Hematologic concerns in extracorporeal membrane oxygenation

Jonathan Sniderman MD, CM1 | Paul Monagle MBBS, MD, FRACP, FRCPA, FCCP2 | Gail M. Annich MD, MS, FRCPC3 | Graeme MacLaren MBBS, MSc, FCCM, FELSO1,4,5

1Paediatric ICU, Royal Children's Hospital, Melbourne, Vic., Australia
2Department of Paediatrics, Department of Haematology, University of Melbourne, The Royal Children's Hospital, Haematology Research Murdoch Children's Research Institute, Melbourne, Vic., Australia
3Department of Critical Care Medicine, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada
4Department of Paediatrics, University of Melbourne, Parkville, Vic., Australia
5Cardiothoracic ICU, National University Health System, Singapore City, Singapore

Correspondence
Graeme MacLaren, Cardiothoracic ICU, National University Hospital, Singapore, Singapore.
Email: gmaclaren@iinet.net.au

Handling Editor: Dr Pantep Angchaisuksiri

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. 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. The bleeding risk remains, with major hemorrhage rates of 19% being reported in a recent systematic review and meta-analysis. Intracranial hemorrhage rates are a concern on VV ECMO, with rates approaching 16% in patients with severe acute respiratory distress syndrome (ARDS). 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.

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. 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. 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. 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. 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.

All ECMO configurations carry a high risk of infections, with rates between 13% and 40%, and some reporting higher rates in VA ECMO. Infection risk, driven by mediastinitis, is higher with central cannulation. Central cannulation is associated with the highest bleeding risk. Neck cannulation is associated with the most cerebral injuries. 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.

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. 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 pre-existing risk may be exacerbated by ECMO. 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

### 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.
as influencing dosage and clearance of heparin and other medica-
tions.\(^{26-28}\) This will be further compounded by patients being placed
onto additional mechanical support with continuous renal replace-
ment 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 hemoly-
sis.\(^{27,30,31}\) The reason CRRT causes an increase in platelet transfu-
sions 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 dys-
function, and disruption of the hematologic system.\(^{32}\) Blood expo-
sure to artificial surfaces results in fibrinogen, albumin, and other
hematologic proteins coating the artificial surface, platelet activa-
tion, and inflammation.\(^{33-36}\) Current ECMO tubing is made from pol-
yvinyl 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 im-
provements and the availability of heparin-bonded tubing, the need
for systemic anticoagulation has not been eliminated and the sig-
nificant challenges and problems of disrupted hematologic hemo-
stasis 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 ni-
tric 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 re-
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 hepa-
erin need in several studies of cardiopulmonary bypass when
compared to unlined circuits.\(^{45-47}\) Whether PPC is superior to hepa-
erin-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 associ-
ated with reduced platelet aggregation and reduced adsorption of
proteins.\(^{49-51}\) Performance when compared to heparin-bonded cir-
cuity is mixed, with possible reduction in adsorption of fibrinogen
and need for platelet transfusions, but possible increased leukope-
nia, 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      | Reduced platelet consumption and thrombosis in animals, NO release and longevity difficult |
|                         | bonded            |                                                                 |
| Biopassive surfaces     | Phosphorylcholine | Reduced heparin needs in cardiopulmonary bypass, unclear if better than heparin bonded |
|                         | lined             |                                                                 |
|                         | 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.  

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. 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. 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. 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. Research is ongoing in how to design circuit membranes that encourage EPCs to create new endothelium across their surface. 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 XIIIf (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 XIIIf 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.

| TABLE 3 Hematologic and inflammatory consequences of initiating ECMO |
|-----------------------------------------------|
| **Hematologic consequences**                  |
| Factor XIIa and XIIIf 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; XIIIf, 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, thrombospordin, fibronectin, immunoglobulin E, von Willebrand factor, albumin, and hemoglobin. 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.

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. 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. Shear stress may contribute to platelet activation and may also contribute to loss of platelet surface receptors necessary for adhesion. Von Willebrand factor multimers may be lost, particularly with centrifugal pumps, reducing the ability of platelets to bind to von Willebrand factor. 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. 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. 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%. 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 vasconstriction.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. By90 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.84 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,
and hypertriglyceridemia (true also for other assays if optical detection of clot is the test methodology). 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.

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. The normal range for antithrombin levels changes with age and is significantly lower in children in intensive care.

By giving antithrombin, the amount of heparin needed to obtain the therapeutic level is reduced by a variable amount. 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 recently 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
thrombogenic and anticoagulant, especially in an unbalanced hematologic system already in dysregulation. 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. In addition, antithrombin may be associated with significant harm and increased rates of both bleeding and thrombotic events. 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.

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. 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. 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. Dilute thrombin time has been suggested as an alternative monitoring test, but this assay is not readily available in many laboratories. 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. 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.

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. 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. 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. 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.

| TABLE 5 | Issues associated with common heparin monitoring tests |
| 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.

Site of sampling and potential contamination is an issue regardless of test.
single-center retrospective review of neonatal hematocrit transfusion threshold on ECMO, Sawyer et al\textsuperscript{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 hemoglobin or hematocrit.\textsuperscript{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.\textsuperscript{143,144} In a review of 511 children on ECMO, Cashen et al\textsuperscript{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.

