10 ECMO ANTICOAGULATION GUIDELINES

10.1 **Introduction**

Unfractionated heparin is used as a systemic anticoagulant in ECMO. The activated partial thromboplastin time (aPTT) and activated clotting time (ACT) are the standard tests used in our unit to titrate and dose infusions of heparin during ECMO. The anticoagulant effect of heparin is dependent on an adequate antithrombin level.

Anticoagulation strategies vary according to patient diagnosis and status of clotting versus bleeding (e.g. disseminated intravascular coagulation, post-cardiotomy with significant bleeding) and circuit considerations. The principal aim is to achieve sufficient anticoagulation in order to minimize circuit interventions associated with clotting and at the same time minimize the risk for bleeding in the patient.

10.2 **Initiating ECMO**

Prior to cannulation, recommended baseline blood investigations should include: FBC, PT/PTT, Fibrinogen level and ACT where possible.

Heparin is given at various time points during the initiation process:

• Circuit prime: 1 unit of heparin per ml of circuit prime

• Cannulation dose: **50 units/kg heparin bolus is the recommended dose during cannulation**. Lower or higher doses (25-100 units/kg) may be required depending on the clinical situation. Read-back the intended dose to the surgeon before giving the heparin bolus, and ALWAYS use units/kg in communicating the heparin dose.

Repeat ACT 5-10 min after heparin bolus. Consider repeating heparin bolus (25-50u/kg) if the ACT < 250 sec in discussion with cannulating surgeon.

Following cannulation (i.e. flow established), repeat ACT hourly until ACT < 250s and start heparin infusion (see below), guided by the patient's clinical status (e.g. bleeding risk). The presence of clinically significant bleeding may necessitate starting the heparin infusion at a more conservative dose. ACT targets should be discussed with the cannulating surgeon at initiation and whenever there are significant clinical/ circuit concerns.

- In all patients: start heparin infusion at 10 units/kg/hr
  (Note: neonates and infants < 6 months of age, may require higher starting infusion rates)

10.3 **During ECMO run**

Heparin is given as a continuous infusion during the ECMO run, and the rate is titrated accordingly to the goals and guidelines of heparin infusion during ECMO. This is to be reviewed on a daily basis.

10.3.1 **Goals and Guidelines of heparin infusion during ECMO**

- Perform ACT Q2-4 hourly and aPTT Q4-6 hourly for the 1st 24 hours of ECMO run, or more frequently if indicated.
- Maintain ACT 180-220s (suggested range for VA ECMO) with heparin infusion rate 10-40 units/kg/hr. Lower ACTs may be targeted in VV ECMO (160-180) or in situations where

there is clinically significant bleeding. This should ideally correlate with an aPTT value of 60-90 seconds.

- In stable patients on ECMO > 24 hours post initiation, ACT monitoring frequency may be decreased to Q4 – 6 hourly as guided by their clinical status and transfusion requirements. Perform aPTT Q 6-8 hourly during this phase, aiming for target aPTT 60-90 sec.
- Inform ICU consultant if ACT < 140 or > 260 and/or if aPTT < 50 or > 100.

10.3.2 **ECMO Coagulation Tests**

ECMO Coagulation Tests are used in conjunction with the ACT to monitor anticoagulation.

Coagulation Test	**Therapeutic goals**
aPTT	60-90s
Fibrinogen	>1.5 g/L

These tests are ordered in the ECMO Daily Management Orders (see Section 11.2.1).

The following additional tests may be obtained in conjunction with a review by the Haematology team, if heparin requirement is ≤ 10 or ≥ 40 units/kg/hr. See also Table 1 for additional lab tests commonly utilized in ECMO.

- Anti-Xa levels to measure heparin effect may be done if clinically indicated (target 0.3-0.7). **Please order as Anti-Xa (UFH) and NOT Anti-Xa (LMWH)**
- Where Antithrombin III deficiency is suspected, Antithrombin III levels may be requested (turnaround time > 3 days) and replacement with FFP 20ml/kg may be considered
- Von Willebrand panel: Factor VIII activity, von Willebrand antigen, Ristocetin-cofactor

10.3.3 **Blood product support**

Haematological indices are monitored as patients are at risk of bleeding, have frequent blood sampling and often receive blood products to maintain haemoglobin and other haematological targets on ECMO.

