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:
  - 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

Age	Normal aPTT
15 days – 4 weeks	27.6-45.6 seconds
1 – 5 months	24.8-40.7 seconds
> 5 months	25-37 seconds

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**
    - Initiate dose at 0.2 mcg/kg/min
    - Half-life can be extended up to 180 minutes (3 x normal half-life of 39-51 minutes)
  - **In patients with renal impairment**
    - No dosage adjustments required
    - Dialyzable- approximately 20% of drug is removed in 4 hours of hemodialysis
  - **Adjusting argatroban dose based on aPTT:**

aPTT	Directions
< 1.5x patient's baseline aPTT	Increase infusion rate by 0.1-0.25 mcg/kg/min or by 0.05 mcg/kg/min if hepatic impairment
Target Range 1.5- 3x baseline, not to exceed 100 seconds	No change
> 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

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Anticoagulation Safety Committee: Nov 2019
Pediatric Subcommittee: Dec 2019
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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:

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

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

References:

1. Young G. Anticoagulants in children and adolescents. Hematology Am Soc Hematol Educ Program.2015:111-6.
2. Young et al. Pilot dose-finding and safety study of bivalirudin in infants < 6 months of age with thrombosis. J Throm Haemo. 2007;5:1654-59.
3. Rayapudi, et al. Bivalirudin for anticoagulation in children. Pediatr Blood Cancer. 2008;51(5):798-801.
4. Madabushi, R., Cox, D.S., Hossain, M., Boyle, D.A., Patel, B.R., Young, G., Choi, Y.-M. and Gobburu, J.V.S. (2011), Pharmacokinetic and Pharmacodynamic Basis for Effective Argatroban Dosing in Pediatrics. The Journal of Clinical Pharmacology, 51: 19-28. doi:10.1177/0091270010365550

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