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Hematologic concerns in extracorporeal membrane oxygenation

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Abstract

This ISTH "State of the Art" review aims to critically evaluate the hematologic considerations and complications in extracorporeal membrane oxygenation (ECMO). ECMO is experiencing a rapid increase in clinical use, but many questions remain unanswered. The existing literature does not address or explicitly state many pertinent details that may influence hematologic complications and, ultimately, patient outcomes. This review aims to broadly introduce modern ECMO practices, circuit designs, circuit materials, hematologic complications, transfusion-related considerations, age- and size-related differences, and considerations for choosing outcome measures. Relevant studies from the 2019 ISTH Congress in Melbourne, which further advanced our understanding of these processes, will also be highlighted.

KEYWORDS

adult, extracorporeal membrane oxygenation, hemolysis, hemorrhage, pediatric, thrombosis

Essentials

- Extracorporeal membrane oxygenation (ECMO) is a form of life support for patients with severe lung or heart failure. Its use can affect the blood in many complex and poorly understood ways, leading to excessive bleeding or clotting.
- Few ECMO studies comprehensively describe the factors that can affect these complications, such as circuit design or blood product transfusion.
- The best ways of preventing these complications are unknown.
- A common language is needed to better understand them and to facilitate more detailed research.

1 | INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) provides gas exchange and/or circulatory support with an artificial circuit and membrane. It is a potentially lifesaving therapy but is beset with potential problems and complications by virtue of the artificial materials required and its effects on the circulatory, endothelial, hematologic, inflammatory, and immune systems. There has been a substantial increase in ECMO use over the past decade. The increase in clinical practice has mirrored a rapid expansion of research on ECMO. Despite the increasing clinical experience and research data available, much is unknown about best practices and risk minimization.

This paper reviews in detail the hematologic considerations in current ECMO practices, as well as highlight and differentiate what practices are based on clinical or physiologic data and which practices are based on expert opinion and hence high-priority targets for ongoing research. The overall goal is to highlight the effects of ECMO practices and components on the hematologic system.

2 | CONTEMPORARY ECMO USES AND CIRCUIT DESIGNS

ECMO can be used in a number of configurations. Broadly speaking, ECMO is divided into venoarterial (VA) ECMO and venovenous (VV) ECMO. VA ECMO provides circulatory support as well as gas exchange but exposes the patient to the risk of systemic thromboembolism. Other risks associated with VA ECMO vary among patient populations, indications, and cannulation technique. Complications include hemorrhage in 30%-70% of patients, stroke in 4%-12%, limb ischemia in 12%-22%, and left ventricular distention, which both delays separation from ECMO and increases areas of stasis and hematologic complications.[1-7] Assessing the true risk of complications associated with ECMO is difficult because of the differences in populations, indications (including cardiac arrest, low cardiac output, and respiratory failure), cannulation techniques, circuitry, and anticoagulation strategies. In addition, there is a general failure to accurately describe these differences in publications by virtue of a lack of common language and template, making discerning their individual contributions to risk either difficult or impossible.

VV ECMO provides gas exchange and does not carry the same systemic embolic risk as VA ECMO but at the cost of not providing direct circulatory support, though cardiac output may still improve following initiation as a result of improved gas exchange and a reduction in mechanical ventilation pressures.[8] The bleeding risk remains, with major hemorrhage rates of 19% being reported in a recent systematic review and meta-analysis.[9] Intracranial hemorrhage rates are a concern on VV ECMO, with rates approaching 16% in patients with severe acute respiratory distress syndrome (ARDS).[10] Indication and patient population heavily confound risk. In the same study, 8% of non-ECMO patients with ARDS in the same center had intracranial hemorrhage. Risk of intracranial hemorrhage was independently related to length of ventilation and admission fibrinogen level but not the use of ECMO. This same pattern of intracranial hemorrhage being related to severity of illness and patient factors, and not ECMO use, has been demonstrated in other studies.[11]

There are many configurations for ECMO circuitry. Cannulas may be centrally inserted via sternotomy or peripherally inserted via the great vessels of the neck, groin, or, less commonly, the subclavian great vessels.[12] Most ECMO pumps in use are centrifugal, but roller pumps may still be encountered. Centrifugal pumps may be associated with more frequent nonsurgical bleeding and hemolysis.[13] Despite these concerns, centrifugal pumps are generally preferred because they require a smaller circuit, as roller pumps need to have blood fed into them via gravity, which requires extra tubing before pumping, and they have a reduced risk of air emboli and smaller priming volumes.[14] Different surface coatings such as heparin or poly-2-methoxyethylacrylate (PMEA) are available. Tubing comes in different widths, and the overall length of the circuit is highly variable. Different connections within the circuit may exist, such as bridges, pressure monitors, sampling ports, and bladders.[15] Table 1 summarizes these potential differences. Each has the potential to influence hematologic complications. ECMO circuit design and components are rarely discussed alongside ECMO protocols, studies, and complication rates.