Sample targets while on ECMO are stated below:

- Haemoglobin > 10-12g/dL
- Platelets > 80, 000 (recognizing that platelet function may be impaired on ECMO)
- Fibrinogen > 1.5 g/L
- INR < 1.5. Consider optimizing nutritional sources or Vitamin K supplementation in young infants or patients with liver dysfunction

10.3.4 **Titration of Heparin Infusion**

The heparin infusion is titrated to the aPTT and ACT level, keeping in the range of aPTT 60-90 sec, unless otherwise stated. Targets may vary depending on the clinical situation of patient bleeding/clotting or circuit thrombus/ clot build-up. Therefore, a review of aPTT targets and correlating ACT must be done daily and more frequently depending on the clinical situation.

In the case of bleeding or thrombosis, the ACT goals may be different.

Antithrombin III deficiency may cause a degree of heparin resistance, requiring higher doses of heparin or the supplementation of antithrombin with antithrombin concentrate or FFP in order to maintain ACT targets. If heparin infusion exceeds 30 units/kg/h in children (> 10kg) or 40 units/kg/h in neonates (< 10kg), consider antithrombin deficiency. In such cases, consider FFP infusion 20mL/kg to replenish antithrombin stores.

Factors other than Heparin dose that may modify the ACT include the following:

- Administration of platelets have a profound effect on the ACT and decrease the ACT abruptly. Prior to platelet administration, an ACT should be drawn and heparin infusion may need to be increased by 10% before platelets are administered, depending on the ACT level.
- Administration of Fresh Frozen Plasma (FFP) & Cryoprecipitate may also have a transient effect on the ACT and can increase or decrease the ACT.
- Patients with impaired liver function and/or abnormal INRs may have changes in their ACTs unrelated to the doses of heparin.
- Changes in temperature targeted therapy or in diuretic therapy may also affect the steady state of the ACT.

10.4 Bleeding

10.4.1 Definition

- Thoracotomy or haemothorax: drainage > 4 mL/kg/hour for 4 hours
- GI, oral, or nasal bleeding w/ ↓ Hb despite intervention
- Catheter or cannula site bleeding w/ ↓ Hb despite intervention
- New or worsening cranial bleed

Major:

- Hb drop of 2 g/dL over 24 hrs
- >20ml/kg blood loss over 24 hrs
- Retroperitoneal, pulmonary or CNS bleed
- Any bleeding requiring surgical intervention

Minor:

- 10-20ml/kg of bleeding over 24 hrs

In situations where there is excessive bleeding, particularly in post-cardiotomy patients, holding the heparin infusion temporarily may be warranted after discussion with ICU consultant and cannulating surgeon. The circuit must be closely monitored for development of thrombotic complications. Targeting lower aPTT/ ACTs while there is clinically significant bleeding may be necessary till the bleeding is well controlled.

In these situations, consider:

- Accepting lower aPTT/ ACT targets
- Keep Hb > 12g/dL, Platelets ≥ $120x10^9$/L, Normal INR, Fibrinogen > 1.5g/L
- Consider activation of the massive transfusion protocol if > 20mL/kg of PRBC or > 40mL/kg of fluid bolus has been transfused and primary cause of instability is from uncontrolled bleeding

- Frequent re-evaluation and frequency of lab monitoring (Q4-8hourly) and return to routine laboratory monitoring when bleeding subsides
- Consider performing ROTEM (see section on “Thromboelastometry”) if bleeding does not subside after 4 hours of intervention.

In addition, the agents discussed below may be considered on a case-by-case basis.

10.4.2 Anti-fibrinolytic Agents

Tranexamic acid
Loading dose: 10mg/kg IV over 1 hour, followed by 10mg/kg/dose Q8H
Infusion dose: 2.5-10 mg/kg/hr IV infusion

10.4.3 Other Haemostatic Adjuncts:

Activated Factor VII (NOVOSEVEN 1mg Injection)

Activated Factor VII may be considered for patients with severe refractory haemorrhage only after the optimization of coagulation factors, fibrinogen and platelets. The cannulating surgeon must be informed prior and preparations made to manage acute circuit thrombosis, including the preparation of a standby circuit may need to be discussed.

