



2021 ELSO Adult and Pediatric Anticoagulation Guidelines

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Anticoagulation is necessary for most pediatric and adult extracorporeal membrane oxygenation (ECMO) patients to prevent circuit clotting. Inherently, the most common side effect of anticoagulation is bleeding. Anticoagulation during ECMO is complex due to patient critical illness, interactions between the patient and ECMO circuit, and the inflammatory responses of the patient to illness and to the ECMO circuit which all lead to imbalance in normal patient hemostasis.¹

Anticoagulants

Unfractionated heparin (UFH) is currently the most commonly used anticoagulant for pediatric and adult ECMO.^{2,3} Unfractionated heparin is a glycosaminoglycan that binds to antithrombin (AT) to produce a 1,000-fold increase in AT inhibition of thrombin, factor Xa, factor XIIa, and factor IXa.⁴

There are several disadvantages to UFH use in ECMO patients (Table 1). Besides binding to AT, UFH binds to circulating plasma proteins, endothelial cells, and macrophages thus altering its pharmacokinetics and patient dose response. Pharmacokinetics also vary significantly in neonatal and pediatric patients due to lower concentrations of AT, larger volume of distribution, and increased rate of clearance.^{5,6} For example, in healthy adults the half-life of UFH is 1 to 2 hours compared with 35 minutes in neonates.⁷ Although it is rare, UFH can cause heparin induced thrombocytopenia (HIT) in 0.2% to 5% of adult patients.⁸ Heparin induced thrombocytopenia is more common in adults than pediatrics and is a potentially life-threatening immune-mediated prothrombotic disorder, especially in patients exposed multiple times to heparin.^{9,10}

Alternative anticoagulants, such as direct thrombin inhibitors (DTIs), are being increasingly used off-label for both pediatric and adult ECMO patients. Direct thrombin inhibitors are short-acting anticoagulants that directly inhibit thrombin. Theoretically, DTIs should have a more predictable dosing regimen because, unlike UFH, they bind directly to thrombin without the need for AT and do not bind to other plasma proteins. The two DTIs most commonly used in ECMO are bivalirudin and argatroban. Bivalirudin binds to both circulating and clot-bound thrombin compared with UFH that only binds to freely circulating thrombin. Bivalirudin is primarily metabolized by proteolytic enzymes and 20% is renally excreted. Argatroban is a univalent DTI that reversibly binds and inhibits the active site of thrombin. It is metabolized mainly in the liver and primarily excreted in the feces.

Disadvantages of DTIs include the limited availability of specific laboratory monitoring, lack of specific antidote, higher cost, and limited ECMO experience. While no antidote exists

Table 1. Summary of the Mechanism of Action, Advantages and Disadvantages of Anticoagulants During ECMO

Anticoagulant	Mechanism of Action	Half-Life (mins)	Advantages	Disadvantages
UFH	Main: binds to AT to inhibit thrombin and Xa	60–90 (adults) and 35–75 (pediatrics)	Inexpensive; has antidote (protamine)	Binds to other plasma proteins; heparin induced thrombocytopenia
Bivalirudin	Reversibly binds to thrombin	25 (adults) and 15–42 (pediatrics)	Does not require AT	No antidote, caution with blood stasis and renal dysfunction
Argatroban	Reversibly binds to thrombin	39–51	Does not require AT; not degraded by serine proteases	No antidote; variable dosing; caution with hepatic dysfunction

AT, antithrombin; ECMO, extracorporeal membrane oxygenation; UFH, unfractionated heparin.

for DTIs, discontinuation of the agent is often the only treatment necessary given their short half-life (Table 1). In addition, recombinant factor VIIa has been shown to be an effective reversal agent. Furthermore, bivalirudin can be quickly removed by continuous renal replacement therapy and plasmapheresis.¹¹ Nonetheless, caution should be used with bivalirudin in low flow states such as severe cardiac dysfunction due to risk of localized bivalirudin proteolysis and formation of an intracardiac thrombus.¹² It is also common for low flow areas in the circuit (e.g. lab access lines or reperfusion cannulas) to clot when on bivalirudin and they may require frequent changes.

Several retrospective case series have examined the use of DTIs compared with UFH for pediatric and adult ECMO patients.^{13–29} Large, prospective randomized trials are needed to confirm the efficacy and superiority of DTIs before their use as the primary anticoagulant for ECMO patients.

Therapeutic Monitoring of Anticoagulants

The optimal method to measure UFH and DTI efficacy on ECMO is unknown. Anticoagulation monitoring for drug specific effect is done *in vitro*. As such, this does not take into account endothelial responses nor blood/artificial-surface responses to anticoagulation *in vivo* during ECMO. This is a major limitation in understanding how coagulation occurs in the patient. The majority of coagulation tests used to monitor anticoagulation are plasma-based tests. Plasma-based tests such as activated partial thromboplastin time (aPTT) are partial functional measures of coagulation and do not account for platelet function or clot strength. In contrast, some whole blood tests such as viscoelastic tests incorporate platelet function and assess clot strength but are not always routinely performed or available at ECMO institutions. Viscoelastic tests also require expertise in viscoelastic technology to interpret and guide clinical management.

A tailored strategy for each patient which allows for interpretation of their anticoagulation monitoring in the context of their individual baseline (as opposed to laboratory baseline), overall inflammatory state (such as septic shock), end-organ dysfunction (liver and kidney) and platelet function as well as consideration of their unique bleeding and clotting risks is needed for optimal anticoagulation. Anticoagulation monitoring tests are only tests; they do not represent *in vivo* physiology. The clinician must interpret results in the context of their patient and circuit. It is recommended especially in pediatrics or challenging cases to perform both a plasma-based test to measure specific anticoagulant effect and a whole blood test to measure point of care hemostasis.

