models that are more human-like.

Table 2 (continued)

Fibrinolytic dysfunction
Understand mechanisms: conduct research to identify mechanisms underlying fibrinolytic dysfunction and factors contributing to hemorrhagic and thrombotic complications.
Enzymatic function vs clot structure: understand the relative roles of fibrinolytic (enzymatic) balance and clot structure in determining overall fibrinolytic function.
At-risk patient populations: identify patient populations at risk for developing hemorrhagic or thrombotic phenotypes related to fibrinolytic dysfunction.
Diagnostics and therapeutics: develop diagnostics and drugs or other therapies to mitigate or prevent fibrinolytic dysfunction during ECMO.

monitoring and tailored therapeutic interventions complicated by the variability in patient responses. Elucidating the underlying mechanisms by which these forces induce coagulopathy will require sophisticated in vitro and in vivo models that accurately replicate human physiology across the lifespan. Preclinical animal models replicating the age-related differences in the neonatal and infant coagulant require significant resources and support.[100] Developing biocompatible ECMO circuit materials and advanced monitoring technologies remain a critical gap. Finally, the heterogeneity of the patient population treated with ECMO presents challenges to clinical trial design that requires use of novel and sophisticated trials that account for heterogeneity of treatment effect and use tools such as adaptive design to tackle this complex problem.[118] Ultimately, advancing translational and clinical knowledge necessitates a multidisciplinary research approach with insights from hematology, critical care medicine, cardiology physicians, and translational scientists with expertise in cell biology, pharmacology, bioengineering, and other disciplines, as shown in Table 1.

Conclusions

The workshop on ECMO-related coagulopathy convened, leading experts to address the multifaceted challenges of managing coagulation disorders in patients on ECMO. Discussions highlighted the critical need for standardized definitions and protocols, the development of advanced monitoring and diagnostic tools, and the exploration of novel anticoagulation strategies. Emphasis was placed on using "omics" technologies to identify and validate biomarkers, improving animal models to support novel therapeutic and device development, and fostering interdisciplinary collaboration. The workshop underscored the importance of adaptive clinical trials and innovative engineering approaches to enhance ECMO therapy for patients of all ages. Key opportunities and future directions were identified to drive research and improve clinical outcomes, ensuring that advancements in ECMO technology and protocols are informed by robust scientific evidence tailored to diverse patient populations. Table 2 lists key opportunities and future directions for consideration.

Acknowledgments

The authors thank the workshop co-chairs (Crystal Hill-Pryor and Deborah Philp, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute) and National Institutes of Health workshop organizer Julie Panepinto for development and sponsorship of the meeting and Alexandra Tarabolettim for workshop support.

Authorship

Contribution: K.M. is the editor-in-chief of *Blood Vessels, Thrombosis, & Hemostasis*, and as an author of this article, was recused by journal policy from any involvement in its peer review and had no access to information regarding its peer review process; J.H.L. wrote the first draft, and then, with P.M.A.A., further edited it, which was circulated to all the authors for comments and additional reference support; P.M.A.A. further completed the reference additions; and the manuscript was once more circulated among all authors, who participated in additional editing and reviewing of the manuscript.

Conflict-of-interest disclosure: J.H.L. served on steering committees for Bayer, Grifols, Octapharma, Takeda, and Werfen. P.M.A.A. reports funding to her institution from the US Department of Defense, the National Institutes of Health, and the US Food and Drug Administration, and is the treasurer for Extracorporeal Life Support Organization. A.S.W. reports research funding from the National Institutes of Health, Takeda, and 501 Ventures; consulted for 501 Ventures; and served on advisory boards for Takeda and Bayer. O.J.T.M. reports research funding from the National Institutes of Health. A.E.P. has served on an advisory board for Octapharma. M.J.C. reports research funding from the National Institutes of Health, the US Department of Defense, Biomedical Advanced Research and Development Authority, and Defense Advanced Research Projects Agency. W.B. reports research funding from the National Institutes of Health, and served on the scientific advisory board for Haima Therapeutics. M.J.C. served on the scientific advisory board and consulted for Abbott, Anthos, Bristol Myers Squibb, Pfizer, Roche, Sanofi, and Werfen. J.M.C. served on the scientific advisory board and consulted for Abbott, Anthos, Bristol Myers Squibb, Perosphere, Pfizer, Roche, Sanofi, and Werfen. J.H.M. reports research funding from the National Institutes of Health and Kerafast; and served on the scientific advisory board for Cayuga Biotech. M.D.N. serves as chief medical officer of Haima Therapeutics; reports research funding from the National Institutes of Health, the US Department of Defense, Defense Advanced Research Projects Agency, Instrumentation Laboratories, Haemonetics, and Alexion; and has served on advisory boards for Takeda, Octapharma, Haemonetics, and Cellphire. B.A.S. reports research funding from the National Institutes of Health and the US Department of Defense; and served on the scientific advisory board and consulted for Eli Lilly, SomaLogic, Basking Biosciences, Rznomics, and AZURNA Therapeutics. The remaining authors declare no competing financial interests.

