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] The antibody responsible for HIT is an immunoglobulin (Ig)G antibody that binds to heparin-PF4 complexes on the platelet surfaces to form immune complexes. These immune complexes result 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 a 24-hour 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 associated patients types [based on new or remote (>100 days) exposure to heparin]: [2,15]

High Risk (risk of developing HIT is > 1%)[2,59]

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

Intermediate Risk (risk of developing HIT is 0.1 to 1%)[2,18-21]

- Surgical patients receiving prophylactic enoxaparin prophylaxis/treatment or heparin flushes > 4 days
- General intensive care patients
- Medical or obstetric patients receiving treatment doses or prophylactic heparin > 4 days
- Medical or obstetric patients receiving enoxaparin after first receiving heparin
- Patients with neurologic conditions
- Patients undergoing percutaneous coronary intervention for acute coronary syndrome
- Patients undergoing acute hemodialysis
- Newborns and infants after cardiac surgery
- Adolescents treated with UFH for spontaneous thrombosis

Low Risk (risk of developing HIT is < 0.1%)[2,18]

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

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 (≥1%)**	**Intermediate Risk (<1%)**	**Low Risk (<0.1%)**
Heparin	Therapeutic	Baseline, repeat within 24 hr of starting heparin	Every 2 to 3 days from day 4 to 14§	No routine monitoring suggested	No routine monitoring suggested
	Prophylaxis	Baseline, repeat within 24 hr of starting heparin	Every 2 to 3 days from day 4 to 14§	No routine monitoring suggested	No routine monitoring suggested
	Flushes (only applies if patient is receiving ongoing therapy)	Baseline, repeat within 24 hr of starting heparin	No recommendation	No routine monitoring suggested	No routine monitoring suggested
Enoxaparin	Therapeutic	Baseline, repeat within 24 hr of starting heparin	Every 2 to 3 days from day 4 to 14§	No routine monitoring suggested	No routine monitoring suggested
	Prophylaxis	Baseline, repeat within 24 hr of starting heparin	Every 2 to 3 days from day 4 to 14§	No routine monitoring suggested	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
* Heparin/LMWH exposure 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"

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]

If one or more of the following are situations are present (in the absence of another more compelling explanation), HIT should be suspected:[2]

- Thrombocytopenia
  - A decrease in platelets of at least 30 to 50% (even if platelets > 150,000 per μL) occurring between days 5 and 14 following initiation of heparin or enoxaparin (even if the patient is no longer receiving heparin therapy when the thrombocytopenia occurs)
  - A more rapid platelet count fall may be seen within 24 hours of heparin or enoxaparin in the setting of previous heparin exposure (within previous 100 days)
- Thrombosis
  - Newly diagnosed thrombosis between days 5 and 14 following initiation of heparin or enoxaparin (even if the patient is no longer receiving heparin therapy when the thrombosis occurs)
    - Up to 25% of HIT patients will experience a thrombotic event during heparin treatment before HIT-associated platelet fall[6]
  - Thrombosis may also occur due to rapid-onset HIT if heparin is given to a patient who already has circulating HIT-antibodies, usually due to heparin given in the 100 days
  - A delayed thrombotic response may occur up to 100 days post-initial exposure
- Atypical inflammatory skin reactions or necrotizing skin lesions at heparin or enoxaparin injection sites
- Acute anaphylactoid reactions
  - 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.

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 of at least 30% begins 5 to 10 days after start of therapy) or when thrombosis or other sequelae of HIT occur in patients treated with (or recently exposed to) 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.[2,22-24]

Figure 1. Estimating the Probability of HIT[2]

