Guidelines for Recognition and Management of
HEPARIN-INDUCED THROMBOCYTOPENIA

BACKGROUND

Heparin-induced thrombocytopenia (HIT) is a life-threatening immune response to heparin (and its derivatives) that is associated with a high risk of thromboembolic complications; a risk that could increase with delay in diagnosis or increase in heparin dose (to treat unrecognized HIT-associated thrombosis), or through use of warfarin. The frequency of HIT varies from 0.5% to 5%, depending on the patient population studied.[1] It is caused by IgG antibodies that recognize complexes formed between heparin and platelet factor 4, which results in platelet activation, endothelial cell injury, and increased thrombin generation.[1]

MONITORING FOR HIT

HIT can lead to life- and limb-threatening complications where a delay in diagnosis or inappropriate continuation of heparin could increase harm to the patient. These considerations suggest that routine platelet count monitoring for HIT is appropriate in at least some clinical situations, and that the greater the risk of HIT (see Table 1), the stronger the rationale for regular monitoring.[2] It is important to note that a baseline and repeat platelet count should be performed in all patients who have received heparin within the past 100 days or where exposure history is uncertain.[2] In addition, patients should be evaluated for the risk of developing HIT prior to starting heparin or enoxaparin in order to determine the frequency of platelet monitoring.

Table 1. Risk Factors for HIT[2,3]

Risk Factor	Description
Duration of therapy	11 to 14 days > 5 to 10 days > 1 to 4 days
Type of heparin	Unfractionated heparin > low molecular weight heparin* (enoxaparin) > fondaparinux
Dose	Manifesting: therapeutic > prophylaxis > flushes Immunizing: prophylaxis > therapeutic
Recent exposure to heparin	Received within last 100 days
Type of patient	Postsurgical > medical > obstetric
Patient gender	Females > males

* Available randomized controlled trials comparing unfractionated heparin and low molecular weight heparin (LMWH) *treatment* for VTE do not support a lower risk for HIT with LMWH.[4,5] It is unclear if the absolute risk of HIT is so low that a true difference is difficult to prove or if there truly is no difference.[3]

Examples of risk category and patients types:

High Risk (risk of developing HIT is > 1%)[2]

- Surgical patients (especially orthopaedic, cardiac, vascular) receiving prophylactic or treatment doses of heparin > 4 days

Intermediate Risk (risk of developing HIT is 0.1 to 1%)[2]

- Surgical patients receiving prophylactic enoxaparin or heparin flushes > 4 days
- Medical or obstetric patients receiving treatment doses or prophylactic heparin > 4 days
- Medical or obstetric patients receiving enoxaparin after first receiving heparin

Low Risk (risk of developing HIT is < 0.1%)[2]

- Medical or obstetric patients receiving enoxaparin > 4 days or heparin flushes
- Any patient receiving heparin or enoxaparin < 4 days

Another consideration that supports a role for platelet count monitoring is that HIT antibody seroconversion and resulting "typical-onset" HIT usually occur during specific time periods following initiation of heparin (5 to 10 days for seroconversion and initial platelet count fall and 7 to 14 days for reaching the threshold defining thrombocytopenia). Further, "rapid-onset HIT", where platelet count fall begins within 24 hours of staring heparin, is strongly associated with recent heparin exposure (within past 100 days, especially last 30 days).[2]

The decision to perform platelet count monitoring, and the intensity of such monitoring, depends on the patient's risk factors, particularly the type of heparin, duration of heparin therapy, and the type of patient. Therefore, it is appropriate to perform platelet count monitoring in certain clinical situations, and to focus platelet count monitoring during those times when HIT usually occurs (see Table 2).[2]

Table 2. ACCP Recommendations for Platelet Count Monitoring[2]