Dose: 90mcg/kg IV (can titrate to vial size to minimize wastage)

Prothrombin Complex Concentrate (OCTAPLEX 500 unit Injection)

4-factor prothrombin complex concentrate (Octaplex) contains Factors II, VII, IX and X. It can be considered for use when there is bleeding associated with liver dysfunction or a high INR. There is a risk of acute circuit thrombosis similar to when activated Factor VII is used, and the 2 agents should preferably not be used together.

Dose: Depends on the INR prior to infusion or Weight-based: 12.5 - 25 IU/kg/dose (Up to max of 2000 IU). Note: 25 IU = 1ml

Patient weight	Pre-treatment INR < 3	Pre-treatment INR > 3
<10 kg	10 ml	20 ml
10-25 kg	20 ml	30 ml
25-50kg	30 ml	40 ml
Each ml = 25 IU, e.g. 40mL=1000 IU/FIX)		

Human Fibrinogen Concentrate (FIBRYGA /HAEMOCOMPLETTAN P 1g Injection)

Utilized in the treatment of bleeding episodes and perioperative prophylaxis in patients with congenital afibrinogenemia/ hypofibrinogenemia (very rare) or acquired hypofibrinogenemia resulting from disorders of synthesis from severe liver disease, or increased intravascular consumption (e.g. DIC, hyperfibrinolysis) or increased loss in the

setting of massive haemorrhage. To be used with supporting evidence with ROTEM -FIBTEM (suggesting low fibrinogen) or low levels of fibrinogen (based on lab test result).

Dose: 70 mg/kg IV

10.4.4 **ALTERNATIVES TO HEPARIN ANTICOAGULATION: BIVALIRUDIN FOR ECMO GUIDELINES**

Introduction

Bivalirudin is the most common alternative to unfractionated heparin (UFH) for Paediatric ECMO.

There may be specific situations when use of bivalirudin instead of UFH is considered for anticoagulation in ECMO. These include:

- Heparin induced thrombocytopenia
- Heparin resistance and worsening circuit clots despite use of Antithrombin replacement within 12 hours
- An anticipated ECMO run < 7 days (owing to cost considerations, bivalirudin is significantly more expensive)
- Infants or children with critical illness where antithrombin stores may be unpredictable
- Patients without pre-existing severe coagulopathy prior to their ECMO run (as bivalirudin affects PT/INR/aPTT)

Mechanism of Action:

- Direct Thrombin Inhibitor - does not require the presence of antithrombin
- Reversibly binds to the active catalytic site of thrombin and the substrate recognition site on both **circulating and clot bound thrombin**

Pharmacokinetics:

Bivalirudin has a rapid onset of action and demonstrates an anticoagulant effect within 2 mins of administration. It has a short half-life in the setting of normal renal function of approximately 20 mins.

Bivalirudin is cleared primarily by intravascular proteolytic degradation and only about 20% by the kidneys. There is no antidote for bivalirudin and the infusion should be ceased if concerns regarding catastrophic bleeding. Coagulation times return to baseline ~1 hour following discontinuation of infusion.

It can also be removed via plasmapheresis and hemofiltration if necessary.

Bivalirudin will reach steady state in 4 hours.

Monitoring:

Bivalirudin exhibits linear dose and concentration dependent prolongation of aPTT in patients with normal renal function. At higher doses, bivalirudin exhibits a non-linear dose response relationship and an aPTT may underestimate the anticoagulation activity, posing an increased risk of bleeding.

The activated clotting time (ACT) and dilute thrombin time (dTT) have also been used to monitor bivalirudin.

Proposed monitoring when on bivalirudin:

- **aPTT will be used as the main means of monitoring patients on bivalirudin.**
- Dose adjustment of bivalirudin should be based upon the goal of aPTT 60-90 seconds. During the first 24 hours of ECMO, a target aPTT of 50-70 may be targeted if the bleeding risk post-procedure is significant and this target should be reviewed daily, taking into account an individual patient's bleeding and clotting risk.
- Given that Bivalirudin will not reach steady state until 4 hours, it is not recommended to repeat testing and make changes within this timeframe, unless there is a clinical concern. However, on the day of ECMO initiation, we recommend more frequent checks Q2 hourly after initiation and dose adjustment till therapeutic range is achieved.
- ACT and ROTEM may be performed if clinically indicated.
- Dose adjustments may be necessary to maintain the anticoagulation targets within range.

It is suggested that blood draws for aPTT be taken from a heparin naïve line, or to discard an appropriate amount of blood if drawing through a line containing heparin.

