Therapeutic Dosing of Unfractionated Heparin-Pediatric/Neonatal - Inpatient/Emergency Department

Consensus Care Guideline

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Population/Problem:

Unfractionated heparin (UFH) is used intravenously when therapeutic anticoagulation is needed, and low molecular weight heparin is not a suitable option. Intravenous UFH has an immediate onset of action but requires monitoring and infusion rate adjustments to achieve a targeted therapeutic range[1]. Neonates and pediatric patients differ in their pharmacologic response to UFH[2-7]. The following guideline provides recommendations for how to initiate, dose adjust and monitor a UFH infusion in a neonatal and pediatric patient.

Definitions:

UFH is a high alert medication. An additional double-check is required as specified in UW Health Clinical Policy 6.1.19 on all boluses, when IV pump programming is outside of the established IV pump decision support software (Alaris Guardrails®) limits, when a new bag of heparin is hung, and at each shift change.

Recommendations:

UFH intravenous infusions with the intent for titration to a therapeutic goal must be ordered via the IP/ED Heparin Anticoagulation – Pediatric – Supplemental Order Set. Separate order sets are available for extracorporeal membrane oxygenation, ventricular assist devices, and for pediatric neuroendovascular/neurosurgical patients.

The standard heparin concentration is 25,000 units in 500 mL (50 units/mL). There is a higher concentration option for fluid restricted patients of 50,000 units in 500 mL (100 units/mL).

1. Baseline laboratory monitoring: prior to starting the UFH infusion, collect the following baseline labs if not already resulted in the previous 48 hours
   - 1.1 PT/INR *(UW Health low quality evidence, strong recommendation)*
   - 1.2 CBC (*UW Health low quality evidence, strong recommendation)*
   - 1.3 Heparin anti-Xa level: only if a patient received any other anticoagulant (e.g., apixaban, rivaroxaban, enoxaparin) within the previous 48 hours prior to starting the UFH infusion *(UW Health low quality evidence, conditional recommendation)*
   - 1.4 Drug-specific anti-Xa level: only if an oral Xa inhibitor (e.g., apixaban, rivaroxaban) was taken within the previous 48 hours prior to starting the UFH infusion *(UW Health very low quality evidence, conditional recommendation)*
   - 1.5 Labs should be drawn from a fresh venipuncture site prior to initiating UFH infusion

2. Initiation of UFH infusion
   - 2.1 Initial bolus dose of 75 units/kg will result in a therapeutic anti-Xa in 90% of children[2] *(UW Health low quality evidence, weak/conditional recommendation)*
   - 2.2 Bolus doses should be used with caution or avoided in patients who meet the following criteria:[2] *(UW Health low quality evidence, weak/conditional recommendation)*
     - 2.2.1 Neonate or premature neonates
     - 2.2.2 Stroke
     - 2.2.3 Active bleeding
     - 2.2.4 High bleeding risk
   - 2.3 Initial starting infusion rate is based on the age of the patient[2-7] *(UW Health moderate quality evidence, strong recommendation)*
   - 2.4 See Table 1 for recommendations on bolus and initial infusion rate recommendations

Table 1. Initial Heparin Bolus Dose and Infusion Rate[2-7] *(UW Health moderate quality evidence, strong recommendation)*

Age	Bolus Dose (units/kg)	Maximum Bolus (units)	Initial Infusion (units/kg/hr)
Birth to 12 months	75	1,500	28
Children > 1 year to ≤12 years	75	5,000	20
Children > 12 years	80	10,000	18

Initial boluses and infusion rates are based on actual body weight

3. Titration and monitoring of UFH infusion[2,8-12] *(UW Health moderate quality evidence, strong recommendation)*
   - 3.1 Check anti-Xa level 6 hours after initiation of the infusion and every 6 hours thereafter
     - 3.1.1 Each anti-Xa level should be ordered as STAT priority
   - 3.2 Use the nomogram in Table 2 to guide UFH infusion rate adjustments
   - 3.3 Once 3 consecutive anti-Xa levels are therapeutic, it is recommended to check an anti-Xa level every 24 hours with the morning labs
   - 3.4 If a rate adjustment becomes necessary or the infusion is held for any reason and restarted, repeat steps 3.1 to 3.3
   - 3.5 If a therapeutic goal is not reached within 24 hours with correct titration the patient may not be an appropriate candidate for adjustments based on the heparin algorithm. Recommend consultation with Pharmacy and/or Hematology for assistance with dosing.

Table 2. Heparin Infusion Dose Adjustment Nomogram[2,8-12] *(UW Health low quality evidence, weak/conditional recommendation)*

Heparin Level by Anti-Xa (IU/mL)	Bolus/Hold	Infusion Rate Change
< 0.1	Bolus 50 units/kg (see maximum dose in Table 1)	↑ by 3 units/kg/hr
0.1 – 0.29	None	↑ by 2 units/kg/hr
0.3 - 0.7	None	No Change; Therapeutic Range
0.71 - 0.9	None	↓ by 2 unit/kg/hr
0.91 – 1	Hold infusion 30 min	↓ by 2 units/kg/hr
> 1	Hold infusion 1 hour	↓ by 3 units/kg/hr

4. Additional monitoring[1,2] *(UW Health low quality evidence, strong recommendation)*
   - 4.1 Samples should not be drawn from an IV line infusing UFH
   - 4.2 Hemoglobin and platelets must be followed 24 hours after initiating UFH therapy and every other day thereafter for up to 14 days until therapy is discontinued.
   - 4.3 Every 8 hours, inspect line/surgical or wound sites for bleeding and check patient for symptoms indicating bleeding such as: hematomas, bruising, and respiratory symptoms. Contact MD for any signs of bleeding
   - 4.4 Physician should be notified for:

