Review Article

Extracorporeal corporeal membrane oxygenation: indications, technical considerations, and future trends

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Abstract: The extracorporeal membrane oxygenation (ECMO) device was initially developed with the goal of providing extended support in patients experiencing cardiac failure. However, ECMO technology has evolved, and now provides a means to successfully manage patients experiencing cardiac and/or pulmonary failure until such time as the patient's body is able to either heal, or undergo transplantation. In addition, it has been used in the management of multisystem organ dysfunction. The life-saving utility of this therapy for critically ill patients has prompted world-wide implementation particularly in resource-rich settings. Innovations in instrumentation, broad clinical implementation, extensive utilization of blood and blood components, and the catastrophic nature of potential complications, have collectively prompted the evolution of a tremendous body of research. In this comprehensive review we briefly describe the early development of the ECMO device and technology, in addition to outlining the function of the device as it now commonly utilized including veno-arterial (VA) *vs.* veno-venous (VV) and rapid deployment ECMO. This review will also delineate the rationale for ECMO use, common clinical indications, and specialized techniques, in addition to the approaches necessary for their successful implementation. As systemic anticoagulation is frequently utilized to support patients on ECMO, the review also contains an extensive review of anticoagulation management, blood component utilization, and potential hematologic complications of ECMO. The review includes a discussion of more recent trends including the use of ECMO in COVID-19 patients, and the performance of tandem plasma exchange. Finally, areas of current controversy and needed research will be highlighted.

Keywords: Extracorporeal membrane oxygenation (ECMO); extracorporeal life support (ECLS)

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Background

Origin of extracorporeal life support (ECLS) technology

The field of mechanical cardiopulmonary support originated when Dr. John H. Gibbon Jr., a trainee at the Massachusetts General Hospital in Boston, worked on a prototype of a heart-lung machine. He continued refining the instrument, with both engineering and financial support from IBM, after joining the faculty at Thomas Jefferson University in Philadelphia. It was finally used successfully in a cardiac surgery for an 18-year-old girl with atrial septal defect (1). Further modifications of the instrument allowed Dr. John Kirklin of Mayo Clinic in Rochester and Dr. Robert Bartlett of the University of Michigan in Ann Arbor to perform successful operations in an adult and pediatric patient, respectively (1). These, and other similar successes, led to the acceptance of extracorporeal circulation as a safe method for not only cardiac surgery, but also in intensive care units in all patient populations requiring cardiac and/or pulmonary support. The number of centers able to provide ECLS has since grown exponentially, and as of 2020, there were 492 centers in the world that are part of the extracorporeal life support organization (ELSO) registry (2). Historically, ECLS was used as a bridging therapy until the underlying conditions could be resolved or transplantations were performed (1). However, in rare cases, such as in cases of catastrophic pulmonary or cardiac failure, long-term utilization to provide clinical support has been successfully achieved. For further details on the history of ECLS, the reader is referred to excellent reviews published by either by Dalton and Desai; or Makdisi and Wang (3,4).

The term ECLS is frequently utilized to specifically reference extracorporeal membrane oxygenation (ECMO). However, the term ECLS has broader applications and encompasses additional devices/technologies, including ventricular assist devices (VADs) and cardiopulmonary bypass (CPB). There are two distinct ECMO methodologies currently in use: veno-arterial (VA) and veno-venous (VV) ECMO circuits. In a VA circuit, deoxygenated blood (from femoral vein, internal jugular vein, or directly from the right atrium) is oxygenated by a membrane lung (*Figure 1*). Gas exchange occurs by diffusion based on partial pressure differences. The amount of oxygen in the gas supplied to the membrane lung determines the partial pressure (usually at least 100 torr), and as venous blood usually contains only about 40 torr of oxygen, oxygen diffuses through the membrane into the blood. Although the partial pressure difference between the carbon dioxide in the membrane lung

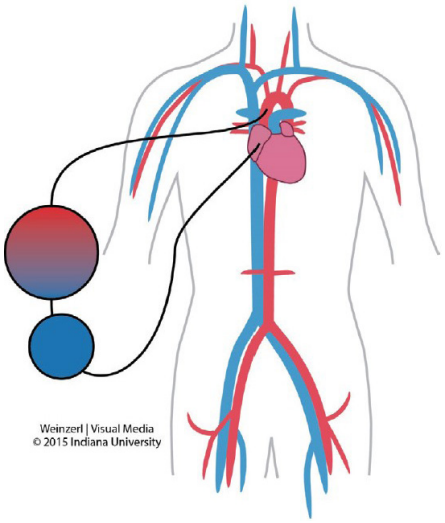

Figure 1 Central VA ECMO cannulation approach. Republished with permission of Nancy International Ltd., Subsidiary AME Publishing Company, Figure 4 in "George Makdisi G, Wang I. Extracorporeal Membrane Oxygenation (ECMO) review of a lifesaving technology. *J Thorac Dis* 2015;7:E166-76"; permission conveyed through Copyright Clearance Center, Inc. (4). VA, veno-arterial; ECMO, extracorporeal membrane oxygenation.

gas (usually 0 torr) and venous blood (usually 40–50 torr) is smaller than oxygen, carbon dioxide is easily exchanged across the membrane lung even at low blood-flow rates. The oxygenated blood is then returned to the body via the arterial cannula (usually in the femoral artery, carotid artery or directly into the aorta—although other vessels may also be used). Hence, VA circuits can be used to provide hemodynamic support in patients having cardiac failure with or without pulmonary compromise (5).

VV ECMO drains venous blood (usually from the femoral vein, internal jugular vein, or directly from the right atrium), and oxygenated return is delivered to the right heart via a venous access. A single cannula with a double lumen to drain and reinfuse blood is also available. Patients with cardiac compromise presumably related to high ventilator settings, can receive VV support; but again, adequate cardiac function to propel blood through the pulmonary circuit and from the left heart to the systemic circulation must exist. With the advent of low resistance, highly gas-permeable membrane lungs, ECMO may also be applied without a pump in the system. This form of support utilizes the systemic blood pressure of the patient to push blood through the circuit and past the membrane

Table 1 Advantages and disadvantages of VA and VV ECMO

ECMO type	Provides cardiac support	Difficulty of cannulation	Maintains pulmonary blood flow	PaO_2 achieved	Safe for patients with cardiac compromise
VA	Yes	Higher, arterial and venous	No, bypasses pulmonary circulation	Higher	Yes
VV	No	Less difficult, venous only	Yes	Lower	No

VA, veno-arterial; VV, veno-venous; ECMO, extracorporeal membrane oxygenation.

lung (usually via the femoral artery and return into the femoral vein). Although only about 1 L of flow can usually be obtained, it is sufficient for carbon dioxide removal in hypercarbic patients. In patients with pulmonary hypertension, the pumping action of the right heart may also drive blood through the circuit and past the membrane lung and oxygenated return can be directed into the left heart for distribution. Smaller systems designed for carbon dioxide removal (referred to as ECCO2R) are also available. The differences in the use of AV *vs.* VV circuits are summarized in *Table 1* (4,6).

While roller-pump systems predominated in the early years of ECMO, new technology now allows centrifugal pumps to be used, and these have replaced roller pump systems in most centers.

Rapid deployment ECMO

Technological improvements have miniaturized ECMO circuits and have led to the ability to reduce circuit priming volumes. This allows for a bloodless prime, which can be initiated within a few minutes, or sterile ECMO systems, which can be stored primed and ready for up to 30–60 days. Studies have shown that pre-priming stand-by ECMO circuits significantly reduces the time to implement ECMO while not compromising circuit sterility (6,7). Significant time savings are achieved because it avoids the need for crossmatch and issuance of blood products from the local transfusion service. This rapid availability of ECMO support has led to one of the largest growing fields in ECMO: that of ECMO applied during active cardiac arrest (ECPR). ECPR has been shown to improve outcomes in both in-hospital and out-of-hospital cardiac arrest in some studies; clinical studies are also in progress (8-10).

Clinical indications and evidence for using ECMO

The ELSO (www.elso.org) is an international society dedicated to supporting ECLS clinical practice, training, and research. The society publishes updated guidelines regarding technical and clinical aspects of ECLS and maintains an international data registry to facilitate research collaboration. The registry contains information regarding pediatric and adult ECLS utilization, including indications, complications, and outcomes (1). Since 1984, the ELSO registry has tracked the number of ECLS procedures, and the number of centers world-wide providing ECLS, with the number of centers providing ECLS growing annually since 2004 (11,12). Although ELSO remains the largest repository of ECMO data, not all centers contribute, which impairs the ability to comprehensively track global ECMO utilization and outcomes.