<u>Dosing</u>

At ECMO cannulation: A systemic unfractionated heparin (UFH) bolus of 25-100 units/kg (typically 50 units/kg) is given, aiming for an ACT target of > 250. Further doses to be discussed with cannulating surgeon if this target has not been achieved.

Following cannulation, monitor the ACT every 1 hour.

Aim to start Bivalirudin when ACT < 250 post cannulation.

Start bivalirudin infusion at 0.15 mg/kg/hr (if renal function is normal, i.e., normal creatinine clearance). Reduce the dose to 0.075 mg/kg/hr in patients with a creatinine clearance < 30 mL/min/1.73 m2.

Consider commencing at 50% of Bivalirudin rate, and lowering aPTT threshold (1.5-2x) if there is a high risk of bleeding

- Target aPTT 60-90s (if no bleeding concerns, goal may be lower if there are bleeding concerns).
- Check aPTT 2 hours after Bivalirudin commenced
- Do not adjust Bivalirudin infusion based on this initial result unless aPTT is supratherapeutic, or there is clinical concern
    - If above the target range consider reducing the infusion rate by 10%

Recheck aPTT 2 hours after the initial check (after Bivalirudin commenced) and 2 hours after any dose change on the day of ECMO initiation (revert to checks 4 hours after dose change from Day 2 ECMO and beyond).

Suggested Bivalirudin dosing table

aPTT (sec)	Rate change	Bolus or Hold	Recheck
<45	Increase dose by 20% **OR** Increase dose by 0.05 mg/kg/hr	**Consider 0.25 mg/kg bolus in discussion with ECMO intensivist and haematologist* if aPTT at baseline e.g 30 seconds	4 hours
45-<60	Increase dose by 10% **OR** Increase dose by 0.03 mg/kg/hr	none	4 hours
60-90	No change	none	4 hours (in first 24 hours then 8 to 12 hourly
90-100	Consider a hold **AND** Decrease dose by 10%	Consider hold: 15 min	4 hours
>100	Hold **AND** Decrease dose by 30%	Hold: 15 min	2 hours

Recheck levels 4 hours after any rate change, or earlier if clinical concern

Monitor aPTT, PT/ INR, Fibrinogen Q6H till stable aPTT achieved (first 24 hours), then reduce frequency to Q8H.

In cases where, achieving therapeutic anticoagulation is challenging, a referral to the haematology team is recommended and further tests e.g., ROTEM may be indicated to guide management.

The target aPTT must be reviewed daily - the goal aPTT may be increased in the presence of circuit clotting and decreased in the presence of bleeding. In case of bleeding, consider correcting platelets and other deficient factors according to laboratory values and revise anticoagulation goals in discussion with CTS.

Weaning/ Decannulation

During weaning, a low flow state is maintained over a variable period of time, in order to make clinical and haemodynamic assessments on a patient's readiness to separate from ECMO.

Bivalirudin does not work well in low flow states or areas of blood stasis due to risk of localized bivalirudin proteolysis. As such, prior to any reduction of ECMO flow (especially if flow is going to be decreased to less than 200ml/min), a discussion must be conducted with CICU/CTS to decide on the need for heparin boluses during the weaning trial/ cessation of bivalirudin and maintenance with heparin, with closer monitoring of ACT/ aPTT during this period. A suggested approach is to give a heparin bolus of 25-50units/kg at the cross-clamping phase and allow it to circulate for three minutes before cross-clamping. Consider redosing heparin if ACT <250.

References:

1. *Snyder CW, Goldenberg NA, Nguyen ATH et al. A perioperative bivalirudin anticoagulation protocol for neonates with congenital diaphragmatic hernia on ECMO. Thromb Res 2020; 193:198-203*
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4. *Ryerson LM, McMichael ABV. Bivalirudin in pediatric extracorporeal membrane oxygenation. Curr Opin Pediatr 2022,34:255-260*
5. *VanderPluym CJ, Cantor RS, Machado D et al. Utilization and Outcomes of children treated with direct thrombin inhibitors on paracorporeal ventricular assist device support. ASAIO J 2020; 66:939-945*
6. *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 2020; 21:827-834*
7. *Schill MR, Doude MT, Burns EL, et al. Is anticoagulation with bivalirudin comparable to heparin for pediatric extracorporeal life support? Results from a high-volume center. Artif Organs 2021.; 45:15-21*
8. *Davidson, S. Assays to Monitor Bivalirudin. In: Favaloro, E.J., Gosselin, R.C. (eds) Hemostasis and Thrombosis. Methods in Molecular Biology 2023;Vol 2663. Humana, New York, NY.*