ORCID profiles: J.H.L., 0000-0003-3766-4962; P.M.A.A., 0000-0003-4837-7598; A.S.W., 0000-0002-2845-2303; O.J.T.M., 0000-0001-9481-0124; A.E.P., 0000-0002-9660-3919; R.R.B., 0000-0003-4362-3462; W.B., 0000-0002-1211-8861; M.J.C., 0000-0003-1402-5869; J.M.C., 0000-0001-6445-582X; J.H.M., 0000-0002-1570-1569; M.D.N., 0000-0001-8931-6236; E.T.T., 0000-0003-3459-2772; K.M., 0000-0001-7340-475X; B.A.S., 0000-0002-5113-5541.

Correspondence: Jerrold H. Levy, Duke University Medical Center, 2301 Erwin Rd, 5691H HAFS, Box 3094, Durham, NC 27710; email: jerrold.levy@duke.edu.

References

1. Tonna JE, Boonstra PS, MacLaren G, et al. Extracorporeal life support organization registry international report 2022: 100,000 survivors. *ASAIO J*. 2024;70(2):131-143.
2. Bartlett RH. The story of ECMO. *Anesthesiology*. 2024;140(3):578-584.
3. Frantzeskaki F, Konstantonis D, Rizos M, et al. Extracorporeal membrane oxygenation (ECMO)-associated coagulopathy in adults. *Diagnostics*. 2023;13(23):3496.
4. Nunez JI, Gosling AF, O'Gara B, et al. Bleeding and thrombotic events in adults supported with venovenous extracorporeal membrane oxygenation: an ELSO registry analysis. *Intensive Care Med*. 2022;48(2):213-224.
5. Kohs TCL, Weeder BR, Chobrutskiy BI, et al. Predictors of thrombosis during VV ECMO: an analysis of 9809 patients from the ELSO registry. *J Thromb Thrombolysis*. 2024;57(3):345-351.
6. Millar JE, Fanning JP, McDonald CI, McAuley DF, Fraser JF. The inflammatory response to extracorporeal membrane oxygenation (ECMO): a review of the pathophysiology. *Crit Care*. 2016;20(1):387.
7. Hatami S, Hefler J, Freed DH. Inflammation and oxidative stress in the context of extracorporeal cardiac and pulmonary support. *Front Immunol*. 2022;13:831930.
8. Dalton HJ, Reeder R, Garcia-Filion P, et al. Factors associated with bleeding and thrombosis in children receiving extracorporeal membrane oxygenation. *Am J Respir Crit Care Med*. 2017;196(6):762-771.
9. O'Halloran CP, Andren KG, Mecklosky J, et al. Mortality and factors associated with hemorrhage during pediatric extracorporeal membrane oxygenation. *Pediatr Crit Care Med*. 2020;21(1):75-81.
10. Masi P, Gendreau S, Moyon Q, et al. Bleeding complications, coagulation disorders, and their management in acute myocardial infarction-related cardiogenic shock rescued by veno-arterial ECMO: a retrospective cohort study. *J Crit Care*. 2024;82:154771.
11. Helms J, Frere C, Thiele T, et al. Anticoagulation in adult patients supported with extracorporeal membrane oxygenation: guidance from the Scientific and Standardization Committees on Perioperative and Critical Care Haemostasis and Thrombosis of the International Society on Thrombosis and Haemostasis. *J Thromb Haemostasis*. 2023;21(2):373-396.
12. McMichael ABV, Ryerson LM, Ratano D, Fan E, Faraoni D, Annich GM. ELSO adult and pediatric anticoagulation guidelines. *ASAIO J*. 2022;68(3):303-310.
