Heparin Induced Thrombocytopenia

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Sample Case

- 64 yo woman with endocarditis
- Platelet count decreases from 161k on day 7 to 60k on day 9
- Been receiving low molecular weight heparin 40k daily since admission
HIT

- Does not induce bleeding
- Paradoxical PROTHROMBOTIC state
- 1 in 5000 patients
- 1 to 3% risk after cardiac surgery
- In 50% of patients with HIT, thrombotic complications occur
**HIT**

<table>
<thead>
<tr>
<th>KEY CLINICAL POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPARIN-INDUCED THROMBOCYTOPENIA</strong></td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia (HIT) is characterized by a decrease in the platelet count of more than 50% from the highest platelet count value after the start of heparin, an onset 5 to 10 days after the start of heparin, hypercoagulability, and the presence of heparin-dependent, platelet-activating IgG antibodies. Use of a scoring system that takes into account the timing and magnitude of the platelet count fall, new thrombosis, and the likelihood of other reasons for thrombocytopenia is helpful in assessing the pretest probability of HIT. Delayed-onset HIT develops after the cessation of heparin, and spontaneous or autoimmune HIT develops in the absence of heparin exposure. Platelet factor 4–heparin antibody tests should be ordered only if clinical features reasonably suggest HIT. These tests have a high negative predictive value but a low positive predictive value. Treatment of acute HIT requires the cessation of heparin and the initiation of therapeutic-dose anticoagulation with an alternative agent (argatroban, danaparoid, fondaparinux, or bivalirudin). Warfarin should be avoided in patients with acute HIT.</td>
</tr>
</tbody>
</table>
Onset of HIT

- 5-10 days after exposure
- Surgery can reset the clock
- Heparin exposure within 90 days
  - Abrupt onset HIT
  - Anaphalactic reaction within 30 min
- Catastrophic HIT
Pathogenesis

- IgG antibodies recognizes neoepitopes on positively charged chemokine PF4 within PF4-polyanion complexes

- PF4 binds heparin
  - Can bond other polyanions
  - Nucleic acids/polysaccharides on bacteria

- PF4-heparin complexes coat platelets
  - Induce IgG response
Pathogenesis

Mechanism of heparin induced thrombocytopenia (HIT)

- PF4
- Heparin
- Platelet
- IgG
- Immune complex
- Fc receptor
- Platelet removal by splenic macrophages
  - Thrombocytopenia

- Platelet activation
  - Platelet release
  - Platelet aggregation
  - Thrombosis

Release of procoagulant microparticles
Risk of HIT

- 10x higher in unfractionated heparin
- Higher risk after major surgery
- Rare on obstetrics
Diagnosis of HIT

- More than 50% drop
- 5-10 days after exposure
- 4 T scoring system
Types of HIT

- **Type 1**
  - Within one to two days
  - Often returns to normal, with continued heparin
  - Non immune mediated platelet aggregation
  - Nadir typically 100k

- **Type 2**
  - Antibodies to PF4 complexed to heparin
  - Clinically significant
Type of HIT

Distinguishing characteristics of the two types of heparin-induced thrombocytopenia

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>10 to 20 percent</td>
<td>1 to 3 percent</td>
</tr>
<tr>
<td>Timing of onset</td>
<td>1 to 4 days</td>
<td>5 to 10 days after start of heparin</td>
</tr>
<tr>
<td>Nadir platelet count</td>
<td>100,000/microL</td>
<td>usually &gt;20,000/microL; median nadir 60,000/microL</td>
</tr>
<tr>
<td>Antibody mediated</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Thromboembolic sequelae</td>
<td>None</td>
<td>30 to 80 percent</td>
</tr>
<tr>
<td>Hemorrhagic sequelae</td>
<td>None</td>
<td>Rare</td>
</tr>
<tr>
<td>Management</td>
<td>Observe</td>
<td>Cessation of heparin, alternative nonheparin anticoagulation to prevent thrombosis</td>
</tr>
</tbody>
</table>


Graphic 50170 Version 2.0
### Table 1. 4T Scoring System for Evaluating the Pretest Probability of Heparin-Induced Thrombocytopenia.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Acute thrombocytopenia</td>
<td>Platelet count decrease of &gt;50% and nadir ≥20,000/mm³</td>
</tr>
<tr>
<td>Timing of onset</td>
<td>Day 5–10, or day 1 if recent heparin exposure</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>New thrombosis or anaphylactoid reaction after heparin bolus</td>
</tr>
<tr>
<td>Other cause of thrombocytopenia</td>
<td>None</td>
</tr>
</tbody>
</table>

* Total score: 6–8, indicating high score; 4 or 5, indicating intermediate score; 0–3, indicating low score.