TABLE 1 Design and configuration variables in ECMO circuits

ECMO type	VA, VV, and variants of
Cannulation strategy	Central vs peripheral
Pump type	Centrifugal vs roller pump
Number of cannula	1, 2, 3, or more
Cannula size	6 Fr to 31 Fr
Cannula connection strategy	Directly inserted vs connected via graft
Circuit connections	Bridge/no bridge, bladder/no bladder
Monitoring sites	Number of pressure monitors, sampling ports
Total length of circuit	Highly variable
Tubing	Width variable, no coating vs heparin or other
Oxygenator model	Variable sizes and models in use

Abbreviations: ECMO, extracorporeal mechanical oxygenation; Fr, French; VA, venoarterial; VV, venovenous.

All ECMO configurations carry a high risk of infections, with rates between 13% and 40%, and some reporting higher rates in VA ECMO.[6] Infection risk, driven by mediastinitis, is higher with central cannulation.[16] Central cannulation is associated with the highest bleeding risk.[17] Neck cannulation is associated with the most cerebral injuries.[18] Femoral cannulation is associated with uneven mixing of blood from the ECMO circuit and the native systemic ventricular ejection, resulting in differential hypoxia (the uneven mixing of oxygenated blood from the ECMO circuit and deoxygenated blood ejected from the systemic ventricle in a patient with respiratory failure and resulting pulmonary venous desaturation), resulting in elevated saturations in the lower body while the upper body has a significantly lower saturation).[19]

When considering ECMO complications, it is important to acknowledge that many of the patients have multiorgan disease. Patients with dysfunction of the left ventricle are at risk of losing myocardial ejection after VA ECMO initiation due to increased systemic afterload, leading to stasis within the ventricle and aortic root.[20-22] Many will have inflammatory states from sepsis or other disease processes, which will change both their hematologic laboratory parameters and their overall clotting and bleeding risk. This preexisting risk may be exacerbated by ECMO.[23-25] Some patients will have acute kidney injury at the time of ECMO cannulation, which in and of itself is a risk factor for adverse events and mortality, as well

as influencing dosage and clearance of heparin and other medications.[26-28] This will be further compounded by patients being placed onto additional mechanical support with continuous renal replacement therapy (CRRT). CRRT may be done through additional large-bore access or connected to the ECMO circuit.[29] CRRT may have hematologic consequences for the patient, including an increase in platelet transfusions and the potential for increased hemolysis.[27,30,31] The reason CRRT causes an increase in platelet transfusions and hemolysis on ECMO, but not typically in other critically ill patients, has yet to be definitively elucidated.

3 | ECMO CIRCUIT MATERIALS

Exposing large volumes of blood to circuit surfaces during ECMO is unavoidable. This exposure results in inflammation, platelet dysfunction, and disruption of the hematologic system.[32] Blood exposure to artificial surfaces results in fibrinogen, albumin, and other hematologic proteins coating the artificial surface, platelet activation, and inflammation.[33-36] Current ECMO tubing is made from polyvinyl chloride, though connectors and hubs may be made of other materials. Attempts to change circuit membrane characteristics to dampen or eliminate the blood-membrane response can be broken into 3 broad categories: biomimetic surfaces, biopassive surfaces, and endothelialization.[32] The most common variants of each and their properties are summarized in Table 2.

Biomimetic tubing is the most commonly known attempt to dampen or prevent the adverse effects of passing blood through an ECMO circuit. The common variant in use is heparin-bonded surfaces. Clinical studies have shown that heparin-bonded tubing reduces cellular activation and release of inflammatory markers in cardiopulmonary bypass.[37-40] Despite the promise from these improvements and the availability of heparin-bonded tubing, the need for systemic anticoagulation has not been eliminated and the significant challenges and problems of disrupted hematologic hemostasis and systemic anticoagulation remain. Nitric oxide biomimetic surfaces are another technology in development. Nitric oxide can inhibit platelet activity via multiple pathways.[41] In vivo testing of nitric oxide–bonding circuitry has shown an ability to prevent platelet consumption and thrombus formation in animal models, though it does not prevent fibrinogen deposition.[42] Attempts have been made to combine multiple strategies into a single biomimetic tubing with promising results.[43] To date, there is no tubing yet developed that can be used in ECMO circuits, which fully dampens the inflammatory and coagulopathic response of blood to a foreign material.

