Heparin Induced Thrombocytopenia

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Heparin Induced Thrombocytopenia

• First recognized as complication of heparin in the 1970's, but the understanding of pathogenesis, diagnosis, and treatment has occurred in the last ten years
• Heparin -induced thrombocytopenia is an antibody-mediated drug reaction that may be complicated not by just low platelets but arterial or venous thrombosis

Heparin Induced Thrombocytopenia

• Heparin –induced thrombocytopenia occurs in up to 5 % of patients receiving unfractionated heparin and in 0.5% receiving low–molecular weight heparin
• It can occur with miniscule amounts of heparin and the clinical situation effects frequency with orthopedic surgery and cardiac surgery more common than medical patients

Temporal Aspects

• In majority of patients the sentinel event thrombocytopenia occurs four or more days after start of heparin
• However, rapid onset within 10 hours can occur in patients who received heparin within the last 100 days
Heparin-Induced Thrombocytopenia

Pathophysiology

- HIT is a hypercoagulability state associated with increased thrombin generation and increased risk of venous and arterial thrombosis
- This risk is maintained unabated for many days after heparin exposure

Pathophysiology

- Heparin induces antibodies of IgG class whose target is multimolecular complexes of platelet factor 4 and heparin bound to platelet surface
- These complexes occupy platelet FcγIIa receptors causing platelet activation and circulating platelet derived microparticles
When to Suspect

- **Thrombocytopenia** with a drop of 50% or greater from baseline is most common clinical finding.
- Rare to have platelet counts less than 15x10^9/L.
- Thrombosis occurs in most patients with DVT more common than arterial.

Factors Influencing the Frequency of HIT

<table>
<thead>
<tr>
<th>Factor</th>
<th>Influence</th>
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<tr>
<td>Type of heparin</td>
<td>Longer HEP &gt; shorter (historical versus modern HEP: &gt;10%) is generally,</td>
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<td>Patient population</td>
<td>Post surgery &gt; medical &gt; hospital</td>
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<tr>
<td>Duration of heparin use</td>
<td>Duration of heparin use typically begins between days 5-10, with</td>
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<td>thrombocytopenia usually reached by day 7-14; thus, each day of</td>
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<td>heparin use beyond 5-10 days increases risk of HIT</td>
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<tr>
<td>Site of heparin use</td>
<td>Change from prophylactic dose to therapeutic dose heparin can cause</td>
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<td></td>
<td>platelet count fall in patients with HIT antibodies</td>
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<tr>
<td>Sex</td>
<td>Males &gt; females</td>
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<tr>
<td>Definition of thrombocytopenia used</td>
<td>Prothrombin platelet count (PLT &gt; 50%) is more sensitive for detecting</td>
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<td>HIT: using absolute platelet count threshold (e.g., &gt;100,000 or &gt;150,000)</td>
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_Aster RH. New England Journal of Medicine 1995; 332:1374 [editorial]_
### Acute Systemic Reactions to Heparin Bolus

- Occurs 5-30 minutes after iv heparin bolus
- Prior heparin use with past 5-100 days
- Abrupt fall but reversible drop in platelet count

### Diagnosis

- Clinical syndrome should be confirmed by lab assay
- May require assay off of heparin
- Two major group of assays a) platelet activation assays b) PF-4 dependent antigen assays
- Neither set of assays perfect
Management

- HIT suspected but low probability follow patient closely consider holding heparin follow platelet count and look for thrombosis? Send assay

- HIT suspected intermediate or high probability stop heparin send assay anticoagulate
Heparin Induced Thrombocytopenia

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Case Presentation #1

- 67 year old male admitted for urgent CABG doing well on post-operative day 3. Chest pain at surgical site and mild fatigue, but otherwise asymptomatic. Noted to have thrombocytopenia beginning 1 day after surgery
  - PMH: triple vessel CAD
  - FH: CAD, DM
  - SH: non-smoker, rare alcohol use

Thought Process

- Relatively abrupt onset of thrombocytopenia after cardiac bypass surgery
  - Exposure to heparin during heart lung bypass
  - Complete blood count otherwise unremarkable
  - Previously normal platelet count prior to surgery
Delayed-onset HIT

