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Anticoagulation during ECMO in neonatal and paediatric patients

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ABSTRACT

Extracorporeal Membrane Oxygenation (ECMO) is a form of Extracorporeal Life Support (ECLS) which is used frequently in the paediatric and neonatal setting to support either the pulmonary, or both the pulmonary and cardiac systems. Management of ECMO requires the use of systemic anticoagulation to prevent patient and circuit based thrombosis, which in turn increases the risk of haemorrhage. A number of coagulation tests, laboratory and point of care based, are used to monitor anticoagulation, however the evidence for correlation of the test results with level of anticoagulant and clinical outcomes in children remains poor.

1. Introduction

Extracorporeal Membrane Oxygenation (ECMO) is a form of Extracorporeal Life Support (ECLS) which supports either the pulmonary system or both the pulmonary and cardiac systems, with the use of an artificial circuit. ECMO provides cardiac and respiratory support whilst reversible pathophysiological processes are allowed time to resolve, spontaneously or through medical or surgical interventions. As such ECMO is not considered a therapeutic intervention, rather a supportive therapy, and should be reserved for those with reversible pathophysiological processes [1].

ECMO involves removal of deoxygenated venous blood from the patient, passing the blood through a membrane oxygenator which includes pressurisation, and then returning the now oxygenated blood to either the venous or arterial side of the circulation. The site of blood collection and return in neonates and children is dependent upon the type of ECMO required and many patient factors. ECMO was first used successfully in a neonate with meconium aspiration and pulmonary hypertension in 1975. [2]. The development and growth of ECMO in neonates appeared to be faster than that in the adult population, which is in contrast to the majority of medical developments and technological interventions [3]. Over the following few decades the number of centres performing ECMO continued to grow, and ECMO within the neonatal and paediatric population became common practice. As the expertise and experience with ECMO increased so too did the survival rates [4]. However, across the different ECMO centres there is significant variation in the circuits used, both in terms of structure and design, oxygenators, pumps as well as the administration and monitoring of anticoagulation. There is no standard language or definitions for reporting of these variables in data and published records, which makes comparison of published literature very difficult.

2. Paediatric & neonatal indications for ECMO

Paediatric and neonatal patients who require ECMO are a heterogeneous group and the underlying pathophysiology of these indications may result in a coagulopathy of varying degrees and aetiologies. Neonates have the best survival rates compared with other ages and disease states [4,5], as listed in Table 1. The indications for ECMO are largely divided into respiratory and cardiac conditions, with the latter being further divided into those who have had cardiac surgery and those who have not.

3. Pathophysiology of ECMO

ECMO changes the blood-endothelial interface to blood-biomaterial, with continuous contact of circulating blood to the plastic tubing, resulting in activation of both the inflammatory and coagulation systems. This activation shifts the balance of normal haemostasis to a pro-coagulant state, as well as a pro-inflammatory state, of which the mechanisms and complexity is poorly understood [9].

Shortly after the commencement of ECMO the artificial surface of the circuit becomes coated with blood proteins, albumin and fibrinogen, followed by glycoproteins and von Willebrand Factor (vWF), which in turn act as an anchor for platelet attachment [10,11]. Platelet activation then results in exposure of Tissue Factor (TF) and subsequent

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Table 1
Paediatric & neonatal indications for ECMO.
Adapted from [6–8].

Neonatal respiratory diseases	Paediatric respiratory diseases
Congenital Diaphragmatic Hernia (CDH)	Acute Respiratory Failure without ARDS
Meconium Aspiration Syndrome (MAS)	Aspiration Pneumonia
Idiopathic Persistent Pulmonary Hypertension of the Newborn (PPHN)	Acute Respiratory Disease Syndrome (ARDS) - Sepsis related - Post-operative - Trauma related
Pneumonia	Status asthmaticus
Sepsis with respiratory compromise	PERTUSSIS pneumonia
Hyaline Membrane Disease (HMD) with PPHN	Pulmonary haemorrhage
Other congenital lung disorders	Influenza
	Drowning injury
	Pneumocystis jirovecii pneumonia
	Fungal pneumonia

