CLINICAL PRACTICE GUIDELINES

Initiation and Maintenance of Heparin Infusion

Disclaimer: These clinical practice guidelines are based upon the opinions of staff members of The Children’s Hospital of Philadelphia. Treatment should be individualized and based upon the clinical conditions of each patient.

General Information

These guidelines apply to the use of unfractionated heparin for the treatment of thromboembolic disorders.

Unfractionated Heparin (uFH) is a well-established anticoagulant for the treatment of venous thromboembolism. It is administered via continuous infusion. It requires very close monitoring and frequent dose adjustments, which is often extremely difficult in young children. Its main advantage over low molecular weight heparins (LMWH) is that it can be immediately and fully reversed.

Baseline Monitoring (To be completed prior (< 48 hrs) to or upon initiation of enoxaparin)

Baseline labs are to be completed to ensure patient has a normal baseline coagulation state:
- CBC
  - Thrombocytopenia is a relative contraindication to anticoagulant therapy and should be corrected to >75,000/mL before use.
- PT
- PTT

If the patient has abnormal coagulation studies, thrombocytopenia, or an elevated Cr, the hematology team should be consulted for further recommendations.

Dosing

Bolus Dose
- Bolus doses of 75 units/kg (max dose: 5,000 units) result in therapeutic PTT values in 90% of children.
- Bolus dose should be infused over 10 minutes.
- Bolus doses should be used with caution or avoided in patients with the following conditions:
  - Sick or Premature Neonates
    - The capacity of neonates to generate thrombin is both delayed and decreased when compared to adults.
  - Stroke
    - Potential increased risk for intracranial bleed
  - Active bleeding or high-risk for bleeding
    - Bleeding is a contraindication to heparin therapy unless secondary to disseminated intravascular coagulation
    - Recent surgery or invasive procedure
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Maintenance Dose – see Table 1 (below)

- In pediatric patients, PTT values correctly predict therapeutic heparin concentrations approximately 70% of the time.
- Maintenance heparin doses are age dependent:
  - Infants having the highest requirements (average dose = 28 units/kg/hour)
  - Children ≥ 1 year of age having lower requirements (average dose = 20 units/kg/hour)
  - Older children (≥ 12 years of age) are similar to the weight-adjusted requirements in adults = 18 units/kg/hour (max initial dose: 1,300 units/hr)

Therapeutic Range

- Recommended therapeutic range is a PTT of 60-85 seconds which should reflect a heparin anti-factor Xa level of 0.3 to 0.7 units/mL.

Table 1. Unfractionated Heparin (uFH) Dosing and Monitoring for Pediatric

<table>
<thead>
<tr>
<th>PTT</th>
<th>Anti-Xa</th>
<th>Bolus (unit/kg)</th>
<th>Hold (min)</th>
<th>Rate change (%)</th>
<th>Repeat PTT/Xa</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>&lt; 0.1</td>
<td>50</td>
<td>0</td>
<td>+10</td>
<td>4 h</td>
</tr>
<tr>
<td>50 – 59</td>
<td>0.1 – 0.29</td>
<td>0</td>
<td>0</td>
<td>+10</td>
<td>4 h</td>
</tr>
<tr>
<td>60 – 85</td>
<td>0.3 – 0.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Next day</td>
</tr>
<tr>
<td>86 – 95</td>
<td>0.71 – 0.9</td>
<td>0</td>
<td>30</td>
<td>-10</td>
<td>4 h</td>
</tr>
<tr>
<td>96 – 120</td>
<td>0.91 – 1</td>
<td>0</td>
<td>30</td>
<td>-10</td>
<td>4 h</td>
</tr>
<tr>
<td>&gt; 120</td>
<td>&gt; 1</td>
<td>0</td>
<td>60</td>
<td>-15</td>
<td>4 h</td>
</tr>
</tbody>
</table>

IV. Obtain blood for PTT 4 h after administration of the heparin loading dose and 4 h after every change in the infusion rate.

V. When at least two consecutive PTT values are therapeutic, a daily PTT is recommended since the heparin effect can fluctuate widely on a given dose. A CBC should be performed at least twice a week in stable patients on heparin.