		Platelet Count Monitoring Based on Patient Risk Category and History			
Medication	**Type of Dose**	**Previous Heparin Exposure* or Exposure History Unknown**	**High Risk**	**Intermediate Risk**	**Low Risk**
Heparin	Therapeutic	Baseline, repeat within 24 hr of starting heparin	Every 2 to 3 days from day 4 to 14§	Every 2 to 3 days from day 4 to 14§	Every 2 to 3 days from day 4 to 14§
	Prophylaxis	Baseline, repeat within 24 hr of starting heparin	Every-other-day from days 4 to 14§	Every 2 to 3 days from day 4 to 14§	Every 2 to 3 days from day 4 to 14§
	Flushes (only applies if patient is receiving ongoing therapy)	Baseline, repeat within 24 hr of starting heparin	No recommendation	Every 2 to 3 days from day 4 to 14§	No routine monitoring suggested
Enoxaparin	Therapeutic	Baseline, repeat within 24 hr of starting heparin	No recommendation	Every 2 to 3 days from day 4 to 14§	No routine monitoring suggested
	Prophylaxis	Baseline, repeat within 24 hr of starting heparin	No recommendation	Every 2 to 3 days from day 4 to 14§	No routine monitoring suggested
Fondaparinux	Any dose	No routine monitoring suggested	No routine monitoring suggested	No routine monitoring suggested	No routine monitoring suggested

ACCP = American College of Chest Physicians
* Previous heparin within previous 100 days
§ Initiation day of heparin/enoxaparin is considered day "0"

Recommendations for platelet count monitoring at UIHC have been modified in order to minimize confusion and maintain patient safety (see Table 3).

Table 3. UIHC Recommendations for Inpatient Platelet Count Monitoring

Medication	Type	Minimum Recommended Platelet Count Monitoring*
Heparin	Therapeutic or prophylaxis	Baseline, repeat within 24 hrs, then every-other-day from day 4 to 14
	Flushes (only applies if patient is receiving ongoing therapy)	Baseline, repeat within 24 hrs, then every 2 to 3 days from day 4 to 14
Enoxaparin	Therapeutic or prophylaxis	Baseline, repeat within 24 hrs, then every-other-day from day 4 to 14
Fondaparinux	Any dose	No routine monitoring suggested

* Initiation day of heparin/enoxaparin is considered day "0"

Patients who are not under close platelet count monitoring (patients who are discharged home on heparin or enoxaparin and/or are continued on therapy after 14 days) should be informed of the most common resulting signs and symptoms of HIT (i.e., new thrombosis and painful skin lesions at the heparin injection sites), and be advised to seek medical advice immediately if these events occur.[2] Furthermore, the American College of Chest Physicians (ACCP) recommends that outpatients receiving prophylaxis or treatment doses of heparin should sign an informed consent which includes HIT and its typical sequelae and the advisement that the patient should seek medical advice if these events occur (Grade 2C recommendation).[2]

WHEN SHOULD HIT BE SUSPECTED?

Because the diagnosis is based on both clinical and serologic grounds, clinicians should consider HIT a clinicopathologic syndrome.[2] Thus, neither thrombocytopenia or thrombosis without the presence of heparin-dependent antibodies, nor the isolated presence of antibodies without thrombocytopenia, thrombosis, or other clinical sequelae, meet the criteria for HIT.[2]

The following are situations where HIT should be suspected:

- Patient presenting to the emergency room with signs / symptoms of DVT or PE five to 100 days after hospital discharge (assumes patient was exposed to heparin on previous admission)
- The American College of Chest Physicians recommends that the diagnosis of HIT should be considered in patients who are receiving heparin or have received heparin within the previous 2 weeks if the platelet count decreases by ≥ 50% (even if platelets > 150,000 per μL)and/or a thrombotic event occurs between days 5 and 14 following initiation of heparin (even if the patient is no longer receiving heparin therapy when the thrombosis or thrombocytopenia has occurred)[2]
- Platelet count fall within 24 hours of heparin or enoxaparin in the setting of previous heparin exposure (within previous 100 days, especially within the last 30 days)
- An otherwise unexplained platelet count fall (defined by various investigators as a minimum platelet count fall of 30%, 40%, or 50%) even if the platelet count nadir remains > 150,000 per μL[2]
- Patient receiving heparin or enoxaparin when a thrombotic event occurs (with or without thrombocytopenia)
  - Up to 25% of HIT patients will experience a thrombotic event during heparin treatment before HIT-associated platelet fall[6]
  - Previous exposure (within previous 100 days): thrombosis may occur immediately[2]
  - A delayed thrombotic response may occur up to 100 days post-initial exposure[2]
- Anaphylactoid reactions[2]

- Rarely, patients develop acute inflammatory (e.g., fever, chills, flushing) or cardiorespiratory (e.g., hypertension, tachycardia, dyspnea, chest pain, cardiorespiratory arrest) symptoms and signs within 30 minutes following an IV heparin bolus (or subcutaneous LMWH).
- This presentation mandates a prompt platelet count measurement and comparison to recent prior platelet counts, as an abrupt platelet count fall in this clinical context supports the diagnosis of HIT. The platelet count drop is frequently transient, and thus a delay in determining the platelet count, especially if heparin is stopped, may result in a missed diagnosis.