Biopassive materials are an attempt to create circuitry lined with a nonreactive surface so that no thrombogenic response is initiated. Phosphorylcholine (PPC) is an asymmetric lipid bilayer used to line circuits. When used, a reduced thrombogenic response can be demonstrated, as evidenced by reduced platelet activation and reduced complement response.[44] Circuits lined with PPC have been shown to be safe and reduce overall heparin need in several studies of cardiopulmonary bypass when compared to unlined circuits.[45-47] Whether PPC is superior to heparin-bonded circuits remains unclear.[48] PMEA uses a hydrophobic polyethylene backbone and mildly hydrophilic tail to line circuits. In cardiopulmonary bypass, its use has been shown to be associated with reduced platelet aggregation and reduced adsorption of proteins.[49-51] Performance when compared to heparin-bonded circuitry is mixed, with possible reduction in adsorption of fibrinogen and need for platelet transfusions, but possible increased leukopenia, similar platelet aggregation, increased systemic inflammatory reaction, and increased complement activation.[50,52-55] Fluid-repellent coatings attempt to create a stable air-liquid interface that acts as a repellent layer between the blood and the circuit. The creation of a stable, clear layer that can self-repair damaged

TABLE 2 Alternative surface coating for tubing in ECMO circuits

Membrane type	Examples	Membrane characteristics
Biomimetic surfaces	Heparin bonded	Reduced cellular activation and inflammation, but systemic anticoagulation still required
	Nitric oxide bonded	Reduced platelet consumption and thrombosis in animals, NO release and longevity difficult [32]
Biopassive surfaces	Phosphorylcholine lined	Reduced heparin needs in cardiopulmonary bypass, unclear if better than heparin bonded
	PMEA	Reduced platelet aggregation and protein adsorption, mixed performance compared to heparin bonded
	Fluid repellant	Air-liquid membrane would avoid contact with tubing, but not yet technically feasible
Endothelialization	In vitro	Reduced thrombosis and stenosis when used in grafts, but currently very slow to create and limited to short devices
	In vivo	Mimics native endothelium, but currently not technically feasible

Abbreviations: ECMO, extracorporeal mechanical oxygenation; NO, nitric oxide; PMEA, Poly-2-methoxyethylacrylate.

areas and bond with circuits has been challenging. While there has been some promising early work in this area both in in vitro and in vivo studies in the lab, it has not yet developed sufficiently as a technology to proceed to larger trials.[56]

Endothelium is the medium that regulates the inflammatory and coagulation response of blood as it is transported around the body. If an endothelium could be applied to ECMO circuitry, this natural regulatory effect could be mimicked. Endothelialization of circuitry can be accomplished via 2 techniques. The first is in vitro pre-endothelialization of the circuit and the second is endothelial progenitor cells (EPCs) based on in vivo induced self-endothelialization.[57-59] In vitro endothelialization directly seeds autologous endothelial cells to form a monolayer along the internal surface of synthetic vascular grafts. While effective at reducing stenosis and thrombosis of grafts, it is a technically difficult process that can take months to years to complete, and it is difficult to achieve complete endothelialization of even modest-length devices such as grafts and stents.[57,60] It is currently not technically feasible due to the large surface area of an ECMO circuit requiring coverage, nor to produce this in an urgent or emergent fashion. Long-term stability, risk of infection, and cost also remain obstacles.[32] In vivo endothelialization is an alternative approach in which EPCs derived from bone marrow are circulated at low concentration to generate a functioning endothelium in hardware.[59] Research is ongoing in how to design circuit membranes that encourage EPCs to create new endothelium across their surface.[57,58] While promising early results have been demonstrated with this technique, and it has the potential to create an ideal circuit surface, this technology has not yet come to a point where it can be effectively tested or used in ECMO.

4 | HEMATOLOGIC COMPLICATIONS OF ECMO

Initiating ECMO triggers a number of hematologic and inflammatory consequences. The details and cascades leading to these consequences are inferred from studies of patients on cardiopulmonary bypass, as the consequences of cardiopulmonary bypass have been more widely and thoroughly studied, and equivalent studies of ECMO have not yet been undertaken. The contact system, made up of high-molecular-weight kininogen (HK), prekallikrein (PK), and factors XI and XII, plays a major role. Surface-bound factor XII is converted to XIIa and XIIf (fragment) when exposed to the combination of HK, PK, and a foreign surface. PK is activated to kallikrein, which then feeds back to cause further activation of factor XII and produces more PK from HK. Factors XIIa and XIIf and kallikrein combined activate the intrinsic pathway via factor XI, the classic and alternate complement pathway, and neutrophils, and presumably stimulate tissue-plasminogen activator. This cascade continues and results in the systemic inflammatory response.[25,34] These changes are summarized in Table 3.

TABLE 3 Hematologic and inflammatory consequences of initiating ECMO

Hematologic consequences	Factor XIIa and XIIf upregulation
	Kallikrein upregulation
	Contact system activation
	Intrinsic pathway activation
	Factor depletion, especially fibrinogen
	Platelet activation and dysregulation
	Hemolysis
Inflammatory consequences	Classic complement system activation
	Alternate complement system activation
	Neutrophil activation
	Free radical production
	SIRS

Abbreviations: ECMO, extracorporeal mechanical oxygenation; SIRS, systemic inflammatory response syndrome; XIIf, factor XII fragment.

