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

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Introduction

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.

UFH is a high alert medication. An additional double-check is required as specified in Hospital Administrative Policy 8.33 must be performed 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.

Scope

Intended User(s):

- Physicians
- Advanced Practice Providers
- Fellows
- Residents
- Pharmacists
- Registered Nurses

Objective(s): This clinical practice guideline is intended to provide a standardized process for the initiation, maintenance and monitoring of intravenous heparin used for therapeutic indications.

Target Population: The recommendations within this guideline would apply to neonatal and pediatric patients receiving intravenous unfractionated heparin infusions with the intent to titrate to a therapeutic goal.

NOTE: Definitions of age: adult (18 years or older), adolescent (11-17 years), pediatric (1 month-17 years, 11-17 years OR 17 years or younger), neonate (birth to 28 days).

Clinical Questions Considered:

- How should intravenous heparin be dosed and adjusted in pediatric and neonatal patients?

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 or ventricular assist devices.

1. Baseline monitoring of UFH infusions *(UW Health low quality evidence, strong recommendation)*
   - 1.1 Collect baseline PT/INR prior to initiating UFH infusion if not already available
   - 1.2 Collect baseline CBC and platelet prior to initiating UFH infusion if not already available
   - 1.3 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)*
     - 2.1.1 Boluses doses are based on actual body weight *(UW Health moderate quality evidence, strong recommendation)*
     - 2.1.2 Round the bolus dose to the nearest 10 units for ease of preparation
     - 2.1.2 Use heparin 1000 units/mL vial from floor stock for bolus dose
     - 2.1.3 See Table 1 for recommendations on bolus dose
   - 2.2 Bolus doses should be used with caution or avoided in patients with the following[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)*
     - 2.3.1 See Table 1 for recommendations on initial infusion rate

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	75	5,000	20
Children > 12 years	80	10,000	18

3. Titration and monitoring of UFH infusion[2,8-12] *(UW Health moderate quality evidence, strong recommendation)*
   - 3.1 Check STAT anti-Xa after initiation of the infusion and every 6 hours after any rate change
   - 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 am labs
   - 3.4 If a rate adjustment becomes necessary or the infusion is held for any reason and restarted, recheck anti-Xa level and repeat the above process

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	↑ 3 units/kg/hr
0.1 - 0.29	0	↑ 2 units/kg/hr
0.3 - 0.7	0	No Change; Therapeutic Range
0.71 - 0.9	0	↓ by 2 unit/kg/hr
0.91 - 1.0	Hold infusion 30 min	↓ by 2 units/kg/hr
> 1.0	Hold infusion 1 hour	↓ by 3 units/kg/hr

- Inform physician of each anti-Xa result for heparin infusion rate adjustment

4. Additional monitoring[1,2] *(UW Health low quality evidence, strong recommendation)*
   - 4.1 Samples should not be drawn from an IV 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 of 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 and heparin infusion rate adjustment
     - 4.4.2 Platelet count decrease > 50% from baseline or if count falls below 100 x 10^9/L
     - 4.4.3 Hemoglobin decreases by > 2 g/dL from baseline
     - 4.4.4 Patient has any deterioration in neurological status
     - 4.4.5 Baseline anti-Xa > 0.1 unit/mL or baseline INR > 1.2
     - 4.4.6 Anti-Xa level is < 0.1 IU/mL or > 0.9 IU/mL

5. Transitioning between anticoagulants[13,17]
   - 5.1 Heparin to enoxaparin – give enoxaparin 2-4 hours after heparin discontinued *(UW Health moderate quality evidence, strong recommendation)*
   - 5.2 Heparin to fondaparinux – give fondaparinux 2-4 hours after heparin discontinued *(UW Health low quality evidence, weak/conditional recommendation)*

Disclaimer

Clinical practice guidelines 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.

Methodology

Development Process

Each guideline is reviewed and updated a minimum of every 3 years. 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.

Methods Used to Collect the Evidence:

The following criteria were used by the guideline author(s) and workgroup members to conduct electronic database searches in the collection of evidence for review.

Literature Sources:

- Electronic database search (e.g., PubMed)
- Databases of systematic reviews (e.g., Cochrane Library)
- Hand-searching journals, external guidelines, and conference publications

Time Period: 2014 - 2018

Search Terms:

- Pediatric
- Neonatal
- Heparin

Methods to Select the Evidence:

The quality of evidence for use of heparin in pediatric and neonatal populations is low. There are no randomized controlled trials available. This guideline update focused on review articles, systematic review articles, case series, and retrospective analyses.

