Heparin-Induced Thrombocytopenia

Recent Advances in Management

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Heparin-induced Thrombocytopenia

- Heparin-induced thrombocytopenia (HIT), an antibody-mediated syndrome, is associated with significant morbidity and mortality
  - considered a rarity in the past
    - unrecognized by many clinicians
    - diagnoses can be difficult to confirm
  - until recently there was no therapeutic options other than discontinuation of heparin
Epidemiology

- Thrombocytopenia is one of the most common laboratory abnormalities found among hospitalized patients.
- 0.76% in therapeutic and less than 0.1% in prophylactic use.
- Serologically proven HIT occurs in 1.5% to 3% of patients with heparin exposure.
- Mortality 20%, 10% require amputation.

Epidemiology

- 12 million patients have heparin exposure
- the chance of significant exposure to heparin exceeds 30-50% in hospitalized patients
  - acute coronary syndrome (UA / MI)
  - pulmonary embolism
  - deep venous thrombosis and prophylaxis
  - stroke / atrial fibrillation
  - heparinized pulmonary wedge catheters
  - heparin flush
Bleeding and Clotting

- present with mucocutaneous bleeding, ranging from petechiae and ecchymoses to life-threatening gastrointestinal and intracranial hemorrhage

- paradoxically, the most feared consequence in these patients with a low platelet count is not bleeding but clotting
Thrombosis

- Thrombosis is mostly venous not arterial
- May result in
  - Bilateral deep venous thrombosis of the legs
  - Pulmonary embolism
  - Venous gangrene of fingers, toes, penis, or nipples
  - Myocardial infarction, stroke
  - Mesenteric arterial thrombosis
  - Limb ischemia and amputation

Circulation 1999;100:587-93
Thromb Haemost 1993;70:554-61
Thrombosis

- thromboembolic complications
  - occurs in at least 30% to 40% of HIT cases
  - mortality estimated at 30%
  - increased length of hospital stay

Circulation 1999;100:587-93
medslides.com/Thromb Haemost 1993;70:554-61
Differential Diagnosis of Acquired Thrombocytopenia

- **Drugs**
  - heparin
  - procainamide
  - diuretics (furosemide)
  - H₂ blockers (cimetidine)
  - thrombolytic therapy
  - GP IIb/IIIa antagonists

- **Devices**
  - membrane oxygenator
  - intra-aortic balloon pump

- **Pseudothrombocytopenia**
  - platelet clumping
  - hemodilution

- **Associated disorders**
  - hypersplenism
  - infections/sepsis
  - hypotension and subsequent disseminated intravascular coagulation

- **Other causes**
  - chronic idiopathic thrombocytopenia purpura with exacerbation
  - antiphospholipid antibody syndrome
Heparin Induced Thrombocytopenia

- HIT
  *(heparin-induced thrombocytopenia)*
- HAT
  *(heparin-associated thrombocytopenia)*
- White-clot syndrome
  first noted in the surgical literature
HIT Syndrome

- **Type I**
  - associated with an early (within 4 days) and usually mild decrease in platelet count (rarely <100 x 10⁹/L)
  - typically recovers within 3 days despite continued use of heparin
  - nonimmunologic mechanisms (mild direct platelet activation by heparin)
  - not associated with any major clinical sequelae
  - occurs primarily with high dose iv heparin
HIT Syndrome

- Type II
  - substantial fall in platelet count (> 50%)
  - count in the 50,000 - 80,000 /mm range
  - typical onset of 4-10 days
  - occurs with any dose by any route
  - induced by immunologic mechanisms
  - rarely causes bleeding (think of alternative Dx)
  - potential for development of life-threatening thromboembolic complications
Risks for HIT

- **Type I**
  - intravenous high-dose heparin

- **Type II**
  - varies with dose of heparin
  - unfractionated heparin > LMWH
  - bovine > porcine
  - surgical > medical patients
  - Female > male
HIT

- An immunoglobulin-mediated adverse drug reaction characterized by:
  - platelet activation
  - thrombocytopenia
  - thrombotic complications
Pathogenesis of HIT

- Most commonly caused by IgG antibodies (designated HIT-IgG) that activate platelets through their Fc receptors
Antigenic Heparin/PF4 Complex

- antigen in HIT is a complex of “-” charged heparin polysaccharide and “+” charged protein tetramer (platelet factor 4 or PF4)
- PF4 is released from platelet storage granules during platelet activation
- unfractionated heparin wraps around PF4 to a greater extent than LMWH
Effects on the coagulation system