Table 2 summarizes the advantages and disadvantages of different monitoring techniques for UFH and DTIs and Table 3 describes a suggested anticoagulation monitoring regimen based on ELSO's recommendations.

Activated Clotting Time

Based on experience with cardiopulmonary bypass and availability as a point of care test, activated clotting time (ACT) was the historical test to monitor ECMO anticoagulation. However, as our understanding of the complexities of anticoagulation and ECMO coagulopathy have evolved, anticoagulation monitoring has intensified in select cases and ACT has been slowly replaced in some centers with other laboratory testing.^{2,3,31} Activated clotting time measures the time in seconds of whole blood to form fibrin clot after the addition of various coagulation activators. Hence, it does not represent solely UFH effect, but rather provides a physical examination of the blood at the specific time the test is done. Activated clotting time does not measure clot strength. Activated clotting time results will vary based on many factors including platelet number and function, fibrinogen level, coagulation factor deficiencies, temperature, hemodilution, as well as technical factors. Different ACT machines yield different results either because of different coagulation activators or because they are measuring different end points and as a result they cannot be used interchangeably. Activated clotting time is not licensed to monitor DTIs, although it can be used to follow the anticoagulation trends once DTIs are established. Expertise in understanding and interpreting ACT results, rather than adhering to a specific number or range, can make it a useful whole blood test if viscoelastic testing is not routinely available.

Activated Partial Thromboplastin Time

Historically, dose monitoring of patients receiving UFH has been done with aPTT. Activated partial thromboplastin time is also the standard monitoring test for DTIs because of its wide availability. The aPTT test is a plasma-based test that measures the time from factor XII activation to fibrin formation, after calcium is added to the plasma, which was exposed to phospholipid and a contact activator. A prospective, non-ECMO, adult study from 1972 demonstrated that an aPTT between 1.5 and 2.5 times normal was associated with a decreased risk of recurrent venous thromboembolism.³² Based on this adult study, the therapeutic range for the aPTT was set at 1.5 to 2.5 times the patient's pretherapy baseline aPTT, however, this was never validated in randomized controlled trials or in ECMO patients. Additionally, in children the baseline aPTT varies with age because of developmental hemostasis.

The use of aPTT for UFH monitoring is based on the assumption that the patient's baseline aPTT is comparable to normal controls and that there is a linear relationship between UFH dose and aPTT. The baseline aPTT in critically ill patients is often different from normal controls which limits the utility of

Table 2. Summary of the Advantages and Disadvantages of Anticoagulation Testing

Test	Advantages	Disadvantages	Use in DTI
ACT	Whole blood test Point of care test Primary method to monitor UFH in ECMO Widely available Inexpensive Examines blood response to all factors influencing hemostasis	Affected by clinical factors including: Thrombocytopenia or platelet dysfunction Elevated d-dimers Low fibrinogen or other coagulation factor deficiencies Hypothermia (shortened with hyperthermia) Hemodilution or anemia Technical factors Measures end point of the clotting cascade, but does not solely represent UFH effect No standardization between different ACT devices Plasma test	Not approved for DTIs
aPTT	Gold standard assay for UFH monitoring outside of ECMO Widely available Point of care now available	High degree of inpatient and interpatient variability especially in infants Less reliable in critical illness Influenced by blood collection techniques (composition of sampling tube, timing of sample collection) No standardization between different aPTT reagents Requires revalidation of aPTT target range with new lot of reagent	Yes, standard test for DTI Underestimates true anticoagulant effect at higher concentration of DTI
Anti-Xa Assay	Specific measure of UFH effect based on the ability of UFH to catalyze AT's inhibition of Factor Xa Reports of better association with UFH dose and less variability than aPTT	Plasma test No standardization between assays Use of exogenous antithrombin or dextran sulphate Chromogenic assay Falsely low anti-Xa result with plasma free hemoglobin > 50mg/dl, triglyceride > 500mg/dl, and bilirubin > 6mg/dl Limited availability	No
TEG/ROTEM	Whole blood test Point of care Provides information about both clot strength and fibrinolysis	Expensive and still considered research for some centers Differences between TEG and ROTEM Limited data describing correlation with conventional UFH and clinical outcomes	Yes, limited data
Plasma dilute thrombin time	Improved sensitivity over aPTT to monitor direct thrombin inhibitors Not affected by antiphospholipid antibodies	Research assay (unavailable at most centers) Not approved by FDA for monitoring of bivalirudin (but approved for dabigatran and argatroban)	Limited availability
Ecarin clotting time	Linear response to DTI concentration Unaffected by variations in clotting factors including fibrinogen	Research assay (unavailable at most centers) Not approved by FDA for monitoring of bivalirudin	Research only

ACT, activated clotting time; aPTT, activated partial thromboplastin time; AT, antithrombin; DTI, dilute thrombin time; ECMO, extracorporeal membrane oxygenation; FDA, food and drug administration; TEG, thromboelastography; UFH, unfractionated heparin; UFH, unfractionated heparin.

aPTT as a measure of UFH effect. Nonspecific acute phase reactants, factor VIII and fibrinogen are often elevated in critically ill patients and may shorten the aPTT masking the true UFH effect.

As a result, aPTT demonstrates a high degree of inpatient and interpatient variability that can result in an increased number of aPTT tests drawn for UFH monitoring and frequent UFH dose changes. Consequently, many clinical laboratories and clinicians have substituted the anti-Xa assay for UFH monitoring.

