Heparin Induced Thrombocytopenia (HIT) Treatment

Disclaimer: *This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson's specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. This algorithm should not be used to treat pregnant women.*

Estimate probability of HIT using the "Four T's"[1]

- Low[1] (score 0-3) →
  - No further testing required
  - Monitor platelet count, and signs and symptoms of thrombosis and continue/restart heparin/LMWH
- Intermediate[1] (score 4-5) or High[1] (score 6-8) →
  - Consider Benign Hematology consult
  - Discontinue all heparin/heparin flushes, low molecular weight heparins, and warfarin
  - If patient on warfarin, consider reversing with vitamin K 10 mg PO **or** 5-10 mg IV
  - Check heparin antibody (Heparin Induced Ab)
  - Document diagnosis of HIT on the problem list and add heparin to the allergy list with a comment noting patient has HIT
  - Initiate therapeutic dose of a non-heparin anticoagulant
    - Critically ill patients or patients with high bleeding risk, potential for urgent procedures, life or limb threatening thrombosis present, or requiring dialysis: Argatroban or bivalirudin (see Appendix B)
    - Stable patients without a high risk for bleeding: Rivaroxaban, apixaban, dabigatran or fondaparinux (see Appendix C)
    - Moderate to severe hepatic dysfunction: AVOID argatroban, rivaroxaban, apixaban, and dabigatran
    - Moderate to severe renal dysfunction: AVOID fondaparinux and dabigatran

Heparin induced Ab negative?

- Yes →
  - Stop non-heparin anticoagulation
  - Monitor platelet count, and signs and symptoms of thrombosis and restart heparin as indicated
  - Remove diagnosis of HIT from the problem list and remove heparin from the allergy list
- No →
  - Intermediate[1] (score 4-5) and heparin induced Ab OD is ≥ 0.4 **or** High[1] (score 6-8) and heparin induced Ab OD = 0.4 - 0.9 →
    - Continue non-heparin anticoagulation
    - Consult Benign Hematology to confirm diagnosis with serotonin release assay (SRA)[2]

SRA negative?

- Yes → Stop non-heparin anticoagulation (see above)
- No →
  - High[1] (score 6-8) and heparin induced Ab OD ≥ 1 →
    - No further testing required. Consider Benign Hematology consult for management.
    - Continue non-heparin anticoagulation
    - Consider bilateral lower extremity ultrasound to screen for deep vein thrombosis (DVT)
    - If non-femoral central venous access present, bilateral upper extremity ultrasound to screen for DVT
    - If started on argatroban or bivalirudin, transition anticoagulant when platelet count ≥ 150 K/microliter (see Appendix D)
    - Discontinue all heparin/heparin flushes and low molecular weight heparins from home medication list
    - Outpatient follow up as clinically indicated

LMWH = low molecular weight heparin
OD = optical density

[1] See Appendix A: The Four T's
[2] Ordering of SRA is restricted to Benign Hematology service

Department of Clinical Effectiveness V13
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APPENDIX A: The Four T's

To calculate the probability score, add the values from each "T" category based on presence of criteria

Score 0-3: Low probability
Score 4-5: Intermediate probability
Score 6-8: High probability

	2	1	0
Thrombocytopenia	Platelet count fall > 50% **and** Nadir ≥ 20 K/microliter	Platelet count fall 30-50% (or platelet fall > 50% due to surgery), **or** Nadir 10-19 K/microliter	Platelet fall < 30% **or** Nadir < 10 K/microliter
Timing[1] of platelet fall onset	Onset between Days 5-10 **or** Platelet count fall ≤ Day 1 with prior heparin exposure within past 30 days	Onset after Day 10 or timing unclear, **or** Platelet count fall ≤ Day 1 with prior heparin exposure in the past 30-100 days	Platelet count fall ≤ Day 4 without prior heparin exposure in the past 100 days
Thrombosis or other sequelae	Proven new thrombosis **or** skin necrosis; or Acute anaphylactoid reaction after IV unfractionated heparin bolus	Progressive **or** recurrent thrombosis; non-necrotizing (erythematous) skin lesions, suspected thrombosis (not proven)	None
O**T**her causes[2]	None evident	Possible	Definite