Neonatal & paediatric cardiovascular diseases	
Cardiac surgery	Without cardiac surgery
Pre-operative stabilisation	Myocarditis
Failure to wean from Cardiopulmonary Bypass (CPB)	Cardiomyopathy
Low cardiac output syndrome in post-operative period	Pulmonary Hypertension
Cardiopulmonary arrest	Intractable arrhythmias
	Respiratory indications
	Cardiopulmonary arrest

initiation of coagulation. In addition, the high shear stress and non-laminar flow of ECMO activates vWF, further enhancing the activation of platelets. Parallel to the initiation of coagulation and resultant production of thrombin, in an attempt to localise clot formation the fibrinolytic system is activated [10]. The final pro-coagulant change which occurs is the stimulation of the contact activation system, which in turn activates the coagulation system via the intrinsic coagulation cascade, as well as the inflammatory and immune responses [10,12].

In an attempt to counteract this imbalance, systemic anticoagulation is introduced into the ECMO circuit, of which the gold standard remains Unfractionated Heparin (UFH). UFH aims to prevent both circuit and patient thrombosis, however anticoagulation can lead to haemorrhagic complications [13,14].

Furthermore, in an attempt to further prevent the activation of this pro-inflammatory and pro-coagulant state, a number of different types of circuits with the addition of Nitric Oxide (NO), impregnation with UFH and direct thrombin inhibitors have been developed, however, all circuits have still required the use of a systemic anticoagulant [15–17].

4. Complications of ECMO

Haemorrhage and thrombosis, remain the most common causes of morbidity and mortality in patients who receive ECMO therapy, despite significant improvements and experience in management. Haemorrhagic complications of ECMO are likely multifactorial, and may be due to both patient and circuit related factors. Thrombosis is defined as the formation of a blood clot, within either a blood vessel, circuit or filter that obstructs the flow of blood. The three aspects of Virchow's triad; hypercoagulability, haemodynamic changes (stasis or turbulence) and endothelial injury or dysfunction, can all be increased in patients due to disease status. However, they can also be increased with the use of the ECMO circuit. Inadequate anticoagulation and low flow states with areas of stasis or turbulence can lead to circuit thrombosis, and patient hypercoagulability from introduction of the circuit can further increase the risk of thrombosis.

The Extracorporeal Life Support Organisation (ELSO), formed in 1989, keeps ECMO related registry data that shows bleeding is common, with up to 11% of paediatric and neonatal ECMO patients having intracranial haemorrhage and 31% with bleeding at surgical or cannula sites. Thrombosis is also common with 17% of paediatric patients found to have a clot within the oxygenator [18]. Deaths related to severe haemorrhagic and thromboembolic complications occur in as many as 30–40% of cases [18–20].

4.1. Haemorrhage

The most common sites for bleeding are the surgical sites, including cannulation sites [21]. A number of guidelines define major bleeding as being one of the following; 4 ml/kg/h for > 4 h, intracranial haemorrhage, gastrointestinal bleeding that requires either endoscopic or surgical intervention and surgical site bleeding requiring surgical intervention. Minor bleeding can be defined as bleeding that does not exceed 4 ml/kg/h and does not persist for > 4 h.

One subset of paediatric patients who represent a unique population for haemorrhagic management, are those who are placed onto ECMO following cardiac surgery, the number of which is increasing over the years. Studies estimate that between 1 and 5% of patients will require ECMO support following cardiac surgery, due to subsequent left ventricular failure, residual lesions, coronary ischaemia, and poor myocardial function [21–23]. These patients often emerge from theatre with multiple surgical sites, dilutional coagulopathies and deranged coagulation systems, further increasing bleeding risk [21,24].

4.2. Thrombosis

The ELSO registry defines a significant thrombosis or clotting complication as an event which requires a change in a portion or the entire circuit. According to the 2015 ELSO Registry data, circuit clots were reported in 40% of ECMO runs, independent of age and disease status, with the oxygenator being the most common site [18]. Additional studies which have analysed post-mortem examinations of paediatric ECMO, revealed higher rates of thrombosis in up to 69% of patients, and 85% of patients with a history of congenital heart disease [25].