Table 3. Suggested Anticoagulation Monitoring Laboratory Schedule*

Laboratory Test	Frequency
ACT	Q1h-Q2h
aPTT	Q6h-Q12h
Anti-factor Xa assay	Q6h-Q12h
Platelets	Q6h-Q12h
INR	Q12h-Q24h
Fibrinogen	Q12h-Q24h
CBC	Q12h-Q24h
Antithrombin level	Daily-PRN
Plasma free hemoglobin	Daily
Thromboelastography/ thromboelastometry	Daily-PRN for bleeding or thrombotic complications

Anti-Xa Assay

The anti-Xa assay is a measure of UFH effect based on the ability of UFH to catalyze AT's inhibition of factor Xa activity. Anti-Xa is not used for DTIs. Anti-Xa is a plasma-based test that evaluates only one chemical reaction of the UFH-AT complex and thus does not measure inhibition of thrombin nor does it incorporate platelet function. However, anti-Xa is used as a surrogate measure of the overall anticoagulant activity of UFH. An adult randomized controlled trial (RCT) of patients with acute venous thromboembolism reported that an anti-Xa of 0.35 to 0.67 U/ml and a PTT of 60 to 85 seconds were equivalent to a heparin level of 0.2 to 0.4 U/ml by a protamine titration.³³ It is important to note that anti-Xa assays vary amongst institutions as to whether exogenous AT is added to the assay or if dextran sulphate is present in the reagent. Calibrators will also vary across institutions. Because it is a colorimetric assay, pigmented

Adapted from Brogan.³⁰

*If patient is clinically stable with no bleeding or clotting, it is reasonable to draw complete blood count and coagulation labs once daily.

ACT, activated clotting time; aPTT, activated partial thromboplastin time; CBC, complete blood count; INR, international normalized ratio.

Table 4. ELSO Suggested UFH Titration and ACT Goal Range Based on Anti-Factor Xa Levels

Anti-Factor Xa Goal Range (units/ml)	Anti-Factor Xa Level (units/ml)	UFH Rate Change	ACT Goal Range (s)
0.3–0.5	<0.3	↑10%–20%	↑10–20
	0.3–0.5	No change	No change
	>0.5	↓10%–20%	↓10–20
0.4–0.6	<0.4	↑10%–20%	↑10–20
	0.4–0.6	No change	No change
	>0.6	↓10%–20%	↓10–20
0.5–0.7	<0.5	↑10%–20%	↑10–20
	0.5–0.7	No change	No change
	>0.7	↓10%–20%	↓10–20

Adapted from Brogan.³⁰

ACT, activated clotting time; UFH, unfractionated heparin.

or opaque plasma, such as that due to high bilirubin, triglyceride or free hemoglobin levels can result in an underestimation of UFH effect.³⁴ Table 4 outlines ELSO's suggested UFH titration based on anti-Xa levels. In addition, Table 5 describes factors to consider when aPTT and anti-Xa testing are discordant.

Viscoelastic Hemostatic Assays

The viscoelastic hemostatic assays (VHA) are whole blood point of care coagulation assays used to measure the viscoelastic properties of the clot (Figure 1). Compared with standard coagulation tests including aPTT, anti-Xa, and ACT, VHAs allow for a global assessment of clot initiation (e.g. clotting time), clot strength or amplitude (e.g. fibrinogen and platelet contribution), and clot stability (e.g. fibrinolysis). The platelet contribution to clot formation can be calculated by the difference between the amplitudes measured after extrinsic or intrinsic activation and fibrinogen assays. While several devices were developed over the past decade, only two have been validated for clinical use: thromboelastometry (ROTEM) and thromboelastography (TEG). Each device comes with multiple assays allowing for extrinsic (EXTEM on ROTEM, RapidTEG on TEG) and intrinsic (INTEM on ROTEM and Kaolin-activated TEG) clot activation, assessment of fibrinogen contribution to formation (FIBTEM on ROTEM and FF-TEG), as well as heparinase assays (HEPTEM on ROTEM and Heparinase Kaolin-TEG).

The use of VHAs is currently recommended to guide the administration of blood products and coagulation factors in the presence of bleeding in patients undergoing cardiac and noncardiac surgery, as well as in trauma.^{35–37} While VHAs have never been validated as tools to predict bleeding, but rather to guide the administration of therapies, recent studies suggest that hypercoagulable states as demonstrated on TEG or ROTEM can predict the risk of thrombotic complications. Because both

devices come with heparinase assays, the ratio between clotting time measures with and without heparinase can be used to estimate the anticoagulation effect of UFH.

Viscoelastic hemostatic assays have been used in several randomized controlled trials in patients undergoing cardiac surgery.^{38,39} The literature regarding use of VHAs in ECMO is increasing and small RCTs and retrospective case series have shown differing results regarding use of VHAs as predictors of clotting and bleeding.^{40–43}

Antithrombin

Monitoring of AT has a strong pharmacologic rationale when using UFH, however, there is not consistent data suggesting that monitoring or replacing AT improves outcomes. Previous retrospective studies described that anticoagulation targets may be reached more easily, although not significantly, and lower doses of UFH may be required when AT supplementation is used.^{44,45} A highly anticipated pilot RCT of adult VV-ECMO patients randomizing patients to receive AT to achieve a goal 80% to 120% versus control found no difference in total UFH dose, bleeding, transfusion need, or thrombosis. However, a posthoc analysis reported that patients who received AT and had an AT level <60% had a decrease in UFH dose.⁴⁶ More evidence is needed before recommending routine AT monitoring and supplementation.

Future Tests for Direct Thrombin Inhibitors

Activated partial thromboplastin time is currently the standard test for monitoring DTIs, but at higher doses of DTIs, such as those used for cardiopulmonary bypass in patients with HIT, aPTT shows a nonlinear response to DTI dose.⁴⁷ Plasma dilute thrombin time and ecarin chromogenic assay may be superior tests, but they are not available at most institutions.^{48,49} When using DTIs, it is strongly suggested to have clinicians with expertise both in anticoagulation and ECMO to aid in dosing, monitoring, clinical management, and complications.

In summary, each anticoagulation monitoring test has merits and disadvantages. For each center an approach that allows for a tailored regimen of anticoagulation (regardless of agent used) and monitoring is necessary. At the very least, both a plasma-based test for anticoagulant effect and whole blood POC test for hemostasis should be available.