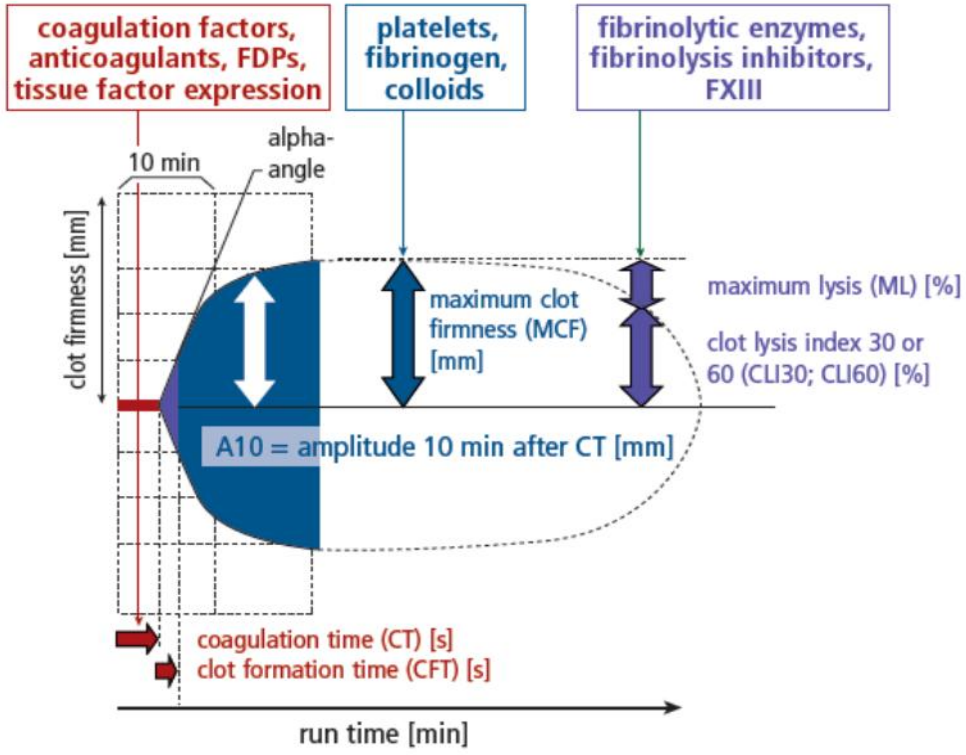
10.4.5 **Thromboelastometry**

In the event that bleeding is not well controlled, ROTEM (Rotational Thromboelastometry) may be used to guide therapy. This is a whole blood POCT of the viscoelastic properties of clot formation that measures the integrity of the coagulation cascade from the time of fibrin formation to fibrinolysis and importantly includes the contribution of platelets. ROTEM provides information relating to multiple phases of coagulation in whole blood, which is extremely relevant to ECLS patients since there may be more than one reason for coagulation abnormalities.