13. Alexander PMA, Bembea MM, Cashen K, et al. Executive summary: the Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE (PEACE) Consensus Conference. *Pediatr Crit Care Med*. 2024;25(7):643-675.
14. Cashen K, Saini A, Brandao LR, et al. Anticoagulant medications: the Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE Consensus Conference. *Pediatr Crit Care Med*. 2024;25(7 suppl 1):e7-e13.
15. Nellis ME, An A, Mahmood H, Prishtina F, Hena Z, Karam O. Epidemiology of anticoagulation for children supported by extracorporeal membrane oxygenation in the United States: a pediatric hospital information system database study. *Perfusion*. Apr 2024;39(3):536-542.
16. Ozment C, Alexander PMA, Chandler W, et al. Anticoagulation monitoring and targets: the Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE Consensus Conference. *Pediatr Crit Care Med*. Jul 1 2024;25(7 Suppl 1):e14-e24.
17. Rintoul NE, McMichael ABV, Bembea MM, et al. Management of bleeding and thrombotic complications during pediatric extracorporeal membrane oxygenation: the Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE Consensus Conference. *Pediatr Crit Care Med*. 2024;25(7 suppl 1):e66-e77.
18. Levy JH, Faraoni D, Almond CS, et al. Consensus statement: hemostasis trial outcomes in cardiac surgery and mechanical support. *Ann Thorac Surg*. 2022;113(3):1026-1035.
19. Alexander PMA, Habet V, Barbaro RP. Realizing potential: pediatric extracorporeal membrane oxygenation needs common adverse event definitions to improve outcomes. *Pediatr Crit Care Med*. 2023;24(6):528-530.
20. Nellis ME, Tucci M, Lacroix J, et al. Bleeding assessment scale in critically ill children (BASIC): physician-driven diagnostic criteria for bleeding severity. *Crit Care Med*. 2019;47(12):1766-1772.
21. Alexander PMA, Di Nardo M, Combes A, et al. Definitions of adverse events associated with extracorporeal membrane oxygenation in children: results of an international Delphi process from the ECMO-CENTRAL ARC. *Lancet Child Adolesc Health*. 2024;8(10):773-780.
22. Martucci G, Giani M, Schmidt M, et al. Anticoagulation and bleeding during veno-venous extracorporeal membrane oxygenation: insights from the PROTECMO study. *Am J Respir Crit Care Med*. 2024;209(4):417-426.
23. Meuwese CL, Levy JH. Optimizing anticoagulation for venovenous extracorporeal membrane oxygenation: finding the right balance. *Am J Respir Crit Care Med*. 2024;209(4):353-354.
24. Barbaro RP, MacLaren G, Boonstra PS, et al. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. *Lancet*. 2020;396(10257):1071-1078.
25. Barbaro RP, MacLaren G, Boonstra PS, et al. Extracorporeal membrane oxygenation for COVID-19: evolving outcomes from the International Extracorporeal Life Support Organization registry. *Lancet*. 2021;398(10307):1230-1238.