4.4.1 Each anti-Xa result, unless the patient is being managed under the UW Health UFH Titration – Adult/Pediatric/Neonatal – Inpatient practice protocol
4.4.2 Platelet count decrease > 50% from baseline or if count falls below 100 K/uL
4.4.3 Hemoglobin decrease by > 2 g/dL from baseline
4.4.4 Patient has any deterioration in neurological status
4.4.5 Baseline anti-Xa (if drawn) > 0.1 IU/mL or baseline INR > 1.2
4.4.6 Prior to administering any heparin bolus or holding the heparin infusion

5. **Table 3. Transitioning between anticoagulants**[13,17] *(UW Health low quality evidence, weak/conditional recommendation)*

Heparin to Enoxaparin	Stop heparin Administer enoxaparin 2-4 hours later
Heparin to DOAC	Stop heparin Give oral anticoagulant at the same time
Heparin to Fondaparinux	Stop heparin Administer fondaparinux 2-4 hours later

6. Heparin and Direct Xa Inhibitors (e.g., apixaban, rivaroxaban) *(UW Health GRADE low quality evidence, conditional recommendation)*
   6.1 In the presence of a direct Xa inhibitor, the measured anti-Xa level may be relatively high in proportion to the antithrombin activity. This may result in over-estimation of the heparin activity by the assay. To account for this, a higher anti-Xa goal may be used for patients with recent use of direct Xa inhibitors.
   6.2 Target a higher anti-Xa range (Table 4) in patients who received a direct Xa inhibitor in the previous 48 hours if the baseline heparin anti-Xa level is elevated.
   6.3 A drug-specific anti-Xa level should be drawn prior to starting the heparin infusion:
      6.3.1 If the drug-specific anti-Xa level is within or elevated outside of the target range, then heparin infusion should not be started.
   6.4 If unable to wait for the drug-specific anti-Xa level to result, then patient risk/benefit for thrombotic and bleeding risks should be weighed prior to starting the heparin infusion.
   6.5 Return to the standard anti-Xa goal 48 hours after the last dose of direct Xa inhibitor (i.e., apixaban, rivaroxaban) was given (see Table 2)

Table 4. Nomogram for Direct Xa Inhibitor in Previous 48 hours and Elevated Baseline Heparin Anti-Xa *(UW Health GRADE very low quality evidence, conditional recommendation)*

Heparin Level by Anti-Xa (IU/mL)	Bolus/Hold	Infusion Rate Change
< 0.1	Bolus 40 units/kg (See maximum dose in Table 1)	↑ by 3 units/kg/hr
0.1 – 0.39	Bolus 20 units/kg (See maximum dose in Table 1)	↑ by 2 units/kg/hr
0.4 – 0.69	None	↑ by 1 unit/kg/hr
0.7 – 1	None	No Change; Therapeutic Range
1.01 – 1.4	None	↓ by 1 unit/kg/hr
1.41 – 1.7	Hold infusion 1 hr	↓ by 2 units/kg/hr
> 1.7	Hold infusion 1½ hr	↓ by 3 units/kg/hr

Disclaimer

Consensus care models assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Conflicts of Interest

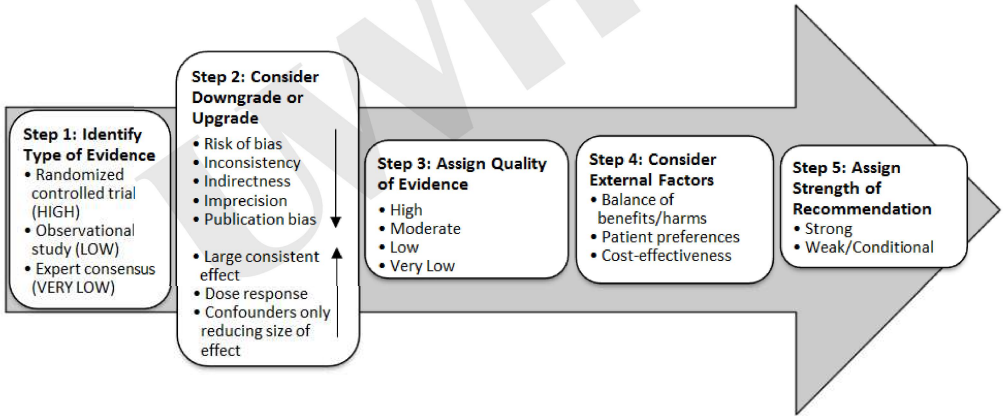
All guideline workgroup members are expected to follow institutional policies and procedures around conflicts of interest. Actions in which a guideline member discloses a conflict of interest relevant to the guideline topic may include, but is not limited to, abstaining from voting, dismissal during comment and voting period, or recusal from requesting and/or participation in the decision-making process.

Methodology

Development Process

Each guideline is reviewed and updated approximately every 3-5 years, but will vary in consideration of the primary literature and relevant practice changes. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

GRADE Methodology adapted by UW Health



Rating Scheme for the Strength of the Evidence/Recommendations:

GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

GRADE Ratings for Recommendations for or Against Practice

Strong (S)	Generally, should be performed (i.e., the net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.)
Conditional (C)	May be reasonable to perform (i.e., may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.)

Collateral Tools & Resources

Metrics
1. VTE Performance Measure – VTE 4 – UFH with dosage and platelet monitored by protocol
2. Guideline adherence
3. Time to achieve a target anti-Xa level
4. % of time with supra or sub-therapeutic anti-Xa levels
5. Event rate for bleeding and thrombotic events during heparin management

Order Sets & Smart Sets
IP/ED Heparin Anticoagulant – Pediatric – Order Set

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