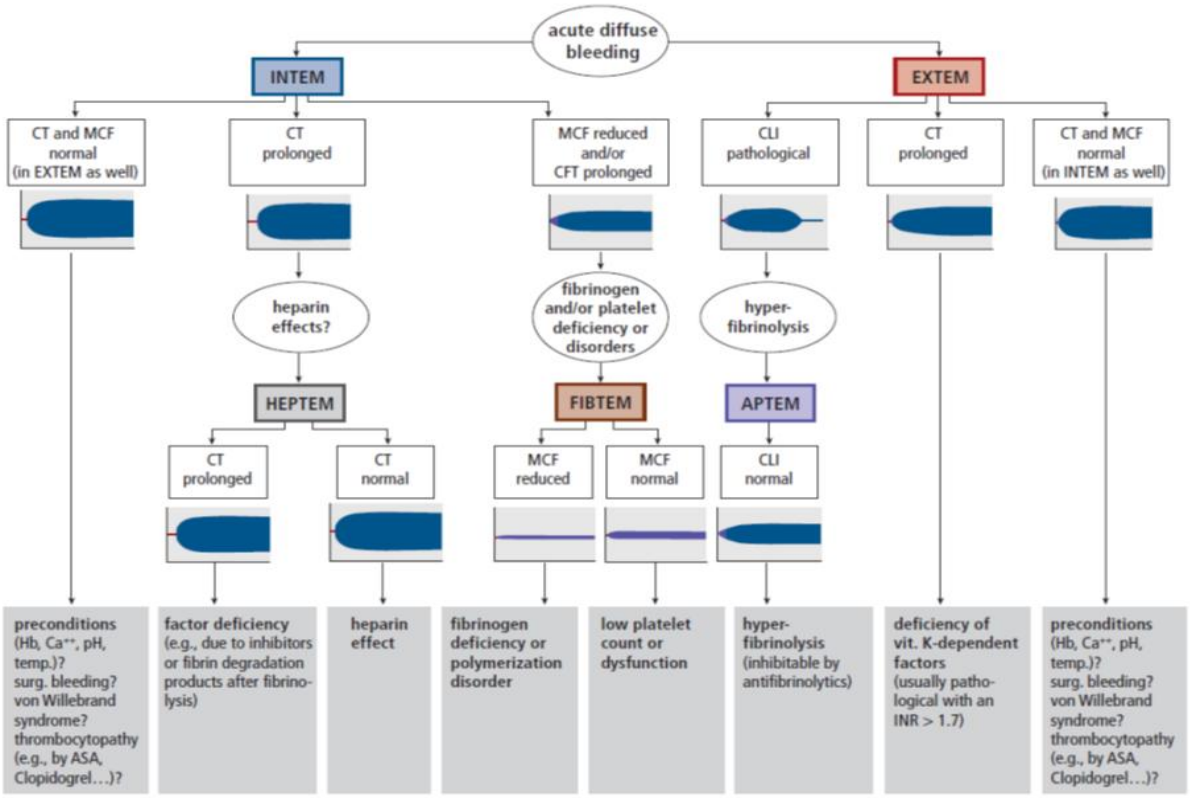
Contact the AU/OT Nurse on-call to arrange for this blood test to be done in OT.

Refer to the CICU Handbook Chapter: ROTEM Guideline - for more detailed information on test interpretation.

<u>ROTEM Tracing, Parameters and Influences</u>



ROTEM Diagnostic Algorithm



Reference: Essener Runde algorithm Hämostaseologie 2013; 33: 51–61

Reference ranges:

ROTEM® parameter	InTEM CT (s)	InTEM CFT (s)	InTEM ALP (°)	InTEM A10 (mm)	InTEM MCF (mm)	ExTEM CT (s)	ExTEM CFT (s)	ExTEM ALP (°)	ExTEM A10 (mm)	ExTEM MCF (mm)	ExTEM CLI60 (%)
Median	184	63	77	55	61	55	95	72	53	60	No data
Reference ranges in adults[5]	137–246	40–100	71–82	44–68	52–72	42–74	46–148	63–81	43–65	49–71	
0–3 months (*n*=51)											
Median	184	44	81	62	66	48	57	78	60	62	87
Reference range	105–285	27–88	74–85	50–72	54–73	38–65	30–105	69–84	51–72	54–74	71–94
4–12 months (*n*=55)											
Median	172	60	78	59	63	53	72	76	57	60	86
Reference range	76–239	37–100	73–83	47–70	52–73	37–77	44–146	68–82	46–68	46–71	71–95
13–24 months (*n*=54)											
Median	161	61	78	59	64	55	75	75	56	60	88
Reference range	99–207	42–112	70–82	45–67	50–72	37–73	46–139	64–81	41–68	46–72	77–94
2–5 yr (*n*=70)											
Median	170	60	78	59	63	56	72	75	58	61	86
Reference range	99–239	40–94	72–82	49–68	53–73	46–97	41–109	69–82	49–68	52–70	74–93
6–10 yr (*n*=79)											
Median	168	64	77	57	62	57	77	74	56	60	87
Reference range	97–212	48–93	72–80	49–66	53–69	43–74	49–114	67–80	49–65	53–68	70–97
11–16 yr (*n*=50)											
Median	171	68	77	56	62	59	81	74	57	62	88
Reference range	128–206	45–106	70–81	48–67	54–71	44–91	53–115	67–80	49–67	53–72	76–94