[1] First day of immunizing heparin exposure = Day 0
[2] Examples of other causes include, but are not limited to: recent chemotherapy, immunotherapy, targeted therapy, or radiation; cancers such as leukemia, lymphoma, myeloma; drug-related; sepsis or other infections; disseminated intravascular coagulation (DIC); liver dysfunction; splenomegaly; post-transfusion purpura (PTP)

APPENDIX B: Direct Thrombin Inhibitor (DTI) Dosing and Monitoring

DTI	Special Dosing Parameters	Initial Dose	Monitoring[1]	Notes and Special Considerations
Argatroban Plasma half-life = 39-51 minutes (in healthy subjects) Primarily hepatic elimination	Normal dosage	2 mcg/kg/minute	• Baseline: Hemoglobin/hematocrit, platelet count, aPTT/PT, creatinine, and hepatic function tests • Therapeutic monitoring: aPTT 2 hours after initiation and dose changes to achieve specified target range per protocol • Adverse effects monitoring: Hemoglobin/hematocrit and platelet count daily	• Use of this medication causes **significant** elevation of PT/INR results due to interference with testing • Do not discontinue this medication based on an elevated INR value • Continue to monitor the patient for signs and symptoms of bleeding
	AVOID or consider dosage reduction with the following: • Child-Pugh[2] score > 6 • Total bilirubin > 1.5 mg/dL • Heart failure • Multi-organ system failure • Severe anasarca • Status post cardiac surgery	0.5 mcg/kg/minute		
Bivalirudin Plasma half-life = 25 minutes (in healthy subjects) Metabolized by proteolytic cleavage with 20% renal elimination	Normal renal function (CrCl > 60 mL/minute)	0.15 mg/kg/hour	• Baseline: Hemoglobin/hematocrit, platelet count, aPTT/PT, creatinine, and hepatic function tests • Therapeutic monitoring: aPTT 2 hours after initiation and dose changes to achieve specified target range per protocol • Adverse effects monitoring: Hemoglobin/hematocrit and platelet count daily	Use of this medication causes mild elevation of PT/INR results due to interference with testing
	CrCl 30-60 mL/minute	0.08 mg/kg/hour		
	CrCl < 30 mL/minute **or** on dialysis	0.05 mg/kg/hour		

CrCl = creatinine clearance

[1] See the Anticoagulant Management and Required Laboratory Monitoring Policy (#CLN0984)

[2] See Appendix E for Child-Pugh Scoring System

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APPENDIX C: Non-heparin Anticoagulants Dosing and Monitoring[1,2]