General indications

ECMO is primarily indicated to support critically ill patients with cardio-pulmonary dysfunction refractory to optimal conventional therapy. A meta-analysis of 12 studies including more than 1,700 patients suggests ECMO is associated with >50% mortality risk (11); as such, it is considered indicated in the setting of cardio-pulmonary failure in patients with a >80% expected mortality (5).

While ECMO was initially primarily used in neonatal conditions, its success in this population has led to its increased use in older children and adults (12). The ELSO registry categorizes indications broadly as pulmonary, cardiac, or ECPR (ECLS Cardio-Pulmonary Resuscitation; ECMO initiated to aid cardiopulmonary resuscitation (CPR) efforts—also known as rapid deployment ECMO described previously). Physiologic criteria for initiation of ECMO in accordance with the current ELSO guidelines for adults are outlined in *Table 2*. Absolute contraindications to ECMO are rare, and limited to either a non-survivable comorbidity, or irreparable cardiac damage in patient unsuitable for transplant or VAD, severe preexisting neurologic damage, or limitation of care orders (5). Relative contraindications

Table 2 Indications for adult ECMO*

Type	Adult Indications for ECMO		
	Physiologic conditions (5)	Clinical conditions (VA ECMO) (4)	Clinical conditions (VA or VV ECMO) (4)
Respiratory	PaO_2/FiO_2 <80 on FiO_2 >90%	Cardiogenic shock	Acute respiratory distress syndrome
	Hypercapnia with PaO_2 >80 mmHg	(Multiple causes)	(Multiple causes)
	Inability to achieve a plateau pressure of 30 cm H_2O or less	Inability to wean from CPB	Lung rest
	Severe air leak syndrome	Post primary transplant failure	(Multiple causes)
	Need for intubation in a patient awaiting lung transplant	Chronic cardiomyopathy	Lung transplant
	Acute cardio/pulmonary collapse (unresponsive to optimal care)	Bridge to VAD support	Primary graft failure
Cardiac	Requirement for cardiopulmonary support	Support for high-risk PCI	Bridge to transplant
	Inadequate tissue perfusion despite adequate intravascular volume	Bridge to cardiac transplant	Intra-operative support
	Persistent shock despite maximum therapy	–	Lung hyperinflation
ECPR	Unsuccessful CPR (ideally to be considered following 10–15 minutes of unsuccessful resuscitation efforts)	–	Pulmonary hemorrhage

*, indications may also pertain to pediatric patients. ECMO, extracorporeal membrane oxygenation; VA, veno-arterial; VV, veno-venous; CPB, cardiopulmonary bypass; VAD, ventricular assist device; PCI, percutaneous coronary intervention; ECPR, Extra-Corporeal Cardiopulmonary Resuscitation; CPR, cardiopulmonary resuscitation.

for adults are shown in *Table 3*.

The most common pulmonary diagnoses reported to the ELSO as indications for ECMO are pneumonia, acute respiratory distress (ARDS), and acute respiratory failure (ARF) (13). Survival to discharge is associated with underlying disease, with rates ranging from 54% for ARDS to 65% for viral pneumonia, and overall survival to discharge of 58%. The most common cardiac diagnoses are cardiogenic shock, cardiomyopathy, and congenital heart disease. The highest survival to discharge was reported for cardiomyopathies (61%), and lowest in adults with congenital heart disease (34–41%); with an overall survival to discharge of 42%. Survival to discharge in the ELSO registry is approximately 29% in the setting of extracorporeal cardiopulmonary resuscitation (ECPR), although recent studies have reported 40–50% survival (13,14).

Evidence supporting ECMO for adult patients with ARF is primarily based on 2 recent randomized controlled clinical trials (RCTs) and multiple observational studies (15-20). The British multicenter CESAR RCT evaluated adult patients with severe, reversible respiratory distress and found patients referred to centers for potential ECMO placement had a significantly higher survival rate without disability, when compared to conventional treatment (63% *vs.* 47%, P=0.03) (19). The EOLIA RCT, focused on adult patients with severe ARDS, demonstrated a trend toward reduced 60-day mortality for patients who were supported with ECMO when compared to those receiving conventional treatment (35% *vs.* 46%). The study additionally found that ECMO was associated with increased incidence of bleeding, severe thrombocytopenia, and ischemic stroke (15).

Evidence supporting ECLS following cardiac arrest, or as part of advanced life support in adult patients comes primarily from observational studies and a single RCT (8,9,21-24). The ARREST study, a recently published single-center RCT that evaluated the efficacy of ECPR for patients with refractory ventricular fibrillation and out of hospital cardiac arrest, demonstrated improved survival in adult patients receiving ECMO compared to standard advanced life support (ALS) (9). These data are additionally supported by observational studies, including a systemic review and meta-analysis demonstrating improved survival in adults supported with

Table 3 Absolute and relative contraindications for adult ECMO*

Clinical and laboratory criteria
Absolute contraindications: adult ECMO
Respiratory
>7 days of mechanical ventilation with FiO_2 of 90% and peak plateau pressure >30 cm H_2O (5)
Immunologic
Absolute neutrophil count <400/μL (5)
Neurologic
Recent or expanding central nervous system hemorrhage (4,5)
Cardiac
Non-recoverable heart in patient not a candidate for transplant or VAD (absolute) (4,5)
Aortic damage (active dissection/severe aortic regurgitation) (4)
Systemic
Severe chronic organ dysfunction (emphysema, cirrhosis, renal failure) (4,5)
Disseminated malignancy (4)
Prolonged unsuccessful CPR (without adequate tissue perfusion) (absolute) (5)
VV-ECMO
Cardiac failure (4)
Severe chronic pulmonary hypertension (mean pulmonary artery pressure >50 mmHg) (4)
Relative contraindications: adult ECMO
Systemic
Advanced age (4,5)
Obesity (4,5)
Inability to receive systemic anticoagulation (4,5)

*, there are very few absolute contraindications to ECLS; patients are considered as candidates in accordance with an assessment of the associated risk, potential survivability, and availability of effective alternative therapeutic modalities. ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device; CPR, cardiopulmonary resuscitation; VV, veno-venous.

ECPR for refractory cardiac arrest (25,26).

Like adult patients, the application of ECLS in pediatric patients has increased in recent decades. However, in neonates, the ELSO registry indicates a steady decrease in the percentage of cases compared to total ECMO cases, from 82% in 1990, to 8.1% between 2011 and 2016 (27). Still, over 800 neonates with respiratory failure receive ECMO each year.

Neonatal indications for ECMO are slightly more complex; ECMO is reserved for term or late preterm neonates with severe cardio/pulmonary failure and a high likelihood of mortality with a potentially reversible etiology. An important criterion for initiating neonatal ECMO is evidence of severe respiratory failure including an elevated oxygenation index (OI) and alveolar-arterial (A-a) gradient. Other physiologic criteria and contraindications for initiation of ECMO in accordance with the current ELSO guidelines for neonates are outlined in *Table 4* (28-30).