Reference: British Journal of Anaesthesia, Sep 2010, Page 1 of 9

Table 1: Laboratory tests utilized in ECMO

	Laboratory Test	
1.	Activated clotting time (ACT)	- time in seconds in which whole blood clots in response to a fibrin activating reagent - influenced by factors other than heparin, such as thrombocytopenia, hypofibrinogenemia etc.
2.	Activated partial thromboplastin time (aPTT)	- assesses intrinsic and final common pathways of coagulation - measures Xa and IIa anticoagulation activity of UFH - influenced by coagulation factors, heparin, and antithrombin levels - performs less reliably in neonatal and pediatric patients compared to adults
3.	Anti-factor Xa assay	- measures the Xa anticoagulation activity of UFH - more specific and less dependent on levels of coagulation factors besides common pathway factors
4.	Thromboelastometry (ROTEM)	- whole blood point of care test of the viscoelastic properties of clot formation that measures integrity of the coagulation cascade from fibrin formation to fibrinolysis; importantly includes the contribution of platelets - can be done with and without an agent that inactivates heparin, so the anticoagulant effect of heparin can be separated from other factors
5.	Antithrombin (AT) III assay	- acquired AT deficiency may contribute to heparin resistance (in infants and children with escalating UNFH requirements, or clinically sub-therapeutic anticoagulation) - target levels to be discussed with haematologist, suggested guidance on range: 50% to 80% *(ELSO Anticoagulation Guidelines 2021)* - treated by giving fresh frozen plasma, cryoprecipitate, or recombinant AT3 concentrates

ECLS Anticoagulation and Blood product administration protocol

Standard protocol

Cannulation - Heparin loading dose - 50units/kg

Post-Cannulation – Commence Heparin infusion at 10units/kg/hr when ACT < 250 sec

Ongoing management- Heparin infusion 10-40 units/kg/hr

Target levels

aPTT 60-90 sec /ACT 180-220 sec (Hourly)

Platelets ⩾ 80 x10⁹/L
Hb ⩾10 g/dL
Fibrinogen > 1.5g/L
INR < 1.5

DAILY Lab Monitoring

Heparin dosing

If Heparin is ⩾40units/kg/hr,
Consider antithrombin deficiency
Give FFP 20mls/kg

Recheck aPTT/ ACT

aPTT> 100/ ACT > 220

Decrease heparin by 10-20% depending on bleeding/ clot status.

Consider FFP transfusion if bleeding is significant.

aPTT < 50/ ACT < 160

Increase heparin by 10-20% depending on circuit clot burden/ patient bleeding status

aPTT 60-90 sec/ ACT 180-220

Continue Current heparin infusion dose.

Daily clinical management should continue to be documented by the ICU Consultant on the ECMO order sheet.
Any variations to the above Protocol should be discussed with the ECMO CICU/NICU Consultant

ECLS Anticoagulation and Blood product administration protocol

Bleeding protocol

Target levels

aPTT 50-70 sec/ ACT 160-180 sec (Hourly)

Platelets ≥120x10⁹/L Fibrinogen > 1.5 g/L

Hb ≥12 g/dL INR normal

If Patient is bleeding ≥ 4mls/kg/hr for ≥ 4 hours.

1. Consider decreasing heparin infusion
2. Maintain Plt, Hb, fibrinogen levels as above. Check aPTT
3. Notify ICU Consultant and Cardiac Surgery Fellow/Consultant.

Blood Products

PRBC –10-15ml/kg before rechecking Hb)

Platelet - 10ml/kg/ 4U/m² of paediatric apheresed platelets (APP)

FFP give 10-20mls/kg

Cryoprecipitate give 5mls/kg

Review HOURLY

Has bleeding reduced?

Yes

Continue to monitor ACTs hourly and assess blood loss.

If remains minimal then increase Heparin infusion as necessary to maintain ACT/aPTT range set as clinically indicated.

No

Bleeding continues – unchanged.

Repeat FBC, fibrinogen and PT/PTT, ensure target levels are met.
Perform **ROTEM** to determine specific deficiency

Liaise with ICU consultant and Cardiac Surgery Consultant to discuss

- surgical re-exploration
- temporarily ceasing heparin
- tranexamic acid or other adjuncts

Review HOURLY

Has bleeding reduced?