Drug	Dosing	Monitoring	Dose Adjustments/Considerations
Fondaparinux (Arixtra®)[3] Indirect factor Xa inhibitor	Actual Body Weight: • < 50 kg: 5 mg subcutaneously daily • 50-100 kg: 7.5 mg subcutaneously daily • > 100 kg: 10 mg subcutaneously daily	• Baseline: Hemoglobin/hematocrit, platelet count, aPTT/PT, and creatinine • Therapeutic laboratory tests: Routine monitoring not required. However, antifactor Xa levels[4] may be useful in certain high-risk patients (*e.g.*, obesity, malnutrition, renal insufficiency, and unexplained bleeding or thrombosis) • Inpatient: Hemoglobin/hematocrit, platelet count, and creatinine at least once weekly • Outpatient: Hemoglobin/hematocrit, platelet count, creatinine, and hepatic function tests at least once yearly ○ If CrCl 30-60 mL/minute, creatinine every 6 months ○ If CrCl < 30 mL/minute, creatinine every 3 months	Use in liver disease: • If Child-Pugh (CP)[5] class C: use with caution Renal: • If CrCl is between 30-50 mL/minute: use with caution • If CrCl is < 30 mL/minute: contraindicated Weight: • For BMI ≥ 40 kg/m^2: no dose adjustment necessary Elderly: • For age > 75 years: may have reduced clearance, use with caution
Apixaban (Eliquis®)[3] Direct factor Xa inhibitor	• **HITT:** 10 mg PO twice daily for 1 week then 5 mg PO twice daily • **Isolated HIT:** 5 mg PO twice daily until platelet recovery of ≥ 150 K/microliter (maximum duration of 21 days)	• Baseline: Hemoglobin/hematocrit, platelet count, aPTT/PT, creatinine, and hepatic function tests • Therapeutic laboratory tests: Routine monitoring not required. ○ Apixaban and rivaroxaban: Antifactor Xa levels[4] may be useful in certain high-risk patients (*e.g.*, obesity, malnutrition, renal insufficiency, and unexplained bleeding or thrombosis) ○ Dabigatran: Thrombin time (TT) may be useful in certain high-risk patients (*e.g.*, obesity, malnutrition, renal insufficiency, and unexplained bleeding or thrombosis) • Inpatient: Hemoglobin/hematocrit, platelet count, and creatinine at least once weekly • Outpatient: Hemoglobin/hematocrit, platelet count, creatinine, and hepatic function tests at least once yearly ○ If CrCl 30-60 mL/minute, creatinine every 6 months ○ If CrCl < 30 mL/minute, creatinine every 3 months	Use in liver disease: • Apixaban: use in CP[5] class C not recommended and there is limited experience for use in class B • Rivaroxaban: CP[5] class B or C: NOT recommended • Dabigatran: No manufacturer recommendations Renal: • Dabigatran: If CrCl is < 30 mL/minute: avoid use Significant drug-drug interactions[6]: • Apixaban and rivaroxaban ○ P-glycoprotein ○ CYP 3A4 • Dabigatran ○ P-glycoprotein Class specific contraindications: moderate to severe mitral stenosis or mechanical heart valve
Rivaroxaban (Xarelto®)[3] Direct factor Xa inhibitor	• **HITT:** 15 mg PO twice daily for 3 weeks then 20 mg PO daily • **Isolated HIT:** 15 mg PO every 12 hours until platelet recovery of ≥ 150 K/microliter (maximum duration of 21 days), then 20 mg PO daily		
Dabigatran (Pradaxa®)[3,7] Direct thrombin inhibitor	• **HITT:** 150 mg PO twice daily after ≥ 5 days of treatment with a parenteral non-heparin anticoagulant • **Isolated HIT:** 150 mg PO twice daily until platelet recovery of ≥ 150 K/microliter (maximum duration of 21 days)		
Edoxaban[8]	No information available, therefore no recommendation can be made		

CrCl = creatinine clearance HITT = heparin induced thrombotic thrombocytopenia

[1] Anticoagulant should continue if indication for long-term anticoagulation present
[2] See the Anticoagulant Management and Required Laboratory Monitoring Policy (#CLN0984)
[3] For concerns regarding affordability, consider submitting a test claim 48 hours prior to discharge via the Pharmacy Test Claim and Pre-Authorization Reports (PECON) (for internal use only)
[4] Fondaparinux, apixaban, and rivaroxaban anti-Xa levels may be ordered as a send out lab using a miscellaneous test order and adding a note for Anti-Xa fondaparinux, Anti-Xa apixaban or Anti-Xa rivaroxaban assay as indicated
[5] See Appendix E for Child-Pugh Scoring System
[6] Assessing for drug-drug interactions: UpToDate®, Lexidrug™ or Micromedex®
[7] Dabigatran capsules should be swallowed whole and NOT opened, broken, crushed, or chewed
[8] Not currently on MD Anderson Formulary

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APPENDIX D: Transitioning Anticoagulants

- For patients with isolated HIT and no thrombosis continue anticoagulation at least until platelet count recovery
- Continue anticoagulation long-term if thrombosis present or other indication for anticoagulation (*e.g.*, active deep vein thrombosis or chronic atrial fibrillation)
  - For patients on direct oral anticoagulant (DOAC) who require long term therapy, DOAC may be continued
  - For patients on argatroban or bivalirudin, see table below on how to transition to warfarin or DOAC or fondaparinux
  - For patients on fondaparinux, may continue therapy for 3-6 months or see table below on how to transition to DOAC or warfarin

