Heparin-Induced Thrombocytopenia

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Disclosures

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• **Consultant positions:** Boehringer Ingelheim, Bristol-Myers/Squibb, Instrumentation Laboratory, CSL Behring, Daiichi Sankyo

• **Off-label medication use:** not applicable
Objectives

• Understand the approach to the clinical diagnosis of heparin-induced thrombocytopenia
• Apply rational laboratory diagnostic strategies based on clinical suspicion
• Explain therapeutic options and strategies for patients with HIT
Patient Presentation

• 64 year old woman presented with unstable angina found to have severe three-vessel CAD with preserved LV function.
• Undergoes coronary artery bypass grafting.
• Post-operative course complicated by several runs of atrial fibrillation, for which heparin was transiently administered.
• Otherwise, she received no anticoagulants.
Platelet Counts

![Graph showing platelet counts over days with a notable decrease and increase.](image-url)
Patient Presentation

- Three days after discharge, she develops progressive dyspnea and mild pain in both legs. She comes to the ED.
- Tachypneic; $O_2$ saturation 90% on room air.
- Bilateral segmental PE on chest CTA, with non-occlusive DVT in both legs by US.
- IV heparin started.
Platelet Counts

![Graph showing platelet counts over time with a note indicating the start of UFH treatment at day 4.](image-url)
Heparin-induced thrombocytopenia

- Thrombocytopenia
  - <150,000 or a 50% drop from baseline
  - Onset 5-14 days after starting heparin
- Exclusion of other causes of thrombocytopenia
- With or without thromboembolic events
- And a positive laboratory test for HIT
Platelet Factor 4/Heparin Antibodies

• Heparin/PF4 complexes are immunogenic in certain patients, resulting in ternary complexes of heparin/PF4/IgG.
HIT antibodies and platelets, monocytes, and endothelial cells

Pathogenesis of HIT and Thrombosis

Warkentin TE. Circulation, 2004; 110: e454-8
Platelet Count Drop is Typically >50%

N=319

Thrombocytopenia is Typically Mild
Timeline of HIT

Warkentin TE. J Thromb Haemost, 2011; 9: 105-17
Timing of Platelet Count Fall

Rapid Onset HIT

“Classic” Timing for HIT

Delayed HIT

Heparin started
Immune Response to Heparin/PF4

- 435 patients treated with SQ heparin
- 244 showed OD change >15% above baseline
- 63 analyzed for individual Ig classes

Rapid onset HIT

• Rapid drop in platelet count and/or thrombotic events, occurring within hours of initiation of heparin
• Reflects pre-formed anti-PF4/heparin antibodies in the circulation, usually from recent heparin exposure
• Therapy consists of stopping heparin and starting an alternative parenteral anticoagulant (argatroban or bivalirudin)
Delayed onset HIT

• Thrombocytopenia and/or thrombotic events that develop days to weeks after heparin has been stopped
• Reflects anti-PF4/heparin antibodies interacting with endogenous glycosaminoglycans and PF4
• Heparin can exacerbate the thrombocytopenia and/or thrombotic events
"4-T" Scoring System

<table>
<thead>
<tr>
<th>Clinical Finding</th>
<th>Score</th>
<th>Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Thrombocytopenia:</strong></td>
<td>&gt;50% fall, or nadir 20-100 X 10^9/L</td>
<td>30-50% fall, or nadir 10-19 X 10^9/L</td>
<td>Fall &lt; 30% or nadir &lt;10 X 10^9/L</td>
</tr>
<tr>
<td><strong>Timing of platelet count fall:</strong></td>
<td>Onset between days 5-10; or &lt;1 day if prior exposure.</td>
<td>Onset after day 10, or &lt;1 day but prior exposure &gt;30 days.</td>
<td>Onset before day 5, with no recent exposure.</td>
</tr>
</tbody>
</table>

Thromboembolism and the Initial Presentation of HIT

- Thromboembolic complications may precede the drop in platelet count in ~30% of patients.

Thromboembolic Complications

- Total of 408 patients with positive laboratory testing for HIT; 227 had 434 TE complications.