Pulmonary dysfunction is the predominant indication for neonatal and pediatric (patients aged 29 days–17 years) ECMO: congenital diaphragmatic hernia (CDH), persistent pulmonary hypertension (PPHN), and meconium aspiration syndrome (MAS) are the most common neonatal pulmonary diagnoses (31). Utilization of ECMO for the treatment of MAS and ARDS has progressively decreased since the 1990s, presumably due to therapeutics developments, such as high-frequency oscillatory ventilation (HFOV),

Table 4 Physiologic indications and contraindications for initiating ECMO in neonates

Potential indications	Contraindications	
	Absolute	Relative
• Oxygenation index >40 for >4 hours	• Lethal chromosomal disorder (includes trisomy 13 and 18, but not 21) or other lethal anomaly	• Irreversible organ damage (unless considered for organ transplant)
• Failure to wean from 100% oxygen despite prolonged (>48 hours) maximal medical therapy or persistent episodes of decompensation	• Irreversible brain damage	• Weight <2 kg
• Severe hypoxic respiratory failure with acute decompensation (PaO_2 <40) unresponsive to Intervention	• Uncontrolled bleeding	• <34 weeks postmenstrual age because of the higher incidence of increased intracranial hemorrhage
• Severe pulmonary hypertension with evidence of right ventricular dysfunction and/or left ventricular dysfunction	• Grade III or greater intraventricular hemorrhage	• Mechanical ventilation >10–14 days
• Pressor-resistant hypotension		• Disease states with a high probability of a poor prognosis

Reproduced with permission Table 15-1 in Pham HP, Staley EM, Wong ECC. Transfusion Support and Hemostatic Monitoring in Patients Connected to Extracorporeal Devices. In: Marques M, Schwartz J, Wu Y, eds. Transfusion therapy: clinical principles and practice, 4th ed. Bethesda, MD: AABB Press, 2019:375-93. ECMO, extracorporeal membrane oxygenation.

surfactant therapy, and inhaled nitric oxide. Survival is largely dependent on underlying disease: data from the ELSO database from 2009–2015 suggests rates as low as 50% for CDH to 93% for MAS, and overall survival to discharge of 67% (27). Infectious disease and ARF represent the most common pediatric diagnoses (>50% of cases reported between 2009–2015). Survival to discharge for pediatric pulmonary indications is similarly associated with diagnosis and ranges from 88% for asthma to 32% for pertussis, with an overall survival to discharge of 60% (31).

The primary cardiac indication for ECMO in pediatric and neonatal patients is congenital heart defects (representing 80% and 52% of diagnoses, respectively), although cardiac arrest, cardiogenic shock, myocarditis, and cardiomyopathy have been reported for both age groups. In terms of survival, myocarditis and cardiomyopathy have the highest rates of survival to discharge in both neonatal (50% and 60%, respectively) and pediatric patients (76% and 65%, respectively). Overall, survival to discharge in pediatric and neonatal patients with a cardiac diagnosis treated with ECMO is 45% (31). The performance of ECMO for ECPR in neonates and pediatric patients is associated with an overall survival to discharge of 43% (31). Improved survival following ECPR when compared to adults may due to the fact that ECPR is predominantly offered to inpatient neonatal and pediatric patients in ICU settings, which is associated with shorter intervals between arrest and initiation of ECPR, and increased utilization of central vessels for cannulation (32).

As with adults, recent RCTs examining the efficacy of ECLS in neonatal and pediatric patients is lacking; supporting data are primarily in the form of controlled studies restricted to neonates published several decades ago and a small number of more recent observational studies (33-36). A recent Cochrane Review of the published literature evaluating the effectiveness of ECMO for neonatal respiratory failure found ECMO support was associated with increased survival to discharge (37). ECMO is considered close to standard of care for neonates with respiratory failure.

While it is unlikely there will be more RCTs of ECMO *vs.* conventional care in children, due to difficulties with design and recruitment for these efforts in the past, more studies may be initiated in adults.

Given the large increase in use of ECMO in the current COVID-19 pandemic, whether ECMO continues to increase in the adult population (the largest expanding group already), remains to be seen. There are on-going RCTs to evaluate the clinical efficacy of ECMO; however, more studies are necessary given the innovations in ECLS equipment and protocols in recent decades, and the relative paucity of modern RCTs. It is worth noting that the management of ECMO patients is often complex, requiring

the care of a highly specialized multidisciplinary team. For centers without dedicated ECLS teams and equipment, early transfer to an ECLS center (with ECMO capability) should be considered. Transport can be arranged prior to ECMO, or ECMO can be applied at the referral site (38).

The use of ECMO in COVID-19

A recently emerging indication for ECMO is cardiopulmonary failure related to coronavirus disease 2019 (COVID-19). The role of ECMO for support of patients with COVID-19 has progressively evolved during the COVID-19 global pandemic. As limited guidance was initially available, ECMO was implemented as clinically indicated in accordance with best practices at a given institution. COVID-19 disease has been associated with myocarditis, pulmonary emboli, cardiac arrhythmias, and stress cardiomyopathies among others, potentially representing indications for mechanical cardiopulmonary support (VA-ECMO). However, the predominant indication, and a key feature of the COVID-19 disease, is ARDS (VV-ECMO) (39). Data from observational cohort studies, suggest that survival for patients with COVID-19 who receive ECMO support is between 30–45%, similar to that of patients requiring ECMO support pre-pandemic. Current ELSO guidelines state that ECMO may be utilized to support patients with COVID-19 with cardiopulmonary failure (although experience with cardiac failure is limited). As COVID-19 patients are known to be hypercoagulable, increased doses of anticoagulant may be considered during ECMO. The most recent COVID-19 surge also is finding more children with cardiac or respiratory failure requiring ECMO support (39).

Anticoagulation protocols used in ECMO

The ECMO circuit has profound effects on the physiologic hemostatic balance because of the systemic anticoagulation typically required to prevent thrombosis in the extracorporeal circuit/tubing, the oxygenator, and/or the cannula. When considering anticoagulation therapy, additional factors that must be evaluated include: the risks for surgical site bleeding, pre-ECMO hemostatic status (i.e., antiplatelet drugs, residual heparinization, and/or postoperative coagulopathies), renal and hepatic function, and/or recent use of factor concentrates and blood products (5). Given extreme clinical heterogeneity of patients, there is a distinct lack of strong evidence-based guidelines for optimal management of anticoagulation during ECMO, which has led to extensive practice variation (1). Often, hemostatic management of these patients is conducted in an interdisciplinary fashion, with consultation from a variety of clinical specialists including perfusionists, hematologists, surgeons, anesthesiologists, and/or critical care specialists.

Heparin-based protocols

The most utilized systemic anticoagulant in ECMO protocols is unfractionated heparin, likely because it is familiar to most providers, has a short-half life, is relatively inexpensive, and is easy to both titrate and reverse (protamine). Heparin induces its anticoagulant effects by potentiating the activity of antithrombin (AT), enhancing its inhibitory effects on thrombin (predominantly). Heparin has also been shown to have an effect not only on activated Factor X, but also on other pro-coagulant factors in the coagulation cascade (40). ELSO has created guidelines for initiation, maintenance, and monitoring of heparin levels during ECMO.

AT use and controversies

AT is a natural anticoagulant that is required for the function of indirect thrombin inhibitors (i.e., unfractionated heparin), and is consumed during thrombosis and heparin therapy. Neonates are at greatest risk of AT deficiency on an ECMO circuit due to immature hepatic synthetic function. AT replacement during ECMO is associated with tighter control of anticoagulation and increased anti-Xa heparin levels (41-43). AT concentrate is the preferred mechanism for AT supplementation per ELSO guidelines, rather than plasma (40). In the U.S., AT is available in either human plasma-derived form (Thrombate III®; Grifols, Research Triangle Park, NC, USA) or recombinant form (ATryn®; LFB, rEVO Biologics, Framingham, MA, USA).

AT plasma activity has been shown to decrease following initiation of ECLS, potentially resulting in a procoagulant state (1). As a result, AT depletion may manifest as a progressive heparin resistance, which is readily detectable depending on the heparin monitoring method utilized. Lehman *et al.* demonstrated that anti-Xa assays depend on the AT sample content, with plasma AT >60% generally being required for reasonable heparin recovery with *in vitro* UFH spiking experiments (44). However, there is significant controversy as to whether AT should be monitored and corrected in pediatric patients from both physiologic and clinical perspectives. Bembea *et al.* showed that the AT was inversely correlated with activated clotting time (ACT), as compared to strong positive correlation of AT and anti-

Xa level (45). From a physiologic perspective, neonatal AT levels, within the 1st week of life range from 39% to 87% (46). To reach adequate levels of anti-Xa activity between 0.3–0.7 IU/mL, a high percentage of infants would need to receive AT infusion. Early studies suggested that in certain conditions, the administration of AT may be beneficial. For example, in a small retrospective study of pediatric patients on CPB, an infusion of 1,000 IU of AT resulted in decreased thrombin formation and reduction of fibrinopeptide A levels, potentially reducing the risk of thrombosis (47). Additionally, Owings *et al.* reported children on CPB had significantly higher thrombin-AT complexes and prothrombin fragment F1.2 than adults, indicating ongoing thrombin production and, thus, possible benefit from AT infusion (48).