- Atypical inflammatory skin reactions at heparin or enoxaparin injection sites

WHAT TO DO IF HIT IS SUSPECTED

1. ***Estimate the probability of HIT***

   Clinicians should consider a diagnosis of HIT when thrombocytopenia occurs with a temporal pattern consistent with heparin-immunization (platelet count fall begins 5 to 10 days after start of therapy) or when thrombosis or other sequelae of HIT occur in patients treated (or recently treated) with heparin.[7] The pretest estimation of the probability of HIT is influenced by the temporal features of the platelet count fall and by the likelihood of other possible alternative diagnoses to explain the thrombocytopenia (see Figure 1).[2] Prospective and retrospective evaluations of the "4 T's" scoring system[8] (a system to help physicians estimate the pretest probability of HIT) have indicated that low scores have very low likelihood of HIT, whereas a high score is associated with moderate to high risk of HIT.[2]

Figure 1. Estimating the Probability of HIT[8]

Estimating the pretest probability of heparin-induced thrombocytopenia: the "4 T's" scoring system

	Points (0, 1, or 2 for each of 4 categories: maximum possible score = 8)		
Date:	2	1	0
Thrombocytopenia score = _____	>50% platelet decrease to nadir ≥20 × 10^9/L	30%–50% platelet count decrease (or >50% directly resulting from surgery) or nadir 10–19 × 10^9/L	<30% platelet decrease or nadir <10 × 10^9/L
Timing[a] of platelet count decrease, thrombosis, or other sequelae (first day of heparin course = day 0)Score = _____	Day 5–10 onset[a] or ≤1 day (with recent heparin exposure within past 5–30 days)	Consistent with day 5–10 decrease, but not clear (eg, missing platelet counts), or ≤1 day (heparin exposure within past 31–100 days), or platelet decrease after day 10	Platelet count decrease ≤4 days without recent heparin exposure
Thrombosis (including adrenal infarction) or other sequelae (eg, skin lesions)Score = _____	Proven new thrombosis, or skin necrosis (at injection site), or post-IV heparin bolus anaphylactoid reaction	Progressive or recurrent thrombosis, or erythematous skin lesions (at injection sites), or suspected thrombosis (not proven)	None
O**T**her cause for thrombocytopeniaScore = _____	No explanation for platelet count decrease is evident	Possible other cause is evident	Definite other cause is present

Total score = _____ Pretest probability score: 6–8 = high; 4–5 = intermediate; 0–3 = low

Changes to score can occur, based upon new information (eg, further decrease in platelets, new thrombosis, other causes for platelet decrease).
The scoring system shown has undergone minor modifications from previous publications.
Abbreviation: IV, intravenous.
[a]First day of immunizing heparin exposure considered day 0; the day the platelet count begins to decrease is considered the day of onset of thrombocytopenia (it generally takes 1 to 3 more days until an arbitrary threshold that defines thrombocytopenia is passed. Usually, heparin administered at or near surgery is the most immunizing situation).

2. Determine action based on probability of HIT

Table 4. UIHC Recommended Action Based on Probability of HIT [2,3,9-11]