<table>
<thead>
<tr>
<th>Type of TE</th>
<th>n (%)</th>
<th>Type of TE</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial (all)</td>
<td>126 (29.2%)</td>
<td>Venous (all)</td>
<td>306 (70.8%)</td>
</tr>
<tr>
<td>Limb artery</td>
<td>71 (16.4%)</td>
<td>Proximal DVT</td>
<td>114 (26.4%)</td>
</tr>
<tr>
<td>Thrombotic stroke</td>
<td>26 (6%)</td>
<td>Pulmonary embolism</td>
<td>103 (23.8%)</td>
</tr>
<tr>
<td>Aortic thrombosis</td>
<td>16 (3.7%)</td>
<td>Distal DVT</td>
<td>78 (18.1%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>10 (2.3%)</td>
<td>Cerebral vein thrombosis</td>
<td>7 (1.6%)</td>
</tr>
<tr>
<td>Intra-abdominal artery</td>
<td>3 (0.7%)</td>
<td>Other</td>
<td>4 (0.9%)</td>
</tr>
</tbody>
</table>
## Other Causes of Thrombocytopenia

### Score = 2

- no alternative explanation for platelet fall is evident

### Score = 1

- Possible other cause is evident:
  - sepsis without proven microbial source
  - thrombocytopenia associated with initiation of ventilator
  - other:

### Score = 0

- Probable other cause present:
  - within 72 hours of surgery
  - confirmed bacteremia/fungemia
  - chemotherapy or radiation within past 20 days
  - DIC due to non-HIT cause
  - posttransfusion purpura (PTP)
  - thrombotic thrombocytopenic purpura (TTP)
  - platelet count < 20 AND given a drug implicated in causing D-ITP (see list)
  - non-necrotizing skin lesions at LMWH injection sites (presumed DTH)
  - other:

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

**Relatively Common:** glycoprotein IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban); quinine, quinidine, sulfas antibiotics, carbamazepine, vancomycin

**Less Common:** actinomycin, amitriptyline, amoxicillin/piperacillin/nafcillin, cephalosporins (cefazolin, ceftazidine, 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.

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“4-T” Scoring System

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<tr>
<th>Clinical Finding</th>
<th>Score</th>
<th>Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis or other sequelae:</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>New TE, skin necrosis, or systemic reaction.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive or recurrent TE, skin lesions.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other cause for thrombocytopenia present:</td>
<td>No other cause for fall is present.</td>
<td>Possible cause is present.</td>
<td>Definite other cause is present.</td>
</tr>
</tbody>
</table>

“4-T” Scoring System

Individual scores for each of the ‘4-T’ criteria are added together, giving the likelihood that the patient actually has HIT:

- Score 0-3: Low likelihood
- Score 4-5: Intermediate likelihood
- Score 6-8: High likelihood

Predictive Value of the 4T Score

- Systematic review and meta-analysis of 13 unique studies investigating the 4T Score

<table>
<thead>
<tr>
<th>Reference</th>
<th>High probability</th>
<th></th>
<th>Intermediate probability</th>
<th></th>
<th>Low probability</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIT+</td>
<td>HIT-</td>
<td>HIT+</td>
<td>HIT-</td>
<td>HIT+</td>
<td>HIT-</td>
</tr>
<tr>
<td>Lillo-Le Louët et al17</td>
<td>11</td>
<td>0</td>
<td>24</td>
<td>29</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Lo et al14 (Canada)</td>
<td>8</td>
<td>0</td>
<td>8</td>
<td>20</td>
<td>1</td>
<td>63</td>
</tr>
<tr>
<td>Lo et al14 (Germany)</td>
<td>9</td>
<td>33</td>
<td>11</td>
<td>128</td>
<td>0</td>
<td>55</td>
</tr>
<tr>
<td>Pouplard et al18</td>
<td>8</td>
<td>2</td>
<td>14</td>
<td>115</td>
<td>0</td>
<td>74</td>
</tr>
<tr>
<td>Bryant et al19</td>
<td>4</td>
<td>8</td>
<td>5</td>
<td>87</td>
<td>0</td>
<td>142</td>
</tr>
<tr>
<td>Denys et al23</td>
<td>6</td>
<td>3</td>
<td>4</td>
<td>58</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>Bakchoul et al20</td>
<td>26</td>
<td>28</td>
<td>9</td>
<td>121</td>
<td>0</td>
<td>316</td>
</tr>
<tr>
<td>Crowther et al24</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>8</td>
<td>0</td>
<td>39</td>
</tr>
<tr>
<td>Cuker et al10</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>21</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Berry et al25</td>
<td>6</td>
<td>8</td>
<td>9</td>
<td>23</td>
<td>5</td>
<td>53</td>
</tr>
<tr>
<td>Nellen et al21</td>
<td>39</td>
<td>35</td>
<td>50</td>
<td>308</td>
<td>7</td>
<td>852</td>
</tr>
<tr>
<td>Tawfik et al22</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>24</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Domma et al26</td>
<td>5</td>
<td>0</td>
<td>6</td>
<td>12</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>128</td>
<td>125</td>
<td>148</td>
<td>955</td>
<td>13</td>
<td>1699</td>
</tr>
</tbody>
</table>

Predictive Value of the 4T Score

Predictive Value of the 4T Score

Initial Evaluation and Management in Suspected HIT


- 4Ts score ≥ 4
  - Discontinue heparin. Start alternative anticoagulant. Obtain HIT laboratory testing.

