Pediatric ECMO Anticoagulation with Bivalirudin

Purpose: To establish a standardized guideline for bivalirudin use in pediatric ECMO patients.

Scope: Neonatal and pediatric patients requiring ECMO in UNC Children's Hospital Pediatric Intensive Care Unit (PICU)

Indications: For systemic anticoagulation during veno-venous (VV) or veno-arterial (VA) ECMO

Definitions:

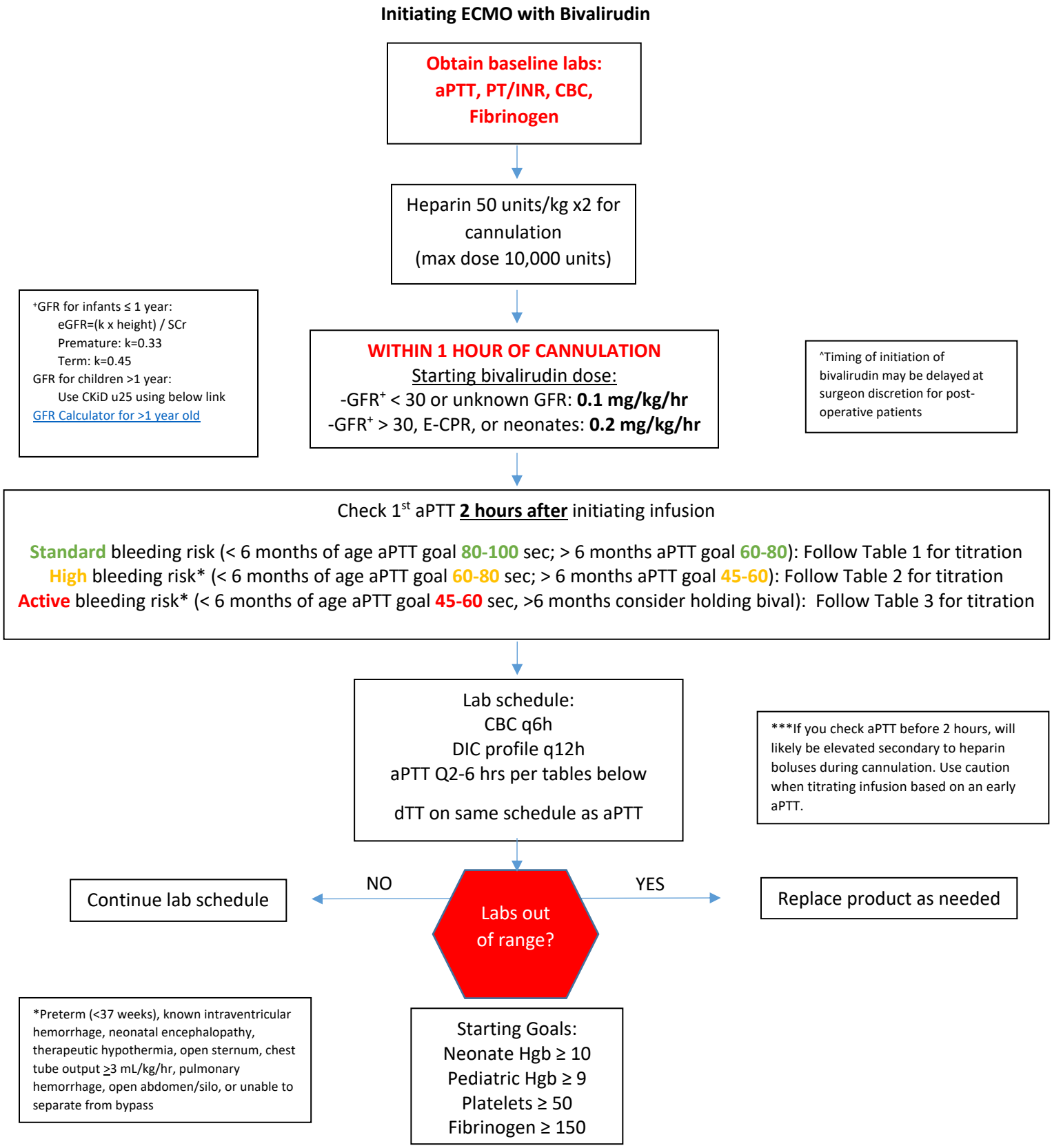
- Bivalirudin: Direct Thrombin Inhibitor (DTI) that works on both clot-bound and circulating thrombin
- Direct Thrombin Inhibitors (DTI): Class of short-acting anticoagulants that binds directly to the active sites on thrombin molecules and expresses more predictable pharmacokinetics and a greater reduction of thrombin generation compared to unfractionated heparin (UFH).
- Heparin-Induced Thrombocytopenia (HIT): An immune complication of heparin therapy caused by antibodies to complexes of platelet factor 4 (PF4) and heparin. HIT diagnosis is made with laboratory evidence of anti-PF4/heparin antibodies.
- aPTT: Activated partial thromboplastin time that measures time to clot
- ROTEM (rotational thromboelastometry): a viscoelastic method which provides a graphical and numerical representation of induced hemostasis in whole blood samples. Can help quickly assess the state of hemostasis in the management of bleeding.