- Binding of heparin to PF4 neutralizes the anticoagulant effect of heparin
- Immune complexes composed of heparin, PF4, and IgG binds to platelet Fc receptors, resulting in strong platelet activation, and ultimate increase in thrombin generation
Cascade of events leading to formation of HIT antibodies and prothrombotic components
Diagnosis of HIT

- absence of another clear cause for thrombocytopenia
- the timing of thrombocytopenia
- the degree of thrombocytopenia
- adverse clinical events (most often thrombocytopenia)
- positive laboratory tests for HIT antibodies
# 4Ts HIT score

<table>
<thead>
<tr>
<th>Category</th>
<th>2 points</th>
<th>1 point</th>
<th>0 point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>&gt; 50% fall, or nadir ≥ 20 x 10^9/L</td>
<td>30–50% fall, or nadir 10-19 x 10^9/L</td>
<td>&lt; 30% fall, or nadir &lt; 10 x 10^9/L</td>
</tr>
<tr>
<td>Timing of the decrease in platelet count</td>
<td>Days 5 to 10, or &lt; day 1 with recent heparin (past 30 days)</td>
<td>&gt; Day 10 or timing unclear, or &lt; day 1 if heparin exposure within past 30-100 days</td>
<td>&lt; Day 4 (no recent heparin)</td>
</tr>
<tr>
<td>Thrombosis or other sequelae</td>
<td>Proven thrombosis, skin necrosis, or acute systemic reaction after heparin bolus</td>
<td>Progressive, recurrent, or silent thrombosis; erythematous skin lesions</td>
<td>None</td>
</tr>
<tr>
<td>Other causes of thrombocytopenia</td>
<td>None evident</td>
<td>Possible</td>
<td>Definite</td>
</tr>
</tbody>
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Pretest probability score: 6–8 = High; 4–5 = Intermediate; 0–3 = Low
Characteristic features of HIT

- platelet count typically begin to fall 5-8 days after heparin therapy is started
- may develop within the first day with repeat exposure
- consider other causes if occurs after 2 wks of therapy
- thrombocytopenia is usually mild to moderate, with platelet counts ranging from 20 to 150 x 10^9/L (threshold for thrombocytopenia)
Unusual Clinical Events Suspicious for HIT

- mild to moderate thrombocytopenia, often in conjunction with thrombosis
- adrenal hemorrhagic infarction (caused by adrenal vein thrombosis)
- warfarin-induced venous limb gangrene
- fever, chills, flushing, or transient amnesia beginning 5 to 30 minutes after an IV heparin bolus
- heparin-induced skin lesions associated with HIT antibodies, even in the absence of thrombocytopenia
Clinical Syndromes Associated with HIT

- Venous thromboembolism
- Arterial thrombosis
- Skin lesions at heparin injection site
- Acute platelet activation syndromes
Venous Thromboembolism

- Deep vein thrombosis *
- Pulmonary embolism *
- Venous limb gangrene
- Adrenal hemorrhagic infarction
- Cerebral sinus thrombosis

* most common complication of HIT

Arterial thrombosis

- Lower limb involvement
- Stroke
- Myocardial infarction
- Other

Venous thrombotic events predominate over arterial events by 4:1 ratio. Usually involving large vessels.

Other Clinical Syndromes

- Skin lesions at heparin injection site
  - Skin necrosis
  - Erythematous plaques
- Acute platelet activation syndrome
  - Acute inflammatory reactions (fever, chills, etc.)
  - Transient global amnesia
Skin lesions associated with HIT

LEFT: Heparin-induced erythematous plaques.
RIGHT: Heparin-induced skin necrosis
Common Laboratory Tests for HIT

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAA</td>
<td>Rapid and simple</td>
<td>Low sensitivity - not suitable for testing multiple samples</td>
</tr>
<tr>
<td>SRA</td>
<td>Sensitivity &gt;90%</td>
<td>Washed platelet (technically demanding), needs radiolabeled material $^{14}$C</td>
</tr>
<tr>
<td>HIPA</td>
<td>Rapid, sensitivity &gt;90%</td>
<td>Washed platelets</td>
</tr>
<tr>
<td>ELISA</td>
<td>High sensitivity,</td>
<td>High cost, lower specificity for clinically significant HIT detects IgA and IgM</td>
</tr>
</tbody>
</table>

Thromb Haemost 1998;79:1-7
Functional Assays

- exploits the ability of HIT antibodies to activate normal platelets
  - platelet aggregation assay (PAA)
  - serotonin release assay (SRA)
  - heparin induced platelet activation (HIPA)
- use of washed donor platelets increase sensitivity and specificity to >90% for SRA and HIPA
Management of HIT