5. Anticoagulation in paediatric & neonatal ECMO

There is a paucity of data and research relating to the pharmacokinetic and pharmacodynamic profile of anticoagulation, as well as inadequate validation of anticoagulation management in children in general [26–28]. The majority of recommendations for the use of anticoagulation in paediatrics comes from prospective paediatric cohort & observational studies, extrapolation from adult research, as well as historical and anecdotal experience within individual centres [29]. In addition to the challenge of developmental haemostasis, other factors impact the ability of adult anticoagulation programs being extrapolated to paediatric use. For example, the varying distribution, binding and clearance of antithrombotic drugs amongst children of different ages, different aetiology of thromboembolism, limited vascular access which may impair delivery and monitoring of drugs, and lack of specific paediatric formulations of antithrombotic drugs [26] all point to inadequacies of interpolation between adult and paediatric anticoagulation protocols.

The current standard of care for anticoagulation in ECMO is a continuous infusion of UFH, which aims to prevent both circuit and patient thrombosis [13,14]. UFH is a complex glycosaminoglycan and its activity is dependent upon its binding to Antithrombin (AT) and results in a conformational change which enhances the inhibitory activity of AT, inactivating thrombin and preventing further thrombin generation [9,14,19,30]. The UFH-AT complex is able to inactivate free thrombin, however thrombin bound to fibrin or the subendothelial

matrix is not affected by these complexes, and as such is able to further stimulate the haemostatic system [19]. In addition to binding to AT, UFH binds to endogenous plasma proteins, platelet factor 4 and to high molecular weight multimers of vWF; collectively referred to as Heparin Binding Proteins (HBPs). Some HBPs are acute phase reactants released during activation of the inflammatory system, and others such as vWF and Platelet Factor 4 (PF4) are released during activation of the coagulation system, both of which states are induced by both the ECMO circuit and underlying patient pathophysiology [30]. Binding of UFH to these proteins reduces the anticoagulant activity of UFH. There is wide variability in plasma concentrations of these HBPs in patients on ECMO, as well as variation in age, and as a result the response of UFH is unpredictable at times and needs to be closely monitored [31]. UFH is eliminated in two phases in a dose-dependent fashion, with an initial rapid phase of hepatic uptake, followed by a slower phase involving renal clearance [32].

Overall anticoagulation protocols appear to be similar for those who require emergency therapy with ECMO, and also for those who are placed onto ECMO post-cardiac surgery. At the time of ECMO cannulation a bolus of UFH (50–100 units/kg) is given as a loading dose, and is usually followed by an UFH infusion (10 units/kg/h). The ongoing UFH infusion is maintained within the dose range of 10-40 units/kg/h, and is titrated based on regular monitoring tests [33].

A number of studies have reported that UFH has an age-dependent variation in activity within neonatal and paediatric patients [27,34–36]. There is a paucity of paediatric research in this area, and as such appropriate dosing, therapeutic ranges and monitoring protocols remain unclear and vary between different ECMO institutions, with limited evidence base for the protocols utilised.

Despite these disadvantages continuous UFH remains the anticoagulant of choice in paediatric and neonatal ECMO, with only a few alternatives which are listed in Table 2. Of these alternatives there exists only a few ‘single centre experiences’ or published case reports and series detailing their use in paediatrics, which have primarily emerged in an attempt to reduce haemorrhage, heparin resistance due to low AT levels and from rare cases of Heparin Induced Thrombocytopenia and Thrombosis (HITT).

6. Antithrombin (AT)

Antithrombin (AT) is a serine protease and naturally occurring anticoagulant, which inhibits thrombin (Factor IIa), Factor Xa and other serine proteases which are involved in the coagulation pathway. AT levels in neonates and paediatric patients are physiologically lower, and do not reach adult levels until 3–6 months of age. [36,44]. As AT is required for UFH to function as an anticoagulant, there is a concern that replacement of AT would increase bleeding risks in paediatric patients on ECMO [45]. An international ECMO survey performed by Bembea and colleagues, demonstrated that 51% of ECMO centres routinely monitored AT activity, however, both the frequency of monitoring, the threshold for replacement and in addition the product used for replacement varied amongst respondents [46]. A number of studies have evaluated the use of AT replacement, and have found varying results, however these studies are unified by the lack of evidence suggesting an improved clinical outcome [47]. Some studies have demonstrated an increase in frequency of circuit failure, but were unable to demonstrate a change in UFH infusion, or Activated Clotting Time (ACT) levels or haemorrhage. [48,49]. Ryerson and colleagues showed that AT supplementation increased AT levels and Anti-Xa levels to within therapeutic range, with a subsequent a reduction in UFH dose without a change in APTT. Todd Tzanetos et al. also demonstrated increased Anti-Xa levels to within therapeutic range following AT supplementation, however there was no correlation with UFH dose. Neither study showed a correlation with AT level and clinical events of thrombus or bleeding [45,50]. Most recently, in the largest analysis to date, Wong et al. showed that neonates and children who received AT during ECMO had an increased number of thrombotic and haemorrhagic events, and longer length of stays without an associated difference in mortality. The authors concluded that over half of paediatric patients on ECMO are currently receiving AT without clear benefit, with extra cost, and potential harms [51]. As such the current frequent use of AT during ECMO therapy is hard to justify [52].