Guideline:

- **Proposed use:** neonatal and pediatric patients requiring ECMO support, especially those with the following diagnoses or clinical concerns:
    - Suspected or confirmed HIT
    - Congenital diaphragmatic hernia (CDH)
    - Difficulty achieving adequate anticoagulation on heparin (heparin infusion > 50 units/kg/hr) with high fibrin deposition and elevated plasma free hemoglobin
    - Laboratory derangements making heparin management problematic (i.e. elevated bilirubin)
    - COVID-19 positive
    - Concern for post-operative bleeding
    - Attending physician discretion
- **Exclusions: (start anticoagulation with heparin)**
    - Allergy to bivalirudin (rare)
    - Bivalirudin resistance: Failure to achieve therapeutic anticoagulation within 24 hours of initiation
    - Prolonged low flow states
        - Patients with severely impaired cardiac function (myocarditis, post-cardiopulmonary bypass, ECPR) or asystole on ECMO due to low flow state within the heart.
        - On flows less than rated flow of oxygenator (PediMag <0.25 LPM, CardioHelp <0.5 LPM)

Process owners: Lauren Brown DO, Katherine Clement MD, Wesley Scercy RN/ECMO specialist
Updated January 22nd, 2025

Algorithm for initiating ECMO with Bivalirudin



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- **Bleeding Risk Categories:**
  - Standard Bleeding Risk: < 6 months Goal aPTT 80 to 100 seconds – refer to Table 1a
  - Standard Bleeding Risk: > 6 months Goal aPTT 60 to 80 seconds – refer to Table 1b
  - High Bleeding Risk: < 6 months Goal aPTT 60 to 80 seconds – refer to Table 2a
  - High Bleeding Risk: > 6 months Goal aPTT 45-60 seconds – refer to Table 2b
  - Actively Bleeding: Goal aPTT 45 to 60 seconds – refer to Table 3

- ***Important Note*** for patients with a **true baseline aPTT level** (not in DIC, septic shock, post-cardiac arrest, etc) try to **ensure that goal aPTT is at least 1.5 times the baseline aPTT level**
- *When available, send dilute thrombin time (dTT) on the same schedule as the aPTT*

Table 1a. **Standard Bleeding Risk for age < 6 months**

aPTT	Hold Infusion	Bivalirudin Dose Titration	Acute* Phase Repeat aPTT	Maintenance+ phase Repeat aPTT
< 50	No	Increase dose by 30%	2 hours	6 hours
50-64	No	Increase dose by 25%	2 hours	6 hours
65-79	No	Increase dose by 15%	2 hours	6 hours
80-100	No	No change	4 hours, if in range x24 hours, then recheck every 6 hours	Every 12 hours or if clinically indicated
101-115	No	Decrease dose by 15%	2 hours	6 hours
116-140	30 min	Decrease dose by 25%	2 hours	6 hours
> 140	60 min	Decrease dose by 30%	2 hours	6 hours

*Acute phase = first 24 hours of infusion, clinical instability, frequent titration of infusion
+Maintenance phase = >24 hours of infusion, clinical and anticoagulation stability

Table 1b. **Standard Bleeding Risk for age > 6 months**

aPTT	Hold Infusion	Bivalirudin Dose Titration	Acute* Phase Repeat aPTT	Maintenance+ phase Repeat aPTT
< 40	No	Increase dose by 25%	2 hours	6 hours
40-59	No	Increase dose by 15%	2 hours	6 hours
60-80	No	No change	4 hours, if in range x24 hours, then recheck every 6 hours	Every 12 hours or if clinically indicated
81-105	No	Decrease dose by 15%	2 hours	6 hours
106-120	30 min	Decrease dose by 20%	2 hours	6 hours
> 120	60 min	Decrease dose by 30%	2 hours	6 hours
< 40	No	Increase dose by 25%	2 hours	6 hours

*Acute phase = first 24 hours of infusion, clinical instability, frequent titration of infusion
+Maintenance phase = >24 hours of infusion, clinical and anticoagulation stability