Recommendations Specific to Adult ECMO Patients

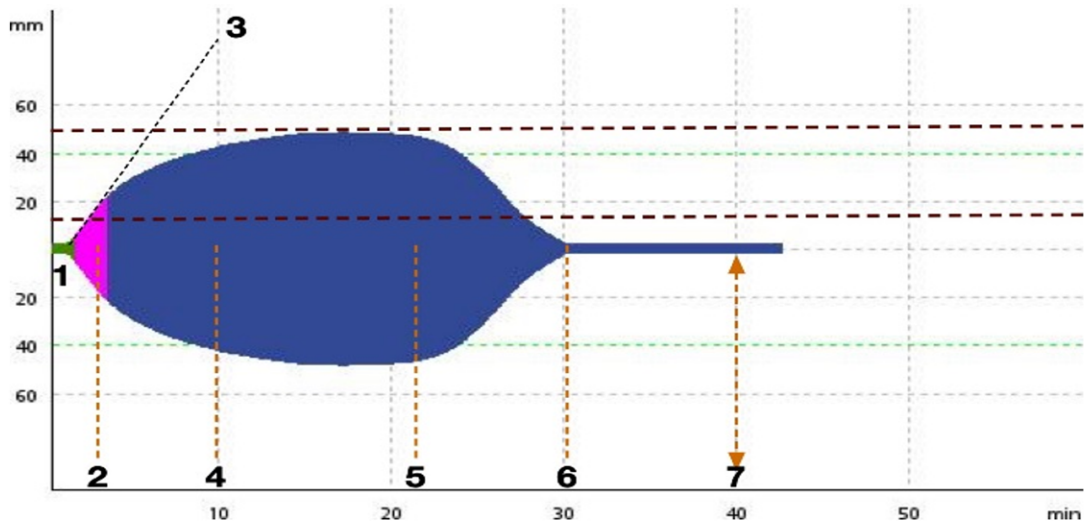
There is variability in anticoagulation practices for adults supported with ECMO and as in pediatric ECMO this remains an area of active investigation. Importantly, some issues related

Table 5. Algorithm for Discrepant Anticoagulation Tests

Anti-Factor Xa (0.3–0.7 IU/ml)	aPTT (60–90 s)		
	Low	Normal	High
Low	Increase heparin	Increase heparin	Consider factor deficiency and repletion with FFP
Normal	Consider hypercoagulable state	No change	Repeat aPTT, consider FFP if still high
High	Unlikely to occur; consider repeating labs	Consider repeating labs, consider hypercoagulable state	Decrease heparin

aPTT, activated partial thromboplastin time; FFP, fresh frozen plasma.

Extrinsic Pathway



Example of VHA testing: Extrinsic pathway for ROTEM and TEG
 First parameter denotes ROTEM with its corresponding TEG value (if applicable)

1. Clotting time (CT, sec)/R (min)
2. Clot Formation Time (CFT, sec)/K (min)
3. Alpha-angle (α , degree)/Alpha-angle (α , degree)
4. Amplitude 10 min after CT (A10, min)
5. Maximum Clot Firmness (MCF, mm)/Maximum Amplitude (MA, mm)
6. Lysis Index 30 min after CT (LI30, %)/Lysis Index 30 min after MA (LY30, %)
7. Maximum Lysis (ML, %)

Figure 1. Example of VHA testing. TEG, thromboelastography; VHA, viscoelastic hemostatic assays.

to developmental hemostasis or to the use of lower blood flows associated with pediatric ECMO are less of a concern in adults, making typical anticoagulation strategies easier. Nevertheless, the rate of bleeding and thrombotic complications is still a concern and is the motivation for the development of new strategies.

There is currently a paucity of evidence to guide optimal anticoagulation management in adult ECMO patients. The current tendency is towards less anticoagulation especially in VV-ECMO where multiple retrospective studies suggest that either lower (or no) anticoagulation is safe and feasible.^{50,51} Although these data are encouraging, we cannot yet recommend the routine use of no anticoagulation for VV-ECMO. The most recent pilot randomized study of low heparin *versus* usual care showed a significant decrease in the dose of heparin and in the mean aPTT and anti-Xa without increasing the rate of complications.⁵² However, this study did not conclude on the superiority of a low-dose heparin protocol for ECMO. Fortunately, there are both ongoing (NCT04496362) and planned (NCT04273607) studies that will help to answer

the question regarding the safety of a no anticoagulation strategy for adult VV-ECMO.

For VA-ECMO, given the concerns of systemic emboli, the routine use of anticoagulation is currently recommended. A recent retrospective study on VA-ECMO patients suggested that the absence of anticoagulation is safe in adult VA-ECMO patients and is associated with decreased transfusion and hemorrhagic complication without an increase in thrombotic events.⁵³ However, well-powered randomized controlled trials are still needed to draw definitive conclusions on the safety and feasibility of VA-ECMO without anticoagulation.

Management of Bleeding and Thrombotic Complications

Optimal Blood Product Replacement

There is a lack of studies to guide blood product transfusion practices in ECMO patients. Table 6 describes one approach for blood product replacement based on clinical experience and local center clinical guidelines.

Table 6. Blood Product Goal and Replacement

	Goal	Product to Transfuse
Platelets	≥100,000 × 10 ⁹ /L (bleeding patient) ≥50,000–100,000 × 10 ⁹ /L (nonbleeding patient)	Platelets 10 ml/kg (max 2 units)
INR	<1.5 (bleeding patient) <3 (nonbleeding patient)	Fresh frozen plasma 10 ml/kg (max 2 units)
Fibrinogen	>1.5 g/L (bleeding patient or before surgical intervention) >1 g/L (nonbleeding patient)	Cryoprecipitate 1 unit/5 kg (max 6 units)
Hemoglobin	>70–90 g/L (consider higher goal for neonates and children with cyanotic congenital heart disease or lower goal for stable, adult patients)	Packed RBCs 10 ml/kg (max 2 units)
Antithrombin	>50%–80% (>0.5–0.8 U/ml), consider AT replacement if on maximum dose of UFH and unable to obtain anticoagulation goals	AT concentrate: Thrombate III dose (IU) = [desired AT – current AT] × weight (kg)
		1.4

AT, antithrombin; RBCs, red blood cells; INR, international normalized ratio; UFH, unfractionated heparin.