- Risk for thrombosis is high in HIT, prevention of thrombosis is the goal of intervention
- Heparin is contraindicated in patients with HIT
- Discontinuation of heparin - all sources of heparin must be eliminated
- Most patients will require treatment with an alternate anticoagulant for
  - Initial clinical problem
  - HIT induced thrombosis
Antithrombotic Treatment

- LMWH (enoxaparin and dalteparin)
  - in vitro studies showed virtually 100% cross-reactivity with HIT antibodies
  - lack large, controlled studies
  - anecdotal reports of persistent or recurrent thrombocytopenia during treatment
Antithrombotic Treatment

- **Warfarin**
  - caution if INR >4
  - high INR corresponds to a marked reduction in protein C levels, i.e., there is insufficient protein C activity to regulate the ↑thrombin generation found in HIT
  - associated with progression of deep venous thrombosis to venous limb gangrene
  - considered contraindicated in acute HIT, but reasonable to use in longer-term anticoagulation
  - Should be started when plt exceeds 150

Thromb Haemost 1998;79:1-7
Ann Intern Med 1997;127:804-812
New Antithrombin Drugs

Agents that reduce or inhibit thrombin

- bivalirudin
- danaparoid sodium (Orgaran)
- Fondaparinux (indirect factor X inhibitor)
- Argatroban
Danaparoid (Orgaran®)

- a low-molecular-weight heparinoid
  - mixture of anticoagulant glycosaminoglycans (heparin sulfate, dermatan sulfate, and chondroitin sulfate) with predominant anti-factor Xa activity
- rapid anticoagulant effect with IV bolus
- long half-life (~25 hours) for anti-Xa activity
- in vitro cross-reactivity with the HIT antibody (10% to 40%) does not predict development of thrombocytopenia or thrombosis

Blood 1996;88(Suppl 1):626a
Thromb Haemost 1993;70:554-561
Argatroban (Novastan®)

- a small synthetic non-polypeptide molecule
- a direct thrombin inhibitor
- FDA approved June 30, 2000
- has the same theoretical advantages of lepirudin
  - short half-life (< 1 hr)
  - lack of cross-reactivity for HIT antibodies
  - potent antithrombin activity
- metabolized predominantly by the liver, may require dose adjustment
- excreted normally even in severe renal failure
- 2 mic/kg/min over 1-3 hours PTT 1.5 -3 times
Adjunctive Therapies for HIT

- Plasmapheresis
  - can reduce the concentration of HIT antibodies
  - replace deficient plasma anticoagulant factors
- Aspirin/Clopidogril/Gp2b3a inhibitors
  - can inhibit platelet activation by HIT antibodies
Patients who are to receive any heparin should have a baseline platelet count (2C).

- Post-operative patients including obstetric cases receiving unfractionated heparin (UFH) should have platelet count monitoring performed every 2–3 d from days 4 to 14 or until heparin is stopped (2C).

- Post-cardiopulmonary bypass patients receiving low molecular weight heparin (LMWH) should have platelet count monitoring performed every 2–3 d from days 4 to 14 or until heparin is stopped (2C).

Post-operative patients (other than cardiopulmonary bypass patients) receiving LMWH do not need routine platelet monitoring (2C).
BJH guideline

- Post-operative patients and cardiopulmonary bypass patients who have been exposed to heparin in the previous 100 d and are receiving any type of heparin should have a platelet count determined 24 h after starting heparin (2C).

- Medical patients and obstetric patients receiving heparin do not need routine platelet monitoring (2C).

- If the platelet count falls by 30% or more and/or the patient develops new thrombosis or skin allergy or any of the other rarer manifestations of heparin-induced thrombocytopenia (HIT) between days 4 and 14 of heparin administration, HIT should be considered and a clinical assessment made (2C).

- HIT can be excluded by a low pre-test probability score without the need for laboratory investigation (2B).
If the pre-test probability of HIT is not low, heparin should be stopped and an alternative anticoagulant started in full dosage whilst laboratory tests are performed (1C).

Platelet aggregation assays using platelet-rich plasma (PRP) lack sensitivity and are not recommended (2C).

- Platelet activation assays using washed platelets [heparin-induced platelet activation assay (HIPA) and serotonin release assay (SRA)] have a higher sensitivity than platelet aggregation assays using PRP and are regarded as the reference standard, but are technically demanding and their use should be restricted to experienced laboratories (2C).
Non-expert laboratories should use an antigen assay of high sensitivity. Only the IgG class needs to be measured. Useful information is gained by reporting the actual optical density, degree of inhibition by high dose heparin, and the cut-off point for a positive test rather than simply reporting the test as positive or negative (1B).

