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

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Pharmacy and Therapeutics: August 2012; November 2015

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Executive Summary
Guideline Overview
This clinical practice guideline is intended to provide a standardized process for the initiation, maintenance and monitoring of intravenous unfractionated heparin used for therapeutic indications. Practices considered include guidance on selection of initial dosing nomograms, maintenance dose adjustments, laboratory monitoring and transitioning to alternative anticoagulants.

Key Practice Recommendations
1. Initial Heparin Bolus
   1.1. Initial bolus dose of 75 units/kg will result in a therapeutic anti-Xa in 90% of children
       1.1.1. Bolus doses are based on actual body weight
   1.2. Boluses should be used with caution or avoided in patients with the following:
       1.2.1. Neonates and premature neonates
       1.2.2. Stroke
       1.2.3. Active bleeding
       1.2.4. High bleeding risk

2. Initiation of Heparin Infusion
   2.1. Initial infusion rate is based on the age of the child
   2.2. Document infusion rates in units/kg/hr

Table 1. Initial Heparin Infusion Rates
<table>
<thead>
<tr>
<th>Age</th>
<th>Bolus Dose (units/kg)</th>
<th>Maximum Bolus (units)</th>
<th>Initial Infusion (units/kg/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 12 months</td>
<td>75</td>
<td>1,500</td>
<td>28</td>
</tr>
<tr>
<td>Children &gt; 1 year</td>
<td>75</td>
<td>5,000</td>
<td>20</td>
</tr>
<tr>
<td>Children &gt; 12 years</td>
<td>80</td>
<td>10,000</td>
<td>18</td>
</tr>
</tbody>
</table>

3. Algorithm for adjusting therapeutic heparin infusion

Table 2. Heparin Infusion Dose Adjustments
<table>
<thead>
<tr>
<th>Heparin Level by Anti-Xa (IU/mL)</th>
<th>Bolus/Hold</th>
<th>Infusion Rate Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.1</td>
<td>Bolus 50 units/kg</td>
<td>↑ 3 units/kg/hr</td>
</tr>
<tr>
<td>0.1 – 0.29</td>
<td>0</td>
<td>↑ 2 units/kg/hr</td>
</tr>
<tr>
<td>0.3 - 0.7</td>
<td>0</td>
<td>No Change; Therapeutic Range</td>
</tr>
<tr>
<td>0.71 - 0.9</td>
<td>0</td>
<td>↓ by 2 unit/kg/hr</td>
</tr>
<tr>
<td>0.91 – 1.0</td>
<td>Hold infusion 30 min</td>
<td>↓ by 2 units/kg/hr</td>
</tr>
<tr>
<td>&gt; 1.0</td>
<td>Hold infusion 1 hour</td>
<td>↓ by 3 units/kg/hr</td>
</tr>
</tbody>
</table>

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

Companion Documents
1. IP/ED Heparin Anticoagulant – Pediatric – Order Set

Pertinent UW Health Policies & Procedures
1. UWHC Policy #: 8.33 High Alert Medication Administration
Patient Resources
1. Health Facts For You #6915: Heparin (Unfractionated and Low Molecular Weight)

Scope

Disease/Condition(s):
Hospitalized neonatal and pediatric patients receiving intravenous unfractionated heparin intended for therapeutic dosing.

Intended Users:
- 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.

Interventions and Practices Considered:
The clinical interventions and practices recommended in this guideline are intended for patients receiving therapeutic intravenous unfractionated heparin. Practices considered include guidance on selection of initial dosing nomograms, maintenance dose adjustments, laboratory monitoring and transitioning to alternative anticoagulants.

Major Outcomes Considered:
The major outcomes considered in this guideline are for the safe and effective dosing of IV unfractionated heparin through the use of standardized dosing and monitoring nomograms, and documentation. Efficacy is measured by achieving a therapeutic goal within 24 hours of initiation and safety is measured by bleeding outcomes and critical values.