- Discontinue heparin administration
  - including unintended heparin exposures for catheter flushes, arterial line flushes, etc.
  - avoid low molecular weight heparin as well given potential for cross-reactivity
- Is this enough?
  - Incidence of new thrombotic events ranging 19%-52% in patients with discontinuation of heparin alone without additional anticoagulation

Heparin Induced Thrombocytopenia-Treatment

- Systemic anticoagulation with a direct thrombin inhibitor
  - argatroban and lepirudin approved for treatment by the United States FDA
  - Cannot wait for results of serologic testing
- Initiation of warfarin therapy
  - Delay warfarin until substantial platelet recovery
  - Avoid unopposed warfarin therapy
  - Duration of therapy 3-6 months
Laboratory testing positive (functional assay) for the diagnosis of HIT

Clinically asymptomatic, placed on systemic anticoagulation with Argatroban

- Doppler study positive for lower extremity DVT
- After normalization of platelet count started on warfarin therapy
- Received 4 months of warfarin therapy

PMH: chronic MRSA
FH: CVA, CHF
SH: non-smoker, no alcohol use

Case Presentation #2

- 59 year old male, small bowel obstruction, exploratory laparotomy with removal of infected mesh

More pronounced drop in platelet count after IV UFH

Which came first?

Diagnosis

- Noted to have the development of thrombocytopenia 5-6 days after SQ UFH

- Started on IV heparin on day 4 after diagnosis of lower extremity DVT

- More pronounced drop in platelet count after IV UFH

- DVT versus HIT
Platelet Count

Days

SQ UFH
DVT Diagnosed
IV UFH
HIT Testing

Heparin and Thrombocytopenia

• Many possible etiologies of thrombocytopenia in patients acutely ill
  ✓ Drug-induced, immune-mediated thrombocytopenia (ITP), sepsis, DIC, consumptive process

Heparin and Thrombocytopenia

• Study by Oliveira et al of 2,420 patients treated with heparin for 4 days or longer
  ✓ 881 patients (36%) developed thrombocytopenia
  ✓ Minority of patients (9%) with clinically suspected HIT
  

Clinical Suspicion for HIT

• Time course of thrombocytopenia could be consistent with HIT
  ✓ Starting with SQ UFH or IV UFH
  ✓ New thrombotic event
  • ? Too close to initiating SQ heparin
## Clinical Suspicion for HIT

- Exposure to heparin after surgical procedure
- If sufficient clinical suspicion:
  - Need to start direct thrombin inhibitor

## Diagnostic Questions

- Was the DVT unrelated to HIT, but more due to risk of DVT after surgery and inpatient hospitalization?
  - Either way needs systemic anticoagulation

## Treatment

- Laboratory testing (functional assay) positive for HIT
- Systemic anticoagulation with a direct thrombin inhibitor (argatroban)

## Diagnostic Questions

- After sufficient recovery of platelet count to near normal:
  - Warfarin started concurrently with argatroban
  - Argatroban discontinued after INR therapeutic
- Warfarin therapy continued for 4-6 months
**Case Presentation #3**

- 59 year old female admitted for unstable angina. Underwent cardiac catherization and subsequently a stenting procedure. Received heparin and abciximab (gp IIbIIIa agent) as a part of procedure, and subsequently placed on antiplatelet therapy
  - PMH: CAD
  - FH: CAD, DM

**Thought Process**

- Abrupt and severe thrombocytopenia that developed 6 days after therapy with both abciximab and heparin
- Acute drop in platelet count
  - Time course of thrombocytopenia
  - Severity of thrombocytopenia
  - Which is the potentially offending agent?
### Differential Diagnosis

- Severe thrombocytopenia related to the use of glycoprotein IIb/IIIa agent versus HIT
- Timing of thrombocytopenia
  - Thrombocytopenia abruptly occurred 7 days after abciximab and heparin

### Diagnosis

- Overall clinical course and laboratory findings more suggestive of abciximab induced thrombocytopenia
  - Direct thrombin inhibitor not started
- Gradual improvement in platelet count over the next 5-7 days
  - Supportive care with platelet transfusions
  - PF4 Antibody testing negative

### Differential Diagnosis

- Timing does not differentiate
  - Severity of thrombocytopenia more consistent with abciximab induced thrombocytopenia
  - Can occur within hours, or 5-8 days after therapy
    - Much sooner if recent exposure/sensitization