Several retrospective clinical studies have been conducted to address this question. One single-institution retrospective study of 40 patients ranging from 0–18 years of age found that neither heparin responsiveness nor circuit life was enhanced by daily AT infusion for activity <70% (49). In another single-institution retrospective study, 64 neonates and pediatric patients were examined to determine the impact of on-demand dosing of AT concentrate (50). Although AT levels were significantly increased, target levels were frequently not achieved, and no statistical differences were noted in the number of circuit changes, *in vivo* clots or hemorrhages, transfusion requirements, hospital or ICU length-of-stay, or in-hospital mortality (50). Furthermore, in a study using the Pediatric Health Information System database study, patients who received AT during ECMO had a significantly higher number of thrombotic and hemorrhagic events during hospitalization and longer length of-stay without an associated difference in mortality (51). In contrast, a recent retrospective study of 162 neonates by Stansfield et. al. found that routine administration of AT in neonates receiving ECMO was associated with tighter control of ACTs within the first 3 days on ECMO, increased anti-Xa activity, and a reduction in thrombotic complications, without increasing unwanted bleeding (52). Additionally, circuit lifespan was unaffected and blood product usage was significantly decreased. However, the results of this retrospective study must be viewed with caution, as several changes to the ECMO circuit occurred during the study period and may have confounded the results. In addition, patient-specific outcomes were not different between the control and the AT cohorts (52). Confounding this issue further is the manner of AT repletion. In a recent retrospective case-controlled study of pediatric patients on VA ECMO, patients who received continuous AT *vs.* intermittent AT infusion had a significantly higher frequency of being within the ACT goal range (53). This was associated with lower heparin dosing without an increase in hemostatic complications and with a trend toward lower blood usage (53).

Currently, the AT level used to trigger supplementation in ECMO is highly variable. In a survey of international adult ECMO centers, only 50% had any trigger for AT supplementation. Of those that did, most targeted a level between 51–99% (54). In a mixed survey of adult and pediatric ECMO centers, 82% reported at least occasional AT testing. The median AT goal in that study was 70% (45). In pediatric ECMO centers, the goal AT level transitions from 80% in neonates to 60% in infants and older children (55). Furthermore, in a retrospective study of neonatal/infant ECMO, the measured increment after AT supplementation was generally small (median 8%) (56). Furthermore, in the event of bleeding, which can occur in approximately 33% of ECLS patients, strategies for transfusion and monitoring of AT have not been defined (51).

While retrospective analysis of AT supplementation in pediatric ECMO in the U.S. showed consistent increase in AT use from 2005 to 2012, resulting in over 16% of ECMO courses involving AT supplementation, usage declined from 2012–2015 (57). In that retrospective database study of US pediatric ECMO centers, AT supplementation during ECMO was associated with decreased thrombosis (without an increase in hemorrhage), increased inpatient mortality, a shorter length of stay, and decreased billing cost (57). A recent survey, however, found that routine use of AT in pediatric ECLS patients has dropped significantly, likely largely due to lack of data that has shown it to be associated with better outcomes or need for lower heparin doses (51,55). It is likely that AT is not indicated for all ECMO patients, and factor costs can be substantial (58).

Considering the significant cost of AT replacement and potential impact on circuit lifespan and patient outcomes, a prospective randomized trial to determine efficacy, dosing, and cost effectiveness of AT for ECMO patients is warranted to resolve this controversy in both adult and pediatric populations. Currently, in adults, an RCT of AT supplementation is underway for VV ECMO patients to clarify its use in this patient population (59).

Heparin-coated circuits

Heparin-coated circuits have also been used with promising results during CPB in patients requiring support during

cardiac surgery, demonstrating reduced hemolysis as well as reduced complement and granulocyte activation (1). However, these observations may not extrapolate to ECMO, as the impregnated heparin is leached from the circuit over time and given the prolonged use of ECMO compared to CPB. This may be the result of the Vromen effect, wherein pro-coagulant proteins initially deposited on the circuit are exchanged for proteins with less hemostatic potential (1). Thus, the use of heparin-coated circuits may be effective at critical periods of increased thrombogenicity, which remain undefined in the context of ECMO.

Non-heparin-based anticoagulation protocols

A variety of alternative anticoagulant protocols have been used during ECMO, mostly driven by necessity in patients with heparin-induced thrombocytopenia (HIT), or patients with heparin resistance. HIT involves the formation of an antibody to the heparin-platelet factor 4 (PF4) complex, inducing thrombocytopenia and possibly life-threatening thromboembolic events (1). A recent meta-analysis reported an overall HIT incidence of 2.6% in patients exposed to heparin; however, in patients on ECLS, presumably as a result of long-term exposure, the incidence is believed to be much higher (60). Since patients on ECMO are commonly thrombocytopenic, it can be very difficult to differentiate HIT from alternative causes of thrombocytopenia. Anticoagulation protocols using the direct thrombin inhibitors (DTI), such as bivalirudin and argatroban, have been safely utilized (1). Several studies have suggested that bivalirudin may be an attractive, effective option for patients undergoing ECMO; not only because of its lack of dependence on AT but also because it is metabolized mainly via intravascular proteolytic degradation and undergoes minimal (~20%) renal clearance. While there is no available reversal agent for bivalirudin, as there is for heparin, half life is short (25–35 min). Currently, safety and efficacy data for neonatal and pediatric patients are undergoing clinical trials.

One small single-center study found that bivalirudin was associated with decreased bleeding and better coagulation profile compared to support with a heparin protocol (61). Another study found that bivalirudin was associated with less variation in activated partial thromboplastin time (aPTT) results during ECMO, likely due to its specific mechanism of action as a DTI (62). While bivalirudin has replaced heparin as the primary anticoagulant during ECLS in many centers, it is more expensive and comparative data against heparin in terms of bleeding, thrombosis, other outcomes, and costs are needed.

Role of anticoagulation monitoring

Patients on ECMO are at risk of both hemorrhage and thrombosis, so anticoagulation must be carefully titrated. ACT has been historically utilized for anticoagulant monitoring of patients on ECMO as it is readily available and can be performed as a point-of-care (POC) test using whole blood. ELSO guidelines describe anticoagulation monitoring using ACT, aPTT, or anti-Xa which are commonly available at ECLS centers (1). All of the tests rely on activation of the clotting cascade by means of contact activation; activation may be initiated by a variety of substances that vary in accordance with the testing platform. ACT was originally developed for use during CPB due to the unreliability of the aPTT when high heparin concentrations are present (1). ACT results are additionally affected by a variety of factors likely present in ECMO patients including anemia, thrombocytopenia, coagulation factor deficiencies, hypothermia, and/or hemodilution, in addition to prior use of oral anticoagulants and/or anti-platelet agents, and conditions associated with platelet dysfunction (either congenital or iatrogenic). This makes ACT a less-than ideal test for anticoagulation monitoring (63). To add to the complexity of monitoring, there are inconsistencies among the ACT platforms regarding the correlation to measured heparin levels, particularly in the low range targeted for patients on ECMO (often 180–220 seconds) (64,65). When systemic anticoagulation is performed requiring minimal heparin dosing, some centers rely on the aPTT for monitoring anticoagulation, typically targeting an aPTT 1.5–2.0 times the normal value (66). However, the aPTT assesses the intrinsic pathway of coagulation and thus, is not specific for heparin effect. As such, the ability of aPTT to monitor heparin is decreased in the setting of inflammation and pregnancy, as well as disseminated intravascular coagulation (DIC), lupus anticoagulant, liver disease, and/or hemodilution-acquired coagulation factor deficiencies (1). In some ECMO centers, the anti-Xa assay is the preferred method for heparin monitoring in the setting of ECMO, proposed as being superior to the aPTT, as it assesses heparin inhibition of Factor Xa and is unaffected by conditions that affect clot formation. However, because anti-Xa assays rely on the measurement of released chromogenic substances, the results can be affected by gross hemolysis, severe hyperlipidemia, and hyperbilirubinemia. The anti-Xa assay typically targets values equivalent to