Guideline Metrics:
The Anticoagulation Stewardship Program periodically completes a review of our intravenous heparin infusion administrations. This review is done to assess adherence to the dosing and monitoring nomograms, assess time to achieving therapeutic ranges, evaluate critical values, and bleeding outcomes. Additionally, PSN related to heparin infusions are reviewed throughout the year.
Methodology
A modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) developed by the American Heart Association and American College of Cardiology Foundation has been used to assess the Quality and Strength of the Evidence in this Clinical Practice Guideline (Appendix A).\(^1\)

A literature search conducted in Pubmed was completed to include the following search terms: 'pediatrics,' 'unfractionated heparin monitoring', and 'heparin monitoring anti-Xa'

Introduction
Unfractionated heparin (UFH) is used intravenously when therapeutic anticoagulation is warranted 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 in order to achieve a targeted therapeutic range\(^2\). Neonates and pediatric patients differ in their pharmacologic response to UFH\(^3\-6\). 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\(^\text{®}\)) 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 or ventricular assist devices.

1. Baseline monitoring of UFH infusions
   1.1 Collect baseline PT/INR prior to initiating UFH infusion if not already available (Class I, Level C)
   1.2 Collect baseline CBC and platelet prior to initiating UFH infusion if not already available (Class I, Level C)
   1.3 Labs should be drawn from a fresh venipuncture site prior to initiating UFH infusion (Class IIb, Level C)

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\(^3\) (Class IIb, Level C)
     2.1.1 Bolus doses are based on actual body weight (Class IIb, Level C)
     2.1.2 Round the bolus dose to the nearest 10 units for ease of preparation
     2.1.3 Use heparin 1000 units/mL vial from floor stock for bolus dose
     2.1.4 See Table 1 for recommendations on bolus dose
1.2 Bolus doses should be used with caution or avoided in patients with the following:
   (Class I, Level C)
   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
   2.3.1 Document infusion rate in unit/kg/hr
   2.3.2 See Table 1 for recommendations on initial infusion rate

Table 1. Initial Heparin Bolus Dose and Infusion Rate (Class IIb, Level C)

<table>
<thead>
<tr>
<th>Age</th>
<th>Bolus Dose (units/kg)</th>
<th>Maximum Bolus (units)</th>
<th>Initial Infusion (units/kg/hr)</th>
</tr>
</thead>
<tbody>
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<td>10,000</td>
<td>18</td>
</tr>
</tbody>
</table>

3. Titration and monitoring of UFH infusion (Class IIb, Level C)
   3.1
   3.2 Check STAT anti-Xa after initiation of the infusion and after any rate change
   3.2.1 Every 8 hours for children < 1 year of age
   3.2.2 Every 4 hours for children > 1 year of age
   3.3 Use the nomogram in Table 2 for UFH infusion rate adjustments
   3.4 Once 3 consecutive anti-Xa levels are therapeutic it is recommended to check an anti-Xa level every 24 hours with the am labs
   3.5 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
   3.6 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 (Class IIb, Level C)

<table>
<thead>
<tr>
<th>Heparin Level by Anti-Xa (IU/mL)</th>
<th>Bolus/Hold</th>
<th>Infusion Rate Change</th>
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<tbody>
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<td>↓ by 3 units/kg/hr</td>
</tr>
</tbody>
</table>

- Inform physician of each anti-Xa result for heparin infusion rate adjustment
4. Additional monitoring\(^2,3\) *(Class IIb, Level C)*
   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\(^12-16\)
   5.1 Heparin to enoxaparin – give enoxaparin 2-4 hours after heparin discontinued *(Class IIb, Level C)*
   5.2 Heparin to fondaparinux - give fondaparinux 2-4 hours after heparin discontinued *(Class IIb, Level C)*
   5.3 Heparin to direct oral anticoagulant – give oral anticoagulant at the time of heparin discontinuation *(Class IIb, Level C)*

**UW Health Implementation**

**Potential Benefits:**
The benefits of implementation of this guideline include providing a standardized approach for the management and monitoring of UFH.

**Potential Harms:**
While it is anticipated that the overall safety and quality of UFH management will be improved after guideline implementation there is a risk for acute bleeding with any anticoagulant. The risk for bleeding associated with UFH increased as the UFH dose increases.