Methods Used to Formulate the Recommendations:

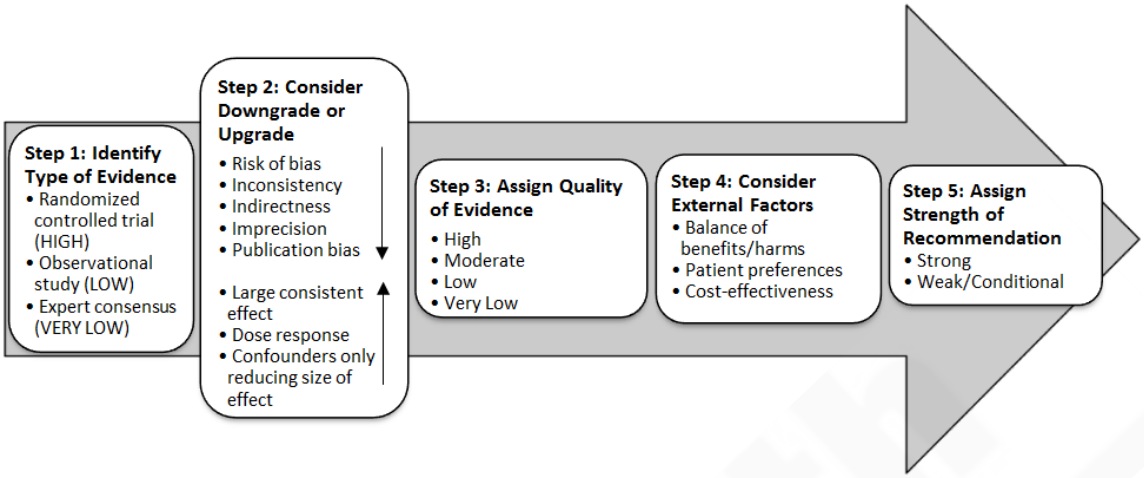
The workgroup members agreed to adopt recommendations developed by external organizations and/or created recommendations internally via a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:

Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see **Figure 1**).

Figure 1. 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

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.)
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.)

Cost Analysis: Not applicable

Recognition of Potential Health Care Disparities: Not applicable

Collateral Tools & Resources

The following collateral tools and resources support staff execution and performance of the evidence-based guideline recommendations in everyday clinical practice.

Metrics

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

Order Sets & Smart Sets

IP/ED Heparin Anticoagulant – Pediatric – Order Set

Appendix A. Heparin Dosing Tables

The following tables provide guidance for the initiation and titration of heparin in neonatal/pediatric population.

Table 1. Initial Heparin Bolus Dose and Infusion Rate[3-6] *(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	75	5,000	20
Children > 12 years	80	10,000	18

Table 2. Heparin Infusion Dose Adjustment Nomogram[3,7-11] *(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	↑ 3 units/kg/hr
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- Inform physician of each anti-Xa result for heparin infusion rate adjustment

References

1. Garcia DA, Baglin TP, Weitz JI, et al. Parenteral anticoagulants: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence based clinical practice guidelines. *CHEST* 2012;141:24s-43s.
2. Monagle P, Chan A, Goldenberg N, et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th edition: American College of Chest Physicians evidence based clinical practice guidelines. *CHEST.* 2012; 141e737s-e801s.
3. Igniatovic V, Summerhayes R, Than J, et al. Therapeutic range for unfractionated heparin therapy: age-related differences in response in children. *J Thromb Haemost.* 2006;4(10):2280-82.
4. Ignjatovic V, Furmedge J, Newall F, Chan A, Berry L, Fong C, et al. Age-related differences in heparin response. *Thromb Res;* 2006;118:741–5.
5. Andrew M, Marzinotto V, Massicotte P, et al. Heparin therapy in pediatric patients: a prospective cohort study. *Pediatr Res*; 1994:35:78-83.
6. Bhatt MD, Paes BA, Chan AK. How to use unfractionated heparin to treat neonatal thrombosis in clinical practice. *Blood Coagul Fibrinolysis.* 2016; 27(6):605-14
7. Dabbous MK, Sakr FR, Malaeb DN. Anticoagulant therapy in pediatrics. *J Basic Clin Pharm.* 2014; 5(2): 27-33
8. Newall F, Ignjatovic V, Summerhayes, et al. In vivo age dependency of unfractionated heparin in infants and children. *Throm Res* 2009; 123:710-14.
9. Newall F, Ignjatovic V, Johnston L, et al. Age is a determinant factor for measures of concentration and effect in children requiring unfractionated heparin. *Thromb Haemost.* 2010; 103(5):1085-1090.
10. Igniatovic V, Summerhayes R, Than J, et al. Therapeutic range for unfractionated heparin therapy: age-related differences in response in children. *J Thromb Haemost.* 2006;4(10):2280-82.
11. Schechter T, Finkelstein Y, Ali M, et al. Unfractionated heparin dosing in young infants: clinical outcomes in a cohort monitored with anti-factor Xa levels. *J Thromb Haemost.* 2012;10:368-74.
12. Igniatovic V, Summerhayes R, Gan A, et al. Monitoring unfractionated heparin (UFH) therapy: which antifactor Xa assay is appropriate? *Thromb Res .*2007;120(3): 347-351.
13. Enoxaparin. In: DRUGDEX® System (internet database). Thomson Micromedex, Greenwood Village, Colorado, USA. Available at http://www.thomsonhc.com (cited March 24, 2014)
14. Eliquis [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 8/2014.
15. Pradaxa [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 12/2014
16. Xarelto [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 12/2014.
17. Fondaparinux. In: DRUGDEX® System (internet database). Thomson Micromedex, Greenwood Village, Colorado, USA. Available at http://www.thomsonhc.com (cited March 24, 2014)