* Adapted from Lo et al. A low 4T score (0 to 3 points) has a high negative predictive value. The day that heparin was started is considered as day 0. The onset of heparin-induced thrombocytopenia (HIT) is defined as the day that the platelet count begins to decrease. Patients in whom the score is difficult to apply, owing to missing platelet count values or coexisting conditions causing thrombocytopenia, and those with an intermediate or high score require further evaluation.
HIT

HIT suspected

Stop ALL forms of heparin

Ongoing anticoagulation indicated?

Yes

New or pre-existing arterial or venous thrombosis

Argatroban, danaparoid, or fondaparinux

See note*

Yes

Other indications for anticoagulation

Thrombocytopenia without thrombosis

Observation*

? Yes/No

Confirm diagnosis:
- HIPA
- Serotonin release assay
- Heparin-PF4 Ab ELISA

Negative

Re-evaluate for other causes of thrombocytopenia
Delayed Onset HIT

- Thrombosis after heparin has been withdrawn
- > than 5-10 days after exposure
- High morbidity, can present with thrombosis on readmission
  - If treated with heparin, higher complication rate
HIT

- Subclinical HIT
  - Refers to patient has recovered from HIT
  - Still present antibodies
HIT

- Spontaneous HIT
  - Has been described without heparin exposure
  - Associated with venous and arterial thrombosis
  - Typical previous infectious (gram neg bacteria) or inflammatory event
  - Pos immunoassay
  - Significant inflammatory response causing activation of PF4 without need for heparin, causing platelet activation
  - Non heparin polyanions causing activation of PF4 directed antibodies
Complications
Complications

- Venous more common than arterial events
- Complications of thrombosis
  - Skin necrosis
  - Gangrene
  - Organ ischemia
### Testing after surgery

#### Patient population, frequency of HIT-IgG antibodies, and clinical HIT

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Days of treatment</th>
<th>Frequency heparin-induced antibodies</th>
<th>Frequency of clinical HIT, percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac, UFH</td>
<td>5.1 ± 2.2 (SD)</td>
<td>20.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Orthopedic, UFH</td>
<td>9.2 ± 2.2</td>
<td>9.3</td>
<td>14.1</td>
</tr>
<tr>
<td>Orthopedic, LMWH</td>
<td>9.5 ± 3.0</td>
<td>3.2</td>
<td>7.5</td>
</tr>
</tbody>
</table>
Lab Testing for HIT

- ELIZA testing: Anti PF4 heparin enzyme immunoassay
  - Low positive predictive value
  - Can lead to overdiagnosis/treatment
  - Antibodies typically present before drop in platelets
Lab testing for HIT

- Functional Assays
  - Increase specificity
  - Longer time to get results

- Serotonin Release Assay
  - Negative value essentially rules out HIT

- Use of T score and ELIZA to help determine need of treatment
Bleeding

- Typically low complications of bleeding
- No need for prophylactic transfusions
- Rarely < 20k
- Platelets can be transfused if needed/bleeding
Differential Diagnosis

- Disseminated Intravascular Coagulation
- Thrombotic microangiopathic process
- ITP
- Thrombocytopenia from medications
Treatment of HIT

- Prompt cessation of heparin products
- Alternative anticoagulation at a therapeutic dose
  - Prophylactic dosing not sufficient
Timing of alternative anticoagulation

- Plt count > 150 x 2 days
- Then consider Vit K antagonists
- Risk of gangrene/limb loss
  - Decreasing protein C
Treatment of alternative anticoagulation

- Overlap of second anticoagulant needed
- At least 5 days!
Treatment

- Argatroban
  - FDA approved HIT

- Danaparoid
  - FDA approved HIT

- Fondoparinux
  - Not FDA approved

- Bivalrudin
  - FDA approved more in HIT patients undergoing PCI
Argatroban

- Used in critically ill patients
- Requires IV administration
- Affects INR
  - Makes bridging difficult
  - Recall need baseline INR, may need to keep on argatroban until INR > 4
  - Need to bridge x 5 days
Danaparoid

- IV or subcutaneous administration
- Can be monitored using Xa levels
Fondaparinux

- Nice alternative in outpatient setting
- Not approved
  - Retrospective Data
Direct thrombin inhibitors

- No studies
- Theoretically could be considered but need more data
- Some case reports
  - Possibly consider if no other options.....
Length of anticoagulation

- If no thrombosis
  - Unclear need for length of anticoagulation
  - At least one month (my preference is 3 months)

- If thrombosis
  - 3 months is the minimum
  - Need to repeat HIT antibodies
Rechallenge

- Avoid if at all possible....

- CPB after HIT
  - Repeat functional assays
  - Consider rechallenge if negative
  - Bivalrudin or Argatroban if urgent or positive assay
Patience....

"Your insurance has run out. We're discharging you from the 'Observation Care' floor to the 'Who Cares?' room in the basement."
Case

- Decrease in platelet count after LMWH
- T score 5 (decrease in platelet count 2, timing 2, thrombosis 0, and likelihood of other reasons 1)
- Testing and then treatment
THANK YOU !!!!