

P & T News

Published by the Pharmacy and Therapeutics Subcommittee of the University Hospital
Advisory Committee and the Department of Pharmaceutical Care

Volume 29 Number 5

March 2009

Edited by
Janet Schlechte, M.D.
Kevin Bebout, R.Ph.
Mary Ross, M.B.A.

Pharmacy and Therapeutics
Subcommittee Members:

- J. Schlechte, M.D., Chair
- P. Abramowitz, Pharm.D.
- J.A. Buckwalter, M.D.
- C. Dawson, A.P.N.
- E. Ernst, Pharm.D.
- M.A. Granner, M.D.
- W. Haynes, M.D.
- R. Hohl, M.D.
- D. Hornick, M.D.
- J.L. Jensen, R.N., M.S.
- P. Kaboli, M.D.
- M. Kamande, R.N.
- J. Klein, M.D.
- M. Lofgren, A.R.N.P.
- S. Manion, M.D.
- L. Mascardo, Pharm.D.
- D. Miller, M.D.
- S. Nelson, R.Ph., M.S.
- J. Niebyl, M.D.
- M. Olsen, M.D.
- P. Polgreen, M.D.
- M.B. Ross, R.Ph., M.B.A.
- V. Sharp, M.D.
- J. Smelser, Pharm.D.
- J. Thomas, MBBS, M.P.H.
- D. Weetman, R.Ph., M.S.
- J. Wilbur, M.D.

©2009



INSIDE INDEX

P&T Subcommittee	
Actions.....	29
Alternatives to Drug Samples, Devices, and Vouchers.....	30

GUIDELINES FOR RECOGNITION AND MANAGEMENT OF HEPARIN-INDUCED THROMBOCYTOPENIA

Guidelines for Recognition and Management of Heparin-Induced Thrombocytopenia have been developed by the Anticoagulation Task Force. The following article summarizes key points of the guidelines.

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, 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.

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

The American College of Chest Physicians (ACCP)² recommendations for platelet count monitoring have been modified at UIHC in order to minimize confusion and maintain patient safety (see Table 2).

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

Table 2. 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

WHEN SHOULD HIT BE SUSPECTED?

The following are situations where HIT should be suspected:

- ◆ Patient presenting to the emergency room with signs / symptoms of DVT or PE 5 to 100 days after hospital discharge.
- ◆ Patients who are receiving heparin or have received heparin within the previous 2 weeks if the platelet count decreases by > or equal to 50% (even if platelets > 150,000 per μ L) 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)
- ◆ Patient receiving heparin or enoxaparin when a thrombotic event occurs (with or without thrombocytopenia)
- ◆ Anaphylactoid reactions²
- ◆ 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 administration (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 Lo et al developed a "4 T's" scoring system⁸ (see Table 3) to help estimate the probability of HIT. Low scores have very low likelihood of HIT, whereas a high score is associated with moderate to high risk of HIT.²

Table 3. Estimating the Probability of HIT⁸#

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 $\geq 20 \times 10^9/L$	30%–50% platelet count decrease (or >50% directly resulting from surgery) or nadir $10\text{--}19 \times 10^9/L$	<30% platelet decrease or nadir $<10 \times 10^9/L$
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
Other 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.
^aFirst 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).

Reprinted from Lo et al. Evaluation of pretest clinical score (4 T's) for the diagnosis of HIT. *J Thromb Haemost.* 2006;4:759-65.

Note: At UIHC platelet counts are reported as K/mL³ (e.g., $20 \times 10^9/L$ is equivalent to 20,000 per μL or 20,000/mL³).

2. Determine action based on probability of HIT (see Table 4)

Table 4. UIHC Recommended Action Based on Probability of HIT^{2,3,9-11}

Probability Score	Actions
Low (0 to 3)	<p><u>HIT unlikely</u></p> <ul style="list-style-type: none"> • 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 Table 3)
Intermediate (4 to 5) Or High (6 to 8)	<p><u>HIT possible</u></p> <ul style="list-style-type: none"> • 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 appropriate testing 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. 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 pre-test probability of having this diagnosis.^{3,16} Results of HIT positive or equivocal antibody tests must be interpreted in the appropriate clinical context of pre-test probability and the specific test result obtained;³ Hematology should be consulted for guidance on patient management.