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 were 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.\textsuperscript{169} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{169} We have not yet adequately elucidated the effect disease process versus ECMO complications or ECMO techniques has on long-term development. Finding appropriate outcomes to titrate our hematologic parameters should look beyond mortality, bleeding, and thrombosis, to fully appreciate the long-term consequences.

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

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\textsuperscript{153} presented a novel surface coating for ECMO circuitry, which showed promise in reducing platelet adhesion and contact system activation. Visser et al\textsuperscript{154} and Butler et al\textsuperscript{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\textsuperscript{156} demonstrated both age and analyzer and reagent specific normative values for factors VIII and IX, while Keragala et al\textsuperscript{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\textsuperscript{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 Arachchilage et al\textsuperscript{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\textsuperscript{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. 200680053447, “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. 06840527.3, “Enzyme Measurement Assay Using A Modified Substrate Comprising a Substrate Attached to a Macromolecule via a Spacer,” issued 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,” issued December 21, 2006.

ORCID

Graeme MacLaren https://orcid.org/0000-0002-1307-4274

TWITTER

Gail M. Annich @AnnichGail

REFERENCES

1. Werho DK, Pasquali SK, Yu S, Donohue J, Annich GM, Thiagarajan RR, et al. Epidemiology of stroke in pediatric cardiac surgical patients supported with extracorporeal membrane oxygenation. Ann Thorac Surg. 2015;100(5):1751–7.
2. Nasr DM, Rabinstein AA. Neurologic complications of extracorporeal membrane oxygenation. J Clin Neurol. 2015;11(4):383–9.
3. Le Guennec L, Cholet H, Huang F, Schmidt M, Brechot N, Hekimian G, et al. Ischemic and hemorrhagic brain injury during venoarterial-extracorporeal membrane oxygenation. Ann Intensive Care. 2018;8(1):129.
4. Khorsandi M, Dougherty S, Bouamra O, Pai V, Curry P, Tsui S, et al. Extra-corporeal membrane oxygenation for refractory cardiogenic shock after adult cardiac surgery: a systematic review and meta-analysis. J Cardiothorac Surg. 2017;12(1):55.
5. Rao P, Khalpey Z, Smith R, Burkhoff D, Kociol RD. Venoarterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest. Circ Heart Fail. 2018;11(9):e004905.
6. Le Gall A, Follin A, Cholley B, Mantz J, Aissouai N, Pirracchio R. Veno-arterial-ECMO in the intensive care unit: From technical aspects to clinical practice. Anaesth Crit Care Pain Med. 2018;37(3):259–68.
7. Dalton HJ, Reeder R, Garcia-Filion P, Holubkov R, Berg RA, Zuppa A, et al. Factors associated with bleeding and thrombosis in children receiving extracorporeal membrane oxygenation. Am J Respir Crit Care Med. 2017;196(6):762–71.
8. Davis C, Walker G. ECLS cannulation for neonates with respiratory failure. In: Brogan TV, Lequier L, Lorusso R, MacLaren G, Peek G, editors Extracorporeal life support: the ELSO red book. 5th ed. Ann Arbor, MI: Extracorporeal Life Support Organization, 2017; p.159–67.
9. Munshi L, Walkey A, Goligher J, Pham T, Uleryk EM, Fan E. Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. Lancet Respir Med. 2019;7(2):163–72.
10. Lockie CJA, Gillon SA, Barrett NA, Taylor D, Mazumder A, Paramesh K, et al. Severe respiratory failure, extracorporeal membrane oxygenation, and intracranial hemorrhage. Crit Care Med. 2017;45(10):1642–9.
11. Arachchilage DRJ, Passariello M, Laffan M, Aw TC, Owen L, Banya W, et al. Intracranial hemorrhage and early mortality in patients receiving extracorporeal membrane oxygenation for severe respiratory failure. Semin Thromb Hemost. 2018;44(3):276–86.
12. Butt W, Heard M, Peek GJ. Clinical management of the extracorporeal membrane oxygenation circuit. Pediatr Crit Care Med. 2013;14(5 suppl 1):513–9.
13. Halaweish I, Cole A, Cooley E, Lynch WR, Haft JW. Roller and centrifugal pumps: a retrospective comparison of bleeding complications in extracorporeal membrane oxygenation. ASAIO J. 2015;61(5):496–501.
14. Dalton HJ, Butt WW. Extracorporeal life support: an update of Rogers’ Textbook of Pediatric Intensive Care. Pediatr Crit Care Med. 2012;13(4):461–71.
15. Valencia E, Nasr VG. Updates in Pediatric Extracorporeal Membrane Oxygenation. J Cardiothorac Vasc Anesth. 2020;34(5):1309–23.
16. MacLaren G, Schlabach LJ, Alken AM. Nosocomial infections during extracorporeal membrane oxygenation in neonatal, pediatric, and adult patients: a comprehensive narrative review. Pediatr Crit Care Med. 2020;21(3):283–90.
17. Raffa GM, Kowalewski M, Brodie D, Ogino M, Whitman G, Meani P, et al. Meta-analysis of peripheral or central extracorporeal membrane oxygenation in postcardiotomy and non-postcardiotomy shock. Ann Thorac Surg. 2019;107(1):311–21.
18. Teele SA, Salvin JW, Barrett CS, Rycus PT, Fynn-Thompson F, Laussen PC, et al. The association of carotid artery cannulation and neurologic injury in pediatric patients supported with venoarterial extracorporeal membrane oxygenation. Pediatr Crit Care Med. 2014;15(4):355–61.
19. Rupprecht L, Lunz D, Philipp A, Lubnow M, Schmid C. Pitfalls in percutaneous ECMO cannulation. Heart Lung Vessell. 2015;7(4):290–6.