**Qualifying Statements**
Clinical studies are limited in the pediatric population and therefore, therapeutic ranges for UFH in pediatric patients have not been extensively studied. Therapeutic ranges for pediatrics and neonates have been extrapolated from therapeutic ranges used in the adult population.

**Implementation Plan/Tools**
1. Guideline will be housed on U-Connect in a dedicated folder for CPGs and on the external Anticoagulation Stewardship Program Webpage.
2. Links to this guideline will be updated and/or added in appropriate Health Link or equivalent tools, including:
   - IP/ED Heparin Anticoagulant – Pediatric – Order Set
Disclaimer

CPGs are described to assist clinicians by providing a framework for the evaluation and treatment of patients. This Clinical Practice 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.

Appendix A¹

<table>
<thead>
<tr>
<th>LEVEL A</th>
<th>Recommendation that procedure or treatment is useful/effective</th>
<th>Recommendation in favor of treatment or procedure being useful/effective</th>
<th>Recommendation’s usefulness/effectiveness well established</th>
<th>Recommendation that procedure or treatment is not useful/effective and may be harmful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data derived from multiple randomized clinical trials or meta-analyses</td>
<td>Sufficient evidence from multiple randomized trials or meta-analyses</td>
<td>Some conflicting evidence from multiple randomized trials or meta-analyses</td>
<td>Evidence from single randomized trial or nonrandomized studies</td>
<td>Evidence from single randomized trial or nonrandomized studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LEVEL B</th>
<th>Recommendation that procedure or treatment is useful/effective</th>
<th>Recommendation in favor of treatment or procedure being useful/effective</th>
<th>Recommendation’s usefulness/effectiveness well established</th>
<th>Recommendation that procedure or treatment is not useful/effective and may be harmful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data derived from a single randomized trial or nonrandomized studies</td>
<td>Evidence from single randomized trial or nonrandomized studies</td>
<td>Some conflicting evidence from single randomized trial or nonrandomized studies</td>
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<td>Evidence from single randomized trial or nonrandomized studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LEVEL C</th>
<th>Recommendation that procedure or treatment is useful/effective</th>
<th>Recommendation in favor of treatment or procedure being useful/effective</th>
<th>Recommendation’s usefulness/effectiveness well established</th>
<th>Recommendation that procedure or treatment is not useful/effective and may be harmful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only expert opinion, case studies, or standard of care</td>
<td>Only diverging expert opinion, case studies, or standard of care</td>
<td>Only diverging expert opinion, case studies, or standard of care</td>
<td>Only diverging expert opinion, case studies, or standard of care</td>
<td>Only diverging expert opinion, case studies, or standard of care</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COR III: No Benefit</th>
<th>Is not recommended</th>
<th>Is not indicated</th>
<th>Usefulness/effectiveness is unknown/unclear/uncertain or not well established</th>
<th>Treatment/strategy A is probably recommended/indicated in preference to treatment B</th>
</tr>
</thead>
<tbody>
<tr>
<td>COR II: Harm</td>
<td>Potentially harmful</td>
<td>Causes harm</td>
<td>Associated with excess morbidity/mortality</td>
<td>Should not be performed/ administered/other</td>
</tr>
</tbody>
</table>

Suggested phrases for writing recommendations:

- Suggested phrases for writing recommendations:
- Comparative effectiveness phrases:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B
  - May/might be considered useful/effective
  - May/might be reasonable use of treatment
  - May/might be beneficial

Table: Size of Treatment Effect

- CLASS I: Benefit >> Risk
- CLASS IIa: Benefit >> Risk
- CLASS IIb: Benefit >> Risk
- CLASS III: Risk
- CLASS IV: Harm

Procedure/Treatment

- SHOULD be performed/administered
- MAY BE CONSIDERED
- MAY NOT BE CONSIDERED
- IS NOT RECOMMENDED
- IS NOT INDICATED
- IS NOT USEFUL/ BENEFICIAL

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References