26. Iba T, Levy JH, Maier CL, Connors JM, Levi M. Four years into the pandemic, managing COVID-19 patients with acute coagulopathy: what have we learned? *J Thromb Haemostasis*. 2024;22(6):1541-1549.
27. Feth M, Weaver N, Fanning RB, et al. Hemorrhage and thrombosis in COVID-19-patients supported with extracorporeal membrane oxygenation: an international study based on the COVID-19 critical care consortium. *J Intensive Care*. 2024;12(1):18.
28. Neal MD, Lawler PR, Zarychanski R. Emerging clinical trial designs may accelerate translation in hematology: lessons from COVID-19. *Blood Adv*. 2022;6(16):4710-4714.
29. Ekdahl KN, Teramura Y, Asif S, Jonsson N, Magnusson PU, Nilsson B. Thromboinflammation in therapeutic medicine. *Adv Exp Med Biol*. 2015;865: 3-17.
30. Doyle AJ, Hunt BJ. Current understanding of how extracorporeal membrane oxygenators activate haemostasis and other blood components. *Front Med*. 2018;5:352.
31. Goel A, Tathireddy H, Wang SH, et al. Targeting the contact pathway of coagulation for the prevention and management of medical device-associated thrombosis. *Semin Thromb Hemost*. 2024;50(7):989-997.
32. Schlagenhauf A, Kalbhenn J, Geisen U, Beyersdorf F, Zieger B. Acquired von Willebrand syndrome and platelet function defects during extracorporeal life support (mechanical circulatory support). *Hämostaseologie*. 2020;40(2):221-225.
33. Stark K, Massberg S. Interplay between inflammation and thrombosis in cardiovascular pathology. *Nat Rev Cardiol*. 2021;18(9):666-682.
34. Gross-Hardt S, Hesselmann F, Arens J, et al. Low-flow assessment of current ECMO/ECCO$_2$R rotary blood pumps and the potential effect on hemocompatibility. *Crit Care*. 2019;23(1):348.
35. Ki KK, Passmore MR, Chan CHH, et al. Low flow rate alters haemostatic parameters in an ex-vivo extracorporeal membrane oxygenation circuit. *Intensive Care Med Exp*. Aug 20 2019;7(1):51.
36. Wang H, Li D, Chen Y, et al. Shear-induced acquired von Willebrand syndrome: an accomplice of bleeding events in adults on extracorporeal membrane oxygenation support. *Front Cardiovasc Med*. 2023;10:1159894.
37. Kalbhenn J, Schlagenhauf A, Rosenfelder S, Schmutz A, Zieger B. Acquired von Willebrand syndrome and impaired platelet function during venovenous extracorporeal membrane oxygenation: rapid onset and fast recovery. *J Heart Lung Transplant*. 2018;37(8):985-991.
38. Rauch A, Dupont A, Rosa M, et al. Shear forces induced platelet clearance is a new mechanism of thrombocytopenia. *Circ Res*. 2023;133(10): 826-841.
39. Mazzeffi M, Tanaka K, Wu YF, et al. Platelet surface GPIbα, activated GPIIb-IIIa, and P-selectin levels in adult veno-arterial extracorporeal membrane oxygenation patients. *Platelets*. 2022;33(1):116-122.
40. Robinson TM, Kickler TS, Walker LK, Ness P, Bell W. Effect of extracorporeal membrane oxygenation on platelets in newborns. *Crit Care Med*. Jul 1993;21(7):1029-1034.
41. Balle CM, Jeppesen AN, Christensen S, Hvas AM. Platelet function during extracorporeal membrane oxygenation in adult patients: a systematic review. *Front Cardiovasc Med*. 2018;5:157.
42. Reddy EC, Rand ML. Procoagulant phosphatidylserine-exposing platelets *in vitro* and *in vivo*. *Front Cardiovasc Med*. 2020;7:15.
43. Heestermans M, Poenou G, Duchez AC, Hamzeh-Cognasse H, Bertoletti L, Cognasse F. Immunothrombosis and the role of platelets in venous thromboembolic diseases. *Int J Mol Sci*. 2022;23(21):13176.
44. Nesseler N, Gouin-Thibaut I, Parasido A, Flecher E, Mansour A. Early endothelial injury in cardiogenic shock patients on venoarterial ECMO. *Intensive Care Med*. 2024;50(11):1929-1930.
45. Doyle AJ, Retter A, Parmar K, et al. Temporal changes in markers of coagulation and fibrinolysis in adults during extracorporeal membrane oxygenation. *Perfusion*. Published online 25 July 2024. https://doi.org/10.1177/02676591241267218
46. Helms J, Curtiaud A, Severac F, et al. Fibrinolysis as a causative mechanism for bleeding complications on extracorporeal membrane oxygenation: a pilot observational prospective study. *Anesthesiology*. 2024;141(1):75-86.
47. Ki KK, Passmore MR, Chan CHH, et al. Effect of ex vivo extracorporeal membrane oxygenation flow dynamics on immune response. *Perfusion*. 2019; 34(suppl 1):5-14.
48. Levy JH, Greenberg C. Biology of factor XIII and clinical manifestations of factor XIII deficiency. *Transfusion*. 2013;53(5):1120-1131.
49. Noitz M, Brooks R, Szasz J, et al. Acquired factor XIII deficiency is common during ECMO therapy and associated with major bleeding events and transfusion requirements. *J Clin Med*. 2023;12(12):4115.
50. Hekimian G, Masi P, Lejeune M, et al. Extracorporeal membrane oxygenation induces early alterations in coagulation and fibrinolysis profiles in COVID-19 patients with acute respiratory distress syndrome. *Thromb Haemost*. 2021;121(8):1031-1042.
51. Varju I, Longstaff C, Szabo L, et al. DNA, histones and neutrophil extracellular traps exert anti-fibrinolytic effects in a plasma environment. *Thromb Haemost*. 2015;113(6):1289-1298.
52. Staessens S, Moussa MD, Pierache A, et al. Thrombus formation during ECMO: insights from a detailed histological analysis of thrombus composition. *J Thromb Haemostasis*. 2022;20(9):2058-2069.
53. Haus M, Foltan M, Philipp A, et al. Neutrophil extracellular traps - a potential trigger for the development of thrombocytopenia during extracorporeal membrane oxygenation. *Front Immunol*. 2024;15:1339235.
54. Foote CA, Soares RN, Ramirez-Perez FI, et al. Endothelial Glycocalyx. *Compr Physiol*. Aug 23 2022;12(4):3781-3811.