Administration

- Patients must have a dedicated line for heparin infusions.
- The infusion must NOT be stopped or interrupted for other medications.
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Monitoring

- See above table for monitoring recommendations.
- Patients ≥ 18 years of age should have a CBC every 48 hours while on heparin therapy due to the risk of Heparin induced thrombocytopenia.
- Ideally, blood samples for the PTT should be drawn by venipuncture. **Heparin contamination in the central line or IV may affect the level.** In the case where a level is drawn from a line through which heparin has been administered, ensure that an adequate amount of “waste” is withdrawn from the line before drawing the lab [at least twice the volume of the catheter].
- Adequacy of anticoagulation using heparin is usually assessed by PTT. Unfractionated heparin (UFH) anti-Xa levels can be used in certain clinical circumstances (e.g. elevated FVIII >300%, inflammation, lupus anticoagulant) where the PTT is inaccurate. It is important to specify UFH anti-Xa in the order when ordering the test to monitor uFH. When at least two consecutive heparin anti-Xa levels are therapeutic (0.3-0.7 units/ml) a daily heparin anti-Xa level is recommended since the heparin effect can fluctuate widely on a given dose. A CBC should be performed at least twice weekly in stable patients.

Safety

- **Bleeding**
  - The major adverse event related to heparin is bleeding. If a patient on a heparin infusion develops bleeding, stop heparin and consult Hematology.
- Heparin Induced Thrombocytopenia (HIT). HIT is an antibody-mediated, hypercoagulable condition wherein thromboembolic complications, sometimes fatal, develop in 38-76% of affected patients. Though rare, HIT does occur in children. This should be suspected in any patient on heparin with unexplained thrombocytopenia (platelet count <100,000 or 50% of baseline platelet count).
  - Patients ≥ 18 years of age should have a CBC every 48 hours while on heparin therapy due to the risk of Heparin induced thrombocytopenia.
  - **If HIT is suspected, hematology should be consulted immediately.**
  - It is critically important that patients with HIT no longer receive heparin, including: heparin infusions, line flushes, heparin in line carriers, heparin in TPN
  - Heparin should be documented as an allergy in the medical record

- Avoid IM injections and arterial punctures during anticoagulant therapy. When such procedures are clinically necessary, ensure adequate external pressure is applied post-procedure.
- Other invasive procedures that may result in bleeding in a patient who is anticoagulated and should be carefully considered include NG tube insertions, intubation, and rectal temps.
- Avoid drugs that affect platelet function (eg, aspirin, NSAIDs, dipyridamole) as they may potentiate the risk of hemorrhage.
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Heparin Reversal

- If anticoagulation with heparin needs to be discontinued for clinical reasons, termination of the heparin infusion will usually suffice. The PTT usually returns to normal within 4-6 hours.
- If an immediate effect is required, consider administering protamine sulfate. Protamine combines with the strongly acidic heparin to form a stable salt complex neutralizing the anticoagulant activity.
- Protamine requires a high level of caution when being prescribed and administered. Protamine should be administered intravenously in a concentration of 10 mg/mL at a rate not to exceed 5 mg/minute. If administered too quickly it may cause cardiovascular collapse. Patients with known hypersensitivity reactions to fish, and those who have received protamine containing insulin or previous protamine therapy may be at risk of hypersensitivity reactions to protamine sulfate.
- The dose of protamine sulfate is based on the amount of heparin received in the previous 2 hours as follows:

<table>
<thead>
<tr>
<th>Time Since Heparin Discontinued</th>
<th>Protamine Dose (mg) per 100 units of Heparin Received (within the last two hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>1-1.5</td>
</tr>
<tr>
<td>30-60 min</td>
<td>0.5-0.75</td>
</tr>
<tr>
<td>60-120 min</td>
<td>0.375-0.5</td>
</tr>
<tr>
<td>2-6 hr</td>
<td>0.25-0.375</td>
</tr>
<tr>
<td>&gt; 6 hr</td>
<td>Do not give protamine</td>
</tr>
</tbody>
</table>

Max dose: 50 mg

- Obtain blood for PT and PTT 15 min after the administration of protamine sulfate. Do not draw sample from line where protamine was administered.

Converting from Unfractionated Heparin to LMWH:

- In converting from heparin (uFH) infusion to a low-molecular weight heparin (LMWH) e.g. enoxaparin (Lovenox), the dose of the LMWH should be given immediately (or within 1 hour) after discontinuation of the heparin infusion.

Elective Procedures

- Hold heparin a minimum of 6 hours prior to scheduled surgical procedure or lumbar puncture.
Complications

- The attending of record or the attending defined responsible for outpatient management will be responsible for the diagnosis and management of any potential complications (i.e. bleeding, etc) in consultation with the division of hematology as deemed appropriate.
- Reporting of complications, including bleeding requiring transfusion, intracranial hemorrhage, and over-anticoagulation requiring reversal with protamine, into the electronic reporting system, Safety Net, is highly recommended.