Table 5 Anticoagulation and hemostatic monitoring for neonatal ECMO

Test	Utility	Suggest target range	Comments
ACT	Use in monitoring unfractionated heparin activity, and global hemostatic measure	Variable dependent on ACT methodology and instrumentation; however, goal is usually 1.5 times normal (i.e., 180–220 sec)	Coagulation factor deficiencies, thrombocytopenia, infection, and temperature also affect the ACT level. Blood products also lowers ACT level. In contrast, high citrate loads related to plasma exchange using FFP as replacement may lower ionized calcium levels resulting in elevated ACT if not properly adjusted
aPTT	Use in monitoring unfractionated heparin activity, and intrinsic/common coagulation cascade measure	Variable, dependent on institutional practice and reagent sensitivity	Affected by heparin, coagulation factor and AT levels. The normal range for the aPTT is age-related, and neonates have higher values than older children and adults. In neonates, aPTT levels do not correlate with anti-Xa or ACT levels. The aPTT is falsely prolonged in patients with elevated CRP and falsely decreased with elevated factor VIII levels
Anti-Xa activity	Specific monitoring of the anti-Xa activity of heparin	Levels 0.25–0.5 IU/mL may be more appropriate for neonates than 0.3–0.7 U/mL or up to 1.0 IU/mL in older patients; however, little evidence to support this strategy	Neonatal patients tend to have higher requirements for heparin than in adults. Institutions should recognize whether the anti-Xa assay used locally is supplemented with AT or relies on the patient's AT; negatively affected by plasma hemolysis
Thromboelastography, thromboelastometry	Global hemostatic assay that assesses coagulation levels, clot kinetics, clot strength and clot lysis	None recommended, based on institutional practice	See utility comment
Antithrombin	To avoid potential heparin resistance	Normal range for AT level is 80–120%; however, term neonates have AT levels approximately 60% of adult values	Monitoring is important particularly in Anti-Xa assays that rely on the endogenous patient AT
Platelet count	To ensure adequate primary hemostasis	Usual practice is keep platelet count greater than 80,000 or 100,000/μL	Many centers keep platelets >100,000/uL for the first 3 days when the risk of intraventricular hemorrhage is greatest
Fibrinogen	To ensure adequate primary and secondary hemostasis	>150 mg/dL	Maintained either by fresh frozen plasma or cryoprecipitate (contains primarily fibrinogen, factor VIII and vWF and Factor XIII)

Reproduced and modified with permission Table 15-2 in Pham HP, Staley EM, Wong ECC. Transfusion Support and Hemostatic Monitoring in Patients Connected to Extracorporeal Devices. In: Marques M, Schwartz J, Wu Y, editors. Transfusion therapy: clinical principles and practice, 4th ed. Bethesda, MD: AABB Press, 2019:375-93. ECMO, extracorporeal membrane oxygenation; ACT, activated clotting time; aPTT, activated partial thromboplastin time; AT, antithrombin; CRP, C-reactive protein; VWF, von Willebrand factor.

0.3–0.7 IU/mL (67) with a typical goal of 0.5 IU/mL according to the ELSO guidelines (12). Available assays vary as to the incorporation of exogenous AT, which in turn affects the assay's ability to assess *in vivo* heparin activity. Anti-Xa assays may not be available at all times, at all institutions (68).

Anticoagulation monitoring in neonatal and pediatric ECLS patients

Similar to adults, there is extensive practice variation regarding anticoagulation/hemostasis monitoring in neonatal and pediatric ECMO (45). A recent survey of pediatric and neonatal intensive care medical directors found that 68% used ACT and anti-Xa monitoring, with 43% using ACT, anti-Xa, and aPTT; 16% using ACT, anti-Xa, aPTT, and TEG; 7% using anti-Xa and aPTT; and 5% using ACT, anti-Xa, aPTT, thromboelastography (TEG), and rotational thromboelastography (ROTEM) (63). Regarding neonates, *Table 5* shows the type,

utility, and frequency of testing as described in the recent neonatal ELSO guidelines (46,55).

Role of viscoelastic monitoring

Some institutions have used viscoelastic monitoring via TEG or ROTEM during ECMO, with the goal of deciding on interventions using a global assessment of hemostasis. These assays not only assess coagulation, but also evaluate platelet function and fibrinolysis. A heparin effect is easily detected with viscoelastic monitoring and may be eliminated using heparinase, allowing for the assessment of potential underlying hyper- or hypocoagulable states (1). A recent study found viscoelastic monitoring, using R time (TEG), was equally efficacious when compared to aPTT monitoring for patients on ECMO. The study reported similar rates of hemorrhagic and thrombotic complications and similar blood transfusion volumes when anticoagulation was assessed with either aPTT or viscoelastic monitoring (66).

However, because different hemostatic parameters are measured, the results of ACT, aPTT, anti-Xa assays, and viscoelastic testing do not correlate well with each other. This lack of correlation might easily be explained by patient specific parameters; for instance, thrombocytopenia or anemia have a profound effect on viscoelastic testing, while chromogenic assays are affected by the presence of hemolysis/plasma-free hemoglobin. These discrepancies have led some to suggest that anticoagulation monitoring strategies should optimally incorporate multiple assays (68). However, an increasingly disappointing fact of anticoagulant management is the multiple reports that find no testing regimen is associated with decreased bleeding, thrombosis, or improved outcomes in ECMO. Several small studies in adults have also noted that use of ECMO without anticoagulation or with a fixed-dose of heparin have outcomes that are comparable to regimens that incorporate testing and dose adjustment (65). Others have suggested a combination of viscoelastic testing and a common monitoring test (aPTT or other) may be optimal, but no agreement on this approach exists. While monitoring is complex, there is currently no national/international standardized protocol for patients on ECMO, representing an area of needed research.

Transfusion thresholds and ECMO

Patients on ECMO require transfusion of blood components due to a multitude of causes: hemodilution during circuit initiation, complications from their underlying condition, consumption by the ECMO circuit itself, or bleeding related to anticoagulation or circuit changes. Specifically, one meta-analysis identified the average major bleeding rate as 40.8% in adult cardiac ECMO cases (69). In a prospective observational cohort study of pediatric ECMO at eight U.S. hospitals, bleeding occurred in 70.2% of patients, and was independently associated with mortality (hazard ratio, 1.75) (70). Bleeding risk is affected by age, ECMO indication, underlying organ dysfunction, and local ECMO practices (71).

As would be expected based on the correlation of bleeding, underlying illness severity, and transfusion, a 2019 retrospective evaluation of French national ECMO data showed clear correlation of RBC/plasma/platelet transfusion volume and mortality (72). In that study, mortality exceeded 80% in ECMO patients who received more than 19 RBC, 12 plasma, and/or 5 platelet units (72). While VA ECMO is associated with greater patient illness severity and increased mortality as compared to VV ECMO, blood consumption did not significantly differ between the two procedure types in French national data (72).

Currently, there is no consensus on best transfusion practice for patients undergoing ECLS, and again, practices vary significantly among institutions (54). Observational studies have shown increased transfusion utilization in pediatric ECMO as compared to adult, especially for platelets (73). There have been numerous calls for increased use of evidence-based transfusion practice in ECMO (74). As blood component transfusion is associated with worse outcomes, many centers have lowered transfusion requirements from historical levels. Recently, a review by Karam and Nellis described the current gaps in knowledge of blood product use in pediatric ECMO (71).

Blood component usage and transfusion thresholds

Red blood cell usage

The objective of ECMO is to normalize oxygen delivery to the tissues. This is accomplished by adjusting the flow rate, oxygenation of the returned blood, and/or the hemoglobin concentration (75). ECMO patients receive large volumes of RBC transfusions (*Table 6*).

Several observational studies have shown that increased RBC transfusions in ECMO patients is associated with worsened clinical outcomes (72,73,76,79,81,83,84); this is of course likely confounded by the fact that sicker patients receive more transfusions. In adult VV ECMO, each increasing increment of 100 mL/day RBC transfusion was associated with odds ratio of 1.9 for ECMO mortality (83).