20. Chung M, Shiloh AL, Carlese A. Monitoring of the adult patient on venoarterial extracorporeal membrane oxygenation. Scientific World J. 2014;2014:392258.

21. Xie A, Forrest P, Loforte A. Left ventricular decompression in veno-arterial extracorporeal membrane oxygenation. Ann Cardiothorac Surg. 2019;8(1):9–18.

22. Cevasco M, Takayama H, Ando M, Garan AR, Naka Y, Takeda K. Left ventricular distention and venting strategies for patients on venoarterial extracorporeal membrane oxygenation. J Thorac Dis. 2019;11(4):1676–83.

23. Esmon CT. Inflammation and thrombosis. J Thromb Haemost. 2003;1(7):1343–8.

24. Doyle AJ, Hunt BJ. Current understanding of how extracorporeal membrane oxygenators activate haemostasis and other blood components. Front Med (Lausanne). 2018;5:352.

25. 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;13(3):387.

26. Askenazi DJ, Ambalavanan N, Hamilton K, Cutter G, Laney D, Kaslov R, et al. Acute kidney injury and renal replacement therapy independently predict mortality in neonatal and pediatric noncardiac patients on extracorporeal membrane oxygenation. Pediatr Crit Care Med. 2011;12(1):e1–6.

27. Lou S, MacLaren G, Paul E, Best D, Delzoppo C, Butt W. Hemofiltration is not associated with increased mortality in children receiving extracorporeal membrane oxygenation. Pediatr Crit Care Med. 2015;16(2):161–6.

28. Smith AH, Hardinson DC, Worden CR, Fleming GM, Taylor MB. Acute renal failure during extracorporeal support in the pediatric cardiac patient. ASAIO J. 2009;55(4):412–6.

29. de Tymowski C, Desmard M, Lortat-Jacob B, Pellenc Q, Alkhoder S, Alouache A, et al. Impact of connecting continuous renal replacement therapy to the extracorporeal membrane oxygenation circuit. Anaesth Crit Care Pain Med. 2018;37(6):557–64.

30. Chen H, Yu RG, Yin NN, Zhou JX. Combination of extracorporeal membrane oxygenation and continuous renal replacement therapy in critically ill patients: a systematic review. Crit Care. 2014;18(6):675.

31. Ostermann M, Connor MJr, Kashani K. Continuous renal replacement therapy during extracorporeal membrane oxygenation: why, when and how? Curr Opin Crit Care. 2018;24(6):493–503.

32. Ontaneda A, Annich GM. Novel surfaces in extracorporeal membrane oxygenation circuits. Front Med (Lausanne). 2018;5:321.

33. Reynolds MM, Annich GM. The artificial endothelium. Organogenesis. 2011;7(1):42–9.

34. Besser MW, Klein AA. The coagulopathy of cardiopulmonary bypass. Crit Rev Clin Lab Sci. 2010;47(5–6):197–212.

35. Vogler EA, Siedlecki CA. Contact activation of blood-plasma coagulation. Biomaterials. 2009;30(10):1857–69.

36. Edmunds Jr LH. Blood-surface interactions during cardiopulmonary bypass. J Card Surg. 1993;8(3):404–10.

37. Sohn N, Marcoux J, Myczyk T, Krahn J, Meng Q. The impact of different biocompatible coated cardiopulmonary bypass circuits on inflammatory response and oxidative stress. Perfusion. 2009;24(4):231–7.

38. de Vroeghe R, Huybregts R, van Oeveren W, van Klarenbosch J, Linley G, Mutlu J, et al. The impact of heparin-coated circuits on hemodynamics during and after cardiopulmonary bypass. Artif Organs. 2005;29(6):490–7.

39. Wendel HP, Ziemer G. Coating-techniques to improve the hemocompatibility of artificial devices used for extracorporeal circulation. Eur J Cardiothorac Surg. 1999;16(3):342–50.

40. Jansen PG, te Velthuis H, Huybregts RA, Paulus R, Bulder ER, van der Spoel HI, et al. Reduced complement activation and improved postoperative performance after cardiopulmonary bypass with heparin-coated circuits. J Thorac Cardiovasc Surg. 1995;110(3):829–34.