A survey of 187 ECMO centers in 2013 by Bembea et al.³¹ found variable thresholds for blood product transfusion with the majority of centers using a hematocrit of 35% with a range of 25% to 40% as a trigger for transfusion of red blood cells. The current ELSO Red Book recommends maintaining a hemoglobin of 140 to 150 g/L or hematocrit >40%.³⁰ The median platelet count that triggered platelet transfusion in the survey was 100,000 × 10⁹/L with a range of 50,000 to 200,000 × 10⁹/L.³¹ The survey was repeated in 2021 and found that platelet transfusion practices still vary widely amongst pediatric ECMO centers.³ Given concerns about the association of fluid overload and mortality as well as blood product storage issues, some centers are reexamining their transfusion thresholds and suggest that a conservative transfusion strategy may be safe in the adult ECMO population.⁵⁴ Unfortunately, insufficient evidence currently exists to define a safe lower hemoglobin threshold for children.⁵⁵ Given this lack of evidence, recent expert consensus guidelines for pediatric ECMO patients recommended focusing on markers of adequate regional and systemic oxygen delivery such as mixed venous saturation, lactate, systemic oxygen saturation, and cerebral and somatic oximetry in addition to the hemoglobin number.⁵⁵

For adults, the most recent survey on anticoagulation practice demonstrated that more than 75% of the centers ($N = 47$) used a hemoglobin threshold of 100 g/L and 45% of the centers used 80 g/L as a transfusion threshold. The most common platelet threshold was 50,000 × 10⁹/L in 67% of the centers and most common fibrinogen transfusion threshold was 2 g/L.² More recently, a Canadian expert consensus document for the adult VV nonbleeding ECMO patient recommended a transfusion threshold of 70 to 75 g/L for hemoglobin and 50,000 × 10⁹/L for platelets. Although there is a lack of studies, a restrictive strategy seems reasonable in nonbleeding adult ECMO patients.⁵⁶

Hemorrhage and Thrombosis

Both bleeding and thrombotic complications are associated with increased morbidity and mortality.^{57,58} Overall, bleeding complications are more frequent than thrombotic complications.^{57,59–61} If there is excessive bleeding, particularly in post cardiectomy patients, holding the UFH for 4 to 6 hours is reasonable. In some circumstances where bleeding is difficult to control, the UFH may be held up to 12 hours or longer until bleeding is controlled. Case reports in trauma patients with a high risk of bleeding have shown feasibility in running

heparin-free ECMO circuits.^{62–64} If anticoagulation is held, frequent evaluation of the need to restart anticoagulation and the circuit thrombus burden is recommended as thrombosis of the circuit could result in catastrophic complications or death.

Surgical site bleeding may be controlled locally by topical hemostats such as gauze swabs, gelatin sponge (Gelfoam), thrombin soaked gelfoam, thrombin bonded gelatin granules (Flo-Seal), oxidized cellulose (Surgicel), or thrombin and fibrinogen sealant (Tisseel).⁶⁵ For clinically significant bleeding or following major procedures on ECMO, aminocaproic acid (Amicar) and tranexamic acid (TXA) have been shown in some studies to reduce incidence of surgical bleeding when used prophylactically or after surgical operation while others have shown no difference in bleeding outcomes.^{66–70} Both these agents function through the inhibition of plasminogen conversion and thus prevent fibrinolysis. In addition, they optimize platelet functionality. Nonspecific risk of thrombosis is likely increased when antifibrinolytics are administered. Monitoring response with VHA is suggested, if available.

Circuit thrombosis becomes clinically relevant if it requires circuit intervention or is associated with severe hemolysis. Hemolysis is an under-recognized complication as not all ECMO centers measure plasma free hemoglobin. Hemolysis occurs when the red blood cell membrane ruptures because of mechanical trauma, releasing free hemoglobin into the plasma. The circulating free hemoglobin precipitates in renal tubules, which may lead to hemoglobinuria nephropathy. Free hemoglobin in plasma is also cytotoxic leading to endothelial dysfunction and vasoconstriction secondary to the consumption of nitric oxide.⁷¹ The free hemoglobin concentration in ECMO patients is associated with risks of both renal impairment and death.^{71,72} When plasma free hemoglobin is not readily available, other measures routinely performed such as d-dimer, transmembrane pressure, and platelet count can also be used as surrogate markers for potential increase in circuit thrombotic load. In small retrospective studies, increase in d-dimer in particular has been shown to be an early predictor of membrane oxygenator failure.^{73–75}

In conclusion, the current data and practices developed through decades of experience suggest that anticoagulation should be used for most ECMO patients, although there are some clear differences between children and adults. Thrombosis and hemorrhagic management during ECMO should be tailored to the individual patient and condition being supported by ECMO. New developments in circuit materials and an increasing experience in the management of ECMO in large centers may allow for

more restrictive anticoagulation strategies to be developed. We recommend each center develop a local strategy for anticoagulation based on experience as well as availability of different monitoring techniques. Consultation with a hematologist or ECMO experts specializing in anticoagulation should be considered for managing complex hemorrhagic or thrombotic complications or other difficulties in anticoagulation. Multicenter research is vital to uniformize practices and improve patient outcomes.