Probability Score	Actions
Low (0 to 3)	***HIT unlikely*** Heparin or enoxaparin may continue, but consider use of fondaparinux; Consider Hematology consult if inciting incident for suspicion of HIT is thrombosis; Continue to monitor platelets as above (Table 2) and observe for signs/symptoms of thrombosis; and Continue to evaluate the probability of HIT based on the "4T's" scoring system as laboratory values are reported or other signs and symptoms develop (see Figure 1)
Intermediate (4 to 5) **Or** **High (6 to 8)**	***HIT possible*** Discontinue† all heparin* or enoxaparin; Order a heparin platelet factor 4 antibody (PF4 EIA, aka heparin-dependent antibody); List heparin or enoxaparin as allergy in the patient's allergy list in IPR and medical record; Label patient's bedside as having a heparin or enoxaparin allergy; Label all IV sites as "NO HEPARIN OR ENOXAPRIN"; Consider replacing all heparin-coated tubing/catheters/devices with non-heparin coated products; Recommend Hematology consult; Monitor patient closely for signs and symptoms of thrombosis and bleeding§; Order alternative anticoagulation (however, DO NOT USE WARFARIN UNTIL THE PLATELET COUNT HAS RECOVERED TO > 150,000 per µL)^; Perform duplex ultrasonography to investigate for upper & lower limb DVT; and Perform CT scan if patient demonstrates signs/symptoms of PE

† If there is a critical need to continue heparin or enoxaparin a Hematology consult should be requested immediately and rationale for continuation should be written into the patient's record

***** For heparin, this includes drips, subcutaneous injections, flushes, arterial line fluids containing heparin and heparin-coated tubing/catheters/devices

§ Order testing of all suspicious stools for occult blood and monitor for bleeding from all access sites

^ Including argatroban, bivalirudin, or lepirudin, and possibly fondaparinux. DO NOT USE WARFARIN UNTIL THE PLATELET COUNT HAS RECOVERED TO > 150,000 per µL.

3. Choice of alternative anticoagulation (if applicable, see Table 4)

HIT is a prothrombotic condition that is associated with increased *in vivo* thrombin generation and thus can be considered an acquired, hypercoagulability syndrome.[12] The use of alternative anticoagulation are appropriate for patients in whom the diagnosis of HIT is strongly suspected on clinical grounds (pending laboratory confirmation), or has already been confirmed by a strong positive test result for HIT antibodies in the appropriate clinical context of intermediate or high pretest probability.[2]

Although heparin discontinuance is advised, no evidence exists demonstrating that the discontinuance of all heparin-containing solutions decreases the risk of subsequent thromboembolic events.[9,13] Up to 50% of patients with HIT who have not had a thromboembolic event will have one within the subsequent month when taken off heparin and NOT continued on any anticoagulant therapy.[6]

The recommended duration of alternative anticoagulation is contingent on the clinical situation. For isolated thrombocytopenia, therapeutics doses of alternative anticoagulants should be used until the platelet count recovers and for 2 to 4 weeks thereafter. Alternatively, patients who have HIT with associated thrombosis should undergo therapy (direct thrombin inhibitor (DTI) transitioned to warfarin (target INR 2.0 to 3.0)) for 3 to 6 months.[6]

Consider the following when selecting the appropriate alternative anticoagulant[2]:

- **DO NOT USE WARFARIN UNTIL PLATELET COUNT HAS RECOVERED TO > 150,000 per µL**
  - The use of warfarin during the thrombocytopenic phase of HIT is an important risk factor for progression of DVT to severe venous limb ischemia with the potential for limb loss.[9]
  - Administration of vitamin K (10 mg orally once or 5 to 10 mg over 20 minutes by intravenous injection) is advised when HIT is diagnosed after warfarin has already been started.
- Risk of bleeding[14,15]:
  - Recent puncture of lumbar, large vessels, or organ biopsy
  - Anomaly of vessels or organs
  - Recent cerebrovascular accident, stroke, intracerebral surgery, or neuraxial procedures
  - Severe uncontrolled hypertension
  - Bacterial endocarditis
  - Advanced renal impairment (CrCl < 30 mL/min)
  - Hemorrhagic diathesis
  - Recent major surgery
  - Recent major bleeding (intracranial, spinal, gastrointestinal, intraocular, or pulmonary)
  - Recent active peptic ulcer
- Renal function
- Hepatic function
- Half-life of drug
- Factors increasing the activated partial thromboplastin time (aPTT) or INR
- Patients with suspected HIT or history of HIT where a Hematology consult is **strongly** recommended prior to selecting alternative anticoagulation
  - Patients requiring cardiac surgery or procedure
  - Pediatrics
  - Pregnant
  - Patients receiving hemodialysis

Table 5. Comparison of Alternative Anticoagulants for ADULT Patients with Suspected or Documented HIT[2,9]