Protein adsorption onto circuits can lead to reduction or deficiencies in multiple hematologic factors. Extrapolating from cardiopulmonary bypass, the proteins most quickly adsorbed onto the surface of an ECMO circuit are fibrinogen, factor XII, thrombospondin, fibronectin, immunoglobulin E, von Willebrand factor, albumin, and hemoglobin.[33-36] Fibrinogen is initially the most rapidly adsorbed, but the profile of which proteins attach changes over time. Priming the circuit with different blood products can have an impact on this adsorption process. Priming with albumin may reduce platelet activation by decreasing early absorption of fibrinogen.[61]

Thrombocytopenia is common in patients on ECMO. The degree of thrombocytopenia is not related to the duration of ECMO but rather to the severity of illness and platelet count at the time of cannulation.[62,63] The etiology of platelet dysfunction on ECMO is complex and has not yet been definitively elucidated. The artificial surface from the ECMO circuit may induce platelet activation and adhesion.[64] Shear stress may contribute to platelet activation and may also contribute to loss of platelet surface receptors necessary for adhesion.[65,66] Von Willebrand factor multimers may be lost, particularly with centrifugal pumps, reducing the ability of platelets to bind to von Willebrand factor.[24,65,66] The combination of changes in activating and inhibiting factors, and/or changes in local and systemic factors, may explain the paradoxical tendency toward both thrombosis and bleeding on ECMO.[65-67] A recent study demonstrated impaired platelet activation on day 1 of ECMO but not on subsequent days, despite significant differences and variation in activation-dependent surface markers on the platelets of individuals receiving ECMO.[68] One possible explanation of this combination of altered surface markers but equivalent function is the upregulation in the creation of new, young platelets.

Hemolysis is common on ECMO and is associated with significant morbidity. An analysis of 207 pediatric patients on ECMO showed mild hemolysis in 47%, moderate hemolysis in 13%, and severe hemolysis in 7%.[69] In this study, the first plasma free hemoglobin >0.1 g/L was noted at 23.8 hours in cases of mild hemolysis

(interquartile range [IQR], 12.0-58.0 h), 27.0 hours in cases of moderate hemolysis (IQR, 11.5-37.0 h), and 11.5 hours in cases of severe hemolysis (IQR, 10.0-27.0 h). Moderate hemolysis peaked at 51.1 hours (IQR, 32.8-115.4 h) and at 91.9 hours in cases of severe hemolysis (IQR, 34.8-178.1 hours). Severe hemolysis across multiple adult and pediatric studies has been shown to occur at a rate of between 2% and 20%.[69-75] Hemolysis is associated with increased rates of endothelial failure, renal failure, thrombotic events, transfusions, and mortality.[69-74,76] One proposed mechanism for these adverse events is the normal binding of hemopexin and haptoglobin to free hemoglobin becomes overwhelmed. Residual free hemoglobin then binds to endogenous nitric oxide, resulting in vasoconstriction.[77] However, the same complications are not commonly seen in patients with severe hemolysis off ECMO. Whether the link between hemolysis and severe complications is cause, effect, or a parallel phenomenon related to underlying disease and ECMO physiology remains to be determined.

5 | NEONATAL VERSUS PEDIATRIC VERSUS ADULT ECMO

There are obvious physical and maturational differences among neonatal patients, pediatric patients, and adult patients that impact the hematologic considerations in ECMO (Table 4). The small size of the vessels in neonates with low birth weight limits the size of cannulas that can be inserted. The circuit volume of an ECMO circuit is large volume relative to the total blood volume of neonates, giving the priming fluid in ECMO circuits a larger influence on the hematologic status of the patient.[78,79] Neonatal patients have increased rates of intracranial hemorrhage compared to adults, with rates up to 16%-34% compared to 2%-21% for adults.[7,80-84] Neonatal ECMO survivors below 2 kg have been reported, although this population has an increased complication rate, including intracranial hemorrhage, and increased mortality.[85]

TABLE 4 Features of neonatal and pediatric ECMO, as compared to adult ECMO

Smaller cannula(s)
Larger circuit volume relative to blood volume
Lower flows predisposing to hemostasis
Increased dilution of hematologic factors
More cannulations via neck vessels
More CNS injuries
Less predictive response to heparin
Prolonged APTT at baseline
Altered APTT response to heparin
Less available antithrombin in neonates
Less conversion of antithrombin to thrombin in neonates

Abbreviations: APTT, activated partial thromboplastin time; CNS, central nervous system; ECMO, extracorporeal mechanical oxygenation.