41. Radomski MW, Zakar T, Salas E. Nitric oxide in platelets. Methods Enzymol. 1996;269:88–107.

42. Skrzypczak AM, Lafayette NG, Bartlett RH, Zhou Z, Frost MC, Meyerhoff ME, et al. Effect of varying nitric oxide release to prevent platelet consumption and preserve platelet function in an in vivo model of extracorporeal circulation. Perfusion. 2007;22(3):193–200.

43. Wu B, Gerlitz B, Grinnell BW, Meyerhoff ME. Polymeric coatings that mimic the endothelium: combining nitric oxide release with surface-bound active thrombomodulin and heparin. Biomaterials. 2007;28(28):4047–55.

44. De Somer F, Francois K, van Oeveren W, Poelaert J, De Wolf D, Ebels T, et al. Phosphorylcholine coating of extracorporeal circuits provides natural protection against blood activation by the material surface. Eur J Cardiothorac Surg. 2000;18(5):602–6.

45. Ranucci M, Pazzaglia A, Isgro G, Cazzaniga A, Ditta A, Boncilli A, et al. Closed, phosphorylcholine-coated circuit and reduction of systemic heparinization for cardiopulmonary bypass: the intraoperative ECMO concept. Int J Artif Organs. 2002;25(9):875–81.

46. Ranucci M, Isgro G, Soro G, Canziani A, Menicanti L, Frigiol A. Reduced systemic heparin dose with phosphorylcholine coated closed circuit in coronary operations. Int J Artif Organs. 2004;27(4):311–9.

47. Pappalardo F, Della Valle P, Cresceni G, Corno C, Franco A, Torraca L, et al. Phosphorylcholine coating may limit thrombin formation during high-risk cardiac surgery: a randomized controlled trial. Ann Thorac Surg. 2006;81(3):886–91.

48. Thiara AS, Andersen YV, Videm V, Molines TE, Svennevig K, Hoel TN, et al. Comparable biocompatibility of Phisio- and Bioiline-coated cardiopulmonary bypass circuits indicated by the inflammatory response. Perfusion. 2010;25;1:9–16.

49. Tanaka M, Motomura T, Kawada M, Anzai T, Kashi Y, Shirota Y, et al. Blood compatible aspects of poly(2-methoxyethylacrylate) (PMEA)–relationship between protein adsorption and platelet adhesion on PMEA surface. Biomaterials. 2000;21(14):1471–81.

50. Saito N, Motoyama S, Sawamoto J. Effects of new polymer-coated extracorporeal circuits on biocompatibility during cardiopulmonary bypass. Artif Organs. 2000;24(7):547–54.

51. Gunaydin S, Farsak B, Kokakul M, Sari T, Yorgancioglu C, Zorlutuna Y. Clinical performance and biocompatibility of poly(2-methoxyethylacrylate)-coated extracorporeal circuits. Ann Thorac Surg. 2002;74(3):819–24.

52. Hosoyama K, Ito K, Kawamoto S, Kumagai K, Akiyama M, Adachi O, et al. Poly-2-methoxyethylacrylate-coated cardiopulmonary bypass circuit can reduce transfusion of platelet products compared to heparin-coated circuit during aortic arch surgery. J Artif Organs. 2016;19(3):875–81.

53. Suhara H, Sawa Y, Nishimura M, Oshiyama H, Yokoyama K, Saito TN, et al. Efficacy of a new coating material, PMEA, for cardiopulmonary bypass circuits indicated by the inflammatory response. Perfusion. 2010;25(1):9–16.

54. Rupprecht L, Lunz D, Philipp A, Lubnow M, Schmid C. Pitfalls in percutaneous ECMO cannulation. Heart Lung Vessell. 2015;7(4):290–6.