	Score = 2	Score = 1	Score = 0
Thrombocytopenia Compare the highest platelet count within the sequence of declining platelet counts with the lowest count to determine the % of platelet fall. **(Select only 1 option)**	o > 50% platelet fall AND nadir of ≥ 20 AND no surgery within preceding 3 days	o > 50% platelet fall BUT surgery within preceding 3 days OR o any combination of platelet fall and nadir that does not fit criteria for Score 2 or Score 0 (eg, 30-50% platelet fall or nadir 10-19)	o < 30% platelet fall o any platelet fall with nadir < 10
Timing (of platelet count fall or thrombosis*) Day 0 = first day of most recent heparin exposure **(Select only 1 option)**	o platelet fall day 5-10 after start of heparin o platelet fall within 1 day of start of heparin AND exposure to heparin within past 5-30 days	o consistent with platelet fall days 5-10 but not clear (eg, missing counts) o platelet fall within 1 day of start of heparin AND exposure to heparin in past 31-100 days o platelet fall after day 10	o platelet fall ≤ day 4 without exposure to heparin in past 100 days
Thrombosis (or other clinical sequelae) **(Select only 1 option)**	o confirmed new thrombosis (venous or arterial) o skin necrosis at injection site o anaphylactoid reaction to IV heparin bolus o adrenal hemorrhage	o recurrent venous thrombosis in a patient receiving therapeutic anticoagulants o suspected thrombosis (awaiting confirmation with imaging) o erythematous skin lesions at heparin injection sites	o thrombosis suspected
oTher cause for Thrombocytopenia** **(Select only 1 option)**	o no alternative explanation for platelet fall is evident	**Possible other cause is evident:** o sepsis without proven microbial source o thrombocytopenia associated with initiation of ventilator o other	**Probable other cause present:** o within 72 h of surgery o confirmed bacteremia/ fungemia o chemotherapy or radiation within past 20 days o DIC due to non-HIT cause o posttransfusion purpura (PTP) o platelet count < 20 AND given a drug implicated in causing D-ITP (see list) o non-necrotizing skin lesions at LMWH injection site (presumes DTH) o other

Drugs implicated in drug-induced immune thrombocytopenia (D-ITP)

Relatively Common: glycoprotein IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban); quinine, quinidine, sulfa antibiotics, carbamazepine, vancomycin
Less Common: actinomycin, amitriptyline, amoxicillin/piperacillin/nafcillin, cephalosporins (cefazolin, ceftazidime, ceftriaxone), celecoxib, ciprofloxacin, esomeprazole, fexofenadine, fentanyl, fucidic acid, furosemide, gold salts, levofloxacin, metronidazole, naproxen, oxaliplatin, phenytoin, propranolol, propoxyphene, ranitidine, rifampin, suramin, trimethoprim. Note: This is a partial list.

It is important to note that cardiac surgery patients represent a patient population in which the diagnosis of HIT is particularly challenging. In this context, a decrease in platelet count of approximately 40 to 60% occurs during the first 72 hours after cardiac surgery secondary to hemodilution, platelet dysfunction, and consumption of platelets in the extracorporeal circuit, unrelated to the development of HIT (and thus would be considered a definite other cause of thrombocytopenia).[25-27] Glycoprotein IIb/IIIa inhibitors may also cause drug-induced thrombocytopenia.[28] In addition, up to 70% of patients develop anti-platelet factor 4-heparin antibodies detectable by immunoassays with up to 20% of these patients testing positive by platelet activation assay (SRA) during the 10 days post-cardiac surgery[26,31,36-39] with most having clinically irrelevant seroconversion (i.e., not associated with the development and presentation of HIT).[10,29-30] Furthermore, several studies have shown that these antibodies are present in up to 22% of patients before surgery[29,31-34] suggesting that inflammation, and not heparin, is the cause of antibodies.[35] Therefore, due to the low risk of clinically relevant HIT in these patients,

there may be a rationale for considering continued heparin therapy, even if a PF4–heparin antibody test result is positive.[40] Maintaining heparin should be particularly considered when there is a reasonable alternative explanation for the thrombocytopenia, there is no new thrombosis (which would increase the likelihood of true HIT), and no additional platelet count decrease of at least 30% occurs during the characteristic HIT window (i.e., between days 5 and 10 post-surgery).[40]

However, evidence suggests that a 50% or greater platelet count decrease beginning 5 to 10 days post-cardiac surgery is highly predictive for HIT and should prompt a change in anticoagulation before the results of antibody tests become available.[29,41-43]

2. Determine action based on probability of HIT

Table 4.
UIHC Recommended Action Based on Probability of HIT (Calculation of the "4Ts" Score) [2,3,9-11]