Table 6 Blood component utilization in ECMO: selected published studies

Blood component	ECMO patients transfused RBC (%)	RBC units per ECMO run	Volume RBC transfused per kg per day (mL/kg/day)	RBC donor exposures per ECMO course
Packed RBC				
Adult	83% (72)	12.7–29.0 (69) (meta-analysis average range)	N/A	N/A
		11.4 mean (72)		
Pediatric	Nearly all neonatal and young pediatric ECMO patients receive RBC	N/A	Studies show averages from 29 mL/kg/day to 39 mL/kg/day, to up to 105 mL/kg/day (76-78)	Medians from 1.4 to 10.9 per ECMO course (78)
	Blood prime used in 64% of pediatric runs (77)		Cardiac and ECPR indications had significantly higher median RBC requirements (105 mL/kg/day and 66 mL/kg/day respectively) relative to patients supported for non-cardiac indications (20 mL/kg/day, P<0.001) (79)	
Platelets				
Adult	57% (72)	N/A	N/A	N/A
Pediatric	95–100% (73,77)	median 8 platelet transfusions, median cumulative dose of 92 mL/kg (80)	12 mL/kg/day platelet products (76)	68% (81)
				Declined from ~65% to ~40% over 2011–2017 (82)
Plasma				
Adult	55% (72)	N/A	N/A	N/A
Pediatric	91% and 99% of pediatric and neonatal ECMO patients receive plasma, respectively (73)	N/A	7–16 mL/kg/day plasma products (76,81,83)	34% (81)
Cryoprecipitate				
Adult	25% (73)	N/A	N/A	N/A
Pediatric	54% pediatric, 53% neonatal (73)	N/A	0.4 mL/kg/day (76)	14% (81)

ECMO, extracorporeal membrane oxygenation; RBC, red blood cell; ECPR, Extra-Corporeal Cardiopulmonary Resuscitation.

Taiwanese data shows that adult ECMO patients that receive greater than 10 RBC units during ECMO support had significantly greater mortality; interestingly, among patients who received >10 total RBC, an RBC:plasma ratio of >1 was associated with improved mortality compared to a ratio of <1 (82). This contrasts with the findings in the trauma literature on the benefit of a reduced RBC:plasma ratio. One pediatric ECMO study noted that red blood cell transfusion did not improve venous oxygen saturation and that the majority of transfusions were given when central venous saturation (an indicator of adequate delivery/extraction) was normal (85).

The 2014 ELSO guidelines state that the threshold for the transfusion of RBC is generally a hematocrit of 35–40%, although many ECMO centers would accept lower hematocrit thresholds for transfusion (86). 2017 ELSO guidelines state that maintaining the hematocrit over 40% will optimize oxygen delivery while allowing the lowest reasonable blood flow (87). According to a 2017 survey of adult ECMO centers, the most common threshold for RBC transfusion was 7.1–8.0 g/dL for VA ECMO and 8.1–10.0 g/dL for VV ECMO, though there was significant

spread in both groups (54). In a group of 82 adult patients on VV ECMO, the hematocrit goal was 24–30% (83).

Similarly, there was wide variation in practice regarding the reported hemoglobin/hematocrit threshold for RBC transfusion in pediatric ECMO in a 2013 survey (45). The median RBC goal was hematocrit >35% (45). An observational study of pediatric ECMO patients showed median daily hematocrit values from 35–39% (higher in neonatal ICU patients) (76,77). To date, RCTs addressing appropriate thresholds for RBC transfusion in ECMO have not been completed.

Platelet usage

Initial ECMO cannulation and hemodilution are associated with a significant decline in platelet count, more so in neonates and small children (71,80). In one large multicenter study, neonates had an average 59% decline in platelet count upon ECMO initiation, while older pediatric patients had an average 38% decline (88). Although not supported by a large trial, inclusion of platelets in the neonatal ECMO prime was associated anecdotally with less decline in platelet count after ECLS initiation; however, further study is needed to confirm these findings (88). ECLS can also cause platelet activation and consumption, leading to quantitative and qualitative platelet dysfunction. Shear stress from the ECMO device may also lead to consumption of larger von Willebrand factor (VWF) multimers [e.g., predispose to acquired Von Willebrand Syndrome (avWS)] and lead to ineffective binding of platelets. Therefore, ECMO patients receive frequent platelet transfusions (*Table 6*).

The 2014 ELSO guidelines recommend frequent platelet transfusions of 10 mL/kg, to maintain a platelet count at least 100×10^9/L, especially in neonates (86). That was the median platelet goal in pediatric centers surveyed in 2013 (45). The threshold for platelet transfusion may be reduced in older patients with a lower risk of intracranial hemorrhage (86). The 2017 ELSO guidelines recommend maintaining a platelet count of at least 80×10^9/L (87). In a survey of actual practice, most adult ECMO centers target a platelet count of at least 50×10^9/L (54). Platelet targets are often increased in bleeding patients (71,89).

In a multi-national survey of pediatric ECMO centers, 79% of platelet transfusions during ECMO were given for prophylaxis of bleeding (89). The median platelet count prior to transfusion was 70×10^9/L. The median increase in platelet count in response to transfusion was 34×10^9/L. Despite frequent platelet transfusions, there may still be significant platelet dysfunction in ECMO patients. Platelet function tests can be performed to measure platelet activity and aggregation, but this is poorly reported in ECMO to date.

The volume of platelet transfusion was associated with the volume of RBC transfusion in a neonatal ECMO population [Spearman ρ 0.60 (P<0.001)] (84) and was also associated with worsening of the oxygenator function (likely due to clumping/clotting on the oxygenator surface) (71). Greater intensity of platelet transfusion was associated with increased mortality in a retrospective study of 110 neonatal ECMO patients (84). The Collaborative Pediatric Critical Care Research Network showed that, in 511 children on ECMO, average daily platelet transfusion volume was independently associated with mortality (per 1 mL/kg; odds ratio, 1.05; 95% CI: 1.03–1.08; P<0.001), whereas average daily platelet count was not (per 1×10/L up to 115×10/L; odds ratio, 1.00; 95% CI: 0.98–1.01; P=0.49) (88).

Plasma usage

Plasma transfusion replenishes all circulating coagulation factors (*Table 6*), though large transfusion volumes can be required for significant coagulopathy. The 2014 ELSO guidelines state that plasma may be administered in aliquots of 10 mL/kg as needed if the INR is >1.5–2.0 and/or if there is significant bleeding (86). In an international survey of pediatric ECMO centers, seventy-six percent (16/21) of the protocols recommended a more liberal plasma transfusion threshold for bleeding patients: median INR threshold for bleeding patients was 1.5 *vs.* 2.0 for non-bleeding patients (P=0.004) (89).

Nellis *et al.* showed that 60% of plasma transfusions were given for prophylaxis of bleeding. The median INR prior to transfusion was 1.45 (89). As is well known, patients who received plasma transfusion with only mild to moderate pre-transfusion coagulopathy (INR ≤2.0) showed only a small reduction in their post-transfusion INR (delta 0.1) (89). A randomized trial of scheduled (Q48 hours) plasma transfusions (versus usual care) in 31 pediatric ECMO patients showed no difference in the need for ECMO circuit change, UFH dose, bleeding/clotting events, or transfusion of other blood components (90). Of note, the study was small, and the total amount of plasma used in these patients did not significantly differ by intervention group.

Similar to red-cell transfusions, plasma transfusion has been associated with worse patient outcomes in non-randomized observational trials that are likely confounded by indication bias. Greater intensity of plasma transfusion was associated with increased mortality in a retrospective

Table 7 Common blood preparation protocols for ECMO

Clinical scenario	Urgency to issue blood products	Components	RBC freshness
Cardiac arrest (ECPR)	5–10 min*	2 units RBC	<14 days (ideally)
ECMO crash circuit change	5–10 min*	2 units RBC	<14 days (ideally)
Rapidly progressive shock	30 min^	2 units RBC	<14 days (ideally)
New neonatal ECMO activation	1 hour#	2 units RBC	<10 days (78)
		1 unit plasma	
		1 plateletpheresis	
New pediatric/adult (>10 kg) ECMO activation	1 hour	3 units RBC	<14 days (ideally)
		1 unit plasma	
Gradual respiratory or cardiac failure on conventional support	Hours to days**	2 units RBC	<10 days

*, rapidity will require use of emergency release group O RBC; ^, rapidity may require use of emergency release group O RBC; #, institutional neonatal transfusion guidelines will likely use irradiated group O HgbS negative RBC and group AB plasma; **, may allow use of type specific, crossmatched RBC. ECMO, extracorporeal membrane oxygenation; RBC, red blood cell; ECPR, Extra-Corporeal Cardiopulmonary Resuscitation.

study of 110 neonatal ECMO patients (84).

