

BIVALIRUDIN DOSING AND MONITORING GUIDELINE

PURPOSE:

To provide standardized dosing and monitoring guidelines for patients receiving bivalirudin therapy for anticoagulation.

The guidelines provided below are recommendations to assist the medical staff in appropriate administration and monitoring of bivalirudin therapy. The final decision by the medical staff to follow the guidelines is left to their discretion. However, documentation of this decision is recommended.

BACKGROUND:

Parenteral direct thrombin inhibitors (DTIs) can be used as an alternative to unfractionated heparin (UFH) when the intravenous route and/or an anticoagulant with a very short half life is indicated.

Published use of DTIs in pediatric patients is limited to case reports, case series or smaller retrospective reviews. Potential advantages of DTIs over UFH are that they:

- Act independently of antithrombin (no antithrombin replacement needed)
- Inhibit circulating and clot-bound thrombin
- Have less binding to plasma proteins (more predictable pharmacokinetics)
- Are used in patients with heparin-induced thrombocytopenia.

In addition to safety, studies have shown that patients receiving bivalirudin on mechanical circulatory support (MCS) have less blood loss; require fewer transfusions of platelets and plasma with a trend toward decreased packed red blood cell (pRBC) transfusions, as well as avoiding the need for anti-thrombin III (AT-III) concentrate, leading to a decreased overall cost in the pediatric population compared to heparin.

The onset of action for continuous infusion of bivalirudin occurs in 2 minutes, with half-life of 26 minutes in adults with normal renal function, and up to 4 hours in severe renal failure. Bivalirudin is cleared by plasma proteolysis but there is some contribution from kidney as well. Steady-state is reached in 4 hours. There is no specific antidote for bivalirudin.

Monitoring of bivalirudin has been challenging. Drug concentration can be measured by liquid chromatography/mass spectroscopy (LC-MS/MS), which is impractical for the rapid return of results. Case series report successful monitoring during cardiopulmonary bypass using the ACT. Management of deep vein thrombosis in pediatric patients was monitored by the aPTT; however, the aPTT can be falsely shortened in situations with activation of the contact pathway of coagulation. More recently, the dilute thrombin time (dTT) has been used effectively to monitor bivalirudin treatment in pediatric patients on paracorporeal support. Our institution has successfully used the dTT and also has a bivalirudin-specific dTT (Bivalirudin Monitor) that correlates with a therapeutic range for the dTT.

Bivalirudin Restrictions: (See CCHMC P&T Policy V-144)

Prescriber restrictions: Prescriber obtains Hematology consult except for Cath Lab patients unable to receive heparin, VAD or ECMO patients

Location Restrictions: Critical Care Areas, ACCU, A5

Bivalirudin Recommendations: Note that this guideline has separate recommendations for ECMO and VAD patients vs. general venous thromboembolism (VTE) patients.

A. ECMO and VAD Patients

1. Baseline Laboratory Monitoring

Baseline laboratory tests **prior** to initiation of bivalirudin therapy should include the following. Results should be reviewed prior to initiation whenever possible.

- A. CBC with differential count
- B. PT/INR
- C. aPTT
- D. Fibrinogen
- E. Thrombin time
- F. Dilute Thrombin Time (DTT)
- G. Basic metabolic panel
- H. Optional labs: ROTEM, CRP, LDH, cystatin C

2. Initial Dosing

- A. Start bivalirudin once surgical and coagulopathic bleeding resolved (<2mL/kg of chest tube output for 4 hours and no other sources of active bleeding)
- B. See Table 1 below for initial dosing of bivalirudin

Table 1. Initial Bivalirudin dosing

Renal Function (GFR)	Initial Infusion Rate
Normal function (>60 mL/min/1.73m ²)	0.3 mg/kg/hr IV infusion
Mild-moderate dysfunction (30-60 mL/min/1.73m ²)	0.2 mg/kg/hr IV infusion
Severe dysfunction (<30 mL/min/1.73m ²)	0.1 mg/kg/hr IV infusion

3. Monitoring Parameters during Bivalirudin Therapy

- A. Lab schedule:
 - i. Every 6 hours: aPTT, DTT
 - ii. Every 12 hours: CBC, UFH, PT/INR
 - iii. Every 24 hours: Bival monitor level, LDH, plasma free Hgb
- B. Hematologic goals:
 - i. Hematocrit >30%
 - ii. Platelets >50 x 10⁹/L (unless bleeding >100 x 10⁹/L)
 - iii. See table 2 for aPTT goals for standard and high risk for thrombosis targets

Table 2. aPTT and Dilute PTT Goals for Standard and High Risk of Thrombosis Targets

	Standard Target	High Target
Dilute TT	30-45 sec	35-55 sec
aPTT	60-80 sec	70-90 sec

4. Monitoring and Titration of Bivalirudin Infusion

- a. Obtain blood for DTT and aPTT 3-4 hours after initiation and adjust bivalirudin using the following tables 3 and 4 based on target DTT and aPTT.
 - a. Draw labs from line without heparin or bivalirudin to avoid contamination
 - b. The aPTT may remain elevated with low acute phase reactants (fibrinogen, Factor XII, VIII (>30-40% depletion))
 - c. PT/INR >22/2, consider FFP

Table 3. Monitoring and Titration of Bivalirudin Infusion: STANDARD Target

aPTT (sec)	Rate Change	Repeat aPTT Level
< 45	Increase by 25%	2 hours after dose change
45-59	Increase by 15%	2 hours after dose change
60-80	NO CHANGE	DTT, aPTT Q6h
81-95	Decrease by 15%	2 hours after dose change
96-110	Decrease by 25%	2 hours after dose change
>110	Normal renal function: hold for 15 minutes and decrease infusion by 30% Mild/Moderate renal dysfunction: hold for 45 minutes and decrease infusion by 40% Severe renal dysfunction: hold for 2 hours and check aPTT before restarting	2 hours after dose change