4Ts Score	Actions
Low (0 to 3)	***HIT unlikely*** • A heparin platelet factor 4 antibody (PF4 EIA, aka Heparin Dependent Antibody Test) is not necessary • Heparin or enoxaparin may continue (if a PF4 EIA is drawn, consider use of fondaparinux) • Consult Hematology if inciting incident for suspicion of HIT is thrombosis • Continue to monitor platelets as above (Table 3) and observe for signs/symptoms of thrombosis • Continue to evaluate the probability of HIT based on the "4Ts" 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 PF4 EIA • List heparin and/or enoxaparin as allergy in the patient's allergy list in patient's medical record • Label all IV sites as "NO HEPARIN OR ENOXAPRIN" • Consider replacing all heparin-coated tubing/catheters/devices with non-heparin coated products • Consult Hematology • 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 • 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, 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 5)
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 (intermediate to High 4Ts score) on clinical grounds (pending laboratory confirmation), or has already been confirmed by a strong positive (low dose > 1.0) test result for HIT antibodies in the appropriate clinical context of intermediate or high pretest probability.[2] Initial therapy is typically an injectable anticoagulant (e.g., argatroban intravenously or fondaparinux SQ), see **Table 5** for more information on initial choice of therapy. Due to the growing amount of literature (though still rather low quality) supporting the efficacy[65-67,78-86] of fondaparinux in certain patient populations, the broad adoption of its use among other institutions, expert opinion, and the pharmacoeconomic and logistical benefits of use, fondaparinux **may be considered as a 1st line** alternative anticoagulant for suspected or documented HIT if the following criteria are met:

- Normal renal function (CrCl >50 ml/min; see dosing and adjustments in Table 5)
- No invasive procedure scheduled, or the likelihood of one is low

Fondaparinux, a selective indirect inhibitor of factor Xa, is thought to have a negligible risk for development of heparin induced thrombocytopenia. Though there have been a small amount of case reports describing fondaparinux-associated HIT,[68-71] and because fondaparinux can initiate the production of anti-PF4 antibodies, these antibodies have shown to be non-reactive towards the PF4/fondaparinux complex and does not produce platelet activation.[72-77] Fondaparinux is renally cleared and therefore not recommended in patients with renal dysfunction as it may increase the risk of bleeding. Also, its extended half-life (17-20 hours in patients with normal renal function) is not ideal for patients requiring acute procedures that necessitate little to no anticoagulation. In both of the above circumstances, argatroban is the preferred agent.

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]

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)
- Renal and hepatic function
- Half-life of drug
- Factors increasing the activated partial thromboplastin time (aPTT) or INR
- Hematology consult is **strongly** recommended prior to selecting alternative anticoagulation in the following:
  - Patients requiring cardiac surgery or procedure
  - Pregnancy
  - Patients receiving hemodialysis

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

Table 5. Alternative Anticoagulants for ADULTS with Suspected or Documented HIT[2,9]

	Argatroban	Fondaparinux[#]
Elimination	Hepatobiliary	Renal
Half-life*	40 to 50 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)	Baseline renal function, then as clinically indicated
Target Range^	aPTT: 1.5 to 3.0 times the patient's baseline (or mean normal range)	n/a
Effect on INR	Moderate to significant	None
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	< 50 kg: 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	CrCl 30-50 ml/min: use with caution CrCl <30 ml/min: contraindicated

[#] Not FDA-approved for heparin-induced thrombocytopenia
* Half-lives reported in patients with normal renal and hepatic function
^ 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
[§] Recommendation from *Chest.* 2012;141:495S-530S[2], although 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. Alternative Anticoagulants for ADULTS with Suspected or Documented HIT[2,9] (continued)

<table>
<tr><th></th><th>Argatroban</th><th>Fondaparinux[#]</th></tr>
<tr><td rowspan="3">Management of Overlap with Warfarin</td><td>• 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</td><td rowspan="3">• Begin warfarin ONLY after platelet count has recovered to > 150,000 per µL
• Fondaparinux does NOT affect the INR. Monitor warfarin as in usual course of therapy.
• Fondaparinux + warfarin overlap should continue for a minimum of 5 days and at least until the INR has reached the intended target range for 2 consecutive results.</td></tr>
<tr><td>◆ Reduce infusion rate of DTI gradually to achieve aPTT value of the minimum aPPT goal
◆ Determine baseline INR with aPTT values while patient is on DTI prior to starting warfarin.
◆ Initiate 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)</td></tr>
<tr><td>◆ 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 LIP to adjust warfarin dose if above therapeutic range.
Argatroban order may be discontinued after 2 consecutive days of INR values ≥ 2.0.</td></tr>
<tr><td>Special Considerations</td><td>◆ Half-life rises greatly in hepatic failure
◆ For dose > 10 mcg/Kg/minute, call Hematology
◆ If <u>not</u> transitioning to warfarin, discontinue argatroban once platelets recovers to > 100,000 platelets/µL.
◆ Argatroban increases the INR, and thus a higher INR therapeutic range may be required during overlapping argatroban/warfarin therapy</td><td>◆ Fondaparinux may be useful for avoiding problems during transition from DTI to warfarin therapy in patients with HIT-associated thrombosis
◆ Not ideal for patients expected to surgical intervention or with moderate to severe renal insufficiency</td></tr>
</table>

[#] Not FDA-approved for heparin-induced thrombocytopenia.
[∞] 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.