Table 2a. **High Bleeding Risk for age < 6 months**

aPTT	Hold Infusion	Bivalirudin Dose Titration	Acute Phase* Repeat STAT aPTT	Maintenance+ Phase Repeat STAT aPTT
< 40	No	Increase dose by 25%	2 hours	6 hours
40-59	No	Increase dose by 15%	2 hours	6 hours
60-80	No	No change	4 hours, if in range x24 hours, then recheck every 6 hours	Every 12 hours or if clinically indicated
81-105	No	Decrease dose by 15%	2 hours	6 hours
106-120	30 min	Decrease dose by 20%	2 hours	6 hours
> 120	60 min	Decrease dose by 30%	2 hours	6 hours

*Acute phase = first 24 hours of infusion, clinical instability, frequent titration of infusion
+Maintenance phase = >24 hours of infusion, clinical and anticoagulation stability

Table 2b. **High Bleeding Risk for age > 6 months**

aPTT	Hold Infusion	Bivalirudin Dose Titration	Acute Phase* Repeat STAT aPTT	Maintenance+ Phase Repeat STAT aPTT
< 35	No	Increase dose by 15%	2 hours	6 hours
35-44	No	Increase dose by 10%	2 hours	6 hours
45-60	No	No change	4 hours, if in range x24 hours, then recheck q6 hours	Every 12 hours or if clinically indicated
61-75	No	Decrease dose by 10%	2 hours	6 hours
76-85	30 minutes	Decrease dose by 20%	2 hours	6 hours
>85	60 minutes	Decrease dose by 30%	2 hours	6 hours

*Acute phase = first 24 hours of infusion, clinical instability, frequent titration of infusion
+Maintenance phase = >24 hours of infusion, clinical and anticoagulation stability

Table 3. **Actively Bleeding for age < 6 months. *Consider holding bivalirudin for >6 months**

aPTT	Hold Infusion	Bivalirudin Dose Titration	Repeat aPTT
< 35	No	Increase dose by 15%	2 hours
35-44	No	Increase dose by 10%	2 hours
45-60	No	No change	4 hours, if in range x24 hours, then recheck q6 hours
61-75	No	Decrease dose by 10%	2 hours
76-85	30 minutes	Decrease dose by 20%	2 hours
>85	60 minutes	Decrease dose by 30%	2 hours

*Consider ROTEM if actively bleeding and would like additional information

Recommended Lab Schedule

Table 4. Lab Schedule

Lab value	Schedule	Goal
aPTT	Per nomogram table	Per bleeding risk
dTT (dilute thrombin timei)	Send on same schedule as aPTT	trending
CBC	q6h	Hemoglobin: neonate >10, pediatric >9 Platelets: > 50 if no bleeding, >100 if bleeding
DIC profile (PT/INR, fibrinogen, D dimer)	q12h	Fibrinogen > 150
Plasma free hemoglobin	q24h	No recommended goal, marker of hemolysis, useful if concerned for circuit DIC

- **Use of Unfractionated Heparin (UFH) during Bivalirudin therapy**
    - Heparin can contaminate lab draws and should not be used (i.e. no heparin in arterial lines)
    - Remove all heparin from lines and use papaverine only in arterial lines and saline for central line carriers
    - **Heparin use may be necessary during low (<0.25 LPM for PediMag and <0.5LPM for CardioHelp) or idle flow on bivalirudin due to risk of circuit clot**
        - If low flow or idle circuit flow is necessary (i.e. for a clamp trial), bolus heparin 50 units/kg
        - Limit clamp time to ≤ 5minutes if possible
        - Extended clamp trials (>1 hour) may require repeat heparin bolus. Monitor frequently.
        - Patients with Heparin-Induced Thrombocytopenia may require increased bivalirudin dosing during low or idle circuit flow. Consider transition to argatroban if long-term low or idle flow
- **Dose adjustments**
    - Bivalirudin resistance is a phenomenon where aPTT is not increasing despite increasing the dose
        - Primarily occurs 48-72 hours after starting infusion
        - Consider larger dose increases of 40-50% to achieve therapeutic anticoagulation per provider discretion
    - CRRT/Apheresis may increase clearance of bivalirudin
        - Patients may require increasing doses of bivalirudin after initiation of CRRT/apheresis as about 20% of bivalirudin may be cleared by CRRT/apheresis
        - Recommend more frequent aPTTs every 2 hours until stable therapeutic anticoagulation

        - Continue to monitor aPTT every 2 hours after discontinuation of CRRT/apheresis until anticoagulation is stable