In patients <10 kg, the majority of peripheral cannulations are performed via the right internal jugular vein and carotid artery, as the femoral vessels tend to be too small.[86] This is associated with an increase in the number of central nervous system injuries and has implications for the likelihood of an intracranial bleed and or stroke due to carotid artery disruption and possible venous congestion from jugular vein obstruction.[87] Some centers choose to attempt reconstruction of neck vessels at time of decannulation, while other centers routinely ligate the vessels at decannulation. While this procedure is common, some centers report a high rate of thrombosis following neck vessel reconstruction.[88] The smaller cannulas also tend to create flow limitations and attempts to increase the flow may lead to hemolysis through shear stress and the creation of microbubbles.[75]

The hematologic system evolves in patients as they age. Unfractionated heparin has age-dependent variation in activity and different correlation between monitoring tests and dosage.[89,90] Modeling to predict pediatric patients' response to heparin has proven difficult, and the response to single large doses of unfractionated heparin is different from that of lower-dose infusion in pediatric patients.[91] This response is influenced by heparin-binding proteins and renal excretion, which are frequently impaired in patients receiving ECMO. Activated partial thromboplastin time (APTT) is prolonged in neonates and pediatric patients and only approaches adult levels in adolescence.[92-95] The APTT response to heparin varies with age, with younger children showing less prolongation of APTT when given equivalent heparin doses.[92,95,96] Prothrombin appears to have a lower availability in neonatal patients, as well as a lower conversion rate to thrombin.[97] Age-specific norms tend to be overlooked, and adult normative data are used for protocols. Figures 1 and 2 demonstrate the change in normative factor levels and major hematologic proteins from infancy to adulthood.[98]

6 | ANTICOAGULATION: DRUGS AND MONITORING

The optimal test to monitor and titrate coagulation status on ECMO is unclear. Activated clotting time (ACT) is commonly used on ECMO; however, APTT and anti-Xa are also common.[99] Anti-Xa is the test that shows the strongest correlation with heparin infusion dose on ECMO and may reduce bloodletting via sampling on ECMO.[100,101] All tests may suffer in their correlation with heparin dose in part due to the variable fraction of heparin containing the pentasaccharide sequence needed to bind to antithrombin and the variable ratios of long- and short-chain heparin within unfractionated heparin vials.[102] A number of studies have considered assays in relation to specific outcomes, but none have directly compared them or shown superiority of a specific test, and correlation with heparin dosing remains low. Results of all 3 assays (ACT, APTT, Anti-Xa) vary by analyzer and reagent type, and centers must calibrate to the specific assay used in their laboratory.[103] Anti-Xa is less reliable in patients with hyperbilirubinemia, elevated plasma free hemoglobin,

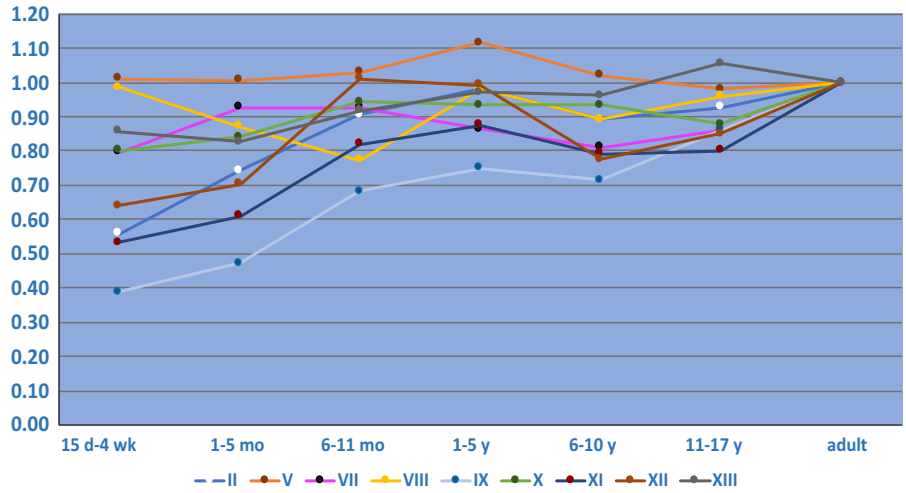

FIGURE 1 Normal factor levels from infancy to adulthood. Adapted from Toulon[98]

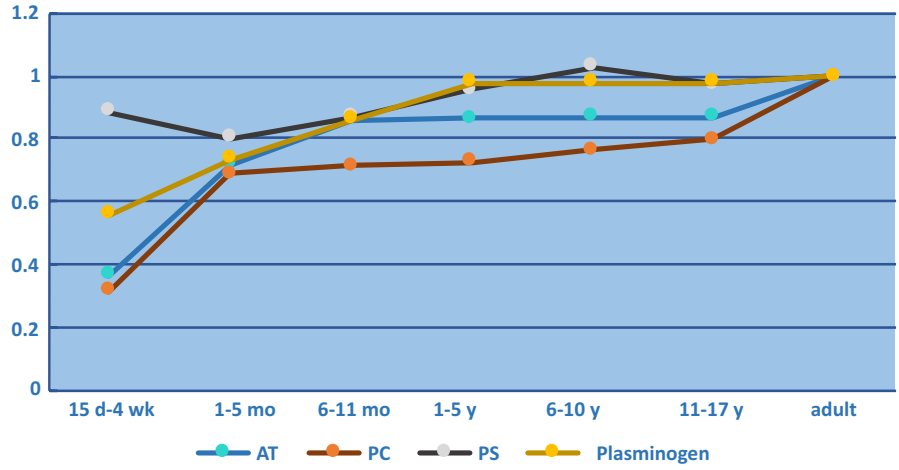

FIGURE 2 Normal coagulation and fibrinolysis protein levels from infancy to adulthood. Adapted from Toulon[98]

