UNFRACTIONATED HEPARIN DOSING AND MONITORING GUIDELINE

PURPOSE:
To provide standardized dosing and monitoring guidelines for patients receiving unfractionated heparin (UFH) therapy. This guideline may not be applicable to patients who are critically ill with multi-organ failure, patients receiving dialysis and patients on mechanical cardiopulmonary support [i.e., extracorporeal membrane oxygenation (ECMO), ventricular assist devices (VADs)].

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

GUIDELINE

1. Hematology Consult is recommended for all patients initiating UFH therapy. (See CCHMC P&T Policy V-144)
   - Consult hematology for patients less than 25 years of age for initiation and management outside of critical care areas.
     i. Exceptions: Fetal Care; Infusions used for circuit anticoagulation by the Center for Acute Care Nephrology or dialysis unit; Patients managed by the VAD team
     ii. Cardiology may manage infusions initiated in the CICU, but initiation outside the CICU requires a hematology consult
   - Consult Hospital Medicine Adult Care Team for initiation in patients > 25 years of age regardless of hospital location
     Exception: Fetal Care

2. Baseline Laboratory Monitoring
   Baseline laboratory tests prior to initiation of UFH therapy should include the following. Results should be reviewed prior to initiation of UFH therapy whenever possible.
   - CBC with differential count
   - Prothrombin Time (PT)
   - Activated Partial Thromboplastin Time (aPTT)
   - Additional testing including antithrombin III (ATIII) level should be considered in consultation with hematology.
   - Consider other tests, in consultation with hematology, for evaluation of thrombophilic disorders as clinically indicated prior to initiation of UFH therapy
3. **Initial Dosing**

- See Table 1 below for initial dosing of systemic therapy with UFH.
- Contact individual services for diagnosis-specific dosing for other indications (i.e., Cardiology Catheterization, CT Surgery, and Liver Transplantation).
- Prophylactic doses are considered 15 units/kg/hour or less, and monitoring is not required for these doses.

**Table 1. Recommendations for UFH Dosing**

<table>
<thead>
<tr>
<th>Patient Type/Age</th>
<th>UFH Loading Dose* Administered IV over 10 minutes</th>
<th>Initial UFH Infusion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>75-100 units/kg, up to a maximum of 5000 units</td>
<td>28 units/kg/hr</td>
</tr>
<tr>
<td>1 to 16 years</td>
<td></td>
<td>20 units/kg/hr</td>
</tr>
<tr>
<td>&gt;16 years**</td>
<td></td>
<td>18 units/kg/hr**</td>
</tr>
</tbody>
</table>

*Lower doses may be considered for patients at risk for bleeding.

**NOTE: Obese patients** may require a decreased starting dose if dosing is based upon their Actual Body Weight. Consider starting these patients at 12 units/kg/hr (based on actual body weight) and titrating dose based upon UFH level results.

4. **Monitoring Parameters during UFH Therapy**

- UFH therapy should be monitored with both “UFH levels” and “Heparin PTT” (HPTT) levels within Epic.
  
  i. **UFH levels** correspond to anti-factor Xa UFH levels in epic, but should be ordered as “UFH Level.” This allows for the correct level to be ordered, so it is not confused with the LMWH level (which is also an anti-factor Xa level, but run for LMWH instead of UFH).
  
  ii. **Heparin PTT levels** correspond to aPTT, but should be ordered as “HPTT” levels within epic once a heparin infusion is running on a patient. This allows the laboratory to extend the reaction time in order to monitor the therapeutic range of UFH, versus standard baseline aPTT levels in a normal patient.
  
  iii. **In general aPTT/HPTT levels should correlate to UFH levels** (Table 2). If a discrepancy between lab values exists, consider a hematology consult.
Table 2. Recommendations for aPTT (HPTT) and UFH Levels during UFH Therapy*

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Baseline aPTT</th>
<th>HPTT and UFH Levels</th>
<th>Goal HPTT Range</th>
<th>Goal UFH Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic UFH Infusion</td>
<td>Yes</td>
<td>Yes</td>
<td>62-94 seconds*</td>
<td>0.3-0.7 units/ml</td>
</tr>
</tbody>
</table>

*UFH infusion of 15 units/kg/hour or less can be considered prophylactic dosing and aPTT/HPTT/UFH levels may not be required. It is recommended to monitor aPTT/HPTT and UFH levels in patients with renal impairment, regardless of the UFH dose.

# aPTT/UFH values in the range of 62 to 94 seconds reflect UFH levels of 0.3-0.7 units/ml in most patients.

5. Monitoring and Titration of UFH Infusion

Obtain blood for UFH level and HPTT 4-6 hours after administration of the heparin loading dose (NOT earlier) and adjust heparin to maintain UFH level of 0.3-0.7 units/ml using the following table.

<table>
<thead>
<tr>
<th>UFH Level (units/ml)</th>
<th>Bolus (units/kg)</th>
<th>Hold (minutes)</th>
<th>Rate Change (units/kg/hour)</th>
<th>Repeat UFH Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.2</td>
<td>50</td>
<td>0</td>
<td>Increase by 10%</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>0.2-0.29</td>
<td>0</td>
<td>0</td>
<td>Increase by 10%</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>0.3-0.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12 hours</td>
</tr>
<tr>
<td>0.71-0.8</td>
<td>0</td>
<td>0</td>
<td>Decrease by 10%</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>0.81-0.99</td>
<td>0</td>
<td>30</td>
<td>Decrease by 10%</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>&gt;1</td>
<td>0</td>
<td>60</td>
<td>Decrease by 15%</td>
<td>4-6 hours</td>
</tr>
</tbody>
</table>

6. Monitoring of therapy, precautions and ongoing follow-up:

- Preferably, blood samples for UFH levels and HPTT should NOT be drawn through lines infusing heparin. However, when drawn from lines infusing heparin, adequate waste should be drawn prior to obtaining sample.