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References

- Saini A, Spinella PC: Management of anticoagulation and hemostasis for pediatric extracorporeal membrane oxygenation. *Clin Lab Med* 34: 655–673, 2014.
- Esper SA, Welsby IJ, Subramaniam K, et al: Adult extracorporeal membrane oxygenation: An international survey of transfusion and anticoagulation techniques. *Vox Sang* 112: 443–452, 2017.
- Ozment CP, Scott BL, Bembea MM, Spinella PC; Pediatric ECMO (PediECMO) subgroup of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network and the Extracorporeal Life Support Organization (ELSO): Anticoagulation and transfusion management during neonatal and pediatric extracorporeal membrane oxygenation: A survey of medical directors in the United States. *Pediatr Crit Care Med* 22: 530–541, 2021.
- Hirsh J, Raschke R, Warkentin TE, Dalen JE, Deykin D, Poller L: Heparin: mechanism of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. *Chest* 102(Suppl 4): 337s–351s, 1992.
- McDonald MM, Jacobson LJ, Hay WW Jr, Hathaway WE: Heparin clearance in the newborn. *Pediatr Res* 15: 1015–1018, 1981.
- Andrew M, Marzinotto V, Massicotte P, et al: Heparin therapy in pediatric patients: a prospective cohort study. *Pediatr Res* 35: 78–83, 1994.
- Newall F, Johnston L, Ignjatovic V, Monagle P: Unfractionated heparin therapy in infants and children. *Pediatrics* 123: e510–e518, 2009.
- Hvas AM, Favaloro EJ, Hellfritsch M: Heparin-induced thrombocytopenia: pathophysiology, diagnosis and treatment. *Expert Rev Hematol* 14:335–346, 2021.
- Lee GM, Arepally GM: Heparin-induced thrombocytopenia. *Hematology Am Soc Hematol Educ Program* 2013: 668–674, 2013.
- Greinacher A: CLINICAL PRACTICE. Heparin-induced thrombocytopenia. *N Engl J Med* 373: 252–261, 2015.
- Preston TJ, Dalton HJ, Nicol KK, Ferrall BR, Miller JC, Hayes D Jr: Plasma exchange on venovenous extracorporeal membrane oxygenation with bivalirudin anticoagulation. *World J Pediatr Congenit Heart Surg* 6: 119–122, 2015.
- Ranucci M: Bivalirudin and post-cardiotomy ECMO: A word of caution. *Crit Care* 16: 427, 2012.
- Ranucci M, Ballotta A, Kandil H, et al; Surgical and Clinical Outcome Research Group: Bivalirudin-based versus conventional heparin anticoagulation for postcardiotomy extracorporeal membrane oxygenation. *Crit Care* 15: R275, 2011.
- Bianchi P, Cotza M, Beccaris C, et al; Surgical and Clinical Outcome REsearch (SCORE) group: Early or late fresh frozen plasma administration in newborns and small infants undergoing cardiac surgery: The APPEAR Randomized Trial. *Br J Anaesth* 118: 788–796, 2017.
- Netley J, Roy J, Greenlee J, Hart S, Todt M, Statz B: Bivalirudin anticoagulation dosing protocol for extracorporeal membrane oxygenation: A retrospective review. *J Extra Corpor Technol* 50: 161–166, 2018.
- Pieri M, Agracheva N, Bonaveglia E, et al: Bivalirudin versus heparin as an anticoagulant during extracorporeal membrane oxygenation: A case-control study. *J Cardiothorac Vasc Anesth* 27: 30–34, 2013.
- Sanfilippo F, Asmussen S, Maybauer DM, et al: Bivalirudin for alternative anticoagulation in extracorporeal membrane oxygenation: A systematic review. *J Intensive Care Med* 32:312–319, 2017.
- Jyoti A, Maheshwari A, Daniel E, Motihar A, Bhatiwala RS, Sharma D: Bivalirudin in venovenous extracorporeal membrane oxygenation. *J Extra Corpor Technol* 46: 94–97, 2014.
- Young G, Yonekawa KE, Nakagawa P, Nugent DJ: Argatroban as an alternative to heparin in extracorporeal membrane oxygenation circuits. *Perfusion* 19: 283–288, 2004.
- Berei TJ, Lillyblad MP, Wilson KJ, Garberich RF, Hryniewicz KM: Evaluation of systemic heparin versus bivalirudin in adult patients supported by extracorporeal membrane oxygenation. *ASAIO J* 64: 623–629, 2018.
- Sin JH, Lopez ND: Argatroban for heparin-induced thrombocytopenia during venovenous extracorporeal membrane oxygenation with continuous venovenous hemofiltration. *J Extra Corpor Technol* 49: 115–120, 2017.
- Menk M, Briem P, Weiss B, et al: Efficacy and safety of argatroban in patients with acute respiratory distress syndrome and extracorporeal lung support. *Ann Intensive Care* 7: 82, 2017.
- Beiderlinden M, Treschan T, Görlinger K, Peters J: Argatroban in extracorporeal membrane oxygenation. *Artif Organs* 31: 461–465, 2007.
- Rougé A, Pelen F, Durand M, Schwebel C: Argatroban for an alternative anticoagulant in HIT during ECMO. *J Intensive Care* 5: 39, 2017.
- Kaseer H, Soto-Arenall M, Sanghavi D, et al: Heparin vs bivalirudin anticoagulation for extracorporeal membrane oxygenation. *J Card Surg* 35: 779–786, 2020.
- Rivosecchi RM, Arakelians AR, Ryan J, et al: Comparison of Anticoagulation Strategies in Patients Requiring Venovenous Extracorporeal Membrane Oxygenation: Heparin Versus Bivalirudin. *Crit Care Med* 49:1129–1136, 2021.
- Hamzah M, Jarden AM, Ezetendu C, Stewart R: Evaluation of bivalirudin as an alternative to heparin for systemic anticoagulation in pediatric extracorporeal membrane oxygenation. *Pediatr Crit Care Med* 21: 827–834, 2020.
- Machado DS, Garvan C, Philip J, et al: Bivalirudin may reduce the need for red blood cell transfusion in pediatric cardiac patients on extracorporeal membrane oxygenation. *ASAIO J* 67: 688–696, 2021.
- Seelhammer TG, Bohman JK, Schulte PJ, Hanson AC, Aganga DO: Comparison of bivalirudin versus heparin for maintenance systemic anticoagulation during adult and pediatric extracorporeal membrane oxygenation. *Crit Care Med* 49: 1481–1492, 2021.
- Brogan T. (ed): Extracorporeal Life Support: The ELSO Red Book. 5 ed, Ann Arbor, MI: Extracorporeal Life Support Organization, 2017.
- Bembea MM, Annich G, Rycus P, Oldenburg G, Berkowitz I, Pronovost P: Variability in anticoagulation management of patients on extracorporeal membrane oxygenation: An international survey. *Pediatr Crit Care Med* 14: e77–e84, 2013.
- Basu D, Gallus A, Hirsh J, Cade J: A prospective study of the value of monitoring heparin treatment with the activated partial thromboplastin time. *N Engl J Med* 287: 324–327, 1972.
- Levine MN, Hirsh J, Gent M, et al: A randomized trial comparing activated thromboplastin time with heparin assay in patients with acute venous thromboembolism requiring large daily doses of heparin. *Arch Intern Med* 154: 49–56, 1994.
- Kostousov V, Nguyen K, Hundalani SG, Teruya J: The influence of free hemoglobin and bilirubin on heparin monitoring by activated partial thromboplastin time and anti-Xa assay. *Arch Pathol Lab Med* 138: 1503–1506, 2014.
- Boer C, Meesters MI, Milojevic M, et al; Task Force on Patient Blood Management for Adult Cardiac Surgery of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA): 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. *J Cardiothorac Vasc Anesth* 32: 88–120, 2018.
- Kozek-Langenecker SA, Ahmed AB, Afshari A, et al: Management of severe perioperative bleeding: Guidelines from the European Society of Anaesthesiology: First update 2016. *Eur J Anaesthesiol* 34: 332–395, 2017.