7. Haemostatic adjuncts

Haemostatic adjuncts, such as Prothrombin Complex Concentrates (PCCs), recombinant activated Factor VII (rVIIa), and antifibrinolytic agent's ε-aminocaproic acid and tranexamic acid, are agents which are used clinically to stop haemorrhage. Although bleeding secondary to anticoagulation on ECMO is common, they are not routinely used in paediatric ECMO patients. The reasons for this are multifactorial, with a lack of dosing strategies and research in paediatric patients, as well as an increased risk of life-threatening thrombosis [19].

7.1. Fibrinolytic agents

Initial reports and studies supported the use of ε-aminocaproic acid in neonates, in an attempt to reduce incidence of intracerebral haemorrhage (ICH), reduce surgical site bleeding and reduce subsequent blood transfusions, however this benefit appeared to be offset by an increased number of circuit changes and thrombotic complications [53–55]. The results obtained varied with some authors reporting a trend, without a statistically significant outcome. However, the increased risk of thromboembolic events has largely precluded their use

Table 2
Anticoagulants in paediatric & neonatal ECMO.

Anticoagulant	Evidence in paediatric & neonatal ECMO
Unfractionated Heparin (UFH)	Most commonly used.
Continuous infusion	Majority of evidence and research based on continuous infusion of UFH.
Unfractionated Heparin (UFH) *Intermittent infusion* combined with continuous Antithrombin infusion (AT)	Single centre experience showed reduction in surgical revision for bleeding [37].
Low Molecular Weight Heparin (LMWH)	Limited reports on its use in paediatric ECMO [38].
Direct thrombin inhibitors	
- Argatroban	- Systematic review identified 4 out of 8 publications detailing the use of Bivalirudin in ECMO, and overall were unable to determine the safety and efficacy of its use [39].
- Bivalirudin	- Retrospective study suggesting Bivalirudin used post-cardiotomy may limit bleeding and blood product transfusions [40].
	- Retrospective case series involving a subgroup of patients who were transitioned to Bivalirudin following initial UFH management. Wide range of doses used and incomplete data available for analysis of clinical outcomes [41].
	- Case report of Argatroban in paediatric ECMO patient with Heparin Induced Thrombocytopenia and Thrombosis (HITT) showed no bleeding complications and resolution of ischaemia and thrombocytopenia [42].
Anti-platelet agents	No formal publications regarding primary use for anticoagulation. Limited case reports have detailed reduction in UFH dose when used to treat Primary Pulmonary Hypertension in patients on ECMO [43].

in routine paediatric ECMO therapy.

7.2. Recombinant activated factor VII

The use of recombinant Factor VIIa in paediatric ECMO has been limited, and there are currently no guidelines or recommendations for its potential use. There is a paucity of data from limited case reports and case series, which demonstrate that administration of rFVIIa may decrease bleeding and reduce subsequent blood transfusions, however as with fibrinolytic agents there is an increased risk of patient and circuit related thrombotic events [19,56,57].

7.3. Prothrombin Complex Concentrates (PCCs)

The use of either 3 or 4 factor Prothrombin Complex Concentrates in ECMO, adult or paediatric, is rare with few published studies, and a single case report suggesting a link between the administration of Activated Prothrombin Complex Concentrate (APCC) and fatal thrombosis in an adult [58]. As a result their use is only recommended in the setting of catastrophic and life-threatening bleeding.

