Pediatric Argatroban Dosing Guidelines

Indications:
For thrombosis prophylaxis and treatment in patients <= 16 years old:
- With suspected or diagnosed HIT, OR
- At risk for HIT and require anticoagulation for the following procedures:
  o cardiac catheterization, cardiac surgery, or hemodialysis
- For patients > 16 years old, use the adult argatroban protocol

Before starting argatroban:
- Consider consulting Pediatric Hematology
- Stop all heparin (including catheter flushes), enoxaparin or dalteparin, and warfarin
- Obtain baselines labs (if none in past 24 hours): CBC, aPTT, PT/INR, Basic Metabolic Profile, LFTs
- If the baseline aPTT is > than the normal range based on the patients age (see table 1 below), do not start argatroban and consult Pediatric Hematology
- Monitor a CBC and aPTT at least daily during treatment

Table 1: Age based aPTT ranges

<table>
<thead>
<tr>
<th>Age</th>
<th>Normal aPTT</th>
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<tr>
<td>15 days – 4 weeks</td>
<td>27.6-45.6 seconds</td>
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<tr>
<td>1 – 5 months</td>
<td>24.8-40.7 seconds</td>
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<tr>
<td>&gt; 5 months</td>
<td>25-37 seconds</td>
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Dosing recommendations:
- Initiate dose at 0.75 - 1 mcg/kg/min
- Target aPTT range = 1.5-3x patient baseline aPTT, not to exceed 100 seconds
- Check aPTT every 2 hours until consecutive values are in range, and at least daily thereafter
  - In patients with multi-system organ failure, anasarca, and post cardiac surgery, dose with caution, as clearance may be impaired by each of these factors.
  - In patients with hepatic impairment
    o Initiate dose at 0.2 mcg/kg/min
    o Half-life can be extended up to 180 minutes (3 x normal half-life of 39-51 minutes)
  - In patients with renal impairment
    o No dosage adjustments required
    o Dialyzable- approximately 20% of drug is removed in 4 hours of hemodialysis
- Adjusting argatroban dose based on aPTT:

<table>
<thead>
<tr>
<th>aPTT</th>
<th>Directions</th>
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<tr>
<td>&lt; 1.5x patient’s baseline aPTT</td>
<td>Increase infusion rate by 0.1-0.25 mcg/kg/min or by 0.05 mcg/kg/min if hepatic impairment</td>
</tr>
<tr>
<td><strong>Target Range 1.5- 3x baseline, not to exceed 100 seconds</strong></td>
<td>No change</td>
</tr>
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</table>
| > 100 seconds OR > 3x patient’s baseline aPTT | Stop infusion for 1 hour and restart at 50% reduced infusion rate  
Recheck aPTT 2 hours after restart |
Conversion to other anticoagulants:

- **Enoxaparin**
  If it is determined that the patient does not have HIT, and that the patient will be converted from argatroban to enoxaparin, stop the argatroban drip and give the 1st enoxaparin injection within 1 hour.

- **Fondaparinux**
  If the decision to switch from argatroban to fondaparinux is made, stop the argatroban drip and give the 1st fondaparinux injection within 1 hour.

- **Direct Oral Anticoagulants (Apixaban and Rivaroxaban)**
  Not FDA approved for patients < 18 years of age
  Contraindicated in patients with antiphospholipid syndrome (APS)

- **Warfarin**
  If the decision is made to continue anticoagulation with oral therapy (warfarin) after argatroban infusion, several steps should be taken to avoid the pro-thrombotic effects of warfarin:
  - Do not use warfarin as monotherapy in acute HIT
  - Do not initiate warfarin until the platelet count has rebounded to >100 K/µL
  - Do not use a loading dose of warfarin; initiate therapy with expected maintenance dose
  - **Overlap** warfarin and argatroban therapy for at least 5 days – to allow for the half–lives of all the clotting factors
  - Measure INR daily; INR will be significantly affected by argatroban as well as by warfarin; however increased INR may not correspond to an increased risk of bleeding
  - To stop argatroban infusion, see table below:

<table>
<thead>
<tr>
<th>For doses ≤ 2 mcg/kg/min</th>
<th>For doses &gt; 2 mcg/kg/min</th>
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<tbody>
<tr>
<td>Discontinue argatroban when the INR is &gt; 4 on combined therapy (&amp; and least 5 days of overlap)</td>
<td>INR cannot be reliably predicted at argatroban doses &gt; 2 mcg/kg/min</td>
</tr>
<tr>
<td>Check INR 4 to 6 hours after stopping argatroban to assure therapeutic goal (INR 2 - 3) is maintained</td>
<td>Temporarily reduce dose of argatroban to 2 mcg/kg/min (in order to predict INR on warfarin alone)</td>
</tr>
<tr>
<td>If repeat INR is below desired therapeutic range (2 - 3) resume argatroban &amp; repeat procedure daily until desired therapeutic range on warfarin alone is reached</td>
<td>Repeat INR 4 to 6 hours after reduction and follow the process outlined for doses up to 2 mcg/kg/min</td>
</tr>
</tbody>
</table>

This is to be used as a guide and should not supersede clinical judgment. For questions call pharmacy or consider consulting Hematology.

References:

Approved by:
Anticoagulation Safety Committee: Nov 2019
Pediatric Subcommittee: Dec 2019
P&T: Jan 2020