• In making a diagnosis of HIT, the clinician’s estimate of the pre-test probability of HIT, together with the type of assay used and its quantitative result [enzyme-linked immunosorbent assay (ELISA) only] and information on reversal using higher doses of heparin should be used to determine the post-test probability of HIT (2B).

• HIT can be excluded in patients with an intermediate pre-test score who have a negative particle gel immunoassay (2B).
BJH guideline

- HIT can be excluded in all patients by a negative antigen assay of high sensitivity (1A).

- • Clinical decisions should be made following consideration of the risks and benefits of treatment with an alternative anticoagulant (1C).

- • For patients with suspected (non-low pre-test probability) or confirmed HIT, heparin should be stopped and full dose anticoagulation with an alternative anticoagulant commenced (1B).

- • LMWH should not be used in the treatment of HIT (1A).

- • Warfarin should not be used until the platelet count has recovered to the normal range. When introduced, an alternative anticoagulant must be continued until the International Normalized Ratio (INR) is therapeutic. Argatroban affects the INR and this needs to be considered when using this drug. A minimum overlap of 5 d between non-heparin anticoagulants and vitamin K antagonist (VKA) therapy is recommended (1B).
BJH guideline

- Platelets should not be given for prophylaxis (1C) but may be used in the event of bleeding (2C).
- If the patient has received a VKA at the time of diagnosis it should be reversed by administering intravenous vitamin K (2C).
- Danaparoid in a therapeutic dose regimen is a suitable alternative anticoagulant for use in patients with HIT (1B).
- Danaparoid at prophylactic doses is not recommended for the treatment of HIT (1B).
- Monitoring the anticoagulant effect of danaparoid using an anti-Xa assay with specific danaparoid calibrators should be considered in patients >90 kg and in patients with renal impairment (glomerular filtration rate <30 ml/min) (2C).
• An argatroban infusion adjusted to an activated partial thromboplastin time (APTT) ratio of 15–30 (but not exceeding 100 s) is a suitable alternative anticoagulant for the treatment of patients with HIT (1C).

• Patients on argatroban undergoing transition to warfarin should have an INR 4 for 2 d prior to discontinuing argatroban (2C).

Therapeutic dose fondaparinux is an acceptable alternative anticoagulant for managing HIT but it is not licensed for this indication. (2C
BJH guideline

- Patients should be therapeutically anticoagulated for 3 months after HIT with a thrombotic complication (1A) and for 4 weeks following HIT without a thrombotic complication (2C).

- Women with HIT in pregnancy should be treated with a non-cross reacting anticoagulant. Danaparoid should be used where available and fondaparinux also considered (2C).

- Patients with previous HIT who are antibody negative (usually so after >100 d) who require cardiac surgery should receive intra-operative UFH in preference to other anticoagulants, which are less validated for this purpose. Pre- and post-operative anticoagulation should be with an anticoagulant other than UFH or LMWH (1B).
Patients with recent or active HIT should have the need for surgery reviewed and delayed until the patient is antibody-negative if possible. They should then proceed as above. If deemed appropriate, early surgery should be carried out with an alternative anticoagulant (1C).

• As an alternative anticoagulant in cases where urgent surgery is required we suggest bivalirudin (2B).

• In patients with previous or present HIT who require coronary intervention including angiography and percutaneous coronary intervention we recommend the use of bivalirudin (2B).
Steps to Prevent HIT

- porcine heparin preferred over bovine heparin
- LMWH preferred over unfractionated heparin
- oral anticoagulation should be started as early as possible to reduce the duration of heparin exposure
- intravenous adapters should not be flush with heparin
- monitoring serial plate counts for developing thrombocytopenia
Long term monitoring

- Use alternative anticoagulants until plt counts recover
- Continue treatment for 4 weeks
- Transit to warfarin when plt > 150
- Overlap with DTI for at least 5 days until INR in the therapeutic range for 48 hours
Patients with history of HIT

- No circulating Ab:
- short term intraoperative heparin for CABG
- Bivalirudin or argatroban for cath and PCI
- Persistent HIT Ab: no heparin

Heparin-induced thrombocytopenia: pathogenesis, frequency, avoidance and management. Warkentin TE. Drug Safety. 1997;17:325-341

Danaparoid (Orgaran) for the treatment of heparin-induced thrombocytopenia (HIT) and thrombosis. Warkentin TE. Blood. 1996;88(Suppl 1):626a


Glycoprotein IIb/IIIa inhibitors can prevent heparin-mediated platelet activation in heparin-induced thrombocytopenia (abst) Blood 1997;90(Supple 2):63b

World Wide Web

www.thrombosite.com