Table 4. Monitoring and Titration of Bivalirudin Infusion: High Target

DTT	Rate Change	Repeat DTT Level
< 25	Increase by 25%	2 hours after dose change
25-35	Increase by 15%	2 hours after dose change
35-55	NO CHANGE	DTT, aPTT Q6h
55-65	Decrease by 15%	2 hours after dose change
>65	Decrease by 25%, send a STAT creatinine	2 hours after dose change

aPTT (sec)	Rate Change	Repeat aPTT Level
< 55	Increase by 25%	2 hours after dose change
55-69	Increase by 15%	2 hours after dose change
70-90	NO CHANGE	DTT, aPTT Q6h
91-105	Decrease by 15%	2 hours after dose change
106-120	Decrease by 25%	2 hours after dose change
>120	Normal renal function: hold for 15 minutes and decrease infusion by 30% Mild/Moderate renal dysfunction: hold for 45 minutes and decrease infusion by 40% Severe renal dysfunction: hold for 2 hours and check aPTT before restarting	2 hours after dose change

5. Considerations Specific to ECMO/VAD Patients

- i. Ongoing monitoring of aPTT should be performed every 6 hours during the first 24-48 hours****. Once therapeutic levels are achieved consistently, aPTT can be spaced at the provider's discretion to a minimum of every 12 hours. However, an aPTT should continue to be checked 2-6 hours following each dose change.
- ii. aPTT may be impacted by the following:
 1. Heparin contamination from the line (increased aPTT)
 2. Traumatic phlebotomy (increased aPTT)
 3. Stasis draw (decreased aPTT)
 4. Low fibrinogen, low Factor XII or VIII (increased aPTT)
 5. Plateau aPTT may be seen at high concentrations of bivalirudin (>1mg/L), consider using PT/INR and/or Dilute TT
 6. High factor VIII, inflammation, activation of the contact pathway (decreased aPTT)

B. Hematology/General Anticoagulation of Venous Thromboembolism (VTE)

1. Baseline Laboratory Monitoring

Baseline laboratory tests **prior** to initiation of bivalirudin therapy should include the following. Results should be reviewed prior to initiation whenever possible.

- a. CBC with differential count
- b. Serum Cr
- c. PT
- d. aPTT
- e. Fibrinogen
- f. Thrombin time
- g. Dilute Thrombin Time
- h. Basic metabolic panel

2. Initial Dosing

Table 1. Initial Bivalirudin dosing

Renal Function (GFR)	Initial Infusion Rate
Normal function (>60 mL/min/1.73m ²)	0.3 mg/kg/hr IV infusion
Mild-moderate dysfunction (30-60 mL/min/1.73m ²)	0.2 mg/kg/hr IV infusion
Severe dysfunction (<30 mL/min/1.73m ²)	0.1 mg/kg/hr IV infusion

4. Monitoring Parameters during Bivalirudin Therapy

- a. Lab schedule:
 - i. First dTT 4 hours after initiation
 - ii. Every 6 hours: dTT (may space to q 12 hr if stable dose and results)
 - iii. Every 12 hours: CBC, PT

- iv. Every 24 hours: dTT, Bival Monitor, serum Cr , fibrinogen, PT, PTT
- b. Hematologic goals:
 - i. Platelets $>50 \times 10^9/L$ (unless bleeding $>100 \times 10^9/L$)
 - ii. dTT of 35-65 seconds

5. Monitoring and Titration of Bivalirudin Infusion

- a. Obtain blood for dTT 4 hours after initiation and adjust bivalirudin using table 3, based on target dTT.
- b. Draw labs from line without heparin or bivalirudin to avoid contamination
- c. The “therapeutic” target dTT could change with new lots of reagents in the main laboratory. This will be revalidated with each lot change, about annually. The Bival Monitor test will also be re-validated quarterly and with reagent lot changes.

Table 3. Monitoring and Titration of Bivalirudin Infusion

dTT (sec)	Rate Change	Repeat dTT
< 20	Increase by 25%	4 hours after dose change
20-34	Increase by 15%	4 hours after dose change
35-65	NO CHANGE	dTT Q6 -12 h
66-80	Decrease by 15%	4 hours after dose change
>81	Normal renal function: hold infusion x 15 minutes, send STAT Cr and repeat dTT and discuss with Hematology about % of rate decrease (suggest 25%) Mild/Moderate renal dysfunction: hold for 45 minutes and decrease infusion by 30% Severe renal dysfunction: hold for 2 hours and check dTT before restarting	2-4 hours after dose change (depending upon renal function)

C. Monitoring of therapy, precautions, and considerations:

- a. Preferably, blood samples (dilute TT, UFH, PT, aPTT) should NOT be drawn through lines infusing heparin or bivalirudin. However, when drawn from lines infusing heparin, adequate waste should be drawn prior to obtaining sample.
- b. Dilute dTT may be impacted by the following:
 - i. Heparin contamination from the line (increased dilute TT)
 - ii. Fibrinogen levels
 - iii. Not impacted by lupus inhibitors or elevated d-dimer

- c. CCHMC uses 2 standard bivalirudin concentrations 0.5mg/mL and 5mg/mL in Dextrose 5% in Water (D5W) for continuous therapeutic infusions.
- d. The bivalirudin infusion should be continued without interruption unless authorized by a physician and should not be paused any longer than 10 minutes under any circumstances unless instructed to do so by the attending physician.
- e. Avoid IM injections and arterial punctures during bivalirudin therapy if possible. If arterial punctures are warranted, appropriate precautions, including the use of extended periods of external pressure, should be considered.

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