55. Levy JH. Antifibrinolytic therapy: new data and new concepts. *Lancet*. 2010;376(9734):3-4.

56. Coleman M, Davis J, Maher KO, Deshpande SR. Clinical and hematological outcomes of aminocaproic acid use during pediatric cardiac ECMO. *J Extra Corpor Technol*. 2021;53(1):40-45.

57. Wilson JM, Bower LK, Fackler JC, Beals DA, Bergus BO, Kevy SV. Aminocaproic acid decreases the incidence of intracranial hemorrhage and other hemorrhagic complications of ECMO. *J Pediatr Surg*. 1993;28(4):536-541 [discussion 540-1].

58. Downard CD, Betit P, Chang RW, Garza JJ, Arnold JH, Wilson JM. Impact of AMICAR on hemorrhagic complications of ECMO: a ten-year review. *J Pediatr Surg*. 2003;38(8):1212-1216.

59. Jakowenko ND, Seelhammer TG, Nabzdyk CGS, et al. Tranexamic acid for bleeding management in adult patients on extracorporeal membrane oxygenation. *ASAIO J*. 2023;69(12):e474-e481.

60. Seelhammer TG, Mangla J, Demirci O. The use of thromboelastography to titrate tranexamic acid therapy for abatement of lysis-induced hemorrhagic complications during venoarterial extracorporeal membrane oxygenation. *J Cardiothorac Vasc Anesth*. 2019;33(4):1059-1062.

61. George B, Parazino M, Omar HR, et al. A retrospective comparison of survivors and non-survivors of massive pulmonary embolism receiving veno-arterial extracorporeal membrane oxygenation support. *Resuscitation*. 2018;122:1-5.

62. Shamanaev A, Ivanov I, Sun MF, et al. Model for surface-dependent factor XII activation: the roles of factor XII heavy chain domains. *Blood Adv*. 2022; 6(10):3142-3154.

63. Zilberman-Rudenko J, Sylman JL, Lakshmanan HHS, McCarty OJT, Maddala J. Dynamics of blood flow and thrombus formation in a multi-bypass microfluidic ladder network. *Cell Mol Bioeng*. 2017;10(1):16-29.

64. Bresette CA, Shea SM, Wagoner S, et al. Novel tubing connectors reduce ECMO circuit thrombosis. *Int J Artif Organs*. 2024;47(5):347-355.

