Heparin-induced thrombocytopenia (HIT)

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Heparin-induced thrombocytopenia (HIT)

- Immune-mediated disorder: heparin-dependent platelet activating IgG Ab (HIT Ab) to heparin/PF4 complex
- Transient strong prothrombotic stage
- HIT: 0.5%-5% of patients receiving heparin
- Thrombosis: 20%-50% of patients with HIT Ab (HITT)
- Surgical (cardiac and orthopedic) > medical > obstetric
- UFH > LMWH
Pathogenesis of HIT

Polyanion: DNA, RNA, bacteria antigens, glycosaminoglycans

UFH, LMWH
Pathogenesis of HIT

- Platelet activation and aggregation
- Platelet decrease > 50%
- Thrombosis (20-50%)

FcγR
Clinical manifestations

• Usually occurs 5-10 days after starting heparin (within 24 hours in cases of recent heparin exposure)
• Median platelet count nadir is about 60 x 10^9/L
• Most patients a ≥ 50% decrease in platelet count
• Complications:
  – Thrombosis (DVT 50%, PE 25%, limb artery 10-15%, stroke 5-10%, MI 3-5%, adrenal v. rare)
  – Warfarin necrosis – venous limb gangrene
  – Anaphylactoid reaction (IV), Skin necrosis (SC)
  – Overt DIC 10-20%
Heparin-induced thrombocytopenia

Summary of 12 HIT patient profiles

- First day of antibody detection
- Beginning of HIT-related platelet count fall
- Platelet count fall ≥50%
- Thrombotic event

EIA-GTI OD (mean +/- SEM)

- Start of heparin
  - Non-HIT (mean day 1.21)
  - HIT (mean day 1.38)

HIT vs. Non-HIT
** P<0.005, * P<0.05

Blood 2009; 113: 4963
Clinical manifestation: Thrombocytopenia

- **Rapid onset HIT**: a decrease in platelet count within 24 hours after receiving heparin $\rightarrow$ presence of circulating HIT Ab (previous exposure within the past few weeks or months)

- **Delayed onset HIT**: decrease of platelet after stopping heparin $\rightarrow$ unusually high level of Ab

- **Spontaneous HIT**: develop of HIT with a highly detected level of HIT Ab but no heparin exposure (classically after orthopedic surgery) = **Autoimmune HIT**
<table>
<thead>
<tr>
<th>Points (0, 1, or 2 for each of four categories: maximum possible score = 8)</th>
<th>2</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>&gt; 50% platelet fall to nadir ≥ 20</td>
<td>30–50% platelet count fall (or &gt; 50% directly resulting from surgery); or nadir 10–19</td>
<td>&lt; 30% platelet fall; or nadir &lt; 10</td>
</tr>
<tr>
<td><strong>Timing</strong>(^a) of platelet count fall, thrombosis, or other sequelae (1st day of putative immunizing exposure to heparin = day 0)</td>
<td>Days 5–10 onset(^a) (typical/delayed-onset HIT); or ≤ 1 day (with recent heparin exposure within past 30 days (rapid-onset HIT))</td>
<td>Consistent with days 5–10 fall, but not clear (e.g., missing platelet counts); or, ≤ 1 day (heparin exposure within past 31–100 days) (rapid-onset HIT); or, platelet fall after day 10</td>
<td>Platelet count fall ≤ 4 days (unless picture of rapid-onset HIT—see two left boxes)</td>
</tr>
<tr>
<td><strong>Thrombosis or other sequelae</strong> (e.g., skin lesions, anaphylactoid reactions)</td>
<td>Proven new thrombosis; or skin necrosis (at injection site); or postintravenous heparin bolus anaphylactoid reaction</td>
<td>Progressive or recurrent thrombosis; or erythematous skin lesions (at injection site); or suspected thrombosis (not proven); hemofilter thrombosis</td>
<td>None</td>
</tr>
<tr>
<td><strong>Other cause for thrombocytopenia</strong></td>
<td>No explanation for platelet count fall is evident</td>
<td>Possible other cause is evident</td>
<td>Definite other cause is present</td>
</tr>
</tbody>
</table>

Pretest probability score: 6–8 = high; 4–5 = intermediate; 0–3 = low
### Table 1 The HIT Expert Probability (HEP) Score (modified from Cuker A, et al. J Thromb Haemost 2010; 8: 2642-2650).