and hypertriglyceridemia (true also for other assays if optical detection of clot is the test methodology).[104-106] There has been no demonstrated difference in either bleeding or thromboembolic events between APTT or Anti-Xa levels. Thromboelastography or thromboelastometry measurements suffer from considerable operator variability in test results and difficulty in clinical interpretation.[107,108] Table 5 summarizes the potential problems with each test. There are no clinical outcome data comparing which test and/or assay best predicts clinical behavior.

Antithrombin transfusion in conjunction with heparin on ECMO is a common but controversial therapy. While antithrombin is most known by the ECMO community for its >1000-fold potentiation of heparin, it has multiple other actions. Antithrombin strongly inhibits thrombin and factors Xa and IXa, and it weakly inhibits factors XIa and XIIa, trypsin, plasmin, kallikrein, and factor VIIa. Antithrombin also exhibits an inhibitory effect on serine proteases and modulates the inflammatory response of the endothelium via the heparan sulfate proteoglycans embedded along its surface.[109] The normal range for antithrombin levels changes with age and is significantly lower in children in intensive care.[93] By giving antithrombin, the amount of heparin needed to obtain the therapeutic level is reduced by a variable amount.[110-113] When giving antithrombin for the purpose of making an anticoagulation test parameter fall in range, it is important to consider that there is poor clinical correlation between heparin measurement assays and bleeding or clotting events on ECMO.

Wong et al[114] retrospectively analyzed nearly 9000 pediatric patients on ECMO at 43 hospitals over a 10-year period. Antithrombin transfusion was used in 2% of patients in 2005 and this increased to 50% by 2012. Some centers never used antithrombin, and others used it in up to 80% of their patients. Patients receiving antithrombin tended to be younger, smaller, and have more chronic conditions. Antithrombin use was associated with increased rates of thrombosis, including pulmonary embolism and acute ischemic stroke (odds ratio [OR], 1.55; 95% confidence interval [CI], 1.36-1.77). There was also an increased risk of hemorrhage associated with antithrombin use (OR, 1.27; CI, 1.14-1.42). There was no demonstrated difference in mortality. There were no temporal data available on when antithrombin was given relative to thrombotic or hemorrhagic events. The majority of antithrombin concentrates presently in use have variable levels of latent antithrombin, with levels up to 40% reported, and therefore are potentially simultaneously

TABLE 5 Issues associated with common heparin monitoring tests[a]

ACT	Least related to heparin dose on ECMO Least responsive to heparin dose changes More frequent sampling Results influenced by reagent used Influenced by thrombocytopenia, hematocrit, and hypothermia
APTT	Over 300 reagents available Reagent changes heparin sensitivity No difference in bleeding or thrombosis risk compared to Anti-Xa Influenced by plasma free hemoglobin and hyperbilirubinemia
Anti-Xa	Assay results influenced by assay type - Exogenous antithrombin - Dextran sulfate additive - Neither Influenced by plasma free hemoglobin, hyperbilirubinemia, and hypertriglyceridemia
TEG/ROTEM	High interoperator variation Results influenced by assay used and plasma free hemoglobin

Abbreviations: ACT, activated clotting time; APTT, activated partial thromboplastin time; CNS, central nervous system; ECMO, extracorporeal mechanical oxygenation; ROTEM, rotational thromboelastometry; TEG, thromboelastography.

[a]Site of sampling and potential contamination is an issue regardless of test.

thrombogenic and anticoagulant, especially in an unbalanced hematologic system already in dysregulation.[89,115,116] Overall, the current literature suggests that antithrombin is being increasingly used to reach therapeutic target ranges for heparin, despite never having been demonstrated to have a clinical benefit in rates of ECMO circuit changes, length of stay, or mortality.[112,114,117] In addition, antithrombin may be associated with significant harm and increased rates of both bleeding and thrombotic events.[114] The use of this potentially harmful and expensive product to reduce the dose of widely available (and cheap) heparin is particularly glaring when considering that higher doses of heparin have independently been associated with improved survival on ECMO.[118]