Argatroban to warfarin	Preferred: • Begin warfarin 2.5-5 mg PO daily (maximum initial dose = 5 mg). Do not use loading dose. • Turn argatroban infusion off and begin fondaparinux at treatment doses ◦ Weight < 50 kg: 5 mg SQ ◦ Weight 50-100 kg: 7.5 mg SQ ◦ Weight > 100 kg: 10 mg SQ • After a minimum 5-day overlap of fondaparinux and warfarin, discontinue fondaparinux when the INR is between 2-3 and continue with warfarin monotherapy Alternate: • Begin warfarin 2.5-5 mg PO daily (maximum initial dose = 5 mg). Do not use loading dose. Overlap with argatroban for a minimum of 5 days. • If argatroban dose ≤ 2 mcg/kg/minute **and** INR > 4, stop infusion and obtain INR 4 hours after stopping infusion ◦ INR 2-3: Continue with warfarin monotherapy ◦ INR < 2: Restart argatroban and repeat above steps the following day • If argatroban dose > 2 mcg/kg/minute, reduce dose to 2 mcg/kg/minute for 4 hours and obtain INR (infusion dose can return to baseline after INR drawn) ◦ If INR ≤ 4: Continue concomitant therapy ◦ If INR > 4: Stop argatroban and obtain another INR 4 hours after stopping infusion - INR 2-3: Continue with warfarin monotherapy - INR < 2: Restart argatroban and repeat above steps the following day	**WARFARIN MONITORING**[1] • General INR goal: 2-3 • Mechanical aortic valve: INR goal: 2-3 • Mechanical mitral valve: INR goal: 2.5-3.5 • Baseline: Hemoglobin/hematocrit, platelet count, PT/INR, and hepatic function tests • Therapeutic laboratory tests: INR to achieve specified target range • Inpatient: Hemoglobin/hematocrit, platelet count, and INR at least once weekly • Outpatient: INR every 3 months at a minimum; Hemoglobin/hematocrit, platelet count, creatinine, and hepatic function tests at least once a year [1] See the Anticoagulant Management and Required Laboratory Monitoring Policy (#CLN0984)
Bivalirudin to warfarin	• Begin warfarin 2.5-5 mg PO daily and overlap with bivalirudin for a minimum of 5 days • Stop bivalirudin infusion and obtain INR 4 hours after stopping infusion ◦ INR 2-3: Continue with warfarin monotherapy ◦ INR < 2: Restart bivalirudin and repeat above steps the following day	
Fondaparinux to warfarin	Overlap fondaparinux with warfarin for at least 5 days and discontinue fondaparinux when INR is in therapeutic range for 24 hours	
Bivalirudin **or** argatroban to DOAC **or** fondaparinux	Stop bivalirudin or argatroban infusion and begin apixaban, rivaroxaban, or fondaparinux within 2 hours (see Appendix B for dosing)	N/A
Fondaparinux to DOAC	Discontinue fondaparinux and start apixaban or rivaroxaban when the next dose of fondaparinux was to be administered	N/A

APPENDIX E: Child-Pugh Scoring System[1]

Chemical and Biochemical Parameters	Points for Increasing Abnormality		
	1	2	3
Hepatic encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Ascites	None	Slight	Moderate
Albumin	> 3.5 g/dL	2.8-3.5 g/dL	< 2.8 g/dL
Total bilirubin	< 2 mg/dL	2-3 mg/dL	> 3 mg/dL
Prothrombin time prolonged or INR	< 4 seconds < 1.7	4-6 seconds 1.7-2.3	> 6 seconds > 2.3

[1] Child-Pugh score is obtained by adding the score for each parameter
Child-Pugh class:
Class A = 5 to 6 points
Class B = 7 to 9 points
Class C = 10 to 15 points

SUGGESTED READINGS

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