- **Pharmacokinetics**
    - Onset of action: Immediate
    - Duration: Coagulation times return to baseline about 1 hour after discontinuing infusion
    - Metabolism: Proteolytic cleavage
    - Half-life:
        - Normal renal function/mild renal impairment: ~25 minutes
        - Moderate renal impairment: ~35 minutes
        - Severe renal impairment: ~60 minutes
    - Excretion: Urine (20%), glomerular filtration, tubular secretion, and tubular reabsorption
- **Bleeding on Bivalirudin**
    - Bivalirudin should be stopped for significant bleeding (i.e. requiring massive transfusion protocol)
    - Consider sending a ROTEM for more information about hemostasis
    - Consider lowering aPTT goals in response to bleeding
- **Transitioning between anticoagulants while on ECMO**
    - Transitioning from heparin to bivalirudin
        - Stop heparin infusion and start bivalirudin infusion
        - Initiate bivalirudin dosing per algorithm—**NO BOLUS**
        - Follow either standard risk, high risk, or active bleeding titration table
        - Check aPTT every two hours for two checks, even if in range, as heparin will affect first aPTT
    - Transitioning from bivalirudin to heparin
        - Recommended in patients with low or idle circuit flow (**except in patients with HIT)** or difficulty meeting anticoagulation goals on bivalirudin
        - Bolus heparin 50-100 units/kg and immediately stop bivalirudin infusion. Initiate heparin infusion per heparin ECMO nomogram, monitor labs per ECMO heparin guidelines

Veno-arterial trial off/clamp trial

- **IF <u>non-cardiac surgery patient</u>, remain on bival and plan for heparin boluses pre/ during clamp trial. Heparin required for clamp trial while on Bivalirudin due to low flow/no flow state increasing risk of circuit thrombosis**
    - Refer to trial off checklist located in ECMO Specialists Binder at bedside for procedure instructions
    - Order heparin bolus **(50 units/kg)** x3 prior to trial off and ensure at bedside
    - ECMO specialist to bring ACT machine and cartridges to bedside
        - ECMO specialist to draw baseline ACT prior to decreasing flows (Goal ACT 180-220). Historically, ACT has been an unreliable predictor of therapeutic anticoagulation.
        - Bolus heparin 50 units/kg **<u>via patient access</u>** (imperative to protect cannulas during clamp trial) at time of low flow (< 0.25 LPM total flow on pedimag oxy; <0.5 LPM total on adult oxy/ tweener)
        - Recheck ACT after 10 minutes
    - Proceed to clamp trial if no further concerns for clot/fibrin burden in ECMO circuit / cannulas
        - Repeat heparin bolus 50 unit/kg x1 at clamp time if concern for circuit integrity
        - Recheck ACT every 15 minutes during clamp trial
        - If further concerns for circuit integrity arise may re-bolus heparin to address circuit integrity changes
    - Keep Bivalirudin infusion running via circuit during trial off
    - Recommend trial off no longer than 1 hour, if possible, to mitigate risk of cannula and circuit thrombosis. Use provider discretion if encountering issues with circuit clotting throughout trial off.

- **IF <u>cardiac surgery patient</u>: Patient will be transitioned to heparin the night before trial off.**
    - Refer to trial off checklist located in ECMO Specialists Binder at bedside for procedure instructions
    - Order heparin bolus **(10-20 units/kg)** x6 prior to trial off and ensure at bedside
    - If anti-Xa is therapeutic, heparin bolus NOT required
    - ECMO specialist to bring ACT machine and cartridges to bedside
        - ECMO specialist to draw baseline ACT prior to decreasing flows (Goal ACT 180-220). Historically, ACT has been an unreliable predictor of therapeutic anticoagulation.
        - Bolus heparin **<u>via patient access</u>** (10-20 units/kg) at time of low flow (< 0.25 LPM total flow on pedimag oxy; <0.5 LPM total on adult oxy/ tweener)
        - Recheck ACT after 10 minutes
    - Proceed to clamp trial if no further concerns for clot/fibrin burden in ECMO circuit / cannulas
        - Repeat heparin bolus (10-20 units/kg) x1 at clamp time if concern for circuit integrity.
        - Recheck ACT every 15 minutes during clamp trial.
        - If further concerns for circuit integrity arise may re-bolus heparin to address circuit integrity changes.
    - Keep Heparin infusion running via circuit during trial off
    - Recommend trial off no longer than 1 hour, if possible, to mitigate risk of cannula and circuit thrombosis. Use provider discretion if encountering issues with circuit clotting throughout trial off

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