With the uncertainty that exists around heparin dosing, monitoring, and antithrombin use, the use of direct thrombin inhibitors as an alternative therapy has been greeted with hope for a simple solution. Bivalirudin is the direct thrombin inhibitor most commonly used. Bivalirudin has a short half-life, helping make it suitable for use in ECMO. However, bivalirudin has no reversal agent, requires dose modification in renal impairment, and is significantly more expensive than heparin.[119,120] While bivalirudin is hailed as being a simpler alternative to heparin, the dose range described in the literature is 0.05 mg/kg/h to 1.6 mg/kg/h, with a range extending up to 2 mg/kg/h being anecdotally shared via correspondence between the authors and clinicians with experience using bivalirudin, making the relative dose range far larger than for heparin.[121-123] Bivalirudin can be monitored by APTT, but a number of studies have suggested loss of linearity within the upper end of the therapeutic range, which is problematic.[124,125] Dilute thrombin time has been suggested as an alternative monitoring test, but this assay is not readily available in many laboratories.[126] There are insufficient data to adequately assign therapeutic targets with other assays, including point-of-care assays. Thus, bivalirudin currently is difficult to effectively monitor, has a much larger relative dose range than heparin, and is more costly, and there are currently no clinical data relating monitoring results to bleeding and clot risk.

Antiplatelet therapies are uncommonly used in ECMO. Dual antiplatelet therapy has been described on VA ECMO in patients with drug-eluting coronary stents. Data are limited by small sample sizes. In these patients, while there was a trend toward more red blood cell transfusions, there was no statistically significant difference in bleeding rates between those on dual antiplatelet therapy and heparin and those only on heparin infusions.[127] There is little in the published ECMO literature on the use of other antiplatelet agents and their effect on coagulation and bleeding, though the use of prostacyclin and nitric oxide are described in ECMO for their effects on pulmonary arterial hypertension and potential modulation of ischemia reperfusion injuries.[128,129]

7 | TRANSFUSION THRESHOLDS

The threshold for red blood cell transfusion on ECMO is an area of debate, with most of the debate centering on oxygen delivery and little consideration for effects of transfusion on rheology of the circuit. The effects of transfusion rheology are likely important but as yet understudied. Randomized control trials have shown benefit in reducing transfusion burden on critically ill patients.[130,131] Hemoglobin and hematocrit targets on ECMO are largely set by expert opinion. On average, neonatal and pediatric patients on ECMO are being transfused between 30 and 105 mL/kg/day of packed red blood cells (PRBCs), depending on age and indication for cannulation.[132-136] Transfusion beyond 30 mL/kg/d in one study was associated with increased mortality in pediatric patients on ECMO, with a 9% increase in mortality for every additional 10 mL/kg/d.[132] Transfused PRBCs have the potential to increase hemolysis due to the increased fragility of stored red blood cells and may be associated with increased thrombosis and infection.[137,138] In a

single-center retrospective review of neonatal hematocrit transfusion threshold on ECMO, Sawyer et al[139] demonstrated that a hematocrit transfusion threshold of 0.35, instead of 0.4, resulted in fewer transfusions for the lower hematocrit group, with no difference in outcomes across the 72 infants reviewed. Similar studies in adults being supported with ECMO for ARDS have demonstrated hemoglobin concentration of 70 g/L can be used without a significant change in clinical outcomes for the patient while reducing transfusion volume.[140,141] An expert panel review in 2018 could find no evidence for any specific target hemoglobin concentration, and recommended that the decision to transfuse should be based on evidence of inadequate cardiorespiratory support, or decreased systemic or regional oxygen delivery, rather than a fixed hemoglobin or hematocrit.[142]

As with hemoglobin, platelet transfusion thresholds are set by expert opinion. In critically ill children, the most common reason platelets are given is prophylaxis for bleeding risk in patients with thrombocytopenia. In the same studies, platelet transfusions are associated with increased mortality.[143,144] In a review of 511 children on ECMO, Cashen et al[145] found that 97.1% were transfused platelets during the course of their ECMO run. They also found that the volume of platelets transfused, but not the platelet count, was independently associated with mortality. There was an increase in mortality with an OR of 1.05 (CI, 1.03-1.08) for each 1 mL/kg/d of platelets transfused on multivariable analysis, whereas average daily platelet count was not associated with mortality; furthermore, platelet counts as low as 56 were not associated with any more risk of bleeding than those over 100. The potential implication is that patients are routinely transfused with platelets for fear of bleeding and intraventricular hemorrhage, when the transfusion of platelets itself is potentially driving worse outcomes. At present, there is little empiric evidence to guide platelet transfusion thresholds.

8 | ECMO OUTCOMES

The traditional outcome measure used in ECMO patients is in-hospital mortality. However, this has obvious limitations, and there have been calls to examine more robust outcome measures, such as 1-year survival with adequate neurologic and functional recovery.[146]

As an example of mortality after decannulation from ECMO, a 2017 review of 400 neonates and children who survived ECMO showed approximately a 10% mortality rate between decannulation and 90 days, with 84% of neonates and 74% of pediatric patients surviving to decannulation, and 76% and 66% alive at 90 days, respectively.[147] Furthermore, a long-term survival review, with a median follow-up time of 7 years for neonates and pediatrics patients who underwent ECMO support in the United Kingdom, demonstrated a 6% mortality >90 days after ECMO.[148] Having congenital heart disease, acquired heart disease, or congenital diaphragmatic hernia represented increased risk for late death, demonstrating again how underlying disease and ECMO risks are intertwined.