55. Vogler EA, Siedlecki CA. Contact activation of blood-plasma coagulation. Biomaterials. 2009;30(10):1857–69.

56. Edmunds Jr LH. Blood-surface interactions during cardiopulmonary bypass. J Card Surg. 1993;8(3):404–10.

57. Sohn N, Marcoux J, Myczyk T, Krahn J, Meng Q. The impact of different biocompatible coated cardiopulmonary bypass circuits on inflammatory response and oxidative stress. Perfusion. 2009;24(4):231–7.
56. Leslie DC, Waterhouse A, Berthet JB, Valentin TM, Watters AL, Jain A, et al. A bioinspired omniphobic coating on medical devices prevents thrombosis and biofouling. Nat Biotechnol. 2014;32(11):1134–40.
57. Liu T, Liu S, Zhang K, Chen J, Huang N. Endothelialization of implanted cardiovascular biomaterial surfaces: the development from in vitro to in vivo. J Biomed Mater Res A. 2014;102(10):3754–72.
58. Goh ET, Wong E, Farhatnia Y, Tan A, Seifalian AM. Accelerating in situ endothelialization of cardiovascular bypass grafts. Int J Mol Sci. 2014;16(1):597–627.
59. Pang JH, Farhatnia Y, Godarzi F, Tan A, Rajadas J, Cousins BG, et al. In situ endothelialization: bioengineering considerations to translation. Small. 2015;11(47):6248–64.
60. Laverty KS, Rhodes C, McGraw A, Eppihimer MJ. Anti-thrombotic technologies for medical devices. Adv Drug Deliv Rev. 2017;112:2–11.
61. Adrian K, Mellgren K, Skogby M, Friberg LG, Mellgren G, Wadenhöv H. The effect of albumin priming solution on platelet activation during experimental long-term perfusion. Perfusion. 1998;13(3):187–91.
62. Abrams D, Baldwin MR, Champion M, Agerstrand C, Eisenberger A, Bachetta M, et al. Thrombocytopenia and extracorporeal membrane oxygenation in adults with acute respiratory failure: a cohort study. Intensive Care Med. 2016;42(5):844–52.
63. Dzierba AL, Roberts R, Muir J, Alhammad A, Schumaker G, Clark J, et al. Severe thrombocytopenia in adults with severe acute respiratory distress syndrome: impact of extracorporeal membrane oxygenation use. ASAIO J. 2016;62(6):710–4.
64. Yoshimoto Y, Hasebe T, Takahashi K, Amari M, Nagashima S, Kamiyo A, et al. Ultrastructural characterization of surface induced-platelet activation on artificial materials by transmission electron microscopy. Microsc Res Tech. 2013;76(4):342–9.
65. Chen Z, Mondal NK, Zheng S, Koenig SC, Slaughter MS, Griffith BP, et al. High shear induces platelet dysfunction leading to enhanced thrombopoeisis and diminished hemostatic capacity. Platelets. 2019;30(1):112–9.
66. Chen Z, Mondal NK, Ding J, Koenig SC, Slaughter MS, Wu ZJ. Paradoxic effect of nonphysiologic shear stress on platelets and von willebrand factor. Artif Organs. 2016;40(7):659–68.
67. 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.
68. Balle CM, Jeppesen AN, Christensen S, Hvas AM. Platelet function during extracorporeal membrane oxygenation in adult patients. Front Cardiovasc Med. 2019;6:114.
69. Lou S, MacLaren G, Best D, Delzoppo C, Butt W. Hemolysis in pediatric patients receiving centrifugal-pump extracorporeal membrane oxygenation: prevalence, risk factors, and outcomes. Crit Care Med. 2014;42(5):1213–20.
70. Okochi S, Cheung EW, Barton S, Zenilman A, Shakoor A, Street C, et al. An analysis of risk factors for hemolysis in children on extracorporeal membrane oxygenation. Pediatr Crit Care Med. 2018;19(11):1059–66.
71. Dalton HJ, Cashen K, Reeder RW, Berg RA, Shanley TP, Newth CJL, et al. Hemolysis during pediatric extracorporeal membrane oxygenation: associations with circuitry, complications, and mortality. Pediatr Crit Care Med. 2018;19(11):1067–76.
72. Omar HR, Mirsaeidi M, Socias S, Sprenger C, Caldeira C, Camporesi EM, et al. Plasma free hemoglobin is an independent predictor of mortality among patients on extracorporeal membrane oxygenation support. PLoS ONE. 2015;10(4):e0124034.
73. Pan KC, McKenzie DP, Pellegrino V, Murphy D, Butt W. The meaning of a high plasma free haemoglobin: retrospective review of the prevalence of haemolysis and circuit thrombosis in an adult ECMO centre over 5 years. Perfusion. 2016;31(3):223–31.
74. Lyu L, Long C, Hei F, Ji B, Liu J, Yu K, et al. Plasma free hemoglobin is a predictor of acute renal failure during adult venous-arterial extracorporeal membrane oxygenation support. J Cardiothorac Vasc Anesth. 2016;30(4):891–5.
75. Lehle K, Philipp A, Zeman F, Luntz D, Lubnow M, Wendel HP, et al. Technical-induced hemolysis in patients with respiratory failure supported with veno-venous ECMO - prevalence and risk factors. PLoS ONE. 2015;10(11):e0143527.
76. Dufour N, Radijou A, Thuong M. Hemolysis and plasma free hemoglobin during extracorporeal membrane oxygenation support: from clinical implications to laboratory details. a review. ASAIO J. 2020;66(3):239–46.
77. Helms C, Kim-Shapiro DB. Hemoglobin-mediated nitric oxide signaling. Free Radic Biol Med. 2013;61:464–72.
78. Arnold P, Jackson S, Wallis J, Smith J, Bolton D, Haynes S. Coagulation factor activity during neonatal extracorporeal membrane oxygenation. Intensive Care Med. 2001;27(8):1395–400.
79. Kern FH, Morana NJ, Sears JJ, Hickey PR. Coagulation defects in neonates during cardiopulmonary bypass. Ann Thorac Surg. 1992;54(3):541–6.
80. Doymaz S, Zinger M, Sweberg T. Risk factors associated with intracranial hemorrhage in neonates with persistent pulmonary hypertension on ECMO. J Intensive Care. 2015;3(1):6.
81. Lorusso R, Barilli F, Mauro MD, Gelsomino S, Parise O, Rycus PT, et al. In-hospital neurologic complications in adult patients undergoing venoarterial extracorporeal membrane oxygenation: results from the extracorporeal life support organization registry. Crit Care Med. 2016;44(10):e964–e972.
82. Cavayas YA, Del Sorbo L, Fan E. Intracranial hemorrhage in adults on ECMO. Perfusion. 2018;33(1_suppl):42–50.
83. Fletcher-Sandersjoo A, Thelin EP, Barta K Jr, Broman M, Sallisalmi M, Elmi-Terander A, et al. Incidence, outcome, and predictors of intracranial hemorrhage in adult patients on extracorporeal membrane oxygenation: a systematic and narrative review. Front Neurol. 2018;9:548.
84. Wiew MA, Whitehead MT, Bulas D, Ridore M, Melbourne L, Oldenburg G, et al. Patterns of brain injury in newborns treated with extracorporeal membrane oxygenation. AJNR Am J Neuroradiol. 2017;38(4):820–6.
85. Rozmiarek AJ, Qureshi FG, Cassidy L, Ford HR, Gaines BA, Rycus P, et al. How low can you go? Effectiveness and safety of extracorporeal membrane oxygenation in low-birth-weight neonates. J Pediatr Surg. 2004;39(6):845–7.
86. Harvey C. Cannulation for neonatal and pediatric extracorporeal membrane oxygenation for cardiac support. Front Pediatr. 2018;6:17.
87. Ij H, Hunfeld M, Schiller RM, Hounes RJ, Hoskote A, Tibboel D, et al. Improving long-term outcomes after extracorporeal membrane oxygenation: from observational follow-up programs towards risk stratification. Front Pediatr. 2018;6:177.
88. Buesing KA, Kilian AK, Schaible T, Loff S, Sumargo S, Neff KW. Extracorporeal membrane oxygenation in infants with congenital diaphragmatic hernia: follow-up MRI evaluating carotid artery reocclusion and neurologic outcome. AJR Am J Roentgenol. 2007;188(6):1636–42.
89. Ignjatovic V, Furmedge J, Newall F, Chen A, Berry L, Fong C, et al. Age-related differences in heparin response. Thromb Res. 2006;118(6):741–5.
90. Newall F, Ignjatovic V, Johnston L, Summerhayes R, Lane G, Cranswick N, et al. Age is a determinant factor for measures of concentration and effect in children requiring unfractionated heparin. Thromb Haemost. 2010;103(5):1085–90.
91. Al-Sallami H, Newall F, Monagle P, Ignjatovic V, Cranswick N, Duffull S. Development of a population
pharmacokinetic-pharmacodynamic model of a single bolus dose of unfractionated heparin in paediatric patients. Br J Clin Pharmacol. 2016;82(1):178–84.