DIAGNOSIS OF HIT

Appropriate use of diagnostic laboratory tests, their limitations, and their clinical utility is instrumental in the diagnosis and treatment of HIT. UIHC offers two diagnostic tests to aid clinicians in assessing the likelihood of HIT in patients.

The first of these, the PF4 EIA (Heparin Dependent Antibody Test), detects serum IgG, IgA and IgM responsive to platelet factor 4 (PF4). These antibodies are present in up to 17% of patients that receive unfractionated heparin, and 8% of patients that receive LMWH.[6] In this context, it is again important to note that heparin/platelet factor 4 antibodies are commonly present perioperatively in cardiac surgical patients who have not been exposed to heparin or LMWH, and are typically not associated with an increased risk of HIT.[44] EIA has been shown to be very sensitive for the presence of clinical HIT (>99%[2]), hence a negative test essentially rules out the diagnosis.[3, 44] Several reports have demonstrated that higher optical density values relate to higher diagnostic probability of clinical HIT[45,28] or the risk of thrombosis[49-50] (due to the likelihood that the patient has heparin-dependent platelet-activating antibodies and, therefore, clinical HIT[44,47,49-50]). The specificity of the EIA is 65-85 %, which may lead to the diagnoses of HIT, when in actuality, the patient does not have HIT.[51] Results of HIT antibody tests must be interpreted in the appropriate clinical context of pretest probability and the specific test result obtained for greater reliability.[3,52-53] Thus, the PF4 EIA test is very useful to exclude the HIT diagnosis. It can be conducted in-house on weekdays, with same-day results if ordered before 1300.

The serotonin release assay (SRA) is the second test for HIT available to UIHC clinicians. This test detects heparin-dependent, platelet-activating antibodies via the release of radiolabeled serotonin from donor platelets placed in patient serum.[44] Available data suggest that this type of "activity assay" may have better specificity than the PF4 EIA for detecting antibodies associated with clinical manifestations.[54-56] The SRA is very specific for HIT (99%), but less sensitive than the PF4 EIA (still thought to be >90%).[44,57] Assays are mailed to an outside lab to be performed. Turnaround time is several days.

Despite the SRA being highly specific and sensitive for the diagnosis of hit, its high cost and lengthy turnaround time, make HIT largely a clinical diagnosis.[6] Therefore, the 4T's scoring system (see Figure 1) is extremely valuable in estimating the probability of HIT in a specific patient.

Table 6 provides recommendations for management of a patient suspected of having HIT based on PF4 EIA results in the context of pretest probability.

The recommended duration of alternative anticoagulation is contingent on the clinical situation.

- For isolated thrombocytopenia, therapeutics doses of alternative anticoagulants or warfarin (**ONLY when the platelet count is >150,000 µL**) should be used for 4 weeks.[2]
- Patients who have HIT with associated thrombosis should undergo therapy (direct thrombin inhibitor (DTI) transitioned to warfarin (**ONLY when the platelet count is >150,000 µL**) (target INR 2.0 to 3.0)) for 3 months.

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

PF4 EIA Result		Actions
Negative		***HIT is ruled out with 99% probability*** • Remove heparin or enoxaparin allergy listing from the patient's medical record • Remove "no heparin or enoxaparin" labels from IV sites • Discontinue alternative anticoagulation • Re-start initial anticoagulation • Monitor platelets as above (Table 3) and observe for signs/symptoms of thrombosis *[ongoing assessment of the pretest clinical probability score (i.e., "4Ts") should be performed]*
Positive	**Low "4Ts" pretest probability score**	***HIT is unlikely*** • Consider Hematology consult • Consider a serotonin release assay (especially in post-cardiac surgery patients) • 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 • Perform CT scan if patient demonstrates signs/symptoms of PE
	Intermediate "4Ts" pretest probability score	***HIT is possible*** • Consider Hematology consult • Consider a serotonin release assay (especially in post-cardiac surgery patients) • 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 • Perform CT scan if patient demonstrates signs/symptoms of PE
	High "4Ts" 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 • 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 • 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.