	Argatroban	Lepirudin	Fondaparinux[#]
FDA-approved for Management of HIT?	Yes	Yes	No
Primary Elimination	Hepatobiliary	Renal	Renal
Elimination Half-life*	40 to 50 minutes	80 minutes	17 to 20 hours
Laboratory Monitoring	**aPTT** (q 2 hr until goal is reached twice consecutively, then daily. Repeat this cycle upon dosage changes) **INR** (baseline) **PT** (baseline) **Hemoglobin/Hematocrit** (baseline, then daily) **Liver function** (baseline)	**aPTT** (q 4 hr until goal is reached twice consecutively, then daily. Repeat this cycle upon dosage changes) **Hemoglobin/Hematocrit** (baseline, then daily) **Renal function** (baseline, then at least every other day)	None
Target Range^	aPTT: 1.5 to 3.0 X patient's baseline (or mean of laboratory normal range)	aPTT: 1.5 to 2.0 X patient's baseline (or mean of laboratory normal range)	n/a
Effect on INR	Moderate to significant	None to slight	None

[#] The literature regarding the use of fondaparinux in the management of HIT is limited to case reports and abstracts. Hematology consult should be obtained if fondaparinux is considered as the alternative anticoagulant because of cases of fondaparinux-induced HIT.
* Half-lives reported in patients with normal renal and hepatic function.
^ These recommendations (based on the ACCP guidelines)[2] differ from the FDA-approved targets listed in the package inserts.

Table 5. Comparison of Alternative Anticoagulants for ADULT Patients with Suspected or Documented HIT[2,9] (continued)

	Argatroban	Lepirudin	Fondaparinux[#]
Initial Dose^	**Normal hepatic function:** 2 mcg/Kg/min IV continuous infusion **Intensive care unit patients or patients with cardiac failure (low cardiac output state)[†]:** 1 mcg/Kg/min IV continuous infusion **Moderately to Severely decreased hepatic function (Child-Pugh score > 6 or bilirubin > 1.5 mg/dL), multiple organ system failure, severe anasarca, postcardiac surgery, or critical care patients starting on CVVH[†]:** 0.5 mcg/Kg/min IV continuous infusion	Bolus[†]: **only give in case of life- or limb-threatening thrombosis** → 0.2 mg/Kg IV push (over 15 to 20 sec) IV Continuous Infusion Rates (based on serum creatinine)[†] **Creatinine ≤ 1.2 mg/dL:** 0.10 mg/Kg/hr **Creatinine 1.3 to 2.0 mg/dL:** 0.05 mg/Kg/hr **Creatinine 2.1 to 5.2 mg/dL:** 0.01 mg/Kg/hr **Creatinine 5.3 to 6.0 mg/dL:** 0.005 mg/Kg/hr	< 50 kg: 2.5 mg SQ daily[§] 50 to 100 kg: 7.5 mg SQ daily[§] > 100 kg: 10 mg SQ daily[§]
Dosage Adjustments	**NOTE: If aPTT > 150, hold argatroban infusion, notify physician, recheck aPTT q 2 hrs until less than maximum goal range and then decrease infusion by 0.25 mcg/Kg/min and restart** **Normal hepatic function:** aPTT < goal: increase by 1 mcg/Kg/min aPTT > goal: decrease by 1 mcg/Kg/min **Intensive care unit patients or patients with cardiac failure (low cardiac output state):** aPTT < goal: increase by 0.5 mcg/Kg/min aPTT > goal: decrease by 0.5 mcg/Kg/min **Moderately to Severely decreased hepatic function (Child-Pugh score > 6 or bilirubin > 1.5 mg/dL), multiple organ system failure, severe anasarca, postcardiac surgery, or critical care patients starting on CVVH:** aPTT < goal: increase by 0.25 mcg/Kg/min aPTT > goal: decrease by 0.25 mcg/Kg/min	**NOTE: If aPTT > 150, hold lepirudin infusion, notify physician, recheck aPTT q 4 hrs until less than maximum goal range and then decrease infusion by 50% and restart** **Creatinine ≤ 1.2 mg/dL:** aPTT < goal: increase by 0.02 mg/Kg/hr aPTT > goal: decrease by 0.02 mg/Kg/hr **Creatinine 1.3 to 2.0 mg/dL:** aPTT < goal: increase by 0.01 mg/Kg/hr aPTT > goal: decrease by 0.01 mg/Kg/hr **Creatinine 2.1 to 5.2 mg/dL:** aPTT < goal: increase by 0.002 mg/Kg/hr aPTT > goal: decrease by 0.002 mg/Kg/hr **Creatinine 5.3 to 6.0 mg/dL:** aPTT < goal: increase by 0.001 mg/Kg/hr aPTT > goal: decrease by 0.001 mg/Kg/hr	n/a