- 4Ts score ≤ 3
  - Continue heparin. Consider alternative diagnoses.
<table>
<thead>
<tr>
<th>Assay</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serologic assays</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF4/heparin polyspecific ELISA:</td>
<td>98-100%</td>
<td>81-89%</td>
</tr>
<tr>
<td>PF4/heparin IgG ELISA:</td>
<td>96-100%</td>
<td>89-94%</td>
</tr>
<tr>
<td>Gel-particle assay:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional assays</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin-release assay:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin-induced platelet activation assay:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet aggregation assay:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diagnostic Testing for HIT

Serologic assays: PF4/heparin polyspecific ELISA has a sensitivity of 98-100% and specificity of 81-89%. PF4/heparin IgG ELISA has a sensitivity of 96-100% and specificity of 89-94%.
Integrating the HIT ELISA result with the 4T score

## Multiple Phases of HIT

<table>
<thead>
<tr>
<th></th>
<th>Suspected HIT</th>
<th>Acute HIT</th>
<th>Subacute HIT A</th>
<th>Subacute HIT B</th>
<th>Remote HIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Thrombotic Risk</td>
<td>?</td>
<td>Increased</td>
<td>Increased?</td>
<td>Increased?</td>
<td>Normal</td>
</tr>
<tr>
<td>Functional HIT assay</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HIT Immunoassay</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

HIT Treatment: General Principles

• For acute HIT:
  • Stop any exposure to heparin or low-molecular weight heparin
  • Initiate an alternative anticoagulant: argatroban, bivalirudin, fondaparinux, or danaparoid

• For suspected HIT:
  • If the 4T score is >3, treat as acute HIT pending laboratory testing results
Approach to management of acute HIT

Is the patient stable?

Yes

Is there renal dysfunction ($Cl_{Cr} < 30 \text{ mL/min}$)?

Yes

Is there hepatic dysfunction ($\text{Bilirubin} > 1.5 \text{ mg/dL}$)?

Yes

Bivalirudin

No

Argatroban

No

Bivalirudin

Danaparoid

No

Danaparoid

Is there renal dysfunction ($Cl_{Cr} < 30 \text{ mL/min}$)?

Yes

Is there hepatic dysfunction ($\text{Bilirubin} > 1.5 \text{ mg/dL}$)?

Yes

Bivalirudin

Danaparoid

No

Arugatroban

Bivalirudin

Danaparoid

No

Bivalirudin

Danaparoid

No

Arugatroban

Bivalirudin

Danaparoid

No

In addition to a DTI or fondaparinux:

• ...we recommend against starting VKA until platelets have substantially recovered (*i.e.*, usually to at least 150 $\times$ 10$^9$/L) ... and that the VKA be initially given in low doses... (Grade 1C).

• ...we recommend that the VKA be overlapped with a non-heparin anticoagulant for a minimum of 5 days and until the INR is within the target range... (Grade 1C).

Treatment in the sub-acute period

• For patients with HIT and thrombosis, we suggest VKA therapy or an alternative anticoagulant be continued for 3 months.

• For patients with HIT [and no thrombosis], we suggest VKA therapy or an alternative anticoagulant be continued for 4 weeks. (ungraded statement)
Antibody Resolution over Time

No. at Risk

Antigen assay  93  36  17  8  6
Activation assay 144  53  23  10  3

## HIT and Surgery

<table>
<thead>
<tr>
<th>Phase</th>
<th>Functional assay</th>
<th>Immuno-assay</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Acute/Subacute A | +                | +            | 1. Delay surgery  
2. If surgery cannot be delayed, use an alternative anti-coagulant (e.g. bivalirudin) or treat with preoperative plasma exchange until functional assay becomes negative |
| Subacute B   | -                | +            | 1. Delay surgery  
2. If surgery cannot be delayed, use heparin |
| Remote       | -                | -            | 1. Heparin |
Can we avoid HIT?

Conclusions

• Diagnosis depends on the relationship between heparin exposure and drop in the platelet count and/or thrombotic events

• Treatment includes stopping heparin and using an alternative anticoagulant

• Antibodies disappear over time and patients may be re-exposed to heparin in certain clinical situations