92. Newall F, Johnston L, Ignjatovic V, Monagle P. Unfractionated heparin therapy in infants and children. Pediatrics. 2009;123(3):e510–e518.

93. Monagle P, Barnes C, Ignjatovic V, Furmidge J, Newall F, Chan A, et al. Developmental haemostasis. Impact for clinical haemostasis laboratories. Thromb Haemost. 2006;95(2):362–72.

94. Andrew M, Vegh P, Johnston M, Bowker J, Ofosu F, Mitchell L. Maturation of the haemostatic system during childhood. Blood. 1992;80(8):1998–2005.

95. Barton R, Ignjatovic V, Monagle P. Anticoagulation during ECMO in neonatal and paediatric patients. Thromb Res. 2019;173:172–7.

96. Ignjatovic V, Summerhayes R, Than J, Gan A, Monagle P. Therapeutic range for unfractionated heparin therapy: age-related differences in response in children. J Thromb Haemost. 2006;4(10):2280–2.

97. Siekmann I, Bjelosevic S, Landman K, Monagle P, Ignjatovic V, Crampin EJ. Mathematical modelling indicates that lower activity of the haemostatic system in neonates is primarily due to lower prothrombin concentration. Sci Rep. 2019;9(1):3936.

98. Toulon P, Berruyer M, Brionne-Francois M, Grand F, Lasne D, Telion C, et al. Age dependency for coagulation parameters in paediatric populations. Results of a multicentre study aimed at defining the age-specific reference ranges. Thromb Haemost. 2016;116(1):9–16.

99. Bembea MM, Annich G, Rycus P, Oldenburg G, Berkowitz I, Pronovost P. Variability in anticoagulation management of patients on extracorporeal membrane oxygenation: an international survey. Pediatr Crit Care Med. 2013;14(2):S77–84.

100. Padhya DP, Prutsky GJ, Nemergut ME, Schears GS, Flick RP, Farah W, et al. Routine laboratory measures of heparin anti-coagulation for children on extracorporeal membrane oxygenation: systematic review and meta-analysis. Thromb Res. 2019;179:132–9.

101. Penk JS, Reddy S, Polito A, Cisco MJ, Allan CK, Bembea M, et al. Bleeding and thrombosis with pediatric extracorporeal life support: a roadmap for management, research, and the future from the pediatric cardiac intensive care society: part 2. Pediatr Crit Care Med. 2019;20(11):1034–9.

102. Penk JS, Reddy S, Polito A, Cisco MJ, Allan CK, Bembea MM, et al. Bleeding and thrombosis with pediatric extracorporeal life support: a roadmap for management, research, and the future from the pediatric cardiac intensive care society: part 1. Pediatr Crit Care Med. 2019;20(11):1027–33.