65. Hastings SM, Ku DN, Wagoner S, Maher KO, Deshpande S. Sources of circuit thrombosis in pediatric extracorporeal membrane oxygenation. *ASAIO J*. 2017;63(1):86-92.

66. Fallon BP, Lautner-Csorba O, Major TC, et al. Extracorporeal life support without systemic anticoagulation: a nitric oxide-based non-thrombogenic circuit for the artificial placenta in an ovine model. *Pediatr Res*. 2024;95(1):93-101.

67. Himebauch AS, Priest JR, Annich GM, et al. The influence of the extracorporeal membrane oxygenation circuit and components on anticoagulation management: the Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE Consensus Conference. *Pediatr Crit Care Med*. 2024;25(7 suppl 1):e1-e6.

68. Cai T, Swaney E, Van Den Helm S, et al. The evolution of extracorporeal membrane oxygenation circuitry and impact on clinical outcomes in children: a systematic review. *ASAIO J*. 2023;69(3):247-253.

69. Levy JH, Staudinger T, Steiner ME. How to manage anticoagulation during extracorporeal membrane oxygenation. *Intensive Care Med*. Aug 2022; 48(8):1076-1079.

70. Graboyes SDT, Owen PS, Evans RA, Berei TJ, Hryniewicz KM, Hollis IB. Review of anticoagulation considerations in extracorporeal membrane oxygenation support. *Pharmacotherapy*. 2023;43(12):1339-1363.

71. Rajsic S, Breitkopf R, Jadzic D, Popovic Krneta M, Tauber H, Treml B. Anticoagulation strategies during extracorporeal membrane oxygenation: a narrative review. *J Clin Med*. 2022;11(17):5147.

72. Fan BE, Favaloro EJ. Counting the carbon cost of heparin: an evolving tragedy of the commons? *Lancet Haematol*. 2022;9(7):e469-e471.

73. Nellis ME, Moynihan KM, Sloan SR, et al. Prophylactic transfusion strategies in children supported by extracorporeal membrane oxygenation: the Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE Consensus Conference. *Pediatr Crit Care Med*. 2024;25(7 suppl 1): e25-e34.

74. Willems A, Anders MM, Garcia AV, et al. Management of extracorporeal membrane oxygenation anticoagulation in the perioperative period: the Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE Consensus Conference. *Pediatr Crit Care Med*. 2024;25(7 suppl 1): e53-e65.

75. Achey MA, Nag UP, Robinson VL, et al. The developing balance of thrombosis and hemorrhage in pediatric surgery: clinical implications of age-related changes in hemostasis. *Clin Appl Thromb Hemost*. 2020;26:1076029620929092.

76. Robinson V, Achey MA, Nag UP, et al. Thrombosis in infants in the neonatal intensive care unit: analysis of a large national database. *J Thromb Haemostasis*. 2021;19(2):400-407.

77. Olson SR, Murphree CR, Zonies D, et al. Thrombosis and bleeding in extracorporeal membrane oxygenation (ECMO) without anticoagulation: a systematic review. *ASAIO J*. 2021;67(3):290-296.

78. Muszynski JA, Bembea MM, Gehred A, et al. Priorities for clinical research in pediatric extracorporeal membrane oxygenation anticoagulation from the Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE Consensus Conference. *Pediatr Crit Care Med*. 2024;25(7 suppl 1): e78-e89.

79. Hodgson CL, Burrell AJC, Engeler DM, et al. Core outcome measures for research in critically ill patients receiving extracorporeal membrane oxygenation for acute respiratory or cardiac failure: an international, multidisciplinary, modified Delphi consensus study. *Crit Care Med*. 2019;47(11): 1557-1563.

80. Hodgson CL, Fulcher B, Mariajoseph FP, et al. A core outcome set for research in patients on extracorporeal membrane oxygenation. *Crit Care Med*. 2021;49(12):e1252-e1254.

81. Franchini M, Focosi D, Pezzo MP, Mannucci PM. How we manage a high D-dimer. *Haematologica*. 2024;109(4):1035-1045.

82. Senoner T, Treml B, Breitkopf R, et al. ECMO in myocardial infarction-associated cardiogenic shock: blood biomarkers as predictors of mortality. *Diagnostics*. 2023;13(24):3683.