Cryoprecipitate usage

In addition to being consumed during clot formation, extracorporeal circuits also deplete fibrinogen as it is deposited onto the circuit surface.

Plasma is an inefficient way to replete fibrinogen and should only be considered for fibrinogen replacement (rather than cryoprecipitate) if concurrent deficiencies of other factors are also being treated. In the observational study of pediatric ECMO by Nellis *et al.*, the median increase in fibrinogen following plasma transfusion was only 20 mg/dL (89).

Cryoprecipitate usage in ECMO is summarized in *Table 6*. While 2014 ELSO guidelines state that cryoprecipitate can be given if the fibrinogen level is <100–150 mg/dL (86), a 2017 update states that plasma fibrinogen should be maintained in the 250–300 mg/dL range (87). Most ECMO centers that do target a plasma fibrinogen level use a range of 151–200 mg/dL and use both cryoprecipitate and plasma as replacement components (45,54). Fibrinogen concentrate was much less frequently reported as being used (54).

Any correlation of mortality and cryoprecipitate transfusion in ECMO patients is not well described in the current literature.

Transfusion services and ECMO

The hospital transfusion service provides blood components for priming and initiation of an ECMO run, as well as meeting ongoing transfusion goals during the run. Components should meet institutional requirements for patient age groups, such as irradiated and Hgb S-negative for neonates.

The complement of blood components sent in an "ECMO pack" will vary by patient, ECMO indication, urgency, and hospital center. Suggested protocols are provided in *Table 7*, derived through personal communication with Dr. David Friedman, and modified by Geoffrey Wool with permission from David Friedman (78).

Reported thresholds for blood component transfusion vary significantly by patient age and indication as well as by hospital/organization. Because there are as yet no prospective RCTs that have identified appropriate thresholds for transfusion, only general ELSO guidelines, survey results, and observational studies are reported in *Table 6*. These triggers should only be viewed as guidance and are limited in terms of their assessment of complex patient physiology (91).

Restrictive blood transfusion strategies in ECMO

A restrictive approach toward RBC transfusion may benefit patients on ECMO. A study of adult ECMO patients showed a statistically significant increase in mortality for patients with median on-ECMO Hct >31% (92). Adoption of an ECMO transfusion protocol (including RBC transfusion trigger of 8.0 g/dL) in adult VA-ECMO resulted

in a decrease in blood component use and complications as well as a statistically significant increase in survival (in a retrospective cohort study) (93). Adult ECMO centers are reporting adoption of restrictive transfusion strategies based on evidence in critically ill patients, with Hgb thresholds as low as 7.0 g/dL, without adverse effects noted (91,94).

Most pediatric ECMO RBC transfusions occurred on days without bleeding (77). A pre- and post-intervention comparison study of neonatal ECMO patients by Sawyer *et al.* showed a reduction in RBC volume usage (from 13.3 to 10.4 mL/kg/day) when a hematocrit trigger for RBC transfusion was reduced from 40% to 35%. No differences were seen in rates of transfusion of other blood components, survival off ECMO, survival to discharge, or complication rate (95).

In the future, transfusions of RBC to ECMO patients may be based on markers of tissue oxygenation rather than a simple blood hemoglobin concentration.

Research into ECMO transfusion practice should ideally be prospective and multicenter, with standardization of blood product usage reporting and outcomes such as bleeding. Such studies are currently on-going for VA-ECMO (NCT03714048) and VV-ECMO (NCT03815773) (96). Contemporary research is particularly important, given significant improvements in ECLS extracorporeal volumes/circuit sizes.

Blood sampling for frequent laboratory monitoring is a clear contributor to transfusion need in ECMO, especially in pediatric patients (70,77). Patient blood management (PBM) for ECMO patients should also focus on limiting phlebotomy and use of pediatric vacutainer tubes, as possible. As no anticoagulation monitoring regimen has proven to be superior, limiting anticoagulation monitoring testing may reduce blood loss from phlebotomy without significant patient harm; further study is necessary.

Use of pharmacologic or novel blood products to enhance hemostasis for ECLS patients

Antifibrinolytics

A 2013 report of an international survey by Bembea *et al.* showed that 67% of ECMO centers (predominantly pediatric) used epsilon aminocaproic acid (EACA), while 22% used tranexamic acid (TXA) (45). In contrast, a 2021 survey report of 51 US pediatric hospitals showed that 22% of ECMO patients received TXA, with increasing use over the 6-year study period; only 7% received EACA (97). Both TXA and EACA are lysine analogues. Some studies have shown TXA to be somewhat more efficacious than EACA for reducing bleeding (98), but TXA is more expensive and has been non-significantly associated with seizure risk (99,100).

In bleeding patients on ECMO with evidence of fibrinolysis (high D-dimer and low fibrinogen levels), EACA may be an effective option to control bleeding and to stabilize clot formation (101). A retrospective cohort study of pediatric cardiac ECMO patients receiving EACA (n=62) showed significantly reduced bleeding rate and reduced transfusions of all components, without increased adverse events. The authors argue for wider consideration for EACA use as a part of a multipronged strategy to manage bleeding during ECMO (102).

Platelet substitutes

Platelet substitutes (103) or modifications of platelet storage (such as cold stored or lyophilized platelets) (104) have not been studied in ECMO patients.

Fibrinogen concentrate

Use of fibrinogen concentrate to treat and prevent bleeding complications is reported in adults on ECMO, but not children (105-107). Advantages of fibrinogen concentrate include more precise dosing due to known fibrinogen concentration, lyophilized product not requiring storage or thawing, and viral inactivation. Disadvantages primarily include cost and lack of other coagulation factors that may be helpful in hemostasis. Further studies are needed to determine its true cost effectiveness and efficacy in ECMO.

Other hemostatic agents

Recombinant activated factor VII (rFVIIa) has been used to treat severe refractory bleeding on ECMO. In complex with tissue factor, FVIIa activates FIX and FX to generate thrombin. The use of rFVIIa to reduce bleeding and transfusion requirements must be balanced with risk of fatal thrombosis (108,109), and such agents should be used only after adequate platelet and factor replenishment (particularly fibrinogen) (80), as well as achievement of normo-thermia and correction of acidosis and hypocalcemia (110). Having an available emergent backup ECMO circuit is strongly recommended when giving agents such as rFVIIa (80).

Sixty-seven percent of ECMO centers (predominantly pediatric) reported use of rFVIIa (45). A 2021 survey report of 51 US pediatric hospitals showed that 3% of ECMO patients received rFVIIa (97). In a small number of case reports, the efficacy of rFVIIa in refractory pediatric

ECMO bleeding is limited (111,112). In contrast, the efficacy of rFVIIa in adult ECMO patients was reported to be 93% (bleeding cessation), with 3% thromboembolic events and 17% circuit change events (110).

Prothrombin complex concentrates (PCC) are used for hemophilia B (3F-PCC) or warfarin reversal (4F-PCC) and off-label for refractory peri-operative bleeding (113), but little literature is available on their use in ECLS.

For bleeding ECMO patients with adequate fibrinogen and platelet counts, avWS and FXIII deficiency should also be considered. Specific factor concentrates are available for those deficiencies (114-116). avWS is induced by the unfolding and consumption of vWF under abnormal/elevated shear stress in the extracorporeal circuit (117) avWS is extremely common in ECMO and has been described in 100% of a pediatric cohort (n=30) receiving ECMO or VAD (118,119). Of note, Humate-P supplementation has not been shown to be effective at reducing transfusion or bleeding in pediatric ECMO patients (120).

ECMO complications

Bleeding vs. thrombotic risks

The ECMO circuit induces significant alternations in the hemostatic balance of the patients due to the inflammatory and thrombotic response induced when blood contacts an artificial surface. The risk of thrombosis is directly proportionate to the time the patients are on ECMO (5). For example, deposition of platelets and monocytes on the circuit surface causes surface-initiated tissue factor exposure and activation of the coagulation cascade (1). This response is amplified in the pro-inflammatory and complement activation states. As many as 20% of patients on ECMO can have deep vein thrombosis (121). Furthermore, ECMO can induce platelet aggregation and platelet-derived microparticle generation. Based on a mathematical model, platelet aggregation is similar between hollow fiber-based circuits and silicon-membrane oxygenator circuits. However, platelet-derived microparticle generation was at least 2.5 times higher using a centrifugal pump compared to a roller-head pump system regardless of oxygenator type (122).