8. Monitoring of anticoagulation

Close monitoring of UFH whilst patients are on ECMO is critical, due to underlying patient factors of coagulopathy, haemodilution and recent or open surgical wounds, as well as the relatively narrow therapeutic window of UFH. The optimal method for monitoring of anticoagulation in paediatric and neonatal patients on ECMO is unknown, with each institution following individual guidelines, with a focus on local experience with assays, laboratory support and clinician interpretation. Having said that, an international survey performed in 2013 by Bembea and colleagues showed the ACT was the parameter of choice for monitoring of anticoagulation in ECMO, with 97% of respondents using this method in some way [46,59]. The majority of centres utilise a combination of ACT, Activated Partial Thromboplastin Time (APTT), Anti-Factor Xa (Anti-Xa) and thromboelastrograms (TEGs) for monitoring of anticoagulation [60] [14].

8.1. Activated Clotting Time (ACT)

The Activated Clotting Time (ACT) measures the time it takes for whole blood to clot, when exposed to an activator such as kaolin or celite, which is in contrast to other tests of coagulation that measure the time plasma takes to clot when exposed to an equivalent activator. The ACT is a point of care test (POCT), and offers a shorter time between sampling and results, compared with formal coagulation tests. In addition point of care testing can reduce blood sample size, reduced sample handling and errors associated with this, decreased sample degradation over time, and can be performed by non-laboratory personnel [61]. The utilisation of the ACT is institution and indication specific, with targets varying depending upon the analyser and activator used and test indication. Within the field of ECMO a lower target compared with cardiopulmonary bypass of 150–170 s is commonly used. However the target is likely reagent and analyser dependent, with work conducted by Andrew and et al. demonstrating that when the same sample is taken from paediatric cardiopulmonary bypass patients and then tested on two different ACT machines, the results are significantly different [62]. Furthermore, research performed by Uden and colleagues demonstrated variability in the ACT result for a single sample, taken from neonatal lambs during ECMO, even when the same analyser is used [63]. Depending upon the ACT result obtained, the UFH infusion is adjusted accordingly and a repeat in 1 h is performed. ACT values are increased by the presence of UFH, however it may also be increased by haemodilution, hypothermia, coagulation factor deficiencies and platelet dysfunction [19,64].

The ACT has revolutionised anticoagulation management during cardiopulmonary bypass (CBP) by reducing postoperative coagulopathy, bleeding and blood product usage [65]. However, a retrospective study performed by Liveris and colleagues showed that within paediatric ECMO patients the ACT was shown to have no correlation to UFH dose, and of the three coagulation tests examined; ACT, APTT & Anti-Xa; ACT was the least effected by change in dose. In addition research conducted by Maul and colleagues found that the ACT was a poor correlate and was insensitive to changes in UFH dosing [66]. The ACT was initially developed for cardiopulmonary bypass which involves higher UFH doses, at which a stronger correlation is shown. Despite these studies, ACT remains the most commonly used test for monitoring of anticoagulation during paediatric and neonatal ECMO [46].

8.2. Activated Partial Thromboplastin Time (APTT)

The APTT is performed using plasma, collected from a citrated tube, and is routinely performed as a clotting based assay. The sensitivity of the APTT to heparin is both analyser and method dependent, and each institution needs to use analyser and reagent specific age appropriate reference ranges [67]. The baseline APTT varies significantly with age, and is prolonged in neonates and young children, approaching adult levels towards the end of puberty and the teenage years [29,36,68]. In addition studies have demonstrated that UFH has an age dependent effect on the prolongation of the APTT, with infants and young children having a smaller prolongation of the APTT compared with adults and older children when given the same dose of UFH [29,34].

A study performed by Ignjatovic and colleagues demonstrated that UFH monitoring using the APTT titrated to an Anti-Xa result of 0.35–0.7 U/ml, also showed significant age related variation, particularly in younger children [34,35]. Further research by Chan et al. and Kuhle et al. reported similar poor correlation between the APTT and Anti-Xa across neonates and children of varying ages [69,70].

8.3. Anti-Factor Xa

The Anti-Factor Xa test, commonly referred to as an Anti-Xa, is a functional assay, primarily used to monitor the use of Heparins, whether they be Low Molecular Weight Heparin (LMWH) or UFH. Some ECMO institutions consider the use of the Anti-Xa to be superior for UFH monitoring and management, however it should be noted that this assay only measures the Anti-Xa effect of UFH, and not the Anti-IIa effect. Furthermore, there is increasing evidence that the ratio of the UFH effect on Anti-Xa and Anti-IIa assays varies with age [35]. In addition the use of the Anti-Xa to monitor UFH in some ECMO centres may not be possible due to familiarity, cost and experience with performing this assay [14,71].