37. Rossaint R, Bouillon B, Cerny V, et al: The European guideline on management of major bleeding and coagulopathy following trauma: Fourth edition. *Crit Care* 20: 100, 2016.
38. Weber CF, Görlinger K, Meiningner D, et al: Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. *Anesthesiology* 117: 531–547, 2012.
39. Karkouti K, Callum J, Wijeyesundera DN, et al; TACS Investigators: Point-of-care hemostatic testing in cardiac surgery: A stepped-wedge clustered Randomized Controlled Trial. *Circulation* 134: 1152–1162, 2016.
40. Panigada M, E lapichino G, Brioni M, et al: Thromboelastography-based anticoagulation management during extracorporeal membrane oxygenation: A safety and feasibility pilot study. *Ann Intensive Care* 8: 7, 2018.
41. Nair P, Hoechter DJ, Buscher H, et al: Prospective observational study of hemostatic alterations during adult extracorporeal membrane oxygenation (ECMO) using point-of-care thromboelastometry and platelet aggregometry. *J Cardiothorac Vasc Anesth* 29: 288–296, 2015.
42. Laine A, Niemi T, Suojäranta-Ylinen R, et al: Decreased maximum clot firmness in rotational thromboelastometry (ROTEM(R)) is associated with bleeding during extracorporeal mechanical circulatory support. *Perfusion* 31: 625–633, 2016.
43. Henderson N, Sullivan JE, Myers J, et al: Use of thromboelastography to predict thrombotic complications in pediatric and neonatal extracorporeal membranous oxygenation. *J Extra Corpor Technol* 50: 149–154, 2018.
44. Morrisette MJ, Zomp-Wiebe A, Bidwell KL, et al: Antithrombin supplementation in adult patients receiving extracorporeal membrane oxygenation. *Perfusion* 35: 66–72, 2020.
45. Sorial MN, Greene RA, Zullo AR, Berard-Collins C, Willis S: Exogenous supplementation of antithrombin III in adult and pediatric patients receiving extracorporeal membrane oxygenation. *Int J Artif Organs* 43: 315–322, 2020.
46. Panigada M, Cucino A, Spinelli E, et al: A Randomized Controlled Trial of antithrombin supplementation during extracorporeal membrane oxygenation. *Crit Care Med* 48: 1636–1644, 2020.
47. Curvers J, van de Kerkhof D, Stroobants AK, van den Dool EJ, Scharnhorst V: Measuring direct thrombin inhibitors with routine and dedicated coagulation assays: Which assay is helpful? *Am J Clin Pathol* 138: 551–558, 2012.
48. Lind SE, Boyle ME, Fisher S, Ishimoto J, Trujillo TC, Kiser TH: Comparison of the aPTT with alternative tests for monitoring direct thrombin inhibitors in patient samples. *Am J Clin Pathol* 141: 665–674, 2014.
49. Love JE, Ferrell C, Chandler WL: Monitoring direct thrombin inhibitors with a plasma diluted thrombin time. *Thromb Haemost* 98: 234–242, 2007.
50. Krueger K, Schmutz A, Zieger B, Kalbhenn J: Venovenous extracorporeal membrane oxygenation with prophylactic subcutaneous anticoagulation only: An observational study in more than 60 patients. *Artif Organs* 41: 186–192, 2017.
51. Kurihara C, Walter JM, Karim A, et al: Feasibility of venovenous extracorporeal membrane oxygenation without systemic anticoagulation. *Ann Thorac Surg* 110: 1209–1215, 2020.
52. Aubron C, McQuilten Z, Bailey M, et al; endorsed by the International ECMO Network (ECMONet): Low-dose versus therapeutic anticoagulation in patients on extracorporeal membrane oxygenation: A pilot Randomized Trial. *Crit Care Med* 47: e563–e571, 2019.
53. Wood KL, Ayers B, Gosev I, et al: Venoaerial-extracorporeal membrane oxygenation without routine systemic anticoagulation decreases adverse events. *Ann Thorac Surg* 109: 1458–1466, 2020.
54. Agerstrand CL, Burkart KM, Abrams DC, Bacchetta MD, Brodie D: Blood conservation in extracorporeal membrane oxygenation for acute respiratory distress syndrome. *Ann Thorac Surg* 99: 590–595, 2015.
55. Bembea MM, Cheifetz IM, Fortenberry JD, et al: Recommendations on the Indications for RBC Transfusion for the Critically Ill Child Receiving Support From Extracorporeal Membrane Oxygenation, Ventricular Assist, and Renal Replacement Therapy Devices From the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. *Pediatr Crit Care Med* 19(9S Suppl 1): S157–S162, 2018.