<table>
<thead>
<tr>
<th>Variables</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>-1</th>
<th>-2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Magnitude of fall in platelet count</strong></td>
<td>( &gt; 50% )</td>
<td>( 30%–50% )</td>
<td>( &lt; 30% )</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Timing of fall in platelet count after heparin exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Typical onset HIT is suspected</em></td>
<td>5–10 days</td>
<td>4 days ( or ) 11–14 days</td>
<td>( &gt; 14 ) days</td>
<td>( &lt; 4 ) days</td>
<td></td>
</tr>
<tr>
<td><em>Rapid onset HIT is suspected (previous heparin exposure in last 100 days)</em></td>
<td>( &lt; 48 ) h after heparin re-exposure</td>
<td>( &gt; 48 ) h after heparin re-exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nadir platelet</strong></td>
<td>( &gt; 20 \times 10^9 /L )</td>
<td></td>
<td></td>
<td>( \leq 20 \times 10^9 /L )</td>
<td></td>
</tr>
<tr>
<td><strong>Thrombosis (Select only one)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Typical onset HIT is suspected</em></td>
<td>New VTE or ATE ( \geq 4 ) days after heparin exposure</td>
<td>Progression of VTE or ATE while receiving heparin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Rapid onset HIT is suspected</em></td>
<td>New VTE or ATE after heparin exposure</td>
<td>Progression of VTE or ATE while receiving heparin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Skin necrosis</strong></td>
<td>At SC heparin injection sites</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acute systemic reaction</strong></td>
<td>After IV heparin bolus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td>Presence of bleeding, petechiae or extensive bruising</td>
<td></td>
</tr>
<tr>
<td><strong>Other causes of thrombocytopenia (Select all that apply)</strong></td>
<td>No other apparent cause</td>
<td>1) Presence of a chronic thrombocytopenic disorder</td>
<td>1) Newly initiated non-heparin medication known to cause thrombocytopenia</td>
<td>2) cardiopulmonary bypass within previous 96 h</td>
<td>2) severe infection</td>
</tr>
</tbody>
</table>
Diagnosis of HIT

N = 50, HIT = 8 (expert consensus), 7 (SRA), (60% surgical patients)
Cuker A. J Thromb Haemost. 2010;8:2642

N = 47, HIT = 10 (HPA), (70.2% medical, 61.7% in ICU)
Uaprasert N. Blood Coagul Fibrinolysis 2013;24:26
Diagnostic test

• 2 classes of assays for detecting HIT antibody
  : PF4 dependent immunoassays (screening test)
    – Detect Ab to PF/anion complex
    – Polyspecific (IgG, IgM, IgA) vs. Monospecific IgG
    – Enzyme, particle gel agglutination, lateral flow immunoassay
  : Platelet activation assays (confirmatory test)
    – Demonstrate platelet activating Ab of PF4/heparin
    – Serotonin release assay, HIPA, aggregometry, flow cyt.
Screening immunoassay

PF4/heparin enzyme-immunoassay (EIA)

1. Patient serum or plasma is added to microtiter plates coated with PF4 and heparin.
2. Wash.
3. Add alkaline phosphatase-conjugated goat antihuman IgG.
4. Wash.
5. Add substrate.
6. Color.

PF4/heparin complex

heparin → PF4/heparin complex

HIT-IgG (from serum or plasma)

Alkaline phosphatase-conjugated goat antihuman IgG
Platelet suspension

Add inactivated plasma or serum
Add heparin 0.1-0.5 U/mL

Activated platelet

Microparticle
Flow cytometry
C$^{14}$ serotonin
SRA
Platelet aggregometry

Heparin 100 U/mL

Fc receptor blocking Ab
Table 4. Number of patients with and without HIT in each 4Ts probability category

<table>
<thead>
<tr>
<th>Reference</th>
<th>High probability</th>
<th>Intermediate probability</th>
<th>Low probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIT⁺</td>
<td>HIT⁻</td>
<td>HIT⁺</td>
</tr>
<tr>
<td>Lillo-Le Louët et al(^{17})</td>
<td>11</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>Lo et al(^{14}) (Canada)</td>
<td>8</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Lo et al(^{14}) (Germany)</td>
<td>9</td>
<td>33</td>
<td>11</td>
</tr>
<tr>
<td>Pouillard et al(^{18})</td>
<td>8</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Bryant et al(^{19})</td>
<td>4</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Denys et al(^{23})</td>
<td>6</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Bakchoul et al(^{20})</td>
<td>26</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td>Crowther et al(^{24})</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cuker et al(^{10})</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Berry et al(^{25})</td>
<td>6</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Nellen et al(^{21})</td>
<td>39</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>Tawfik et al(^{22})</td>
<td>3</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Demma et al(^{26})</td>
<td>5</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>128</strong></td>
<td><strong>125</strong></td>
<td><strong>148</strong></td>
</tr>
</tbody>
</table>

Low-probability 4Ts score (0-3): a high NPV (0.998; 95%CI, 0.97-1)

- **HIT** Suspected
  - **4Ts score ≥ 4**
    - Discontinue heparin. Start alternative anticoagulant. Obtain HIT laboratory testing.
  - **4Ts score ≤ 3**
    - Continue heparin. Consider alternative diagnoses.
Do not follow this diagram, especially in complicated and/or critically ill patients!!!
KCMH experience: 13 HIT