[#] The literature regarding the use of fondaparinux in the management of HIT is limited to case reports and abstracts. Hematology consult should be obtained if fondaparinux is considered as the alternative anticoagulant because of cases of fondaparinux-induced HIT.

^ These recommendations (based on the ACCP guidelines)[2] differ from the FDA-approved dosages listed in the package inserts. Do NOT exceed 140 Kg for argatroban[14] dosing calculations, or 110 Kg for lepirudin[15] dosing calculations.

[†] Further analyses of prospective and retrospective studies, in addition to increasing clinical experience with argatroban and lepirudin have indicated that the currently FDA-approved doses are too high.[2] The doses listed are based on recommendations from the ACCP.[2]

[§] Recommendation from *AJHP* 2008;65:334-9[11], however, the optimal dose of fondaparinux in the treatment of HIT is unclear. Doses in case reports were between 2.5 to 10 mg SQ daily. However, the occurrence of several thrombotic events in a patient who developed HIT while already receiving prophylactic-dose fondaparinux suggests that therapeutic-dose fondaparinux is likely to be required to inhibit severe HIT-associated hypercoagulability.[9]

Table 5.
Comparison of Alternative Anticoagulants for ADULT Patients with Suspected or Documented HIT[2,9] (continued)

	Argatroban	Lepirudin	Fondaparinux[#]
	Begin warfarin ONLY after platelet count has recovered to > 150,000 per µL **DTI + warfarin overlap should continue for a minimum of 5 days and at least until the INR has reached the intended target range**		n/a
	◆ Reduce the infusion rate of DTI gradually to achieve an aPTT value of the minimum aPPT goal ◆ Determine baseline INR with aPTT values while patient is on DTI prior to starting warfarin. ◆ Initiate the appropriate warfarin maintenance dose at a max of 5 mg orally daily (do not use loading doses)[∞] ◆ Identify the desired 1.5 to 2 point increase in the INR (or identify an INR target while considering the INR elevation induced by DTI)		n/a
Management of Overlap with Warfarin	◆ Dosing changes and monitoring of argatroban-warfarin cotherapy o If argatroban dose is ≤ 2.0 mcg/kg/min, draw the INR daily without adjusting the dose. o If argatroban dose is > 2.0 mcg/kg/min, decrease the infusion to 2 mcg/kg/min, draw the INR 6 hours later, and resume at the previous infusion level o Because argatroban may have an effect on the INR independent of warfarin, **monitor INR daily** while patient is receiving argatroban-warfarin cotherapy. ▪ For INR values < 4.0, continue argatroban infusion at current rate. ▪ If INR values ≥ 4.0, stop argatroban infusion and repeat the INR in 6 hours ▪ For repeated INR values < 2.0, restart argatroban after the last dose and repeat the monitoring and interpretation steps. ▪ For repeated INR values ≥ 2.0, do not restart argatroban. Contact the prescriber to adjust the warfarin dose if above the therapeutic range. ▪ Argatroban order may be discontinued after 2 consecutive days of INR values ≥ 2.0.	◆ After a minimum of 5 days of over-lapping therapy and target INR has been reached, withhold lepirudin for 4 to 8 hrs ◆ Recheck the INR and aPTT o If INR is between 2.0 and 3.0, with an aPTT close to baseline (after accounting for warfarin-related elevation), discontinue lepirudin	n/a

[#] The literature regarding the use of fondaparinux in the management of HIT is limited to case reports and abstracts. Hematology consult should be obtained if fondaparinux is considered as the alternative anticoagulant because of cases of fondaparinux-induced HIT.