103. Andrew M, MacIntyre B, MacMillan J, Williams WG, Gruenwald C, Johnston M, et al. Heparin therapy during cardiopulmonary bypass in children requires ongoing quality control. Thromb Haemost. 1993;70(6):937–41.

104. Vera-Aguilera J, Yousef H, Bundalani SG, Teruya J. The influence of free hemoglobin and bilirubin on heparin monitoring by activated partial thromboplastin time and anti-Xa assay. Arch Pathol Lab Med. 2014;138(11):1503–6.

105. Kostousov V, Nguyen K, Hundalani SG, Teruya J. The influence of free hemoglobin and bilirubin on heparin monitoring by activated partial thromboplastin time and anti-Xa assay. World J Pediatr Congenit Heart Surg. 2014;5(2):345–7.

106. Anderson L, Quasim I, Steven M, Moise SF, Shelley B, Schraag S, et al. Interoperator and intraoperator variability of whole blood coagulation assays: a comparison of thromboelastography and rotational thromboelastometry. J Cardiothorac Vasc Anesth. 2014;28(6):1550–7.

107. Solomon C, Sorensen B, Hochleitner G, Kashuk J, Ranucci M, Schoch H. Comparison of whole blood fibrin-based clot tests in thrombelastography and thromboelastometry. Anesth Analg. 2012;114(4):721–30.

108. Wiedermann CJ. Clinical review: molecular mechanisms underlying the role of antithrombin in sepsis. Crit Care. 2006;10(1):209.

109. Ryerson LM, Bauman ME, Kuhle S, Bruce AA, Massicotte MP. Antithrombin concentrate in pediatric patients requiring unfractionated heparin anticoagulation: a retrospective cohort study. Pediatr Crit Care Med. 2014;15(8):e340–6.

110. Diaz R, Moffett BS, Karabinas S, Guffrey D, Mahoney DH Jr, Yee DL. Antithrombin concentrate use in children receiving unfractionated heparin for acute thrombosis. J Pediatr. 2015;167(3):645–9.

111. Niederer RA, Christensen M, Berens R, Wellner H, Mikhailov T, Tweddell JS. Antithrombin replacement during extracorporeal membrane oxygenation. Artif Organs. 2011;35(11):1024–8.

112. Wong TE, Delaney M, Gernsheimer T, Matthews DC, Brogan TV, Mazor R, et al. Antithrombin concentrates use in children on extracorporeal membrane oxygenation: a retrospective cohort study. Pediatr Crit Care Med. 2015;16(3):264–9.

113. Wong TE, Nguyen T, Shah SS, Brogan TV, Wittmer CM. Antithrombin concentrate use in pediatric extracorporeal membrane oxygenation: a multicenter cohort study. Pediatr Crit Care Med. 2016;17(12):1170–8.

114. Karlaftis V, Attard C, Monagle P, Ignjatovic V. Latent antithrombin levels in children and adults. Thromb Res. 2013;131(1):105–6.

115. Karlaftis V, Srithanan G, Attard C, Corral J, Monagle P, Ignjatovic V. Beta (beta)-antithrombin activity in children and adults: implications for heparin therapy in infants and children. J Thromb Haemost. 2014;12(7):1141–4.

116. MacLaren G, Monagle P. Antithrombin administration in extracorporeal membrane oxygenation patients: putting the cart before the horse. Pediatr Crit Care Med. 2016;17(12):1188–9.

117. Baird CW, Zurakowski D, Robinson B, Gandhi S, Burdis-Koch L, Tamblyn J, et al. Anticoagulation and pediatric extracorporeal membrane oxygenation: impact of activated clotting time and heparin dose on survival. Ann Thorac Surg. 2007;83(3):912–20.

118. Runyan CL, Cabral KP, Riker RR, Redding D, May T, Seder DB, et al. Correlation of bivalirudin dose with creatinine clearance during treatment of heparin-induced thrombocytopenia. Ann Pharmacother. 2011;45(10):1185–92.

119. Tsal LV, Dager WE. Bivalirudin dosing adjustments for reduced renal function with or without hemodialysis in the management of heparin-induced thrombocytopenia. Ann Pharmacother. 2011;35(9):850–6.

120. Sanfilippo F, Asmussen S, Maybauer DM, Santonocito C, Fraser JF, Erdoes G, et al. Bivalirudin for alternative anticoagulation in extracorporeal membrane oxygenation: a systematic review. J Intensive Care Med. 2017;32(5):312–9.

121. Ranucci M, Ballotta A, Kandil H, Isgro G, Carlucci C, Baryshnikova V. Beta (beta)-antithrombin activity in children and adults: implications for heparin therapy in infants and children. J Thromb Haemost. 2016;17(12):1170–8.

122. Ryerson LM, Bauman ME, Kuhle S, Bruce AA, Massicotte MP. Antithrombin concentrate in pediatric patients requiring unfractionated heparin anticoagulation: a retrospective cohort study. Pediatr Crit Care Med. 2014;15(8):e340–6.