- 2 cases: 4Ts score = 3
- 1 case: 4Ts score = 2

\[ \begin{align*}
\text{3/13 (23.1\%)}
\end{align*} \]

- Onset of thrombocytopenia: D1, D3 and D4
  Timing = 0
- Platelet count nadirs: 15,000/\(\mu\)L and 4,000/\(\mu\)L
  Thrombocytopenia = 1 and 0
- Low probability 4Ts is unsafe for excluding HIT in complicated and/or critically ill patients
4Ts score

Low

1. Score difficult to apply (missing or unclear data)
2. Patients with coexisting causes of thrombocytopenia

No
Exclude HIT
Continue or restart heparin

Yes

Intermediate
Perform PF4-dependent immunoassays

Negative

Positive

High

1. Function assays
2. Treat as HIT

Negative

Positive

Confirm HIT
Continue HIT treatment
Treatment of HIT
3 Do’s, 3 Don’ts, and 3 Diagnostics

• 3 Do’s:
  – Stop/avoid heparin
  – Give alternative nonheparin anticoagulant (fondaparinux)
  – Indicate potential diagnosis of HIT in the medical record

• 3 Don’ts
  – Give warfarin
  – Give prophylactic PLT Tx
  – Insert an IVC filter

• 3 Diagnostics
  – Test for HIT antibodies
  – Image for lower limb DVT
  – Test for DIC (ICU)
Use of anticoagulant and duration of treatment

• Therapeutic non-heparin anticoagulant
  – Fondaparinux 7.5 mg OD (BW 50-100 kg)
    Dose 5 mg (BW < 50 kg) or 10 mg (BW > 100 kg)
• Start warfarin: PLT recover to > 150,000µ/L or baseline
• Overlap with a non-heparin anticoagulant for at least 5 days and INR 2-3 for at least 48 hours
• Patients without thrombosis: warfarin 4 weeks
• Patients with thrombosis: warfarin 3-6 months
HIT mimicking syndrome

• Acute DIC/hepatic necrosis limb-necrosis syndrome
• Warfarin-induced venous limb ischemia/gangrene complicating cancer
• Protamine (heparin)-induced thrombocytopenia
• DIC with thrombosis
• Catastrophic antiphospholipid syndrome
• Septicemia with thromboembolism e.g., septic endocarditis with embolic stroke
Acute DIC/hepatic necrosis limb-necrosis syndrome

- A postcardiac surgery patient who develops acute onset and persisting thrombocytopenia, DIC, and multiple organ failure, and who then develops symmetrical peripheral gangrene (two- or four-limb acral ischemic necrosis), particularly since postcardiac surgery

- Combination of DIC with preceding shock liver (acute hepatic necrosis) → microvascular thrombosis

- Profoundly disturbed procoagulant–anticoagulant balance: marked increased in thrombin generation with concomitant severely reduced AT and PC levels

- Microvascular ischemic limb necrosis (gangrene with pulses)
Warfarin-induced venous limb ischemia/gangrene complicating cancer

- Warfarin-associated venous limb ischemia in cancer resembles that warfarin-associated venous limb gangrene (VLG) seen in HIT
- Cancer patients with DVT treated with heparin and concomitant warfarin exhibit a characteristic clinical picture
- Platelet count rise on heparin, and platelet count fall after stopping heparin (because of recurrent cancer associated DIC)
- Supratherapeutic INR secondary to warfarin
- Severe venous limb ischemia/gangrene in the limb affected by DVT
- Despite supratherapeutic INRs, patient plasma contained markedly elevated TAT complex levels and PC depletion
Warfarin-induced venous limb ischemia/gangrene complicating cancer

Blood 2015;126:486-93
<table>
<thead>
<tr>
<th>Onset of thrombocytopenia</th>
<th>HIT-associated DIC (incl. warfarin-induced VLG)</th>
<th>Acute DIC/hepatic necrosis-limb necrosis syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-10 days after immunizing heparin exposure</td>
<td>Usually &lt; 4 days after preceding heparin exposure (early onset and persisting thrombocytopenia)</td>
<td></td>
</tr>
<tr>
<td>2-5 days after onset of HIT (or warfarin treatment of Hit)</td>
<td>2-5 days after onset of acute liver dysfunction</td>
<td></td>
</tr>
<tr>
<td>Onset of limb ischemia</td>
<td>Usually yes</td>
<td>Usually no</td>
</tr>
<tr>
<td>Concomitant large vessel thrombosis (DVT)</td>
<td>Strong positive screening and positive functional tests</td>
<td>Negative or weak/moderate positive screening tests</td>
</tr>
<tr>
<td>HIT antibodies</td>
<td>Normal or minor impairment</td>
<td>Severely impaired with preceding “shock liver”</td>
</tr>
<tr>
<td>Liver function</td>
<td>HIT Ab-induced platelet and monocyte activation</td>
<td>Multiple triggers: cardiogenic or hemorrhagic shock, septicemia or both</td>
</tr>
<tr>
<td>Explanation of increased thrombin generation</td>
<td>Decreased production of PC (warfarin); increased consumption of PC and AT (DIC)</td>
<td>Decreased production of PC (liver dysfunction); increased consumption of PC and AT (DIC)</td>
</tr>
<tr>
<td>Explanation of natural anticoagulant depletion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Protamine-(heparin) induced thrombocytopenia (PIT)