[∞] Consider initiating a lower daily warfarin dose in patients with hepatic impairment, heart failure, diarrhea, hyperthyroidism, malignancy, or malnutrition (or NPO > 3 days) as well as in those receiving interacting medications and in the elderly.

Table 5.
Comparison of Alternative Anticoagulants for ADULT Patients with Suspected or Documented HIT[2,9] (continued)

	Argatroban	Lepirudin	Fondaparinux[#]
Special Considerations	◆ Half-life rises greatly in hepatic failure ◆ Doses are based on actual body weight ◆ For any dose exceeding 10 mcg/Kg/minute, call Hematology house officer ◆ If ***not*** transitioning to warfarin therapy, discontinue argatroban once the platelet count recovers to greater than 100,000 platelets/µL. ◆ Argatroban increases the INR, and thus a higher INR therapeutic range may be required during overlapping argatroban/warfarin therapy	◆ Half-life rises greatly in renal failure ◆ Do NOT use lepirudin if serum creatinine is > 6.0 mg/dL (creatinine clearance < 15 mL/min)[17] ◆ Doses are based on actual body weight ◆ For any dose exceeding 0.21 mg/Kg/hr, call Hematology house officer ◆ Risk of anaphylaxis is rare ◆ Avoiding initial bolus may reduce risk of drug accumulation in patients with unrecognized mild renal failure and may reduce the risk or severity of anaphylaxis ◆ If ***not*** transitioning to warfarin therapy, discontinue lepirudin once the platelet count recovers to greater than 100,000 platelets/µL.	◆ Although there have been case reports of fondaparinux-associated HIT, theoretically, lack of *in vitro* cross-reactivity with HIT antibodies suggests it may be useful in HIT ◆ Fondaparinux may be appropriate in patients at low risk of having HIT, but in whom ongoing use of heparin or enoxaparin is not desired. ◆ Fondaparinux may be useful for avoiding problems during transition from DTI to warfarin therapy in patients with HIT-associated thrombosis

[#] The literature regarding the use of fondaparinux in the management of HIT is limited to case reports and abstracts. Hematology consult should be obtained if fondaparinux is considered as the alternative anticoagulant because of cases of fondaparinux-induced HIT.

Note: **Bivalirudin is not an option for treatment of HIT**. Only anecdotal evidence and case series are available regarding the safety and efficacy of bivalirudin in the treatment of HIT.[2] In addition, the dosing recommendations for its use are limited. However, bivalirudin does have an important role for the management of PCI or in cardiac surgery in patients where heparin is contraindicated because of acute HIT.[2] The dose for bivalirudin for cardiac surgery patients is as follows[2]:

- Off-pump
  - Bolus: 0.75 mg/Kg
  - Infusion: 1.75 mg/Kg/hr to maintain ACT > 300 seconds
- Cardio-pulmonary bypass (CBP)
  - Bolus: 1 mg/Kg, in addition to 50 mg bolus added to priming solution of CPB
  - Infusion: 2.5 mg/Kg/hr, additional 0.1 to 0.5 mg boluses to maintain ACT > 2.5-fold baseline ACT

DIAGNOSIS OF HIT

PF4-dependent enzyme immunoassays (EIAs) are sensitive for clinical HIT (about 99%); hence a negative test essentially rules out the diagnosis.[3] Furthermore, the more abnormal the test result, the more likely the patient is to have HIT, given a certain pretest probability of having this diagnosis.[3,16] Results of HIT antibody tests must be interpreted in the appropriate clinical context of pretest probability and the specific test result obtained.[3]

Table 6. Recommended action based on results of PF4 EIA[16,17]