83. Rajsic S, Breitkopf R, Oezpeker UC, Treml B. ECMO in cardiogenic shock: time course of blood biomarkers and associated mortality. *Diagnostics*. 2022;12(12):2963.

84. Caprarola SD, Ng DK, Carroll MK, et al. Pediatric ECMO: unfavorable outcomes are associated with inflammation and endothelial activation. *Pediatr Res*. 2022;92(2):549-556.

85. Birkenmaier C, Dornia C, Lehle K, et al. Analysis of thrombotic deposits in extracorporeal membrane oxygenators by high-resolution microcomputed tomography: a feasibility study. *ASAIO J*. 2020;66(8):922-928.

86. Cai T, Emery-Corbin SJ, McCafferty C, et al. Comprehensive characterization of surface-bound proteins and measurement of fibrin fiber thickness on extracorporeal membrane oxygenation circuits collected from patients. *Pediatr Crit Care Med*. 2024;25(11):1017-1025.

87. Trieu NHK, Mai TA, Pham HM. Critical hematological parameters in bleeding during extracorporeal membrane oxygenation support. *J Artif Organs*. 2025;28(1):25-29.

88. Labarinas S, Norbisrath K, Johnson D, et al. Clinical outcomes in critically ill children on extracorporeal membrane oxygenation with severe thrombocytopenia. *Perfusion*. Published online 16 April 2024. https://doi.org/10.1177/02676591241247981

89. Goh T, Gao L, Singh J, et al. Platelet adhesion and activation in an ECMO thrombosis-on-a-chip model. *Adv Sci*. 2024;11(30):e2401524.

90. Wilm J, Philipp A, Muller T, et al. Leukocyte adhesion as an indicator of oxygenator thrombosis during extracorporeal membrane oxygenation therapy? *ASAIO J*. 2018;64(1):24-30.

91. Otani T, Sawano H, Natsukawa T, et al. D-dimer predicts bleeding complication in out-of-hospital cardiac arrest resuscitated with ECMO. *Am J Emerg Med*. 2018;36(6):1003-1008.

92. Lingel MP, Haus M, Paschke L, et al. Clinical relevance of cell-free DNA during venovenous extracorporeal membrane oxygenation. *Artif Organs*. 2023;47(11):1720-1731.

93. Richter RP, Payne GA, Ambalavanan N, Gaggar A, Richter JR. The endothelial glycocalyx in critical illness: a pediatric perspective. *Matrix Biol*. 2022;14:100106.

94. Siegel PM, Bender I, Chalupsky J, et al. Extracellular vesicles are associated with outcome in veno-arterial extracorporeal membrane oxygenation and myocardial infarction. *Front Cardiovasc Med*. 2021;8:747453.

95. Wallisch M, Lorentz CU, Lakshmanan HHS, et al. Antibody inhibition of contact factor XII reduces platelet deposition in a model of extracorporeal membrane oxygenator perfusion in nonhuman primates. *Res Pract Thromb Haemost*. Feb 2020;4(2):205-216.

96. Meyer AD, Thorpe CR, Fraker T, et al. Factor XI inhibition with heparin reduces clot formation in simulated pediatric extracorporeal membrane oxygenation. *ASAIO J*. 2023;69(12):1074-1082.

97. Weitz JI. Factor XI and factor XII as targets for new anticoagulants. *Thromb Res*. 2016;141(suppl 2):S40-S45.

98. Weitz JI, Fredenburgh JC. Factors XI and XII as targets for new anticoagulants. *Front Med*. 2017;4:19.

99. Povsic TJ, Vavalle JP, Aberle LH, et al. A phase 2, randomized, partially blinded, active-controlled study assessing the efficacy and safety of variable anticoagulation reversal using the REG1 system in patients with acute coronary syndromes: results of the RADAR trial. *Eur Heart J*. 2013;34(31):2481-2489.

100. Reed CR, Bonadonna D, Otto JC, et al. Aptamer-based factor IXa inhibition preserves hemostasis and prevents thrombosis in a piglet model of ECMO. *Mol Ther Nucleic Acids*. 2022;27:524-534.