4. Treatment of HIT: Choice of alternative anticoagulation, if needed

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, therapeutic 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 μ L**
 - 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}
- ◆ 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

A Table outlining the alternative anticoagulants, dosing adjustments, and laboratory monitoring can be found at <https://thepoint.healthcare.uiowa.edu/sites/Policies-UIHCPolicies/Medication%20Management/Anti-coagulation%20Management/2%20-%20Staff%20Education%20Resources/Heparin-Induced%20Thrombocytopenia%20Protocol.doc>

SUMMARY

Recognition of HIT risk factors, ongoing monitoring of patients receiving heparin, and appropriate follow-up when HIT is suspected are key factors for reducing HIT-associated morbidity and mortality. The complete Guidelines for Recognition and Management of Heparin-Induced Thrombocytopenia are available on The Point (through the Clinical Applications Web Links, UIHC Clinical Practice Reference/Anticoagulation Management <https://thepoint.healthcare.uiowa.edu/sites/Policies-UIHCPolicies/Medication%20Management/Anti-coagulation%20Management/2%20-%20Staff%20Education%20Resources/Heparin-Induced%20Thrombocytopenia%20Protocol.doc>) and through the on-line Formulary (Anticoagulation Management link). For patients with suspected or documented HIT, a Hematology consult is strongly recommended for guidance in patient management and selection of alternative anticoagulation, if warranted.

REFERENCES

1. Circulation. 2005;111:2671-83.
2. Chest. 2008;133:S340-80.
3. Hematol Oncol Clin N Am. 2007;21:589-607.
4. Chest. 2007;132:1108-10.
5. Chest. 2007;132:1131-9.
6. Surgery. 2008;142:305-12.
7. Curr Hematol Rep. 2003;2:148-57.
8. J Thromb Haemost. 2006;4:759-65.
9. Semin Respir Crit Care Med. 2008;29:66-74.
10. Pharmacotherapy. 2007;27(4):564-87.
11. Am J Health-Syst Pharm. 2008;65:334-9.
12. Arch Pathol Lab Med. 2002;126:1415-23.
13. 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. Am J Hematol. 2007;82:1037-43.
17. Crit Care Med. 2007;35:1165-76.

Written by Jamie M. Smelser, PharmD, Clinical Pharmacy Specialist, Department of Pharmaceutical Care.

Reviewed by: Donald MacFarlane, MD, Division of Hematology/Oncology; Steven Lentz, MD, Division of Hematology/Oncology; Jeffrey Wilson, MD, Division of Pulmonary/Critical Care/Occupational Medicine; and the Anticoagulation Task Force.

PHARMACY AND THERAPEUTICS SUBCOMMITTEE ACTIONS

DRUGS ADDED TO STOCK

AMBRISENTAN

Ambrisentan (Letairis® - Gilead Sciences) tablets are indicated for the treatment of pulmonary arterial hypertension (PAH) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening.

Cost: \$169 per 5 mg and 10 mg tablets.

BOSENTAN

Bosentan (Tracleer® - Actelion) tablets are indicated for the treatment of PAH in patients with WHO class III or IV symptoms to improve exercise ability and decrease the rate of clinical worsening.

Cost: \$84.57 per 62.5 mg and 125 mg tablets.

BUDESONIDE

Budesonide (Rhinocort Aqua® - AstraZeneca) nasal spray is indicated for the management of nasal symptoms of seasonal or perennial allergic rhinitis in adults and children 6 years of age and older.

Cost: \$80.94 per 60 spray container.

IOBENGUANE I-123

Iobenguane I-123 (AdreView® - GE Healthcare) is a diagnostic radiopharmaceutical for gamma-scintigraphy that is indicated for use in the detection of primary metastatic pheochromocytoma or neuroblastoma.

Cost: \$2200 per 5 ml vial.

METHYLNALTREXONE

Methylnaltrexone (Relistor® - Wyeth) injection is indicated for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care.

Note: Restricted to prescribing for palliative care patients.

Cost: \$38.33 per 12 mg vial.

REGADENOSON

Regadenoson (Lexisan® - Astellas/CV Therapeutics) injection is indicated for radionuclide myocardial perfusion imaging in patients unable to undergo adequate exercise stress testing.

Cost: \$186 per 0.08 mg/ml, 5 ml syringe.

SODIUM FLUORIDE

The 5% topical varnish (Duraflor®, generic) is used to prevent dental caries.

Cost: \$1.88 per 0.25 ml.