Liveris and colleagues demonstrated a strong positive correlation between Anti-Xa and UFH dose, which was in contrast to the ACT and APTT results [60]. Furthermore, low Anti-Xa levels, and therefore low levels of UFH, have been associated with increased risk of circuit/oxygenator change, presumably due to thrombus formation. A study by O'Meara and colleagues which involved introduction of an Anti-Xa monitoring protocol in ECMO, demonstrated less frequent testing and subsequent reduction in iatrogenic blood loss, and more time within therapeutic range compared with standard ACT monitoring [14]. However, there was no difference in either bleeding or thromboembolic events between the two protocols.

Sulkowski and colleagues demonstrated significant differences in how the ACT and APTT reflected heparin anticoagulation, and used the Anti-Xa as a comparator. The APTT appeared to directly correlate with the Anti-Xa level, however there was an inverse correlation with ACT and Anti-Xa levels [72]. Higher APTT levels reflected higher Anti-Xa levels for each patient, however higher ACT levels were reflective of lower Anti-Xa levels.

Overall these studies, and others utilising the ACT, APTT and Anti-

Table 3
Summary of anticoagulation assays used in ECMO.
Adapted from [29].

Assay	Advantages	Disadvantages
ACT	■ Low cost ■ Point of care test (POCT) ■ Rapid result turn-around time ■ Easy to perform ■ Smaller volume of blood required ■ Frequent testing required ■ Measures clotting of whole blood	■ Operator variation ■ Analyser and reagent specific ■ Effected by haemodilution, hypothermia, coagulation factor deficiencies and platelet dysfunction
APTT	■ Low cost ■ Readily available ■ Larger volume of blood required ■ Can detect underlying factor deficiencies, vitamin K deficiency, or Disseminated Intravascular Coagulation (DIC) in presence of UFH (using Heparinase)	■ Analyser and reagent specific ■ Baseline varies with age ■ UFH has an age-dependent effect on prolongation ■ Effected by UFH contamination of sample, haemodilution and coagulation factor deficiencies ■ Depending upon the specific method used this may be effected by increased bilirubin, triglycerides and plasma free haemoglobin (Hb). Prolongation does not equate to effective anticoagulation
Anti-Xa	■ Direct measure of UFH inhibition of Xa ■ Larger volume of blood required	■ Not as readily available in all laboratories ■ Requires experienced staff ■ Higher cost ■ Slower result turn-around time ■ Measures Anti-Xa effect and not Anti-IIa effect ■ Effected by presence of increased bilirubin, triglycerides and plasma free haemoglobin (Hb)

Xa have demonstrated that there is currently no ideal or perfect measurement of anticoagulation. Table 3 summarizes some key points of each assay. Protamine titration is considered the gold standard for monitoring of UFH, however the lack of automation makes this method impractical in the clinical setting. There is a need to not only quantify the amount of UFH in the circuit, but also measure the haemostatic potential of the patient. There exists a delicate balance in these patients between haemorrhage and thrombosis, and a more global measure of coagulation is required, of which thrombin generation has been postulated as a future option.

9. Conclusion

Extracorporeal Membrane Oxygenation (ECMO) is a form of ECLS which provides cardiac and respiratory support for patients with reversible pathophysiological processes. ECMO is most commonly used in neonatal and paediatric patients, and due to both underlying patient factors, as well as introduction of the ECMO circuit, there is activation of both a pro-coagulant and pro-inflammatory state. As a result patients require systemic anticoagulation with UFH to reduce their risk of both circuit and patient based thrombosis, which in addition to the underlying patient pathophysiology increases the risk of haemorrhage. As a result close monitoring of anticoagulation is required, however to date there exists a lack of research and evidence of what is an ideal test of anticoagulation in these patients, as well as a lack of understanding about the basic cellular haemostatic system in paediatric patients on ECMO. Further research is required into the basic haemostatic changes in paediatric ECMO, as well as methods of anticoagulation, which needs to be expanded to include both current techniques as well as newer concepts around global haemostasis such as thrombin generation and platelet activation.

Conflict of interest

None of the authors have any conflicts of interest to declare.

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