101. Larsson M, Rayzman V, Nolte MW, et al. A factor XIIa inhibitory antibody provides thromboprotection in extracorporeal circulation without increasing bleeding risk. *Sci Transl Med*. 2014;6(222):222ra17.

102. Gunaratne R, Kumar S, Frederiksen JW, et al. Combination of aptamer and drug for reversible anticoagulation in cardiopulmonary bypass. *Nat Biotechnol*. 2018;36(7):606-613.

103. Chabata CV, Frederiksen JW, Olson LB, et al. Combining heparin and a FX/Xa aptamer to reduce thrombin generation in cardiopulmonary bypass and COVID-19. *Nucleic Acid Ther*. 2022;32(3):139-150.

104. Yu H, Kumar S, Frederiksen JW, et al. Aptameric hirudins as selective and reversible EXosite-ACTive site (EXACT) inhibitors. *Nat Commun*. 2024;15(1):3977.

105. Wang T, Zhang M, Dong W, et al. Venoarterial extracorporeal membrane oxygenation implementation in septic shock rat model. *ASAIO J*. 2024;70(8):653-660.

106. Kharnaf M, Zafar F, Hogue S, et al. Factor XII promotes the thromboinflammatory response in a rat model of venoarterial extracorporeal membrane oxygenation. *J Thorac Cardiovasc Surg*. 2024;168(2):e37-e53.

107. Tweddell JS, Kharnaf M, Zafar F, et al. Targeting the contact system in a rabbit model of extracorporeal membrane oxygenation. *Blood Adv*. 2023;7(8):1404-1417.

108. Wang T, Yan W, Zhang M, et al. Effects of extracorporeal membrane oxygenation on the coagulation system. *J Vis Exp*. 2024;204:e66433.

109. Pastuszko P, Katz MG, Ebel T, Bozek V, Kubin L, Kubin J. Hypoxia-induced piglet model of cardiac arrest with assisted resuscitation by extracorporeal membrane oxygenation. *Methods Mol Biol*. 2024;2803:227-237.

110. Vincendeau M, Klein T, Groubatch F, Tran N, Kimmoun A, Levy B. Improving oxygenation in severe ARDS treated with VV-ECMO: comparative efficacy of moderate hypothermia and landiolol in a swine ARDS model. *Intensive Care Med Exp*. 2024;12(1):74.

111. Reed CR, Bonadonna D, Everitt J, Robinson V, Otto J, Tracy ET. Coagulopathy characterized by rotational thromboelastometry in a porcine pediatric ECMO model. *J Extra Corpor Technol*. Sep 2020;52(3):203-211.

112. Alexander PMA, Thiagarajan RR. Pediatric oncology-the final frontier for extracorporeal membrane oxygenation in children? *Pediatr Blood Cancer*. 2020;67(10):e28521.

113. Swol J, Cannon JW, Barbaro RP, Fanning JJ, Zonies D. Extracorporeal membrane oxygenation in trauma. *ASAIO J*. 2022;68(4):e62-e63.

114. Lillie J, Boot L, Speggiorin S, Nyman AG. Factors behind decline of venovenous extracorporeal membrane oxygenation to support neonatal respiratory failure. *Pediatr Crit Care Med*. 2020;21(8):e502-e504.

115. O'Neil ER, Lin H, Shamshirsaz AA, et al. Pregnant and peripartum women with COVID-19 have high survival with extracorporeal membrane oxygenation: an extracorporeal life support organization registry analysis. *Am J Respir Crit Care Med*. 2022;205(2):248-250.

116. Ramanathan K, Tan CS, Rycus P, et al. Extracorporeal membrane oxygenation in pregnancy: an analysis of the extracorporeal life support organization registry. *Crit Care Med*. 2020;48(5):696-703.

117. Alexander PMA, Muszynski JA. Clinical trials for pediatric extracorporeal membrane oxygenation: the time is now. *Pediatr Crit Care Med*. 2025;26(1):e118-e121.

118. Goligher EC, Lawler PR, Jensen TP, et al. Heterogeneous treatment effects of therapeutic-dose heparin in patients hospitalized for COVID-19. *JAMA*. 2023;329(13):1066-1077.