- Ongoing monitoring of UFH level and HPTT should be performed every 6-8h during the first 24h. Once a therapeutic UFH level is achieved (0.3-0.7 units/ml), UFH and HPTT can be checked every 12h. However, UFH level and HPTT should continue to be checked 4-6 hours following each dose change.
• CCHMC uses a standard UFH concentration of 100 units/ml in 1/2 Normal Saline (1/2NS) for bolus and continuous therapeutic infusions. A lower concentration of 50 units/ml is available for extremely low birth weight infants.

• The UFH infusion should be continued without interruption through a dedicated catheter unless authorized by a physician.

• If the UFH infusion during the maintenance phase is interrupted for more than 1 hour, obtain blood for an UFH level and HPTT and re-establish the heparin maintenance infusion at the previous rate. Once the UFH level is available, adjust the infusion rate as indicated above (see Table 3).

• CBC’s should be obtained daily until day 14 or until UFH therapy is stopped, whichever occurs first, to monitor for heparin-induced thrombocytopenia (HIT). If the platelet count drops > 50% below baseline or below 100 x 10^9/L, suspect HIT, and notify the Hematologist. The risk of HIT is greater after 5 days of therapy.

• Avoid IM injections and arterial punctures during heparin therapy if possible. If arterial punctures are warranted, appropriate precautions, including the use of extended periods of external pressure, should be considered.

7. **UFH Reversal**:

• If anticoagulation with UFH needs to be discontinued for clinical reasons, termination of the heparin infusion will usually suffice because of the rapid clearance of heparin. In most patients, heparin will be completely cleared within 4 hours of stopping the infusion.

• If an immediate reversal effect is required, IV protamine sulfate rapidly (within 5 minutes) neutralizes heparin activity.

• The dose of protamine sulfate required to neutralize heparin is based on the amount of heparin received in the previous 2 hours. (See Table below).

<table>
<thead>
<tr>
<th>Time since last UFH dose</th>
<th>Protamine sulfate dose per 100 units UFH received</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30 minutes</td>
<td>1 mg</td>
</tr>
<tr>
<td>30 to 60 minutes</td>
<td>0.5 to 0.75 mg</td>
</tr>
<tr>
<td>60 to 120 minutes</td>
<td>0.375 to 0.5 mg</td>
</tr>
<tr>
<td>&gt; 120 minutes</td>
<td>0.25 to 0.375 mg</td>
</tr>
</tbody>
</table>

Developed by CCHMC Anticoagulation and Thrombolytic Therapy Subcommittee.
Please contact the CCHMC Anticoagulation and Thrombolytic Therapy Subcommittee with questions.
• HPTT, UFH and PT may be obtained 15 minutes after the administration of protamine sulfate.

• Protamine sulfate should be administered slowly over 10 minutes. If administered too quickly, protamine sulfate may cause cardiovascular collapse.

• Patients with known hypersensitivity to fish, and those who have received protamine-containing insulin or previous protamine therapy may be at risk of hypersensitivity reactions to protamine sulfate.

8. **Transitioning UFH Therapy**

   UFH should be transitioned to and from other anticoagulant medications as listed below.

   **Table 5. Transitioning UFH Therapy**

<table>
<thead>
<tr>
<th>Transitioning Medication</th>
<th>Stop Current Medication</th>
<th>Start New Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH to LMWH</td>
<td>Stop UFH Zero to 4 hours after first LMWH dose</td>
<td>Start LMWH when clinically indicated</td>
</tr>
<tr>
<td>LMWH to UFH</td>
<td>Stop LMWH after UFH initiation</td>
<td>Start UFH 4 hours after the last LMWH dose. No UFH bolus required if started 4 hours after the last LMWH. Note: If UFH started $&gt;12$ hours following last LMWH dose, an UFH bolus dose is indicated.</td>
</tr>
<tr>
<td>Warfarin to UFH</td>
<td>Stop warfarin when clinically indicated or 5 days prior to procedure</td>
<td>Start UFH on the third day of holding warfarin or when INR $\leq 2.0$</td>
</tr>
<tr>
<td>UFH to Warfarin</td>
<td>Stop UFH after a minimum of 5 days or when warfarin INR is therapeutic 2 days in a row, whichever is longer</td>
<td>Start warfarin when clinically indicated and patient able to tolerate medication</td>
</tr>
</tbody>
</table>

9. **UFH Background Information**

   UFH is a commonly used anticoagulant in pediatric patients. Heparin is heterogeneous with respect to molecular size, anticoagulant activity, and pharmacokinetic parameters. Its molecular weight ranges from 3,000 to 30,000
daltons, with a mean molecular weight of 15,000. Only about one-third of an administered dose of heparin binds to antithrombin (AT), and this fraction is responsible for most of its anticoagulant effect.

Mechanism of Action: Heparin exerts antithrombotic activity by inducing a conformational change in the structure of AT that dramatically augments the ability of AT to neutralize thrombin, and, to a lesser extent, factor Xa and other coagulation factors. Heparin also impairs platelet function.

Plasma levels of AT are physiologically low at birth and do not increase to adult values until 3 months of age. AT levels are even lower in sick premature infants. The clearance of UFH is faster in neonates than that for older children due to a larger volume of distribution. Therefore, the dose of UFH required to achieve a therapeutic aPTT in neonates is higher compared to that in older children.

REFERENCES