123. Pollak U, Yacobobich J, Tamary H, Dagan O, Manor-Shulman O. Antithrombin concentrates use in children on extracorporeal membrane oxygenation: a case report and review of the literature. J Intensive Care Med. 2019;34(5):279–87.
125. Koster A, Faraoni D, Levy JH. Argatroban and bivalirudin for perioperative anticoagulation in cardiac surgery. Anesthesiology. 2018;128(2):390–400.

126. Love JE, Ferrell C, Chandler WL. Monitoring direct thrombin inhibitors with a plasma diluted thrombin time. Thromb Haemost. 2007;98(1):234–42.

127. Staudacher DL, Blever PM, Benk C, Ahrens I, Bode C, Wengenmayer T. Dual antiplatelet therapy (DAPT) versus no antiplatelet therapy and incidence of major bleeding in patients on venoarterial extracorporeal membrane oxygenation. PLoS ONE. 2016;11(7):e0159973.

128. James C, Millar J, Horton S, Brizard C, Molesworth C, Butt W. Nitric oxide administration during paediatric cardiopulmonary bypass: a randomised controlled trial. Intensive Care Med. 2016;42(11):1744–52.

129. Tissot C, Habre W, Soccal P, Hug MI, Blettex D, Pellegrini M, et al. Successful lung transplant after prolonged extracorporeal membrane oxygenation (ECMO) in a child with pulmonary hypertension: a case report. Res Cardiovasc Med. 2016;5(3):e32545.

130. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999;340(6):409–17.

131. Holst LB, Haase N, Wetterson J, Wernerman J, Guttormsen AB, Karlsson S, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med. 2014;371(15):1381–91.

132. Muszynski JA, Reeder RW, Hall MW, Berg RA, Shanley TP, Newth CJL, et al. RBC transfusion practice in pediatric extracorporeal membrane oxygenation support. Crit Care Med. 2018;46(6):e552–9.

133. Tissot C, Habre W, Soccal P, Hug MI, Blettex D, Pellegrini M, et al. Successful lung transplant after prolonged extracorporeal membrane oxygenation (ECMO) in a child with pulmonary hypertension: a case report. Res Cardiovasc Med. 2016;5(3):e32545.

134. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999;340(6):409–17.

135. Holst LB, Haase N, Wetterson J, Wernerman J, Guttormsen AB, Karlsson S, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med. 2014;371(15):1381–91.

136. Muszynski JA, Reeder RW, Hall MW, Berg RA, Shanley TP, Newth CJL, et al. RBC transfusion practice in pediatric extracorporeal membrane oxygenation support. Crit Care Med. 2018;46(6):e552–9.

137. Tissot C, Habre W, Soccal P, Hug MI, Blettex D, Pellegrini M, et al. Successful lung transplant after prolonged extracorporeal membrane oxygenation (ECMO) in a child with pulmonary hypertension: a case report. Res Cardiovasc Med. 2016;5(3):e32545.

138. Lelubre C, Vincent JL. Red blood cell transfusion in the critically ill. Transfusion. 2016;56(11):e159973.

139. Sawyer AA, Wise L, Ghosh S, Bhatia J, Stansfield BK. Comparison of transfusion thresholds during neonatal extracorporeal membrane oxygenation. Transfusion. 2017;57(9):2115–20.

140. Agerstrand CL, Burkart KM, Abrams DC, Bacchetta MD, Brodie D. Blood conservation in extracorporeal membrane oxygenation for acute respiratory distress syndrome. Ann Thorac Surg. 2015;99(2):590–5.

141. Voelker MT, Busch T, Bercker S, Fichtner F, Kaisers UX, Laudi S. Restrictive transfusion practice during extracorporeal membrane oxygenation therapy for severe acute respiratory distress syndrome. Artif Organs. 2015;39(4):374–8.
Extracorporeal Membrane Oxygenation on Coagulation Factors - A Prospective Observational Study. Melbourne: ISTH; 2019.

160. Yaw HPSVH, Barton R, Newall F, D'Udekem Y, Horton S, Maclaren G, et al. Platelet Phenotype and Function in Paediatric Extracorporeal Membrane Oxygenation (ECMO) Circuits. Melbourne: ISTH; 2019.

How to cite this article: Sniderman J, Monagle P, Annich GM, MacLaren G. Hematologic concerns in extracorporeal membrane oxygenation. Res Pract Thromb Haemost. 2020;4:455–468. https://doi.org/10.1002/rth2.12346
Author/s: Sniderman, J; Monagle, P; Annich, GM; MacLaren, G

Title: Hematologic concerns in extracorporeal membrane oxygenation

Date: 2020-05-15

Citation: Sniderman, J., Monagle, P., Annich, G. M. & MacLaren, G. (2020). Hematologic concerns in extracorporeal membrane oxygenation. RESEARCH AND PRACTICE IN THROMBOSIS AND HAEMOSTASIS, 4 (4), pp.455-468. https://doi.org/10.1002/rth2.12346.

Persistent Link: http://hdl.handle.net/11343/246467

File Description: published version

License: CC BY-NC-ND