56. Singh G, Nahiriak S, Arora R, et al: Transfusion thresholds for adult respiratory extracorporeal life support: An expert consensus document. *Can J Cardiol* 36: 1550–1553, 2020.
57. Dalton HJ, Garcia-Filion P, Holubkov R, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network: Association of bleeding and thrombosis with outcome in extracorporeal life support. *Pediatr Crit Care Med* 16: 167–174, 2015.
58. Werho DK, Pasquali SK, Yu S, et al; Extracorporeal Life Support Organization Member Centers: Hemorrhagic complications in pediatric cardiac patients on extracorporeal membrane oxygenation: An analysis of the Extracorporeal Life Support Organization Registry. *Pediatr Crit Care Med* 16: 276–288, 2015.
59. Thiagarajan RR, Barbaro RP, Rycus PT, et al; ELSO member centers: Extracorporeal life support organization registry international report 2016. *ASAIO J* 63: 60–67, 2017.
60. Barbaro RP, Paden ML, Guner YS, et al; ELSO member centers: Pediatric extracorporeal life support organization registry international report 2016. *ASAIO J* 63: 456–463, 2017.
61. Zangrillo A, Landoni G, Biondi-Zoccai G, et al: A meta-analysis of complications and mortality of extracorporeal membrane oxygenation. *Crit Care Resusc* 15: 172–178, 2013.
62. Robba C, Ortu A, Bilotta F, et al: Extracorporeal membrane oxygenation for adult respiratory distress syndrome in trauma patients: A case series and systematic literature review. *J Trauma Acute Care Surg* 82: 165–173, 2017.
63. Moon SH, Kim KN, Jung JJ, Park JH, Byun JH: Heparin-free venovenous ECMO applied to a patient with severe lung contusion and hypovolemic shock due to trauma. *Ulus Travma Acil Cerrahi Derg* 24: 497–500, 2018.
64. Wen PH, Chan WH, Chen YC, Chen YL, Chan CP, Lin PY: Non-heparinized ECMO serves a rescue method in a multitrauma patient combining pulmonary contusion and nonoperative internal bleeding: A case report and literature review. *World J Emerg Surg* 10: 15, 2015.
65. Chiara O, Cimbanassi S, Bellanova G, et al: A systematic review on the use of topical hemostats in trauma and emergency surgery. *BMC Surg* 18: 68, 2018.
66. Downard CD, Betit P, Chang RW, Garza JJ, Arnold JH, Wilson JM: Impact of AMICAR on hemorrhagic complications of ECMO: A ten-year review. *J Pediatr Surg* 38: 1212–1216, 2003.
67. van der Staak FH, de Haan AF, Geven WB, Festen C: Surgical repair of congenital diaphragmatic hernia during extracorporeal membrane oxygenation: Hemorrhagic complications and the effect of tranexamic acid. *J Pediatr Surg* 32: 594–599, 1997.
68. Buckley LF, Reardon DP, Camp PC, et al: Aminocaproic acid for the management of bleeding in patients on extracorporeal membrane oxygenation: Four adult case reports and a review of the literature. *Heart Lung* 45: 232–236, 2016.
69. Horwitz JR, Cofer BR, Warner BW, Cheu HW, Lally KP: A multicenter trial of 6-aminocaproic acid (Amicar) in the prevention of bleeding in infants on ECMO. *J Pediatr Surg* 33: 1610–1613, 1998.
70. Wilson JM, Bower LK, Fackler JC, Beals DA, Bergus BO, Keyv SV: Aminocaproic acid decreases the incidence of intracranial hemorrhage and other hemorrhagic complications of ECMO. *J Pediatr Surg* 28: 536–540; discussion 540–541, 1993.
71. Gbadegesin R, Zhao S, Charpie J, Brophy PD, Smoyer WE, Lin JJ: Significance of hemolysis on extracorporeal life support after cardiac surgery in children. *Pediatr Nephrol* 24: 589–595, 2009.
72. Omar HR, Mirsaeidi M, Socias S, et al: Plasma free hemoglobin is an independent predictor of mortality among patients on extracorporeal membrane oxygenation support. *PLoS One* 10: e0124034, 2015.
73. Di Nardo M, Merli P, Cecchetti C, Pasotti E, Bertaina A, Locatelli F: Progressive increase in D-dimer levels during extracorporeal membrane oxygenation can predict membrane oxygenator failure in children given hematopoietic stem cell transplantation? *J Crit Care* 31: 262–263, 2016.
74. Lubnow M, Philipp A, Dornia C, et al: D-dimers as an early marker for oxygenator exchange in extracorporeal membrane oxygenation. *J Crit Care* 29: 473.e1–473.e5, 2014.
75. Dornia C, Philipp A, Bauer S, et al: D-dimers are a predictor of clot volume inside membrane oxygenators during extracorporeal membrane oxygenation. *Artif Organs* 39: 782–787, 2015.