However, ECMO patients are also at increased risk of bleeding, which can occur in up to 33% of patients on ECMO (11). Bleeding risk is secondary to rapid consumptive coagulopathy along with dilutional coagulopathy at the initiation of ECMO. During ECMO, in addition to consumption of coagulation factors due to inflammation-induced activation of factor X and thrombin generation, patients can also develop avWS, thrombocytopenia, and platelet dysfunction, in addition to factor XIII and fibrinogen deficiencies (1,5). Adding complexity is the need to provide anticoagulation for the extracorporeal circuit, including the oxygenator/heat exchanges, and the various cannular sites. Given this complexity, hemorrhagic or thrombotic events can be extremely challenging for a patient on ECMO (1). When an adverse event occurs, it can be difficult to distinguish if it is due to the patient's underlying condition or an anticoagulation issue (i.e., over- or under-utilization of anticoagulation medications (1).

Other risks

Hemolysis can occur in patients undergoing ECMO, which can be related to the patients' underlying diseases. For example, in patients on ECMO for respiratory failure, adverse event related to hemolysis decreased from 15% to 8.4% between those treated prior to 2000 compared to similar group treated between 2000 and 2016. On the other hand, in patients treated with ECMO for cardiac complications during a similar period, the rate of hemolytic complications increased from 7.5% to 12.4%. This difference was hypothesized to be due to lower-weight neonates who required prolonged ECLS due to complex cardiac surgeries (27).

Another potential complication experienced by patients on ECMO is related to neurological injury, with an incidence between 1.8% to 21%, most likely due to the variation in surveillance practice and/or utilization of medications that can mask neurological problems (1). In fact, neurological injury is the major cause of mortality for infants on ECMO (123,124). This may be related to increased rates of intracranial hemorrhage with rates up to 16–34% compared to 2–21% for adults (74). While intracranial hemorrhage is the most common life-threatening complication for adults undergoing ECMO , other adverse events can include renal complications, limb ischemia, infection and sepsis, air embolism, cannula complications, and device malfunctioning (125,126).

Circuit concerns

The differences among types of pumps and oxygenators adds complexity to the adverse events in pediatric patients. Although centrifugal pumps are smaller and can be more portable compared to roller-head pumps, they

are associated with adverse events related to hemolysis (albeit less so than with roller-head pumps) and negative-pressure generation (127-130). Roller-head pumps, on the other hand, are associated with tubing rupture, which is a high-risk complication. Moreover, although newer generations of ECMO devices are more efficient and better in facilitation of oxygen delivery, they can lead to overventilation and hypocapnia and thus thrombosis, especially in neonates.

Concomitant use of cell separator devices in ECLS

Indications

ECMO is a temporizing therapy utilized in critically ill patients. Patients undergoing ECMO are at risk for, and frequently concurrently treated for, simultaneous severe medical conditions including but not limited to infection, sepsis, shock, and even multi-organ failure (MOF). Treatment of the patient's underlying disease, or even additional temporizing strategies, may include therapeutics that employ an additional form of extracorporeal circulation.

Patients undergoing ECMO frequently have, or develop, acute kidney injury (AKI) often within the first 48 hours of cannulation. Renal replacement therapy (RRT) is often employed to mitigate symptoms of acute renal failure in patients receiving ECMO; it has been estimated that 50% of ECMO patients may require RRT (131,132). While there appears to be significant practice variation with respect to the technical aspects of performing RRT in a patient undergoing ECMO (either through incorporation into the ECMO circuit, or as an independent process), RRT is indicated in the setting of ECLS for the treatment of uremia, fluid overload, acidosis, electrolyte imbalances, and intoxication (131). A survey of 65 ELSO institutions revealed the most common reported RRT indications were fluid overload (59%), AKI (35%), and electrolyte disturbances (4%) (125). Data from a recent meta-analysis suggests that the performance of RRT in ECMO patients was associated with higher mortality, and longer hospitalizations; however, this is likely a reflection of clinical severity (133).

Similarly, although far more rarely, plasma exchange (PE) may be indicated for a patient undergoing ECMO (134-138). In one of the largest cohorts reported to date, a retrospective analysis performed at two US academic medical centers identified only 66 patients over a period of 7 years who received simultaneous PE and ECLS (136). Simultaneous PE may be more commonly performed in pediatric than adult patients. Dyer *et al.* reported the most common indications for simultaneous PE in pediatric patients were MOF and coagulopathy, while in adults it was antibody mediated allograft rejection (136). Due to infrequent clinical need and a relative paucity of published literature on the topic, many apheresis practitioners, particularly at adult medical centers, may be unfamiliar with the required circuit modifications.

Circuit considerations

Although at present no optimized guidelines exist, many centers have PE procedural modifications when performing the procedure using the ECMO circuit that include considerations of patient access, volume calculations, replacement fluid selection, and anticoagulant protocols.

While there is some discrepancy within the literature as to the optimal connection point, the consensus in the field of apheresis is to perform the procedures in parallel, and to insert the PE instrument inlet and return lines into the low pressure side of the ECMO unit, either before or after the pump, but proximal to the oxygenator (135,136,139). This was proposed with the goal that oxygenator would serve to prevent air emboli potentially caused by line manipulation, and the lower pressures would facilitate performance of the procedure (135). As such, if the PE procedure is to be performed in parallel to the ECMO circuit, the patient's calculated blood volume should be increased to account for the volume of the ECMO circuit (135-137).

Replacement fluid

For the performance of PE, generally speaking, albumin is preferred over plasma because it is isosmotic, sterile, stored at room temperature, and is devoid of the infectious risks associated with blood components (140). However, depletion of coagulation factors via PE could potentially exacerbate bleeding at the ECMO cannulation site or any other fresh surgical incisions. It may also affect hemostasis by depleting protein C, protein S, and/or AT, a critical heparin-potentiator (136). Thus, plasma is usually utilized as a replacement fluid of choice during PE to mitigate depletion of critical coagulation factors (135). Selection of replacement fluid in the setting of ECMO should be determined in communication with the clinical teams, as

indicated by the patient's current clinical presentation; optimal fluid selection may vary by procedure.

Anticoagulation considerations

Similarly, there is no optimal protocol with regards to anticoagulation protocols during the performance of simultaneous ECMO and PE procedures (136). Acid citrate dextrose A (ACD-A) is frequently utilized to maintain anticoagulation of the PE circuit; however, given the systemic heparinization that occurs during ECMO, additional anticoagulation maybe unnecessary. Increasing the mean whole blood to anticoagulation ratio (AC Ratio) to 40:1 in actively heparinized patients has been described (135,136). Similar to replacement fluid selection, the anticoagulant protocol should be determined in communication with the patient's clinical team and may vary based on the patient's clinical presentation and in coordination with the patient's current treatment plan.

Adverse events associated with dual procedures are similar to those associated with PE in isolation and are primarily limited to hypotension and hypocalcemia. It is recommended that patients' ionized calcium be assessed throughout the procedure (every 20 minutes for pediatric or at mid-point for adult) to mitigate the risk of hypocalcemia (135). It has been suggested that PE in the setting of ECLS is associated with an increased 30-day mortality; however, this may reflect disease severity (141).

Future directions

The use of ECMO is likely to continue to expand, owing to advances in technology, increased experience in a variety of new patient populations, and success of ECMO support in patient populations historically avoided, such as trauma, cardiac arrest, bridge to transplant, and even intracranial hemorrhage. Bleeding and thrombosis remain the most common complications associated with increased morbidity and mortality. The lack of a standardized, scientifically refined algorithm for anticoagulation monitoring and lack of any testing regimen that is associated with improved outcome, despite many years of experience and research, remains a conundrum and frustration for ECMO providers. Use of blood components, previously driven by historical recommendations rather than scientific rationale, may continue to decrease as our knowledge base expands. RCTs of more conservative red blood cell transfusion thresholds have been proposed, though none have been funded or completed. Similar research is required for other products, such as platelets, plasma, and AT concentrate, to guide appropriate use of these products. Reduced phlebotomy from unnecessary laboratory tests also represents an opportunity for reducing the need for transfusion. Assessing cost savings is also important. Incorporating hematology experts in multidisciplinary teams caring for ECMO patients can improve understanding and care for these complex patients.

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