Some groups have reported on follow-up with survival and neurologic outcomes at ≥1 year. These studies illustrate why long-term follow-up is important when evaluating outcomes. Great Ormond Street Hospital reviewed their ECMO follow-up clinic after 10 years of experience. One-year follow-up is offered to all neonates and pediatric patients who are ECMO survivors. Thirty percent of patients followed up were identified as having neurodevelopmental concerns. Having had an acute neurologic event on ECMO was the only identified risk factor.[149] In a 7-year follow-up of critically ill neonates randomly assigned to ECMO versus non-ECMO treatment, survivors in both groups had similar neuromotor impairment and hearing deficits, and the non-ECMO treatment group had an increased rate of behavioral issues and respiratory problems at the time of follow-up.[150] A follow-up at 8 years of age of children who had received ECMO support as neonates showed normal intelligence scores, with 91% of survivors attending normal schools; however, the ECMO survivors had increased need for special education assistance, slower working speeds, less accuracy, and increased incidence of behavioral and attention problems when compared to their peers.[151]

The best measures of success for ECMO remains unclear. Survival to decannulation misses significant later morbidity and mortality, and as the longest ECMO run reported now has reached 605 days, 30- and 90-day mortality also may miss the significance, difficulties, demands, and consequence of long ECMO runs.[87,152] In pediatric patients, there is good demonstration that while mortality rates on ECMO are high, there is also significant impact and burden from the long-term developmental effects that follow.[149] We have not yet adequately elucidated the effect disease process versus ECMO complications or ECMO techniques has on long-term development.[87] Finding appropriate outcomes to titrate our hematologic parameters should look beyond mortality, bleeding, and thrombosis, to fully appreciate the long-term consequences.

9 | ISTH 2019, MELBOURNE REPORT

ISTH 2019 offered multiple abstracts that further our understanding of ECMO, the hematologic system, and anticoagulation monitoring. Musumeci et al[153] presented a novel surface coating for ECMO circuitry, which showed promise in reducing platelet adhesion and contact system activation. Visser et al[154] and Butler et al[155] both helped advance our understanding of kallikrein, which is a key player in the activation of the contact system by artificial membranes. Cowley et al[156] demonstrated both age and analyzer and reagent specific normative values for factors VIII and IX, while Keragala et al[157] measured baseline and inducible fibrinolytic capacity in children, demonstrating the importance of the details necessary to have comparative values between patients and centers. Bachler et al[158] demonstrated that factor XII is commonly deficient in critically ill patients, leading to possible suboptimal dosing of anticoagulation titrated to APTT in this population. Jayakody Arachchillage et al[159] showed that hemoglobin; platelets; factors II, XI, and XII; and von Willebrand factor all decreased in the first 24 hours on VV ECMO. Yaw et al,[160] in

an effort to elucidate which part of the ECMO circuit is affecting platelets, showed that platelet activation, responsiveness, and von Willebrand factor receptor expression are all increased after oxygenation in an ECMO circuit.

10 | SUMMARY

The interplay of disease, technique, and intervention make it difficult to discern the effect that individual practices have on the rheology of ECMO circuits. To better elucidate how individual components affect outcomes, and how to compare results and differences among centers, a common language is needed. Descriptions of how circuits are constructed and presentation of institutional practices that influence hematologic results should become standard in published academic works on ECMO. Major outstanding research priorities this would help advance include (1) the effects of circuit designs, (2) identification of clinically relevant anticoagulation monitoring targets, (3) evidence-based transfusion practices, (4) identification of appropriate outcome measures, and (5) optimal management of the blood-biomaterial interface. Continued advancement and appreciation for how materials, technique, hematologic parameters, anticoagulation practices, and underlying disease processes interact is needed to reduce morbidity and mortality on ECMO.

RELATIONSHIP DISCLOSURE

JS, GM, and GMA declare nothing to disclose. PM reports a patent on a thrombin generation assay. Inventors: Berry LR, Ignjatovic V, Monagle PT, Chan AKC. US patent no. 8138308, "Modified Peptide Substrate," issued March 20, 2012. India patent no. 244241, "Enzyme Measurement Assay Using a Modified Substrate Comprising a Substrate Attached to a Macromolecule via a Spacer," issued November 25, 2010. Europe patent application, serial no. 06840527.3, "Enzyme Measurement Assay Using A Modified Substrate Comprising a Substrate Attached to a Macromolecule via a Spacer," issued October 2019. China patent application, serial no. 200680053447, "Enzyme Measurement Assay Using a Modified Substrate Comprising a Substrate Attached to a Macromolecule via a Spacer," filed December 21, 2006. Japan patent application, serial no. 2008-547812, "Enzyme Measurement Assay Using a Modified Substrate Comprising a Substrate Attached to a Macromolecule via a Spacer," filed December 21, 2006.

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