PF4 EIA Result		Action
Negative		***HIT unlikely*** Remove heparin or enoxaprin allergy listing from IPR and medical record; Remove allergy alert from patient's bedside; Remove "no heparin or enoxaparin" labels from IV sites; Discontinue alternative anticoagulation; Re-start initial anticoagulation; and Monitor platelets as above (Table 3) and observe for signs/symptoms of thrombosis
Positive	Low "4T" pretest probability	***HIT is possible*** Consider a serotonin release assay (especially in post-cardiac surgery patients); Consider Hematology consult; Continue to monitor patient closely for signs and symptoms of thrombosis and bleeding[§]; Continue alternative anticoagulation[^]; Perform duplex ultrasonography to investigate for upper and lower limb DVT as indicated; and Perform CT scan if patient demonstrates signs/symptoms of PE
	Intermediate or High "4T" pretest probability score	***HIT is probable*** Consider Hematology consult; Continue to monitor patient closely for signs and symptoms of thrombosis and bleeding[§]; Continue alternative anticoagulation[^]; Perform duplex ultrasonography to investigate for upper and lower limb DVT as indicated; and Perform CT scan if patient demonstrates signs/symptoms of PE
Equivocal		***HIT is not ruled out*** Repeat PF4 EIA (new blood draw); Consider a serotonin release assay; Consider Hematology consult; Continue to monitor patient closely for signs and symptoms of thrombosis and bleeding[§]; Continue alternative anticoagulation[^]; Perform duplex ultrasonography to investigate for upper and lower limb DVT as indicated; and Perform CT scan if patient demonstrates signs/symptoms of PE

[§] Order testing of all suspicious stools for occult blood and monitor for bleeding from all access sites

[^] NOTE: the use of warfarin during the thrombocytopenic phase of HIT is an important risk factor for progression of DVT to severe venous limb ischemia with the potential for limb loss. DO NOT USE WARFARIN UNTIL THE PLATELET COUNT HAS RECOVERED TO > 150,000 per µL. If the patient has contraindications to the use of anticoagulation, consult Hematology.

REFERENCES

1. Jang IK, Hursting MJ. When heparins promote thrombosis: review of heparin-induced thrombocytopenia. *Circulation.* 2005;111:2671-83.
2. Warkentin TE, Greinacher A, Koster A, Lincoff AM. Treatement and prevention of heparin-induced thrombocytopenia. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest.* 2008;133:S340-80.
3. Warkentin TE. Heparin-induced thrombocytopenia. *Hematol Oncol Clin N Am*. 2007;21:589-607.
4. Warkentin TE, Greinacher A. So, does low-molecular-weight heparin cause less heparin-induced thrombocytopenia than unfractionated heparin or not ? *Chest.* 2007;132:1108-10.
5. Morris TA, Catrejon S, Devendra G, et al. No difference in risk for thrombocytopenia during treatment of pulmonary embolism and deep venous thrombosis with either low morlecular weight heparin or unfractionated heparin : a meta-analysis. *Chest.* 2007;132:1131-9.
6. Baldwin ZK, Spitzer AL, Ng VL, Harken AH. Contemporary standards for the diagnosis and treatment of heparin-induced thrombocytopenia. *Surgery.* 2008;142:305-12.
7. Warkentin TE, Sheppard JI, Moore JC, et al. Laboratory testing for the antibodies that cause heparin-induced thrombocytopenia. *Curr Hematol Rep.* 2003;2:148-57.
8. Lo GK, Juhl D, Warkentin TE, et al. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost.* 2006;4:759-65.
9. Linkins L, Warkentin TE. The approach to heparin-induced thrombocytopenia. *Semin Respir Crit Care Med.* 2008;29:66-74.
10. Dager WE, Dougherty JA, Nguyen PH, et al. Heparin-induced thrombocytopenia: treatment options and special considerations. *Pharmacotherapy.* 2007;27(4):564-87.
11. Fugate S, Chiappe J. Standardizing the management of heparin-induced thrombocytopenia. *Am J Health-Syst Pharm.* 2008;65:334-9.
12. Warkentin TE. Platelet count monitoring and laboratory testing for heparin-induced thrombocytopenia. *Arch Pathol Lab Med.* 2002;126:1415-23.
13. Wallis DE, Workman DL, Lewis BE, et al. Failure of early heparin cessation as treatment for heparin-induced thrombocytopenia. *Am J Med.* 1999;106:629-35.
14. Argatroban injection prescribing information. Research Triangle Park, NC: GlaxoSmithKline: 2008 May.
15. Refludan (lepirudin (rDNA) for injection) prescribing information. Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc: 2006 December.
16. Lo GK, Sigouin CS, Warkentin TE. What is the potential for overdiagnosis of heparin-induced thrombocytopenia? *Am J Hematol*. 2007;82:1037-43.
17. Selleng K, Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia in intensive care patients. *Crit Care Med*. 2007;35:1165-76.