TREATMENT OF PATIENTS WITH A PREVIOUS DIAGNOSIS OF HIT

In general, exposing a patient with a history of known (or strongly suspected) drug hypersensitivity to the drug in question should not be done. However, there are several reasons why HIT is an important exception to this general rule:

- For patients with a history of typical-onset HIT, there is no trend to earlier onset of HIT. [2,31]
- To prevent rapid-onset HIT, preexisting HIT antibodies that cause the rapid-onset HIT can be tested (PF4 EIA) in patient blood obtained immediately before the repeat heparin exposure. [2,31]
    - For rapid onset HIT, there is a strong association with recent (<100 days), rather than remote (> 100 days) prior heparin exposure. [2,31,32]
- HIT antibodies are transient, with the median time to antibody disappearance of 50 to 80 days.[2,31]
- In situations when patients with a history of HIT have been reexposed to heparin (HIT antibodies were no longer present), recurrence of HIT antibodies usually did not occur. [2,31]
    - In those situations when HIT antibodies were regenerated, they did not occur sooner, or at stronger levels, than in the previous seroconversion that had led to clinical HIT. [2,31]

All these observations argue against the presence of typical immune “memory” response in HIT in which re-exposure to the drug triggers a dramatic and rapid immune-based response such as anaphylaxis.[2]

In general, for patients with a history of HIT who require surgery and heparin or LMWH is to be used peri-surgery or during surgery, the surgery should be delayed, until the PF4 EIA returns a negative result (optimally 100 days after the previous heparin exposure).[2]

For patients with active HIT (i.e., thrombocytopenia and the presence of HIT antibodies), therapy with all forms of heparin should be avoided. This includes all routes of administration of heparin, including heparin flushes, regional anticoagulation therapy, and the use of heparin-coated catheters.[2] If an anticoagulant is needed in these patients, use alternative anticoagulation (see Table 5).

Reexposure to heparin in patients whose platelet counts have recovered but have preexisting antibodies may be associated with the rapid recurrence of thrombocytopenia, recurrent thrombosis, and acute systemic reactions. Therefore, reexposure to any form of heparin should be avoided until there is no evidence of HIT antibodies. However, as the antibody titer falls over time, in the absence of continued heparin exposure, it may at some point become relatively safe to reexpose the patient to heparin. Warkentin and Greinacher[58] have suggested that heparin might be used for cardiac bypass procedures if the result of a sensitive functional assay for HIT antibodies is negative and the result of an enzyme-linked immunosorbent assay (e.g., PF4 EIA) is only weakly positive. There are no published clinical studies regarding reexposure to heparin in patients with an ELISA result that is positive for HIT antibodies; therefore, it may be reasonable to consider short-term heparin reexposure in patients with a negative activity assay result and only a weakly positive ELISA result. However, there are no data regarding the safety of longer term exposure to heparin in these patients, as in the treatment of patients with venous thromboembolism and unstable angina, or in those who require extended prophylaxis for major surgery.

In a patient with a distant history of HIT and no detectable antibodies there is no consensus about the risks of heparin re-exposure. There have been several studies reporting the outcomes of patients who were re-exposed to heparin in the setting of a past history of HIT.[60-64] Very few instances of HIT reoccurrence, with or without thrombosis, occurred.

Table 7 outlines recommendations for anticoagulants for patients with a history of HIT.

Table 7. Recommended Anticoagulation for Patients with Previously Diagnosed HIT

Platelet Count	Antibodies Present via PF4 EIA?	Patient Type				
		Cardiothoracic or Vascular Surgery	PCI or Catheterization	Pregnant	Hemodialysis Flush Solutions‡	Other Patient Types
Not recovered	**Yes**	Bivalirudin	Bivalirudin	Limited data exists for nonheparin anticoagulants (although 10% of the maternal blood concentration of fondaparinux can be measured in the cord blood of a newborn). Fondaparinux is recommended when danaparoid is not available[2]	Saline, citrate, argatroban	Alternative anticoagulation (see table 5)
Recovered	**Yes#**	Bivalirudin	Bivalirudin			
	No	Unfractionated heparin during surgery/procedure only*	Bivalirudin			

Patients with recent HIT whose platelet count has recovered, but who still have detectable HIT antibodies are at risk of developing rapid-onset HIT on heparin reexposure unless a washed platelet activation assay (e.g., serotonin release assay) is negative

* Preoperative and postoperative anticoagulation, if indicated, should be given with a nonheparin anticoagulant

‡ Only anecdotal reports are available

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