TRIAMCINOLONE

Triamcinolone (Triesence® - Alcon) intraocular injection is indicated for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids. It is also indicated for visualization during vitrectomy.

Cost: \$120 per 40 mg/ml, 1 ml vial.

ADDITIONAL ACTIONS

CHOLECALCIFEROL (VITAMIN D-3)

400 unit and 1000 unit tablets were added to stock.

Cost: \$0.01 per each strength.

CHROMIUM (CHROMIC CHLORIDE)

A 4 mcg per ml chromium injection was added to stock.

Cost: \$0.46 per 10 ml vial.

CONJUGATED ESTROGENS

A 0.0625% vaginal cream (Premarin®) was added to stock.

Cost: \$86.34 per 42.5 g tube.

ONDANSETRON

A 4 mg oral disintegrating tablet was added to stock.

Cost: \$1.07 per tablet.

PANCRELIPASE

Creon-20® enteric-coated capsules which contain 20,000 units lipase, 75,000 units protease, and 66,400 units amylase per capsule were added to stock.

Cost: \$1.99 per capsule.

RISEDRONATE (Actonel®)

A 150 mg tablet that is dosed once-monthly was added to stock.

Cost: \$74.40 per tablet.

TETRACAINE

A 0.5% viscous ophthalmic solution (TetraVisc®) was added to stock.

Cost: \$7.02 per 2 ml bottle.

DRUGS DELETED FROM STOCK

BORIC ACID VAGINAL CAPSULES

Discontinued by the manufacturer.

ESTRADIOL (Estrace®) VAGINAL CREAM

Replaced with conjugated estrogens vaginal cream (Premarin®).

GENTAMICIN IRRIGATION SOLUTION

Discontinued by the manufacturer.

LEUPROLIDE ACETATE (Viadur®) IMPLANT

Discontinued by the manufacturer. Histrelin (Vantas®) implant is available.

LEVOFLOXACIN

Replaced with ciprofloxacin and moxifloxacin.

METAPROTERENOL (Alupent®) ORAL INHALER

Discontinued by the manufacturer. Alupent oral inhalers are available.

Alternatives to Drug Samples, Drug Devices, and Drug Vouchers

Effective May 1, 2009, industry-supplied drug samples, drug devices, and vouchers may not be accepted or distributed to patients at UI Health Care. Outlined below are alternatives to the provision of drug samples, drug devices, and drug vouchers for patients who have financial need.

1. Patients who require urgently needed drugs/drug devices and are unable to pay for them should be given a prescription. The pharmacist financial counselor (4-6907) will be consulted and will work with the patient to provide an initial supply of needed medication(s) when appropriate. A payment plan will be established if needed. If the pharmacist financial counselor is not available, the UIHC Ambulatory Care Pharmacies will dispense a 3-day supply, and the patient will be billed.
2. Patients will be referred to the Medication Assistance Center for assistance with obtaining long-term supplies of drugs/drug devices. Patients will be assisted with enrollment into medication assistance programs if eligibility criteria are met. Whenever appropriate, the use of lower cost generic drugs in the therapeutic class will be recommended to the prescriber.
3. The Iowa Prescription Drug Corporation may be contacted to obtain a free supply of medications for patients without other options.
4. Eligible patients will be referred to the IowaCare program.
5. Pharmacists will provide recommendations to prescribers regarding the availability of less expensive therapeutic alternatives, including other generic medications in the same class. The following link directs prescribers to current clinic sample lists and potential alternative agents.
6. If an active medication is needed for administration/education for a clinic patient, one of the following processes should be followed:
 - a. An LIP order to pharmacy should be placed in the Epic system. Pharmacy will label the medication with a label appropriate for take-home use (if the medication is a bulk product containing multiple doses) and send it to the clinic. Administration MUST be documented on eMAR. The LIP must counsel the patient on directions for use and side effects.
 - b. If the medication is floorstocked, an order by the LIP should be placed in Epic. Then the clinic staff MUST label the medication with an appropriate label if sending a bulk product home with the patient. The patient's name, the medication name, strength and directions for use, and LIP's name must be included on the label and affixed to the product. The medication dispensed should be noted by the provider in Epic. The LIP must counsel the patient on directions for use and side effects. Administration MUST be documented in eMAR so the patient is appropriately billed.

Additional information can be obtained by calling Pharmacy Financial Counselor at 384-6907.

Approved: Pharmacy and Therapeutics Subcommittee
Hospital Advisory Committee