- Protamine- arginine-rich, positively-charged protein
- An additive to certain preparations of insulin (NPH) and a rapidly-acting antidote to heparin (particularly to neutralize the effects of high heparin concentrations after cardiac surgery using cardiopulmonary bypass)
- PIT antibody can cause a rapid onset of thrombocytopenia after a reversal of heparin after cardiac surgery
Anti-protamine, anti-protamine-heparin-antibody vs. anti-PF4/heparin (HIT) Ab

- Polyspecific Ab (IgG, IgM and IgA)
- Cross reactivity in immunoassay
- Functional Ab or platelet activating Ab: only IgG
- Functional assay: platelet aggregation
  - Anti-protamine Ab: presence of protamine (2 µg/mL)
  - Anti-protamine-heparin Ab: presence of protamine (2 µg/mL) and enhanced with added UFH (0.2 IU/mL)
  - Anti-PF4/heparin (HIT) Ab: presence of UFH (0.2 IU/mL)
A 67-y-M with STEMI due to LAD and RCA thrombosis underwent CABG

Platelet count ($\times 10^9 \text{L}^{-1}$)

- HIT Ab
  - Immunoassay: +ve
  - Functional: -ve
- PIT Ab
  - Immunoassay: +ve
  - Functional: +ve (protamine) and enhanced with added UFH

Days after hospital admission

LMWH
Protamine-insulin
UFH
LMWH
Argatroban

Backchoul T. J Thromb Haemost 2016;14:1685
Protamine-(heparin) induced thrombocytopenia (PIT)

- Data from the large cohort study: $N = 591$
- Anti-protamine IgG Ab: 14 (2.4%, preoperative) and 19 (3.3%, postoperative by day 10)
- Anti-protamine-heparin IgG Ab: 9.6% (57, preoperative) and 26.6% (154, postoperative by day 10)
- 97/154 (63%): positive for anti-PF4-heparin IgG
- History of DM: a risk factor for preoperative seropositivity (62.0% vs 36.5%; $P < 001$)
Protamine-(heparin) induced thrombocytopenia (PIT)

- 24/154 (15.6%) anti-protamine-heparin IgG induced platelet activation
Protamine-(heparin) induced thrombocytopenia (PIT)

- Of 57 with preoperative anti-protamine-heparin Ab, 7 with platelet-activating Ab showed a more pronounced and prolonged decrease in platelet counts compared with the 50 patients with non–platelet activating Ab.
- One had coronary bypass occlusion of day 2 and one had stroke on day 3 postoperation.
<table>
<thead>
<tr>
<th></th>
<th>HIT</th>
<th>PIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigen</td>
<td>PF4/heparin complexes</td>
<td>Protamine/heparin complexes</td>
</tr>
<tr>
<td>Immunization trigger</td>
<td>Heparin especially given during or soon after surgery</td>
<td>Presumably, protamine-insulin and LMWH in medical patients, UFH reversal by protamine in cardiac surgery patients</td>
</tr>
<tr>
<td>Platelet activation</td>
<td>Yes, IgG Ab via FcγIIaR</td>
<td>Yes, IgG Ab via FcγIIaR</td>
</tr>
<tr>
<td>IgM precedes IgG</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Transience of Ab</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Thrombocytopenia and/or thrombosis early post-cardiac surgery</td>
<td>Unlikely</td>
<td>Yes</td>
</tr>
<tr>
<td>Thrombocytopenia and/or thrombosis beginning 5-10 days post-cardiac surgery</td>
<td>Yes</td>
<td>Unlikely</td>
</tr>
</tbody>
</table>
All 3 types of Abs in one patient

Chulalongkorn University
Backchoul T. J Thromb Haemost 2016;14:1685
Take home message

- Diagnosis of HIT is challenging and requires comprehensive clinical and laboratory review as well as laboratory investigations.
- HIT mimicking syndromes are important differential diagnoses and sometimes very difficult to differentiate from HIT.
- PIT is a new entity of immune-mediated complication causing early onset thrombocytopenia after cardiac surgery.
Thank you for your attention & Open for questions