Heparin-Induced Thrombocytopenia

Kristi J. Smock, MD

Associate Professor of Pathology
University of Utah Department of Pathology
Medical Director, Hemostasis/Thrombosis Laboratory
ARUP Laboratories

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Heparin-Induced Thrombocytopenia (HIT)

What is HIT?

• Immune mediated syndrome that occurs in a small percentage (1-5%) of heparin-exposed patients
• Caused by IgG antibodies to heparin-platelet factor 4 (PF4) complexes
• Immune complexes cause platelet activation
  o Thrombocytopenia
  o High risk of arterial or venous thrombosis
    – ~50% if untreated
Heparin-Induced Thrombocytopenia (HIT)

Pathogenesis

- PF4 released from platelet granules is positively charged
  - Able to form complexes with negatively charged heparin
- Heparin-PF4 complexes are antigenic in some patients, resulting in antibody formation
  - Immune complexes composed of IgG-heparin-PF4 activate platelets via the platelet Fcγ receptor for IgG
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Risk of HIT

• Higher risk in surgical patients than in medical patients
  o Related to amount of circulating PF4 and type and dose of heparin
  o Low risk in pregnancy

• Higher risk with unfractionated heparin (UFH) than low-molecular-weight heparin (LMWH)
  o Related to likelihood of complex formation, creation of HIT antigen
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HIT Diagnosis - Clinical

• Suspected when patient develops thrombocytopenia 5-10 days after heparin exposure
• Evaluation of clinical pre-test probability using clinical scoring system such as the 4T’s system
  o Excellent negative predictive value (NPV) for low scores
    – NPV 97-99%
  o Poor positive predictive value (PPV) for intermediate or high scores
    – PPV for intermediate 10-20%
    – PPV for high 40-80%
Heparin-Induced Thrombocytopenia (HIT) 4T’s scoring system

Thrombocytopenia
- 0 points; <30% drop or nadir <10 x 10^9/L
- 1 point; 30-50% drop or nadir 10-19 x 10^9/L
- 2 points; >50 drop and nadir >=20 x 10^9/L

Timing of platelet drop
- 0 points; <4 days with no recent exposure
- 1 point; suspect 5-10 days but not documented, >10 days, <=1 day with last exposure 30-100 days prior
- 2 points; 5-10 days or <= 1 day if exposed in past 30 days

Thrombosis
- 0 points; none
- 1 point; progressive, recurrent, silent, suspected but not proven
- 2 points; proven new thrombosis or skin necrosis or acute systemic reaction to heparin

Other causes of thrombocytopenia
- 0 points; definite
- 1 point; possible
- 2 points; none

Scoring
Low = <4 points
Intermediate = 4-6 points
High = 6-8 points
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HIT Diagnosis - Laboratory

- 2 categories of tests
  - Immunoassays to detect heparin-PF4 antibodies
    - ELISA is most common
  - Functional assays to detect platelet activation by HIT immune complexes
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HIT Diagnosis - ELISA

- Plates coated with heparin-PF4
- Detect antibodies in patient serum
  - IgG/IgM/IgA – polyspecific
  - IgG only – monospecific
- Diagnostic utility
  - Excellent NPV (~99%)
  - High sensitivity (95-100%)
  - Poor specificity (<90%, possibly well below 90%) and poor PPV since many patients who develop antibodies do not develop the HIT syndrome
  - Specificity somewhat improved with monospecific IgG ELISA
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HIT Diagnosis - ELISA

- Specificity improved by considering the optical density (OD) value of positive results
- Higher OD values correlate with capacity for platelet activation
  - 0.4 to 1.0: ~5% probability of HIT
  - 1.0 to 1.5: ~25% probability of HIT
  - >=2.0: ~90% probability of HIT
- Unclear if repeating positive samples in the presence of a high heparin concentration significantly improves ELISA specificity
  - Possible risk of false-negative results
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HIT Diagnosis – Functional platelet activation assays

- Sensitive (>90%) and more specific (>90%) for HIT than ELISA due to demonstration of antibody platelet activating properties
- Serotonin release assay (SRA) is the most commonly used test and golden standard
  - Further evaluate unexpected ELISA results
  - Further evaluate positive ELISA results
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HIT Diagnosis – SRA

- Combine patient serum with donor platelets and heparin
  - HIT positive sera result in platelet activation and release of serotonin from dense granules
  - Released serotonin is detected and quantified as an indicator of the degree of platelet activation
    - A variety of methods can be used to quantify serotonin
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HIT Diagnosis – SRA results

• Released serotonin expressed as % release
  o Amount of serotonin released divided by total platelet serotonin X 100
  o >= 20% release represents platelet activation
• Each patient specimen is tested at 2 different heparin concentrations and % release values are obtained
  o Low heparin concentration (LH) – therapeutic, supports immune complex formation
  o High heparin concentration (HH) – supra-therapeutic, disrupts immune complex formation
Heparin-Induced Thrombocytopenia (HIT) SRA reaction patterns

<table>
<thead>
<tr>
<th>LH % Release</th>
<th>HH % Release</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;=20%</td>
<td>&lt;20%</td>
<td>Positive</td>
</tr>
<tr>
<td>&lt;20%</td>
<td>&lt;20%</td>
<td>Negative</td>
</tr>
<tr>
<td>&gt;=20%</td>
<td>&gt;=20%</td>
<td>Indeterminate</td>
</tr>
</tbody>
</table>
Heparin-Induced Thrombocytopenia (HIT) Diagnostic algorithm for suspected HIT

Clinical scoring

Low score (<4 points)
- HIT very unlikely; lab testing not routinely performed

Intermediate (4-5 points) or high (6-8 points) score
- HIT possible; order ELISA test; take appropriate clinical action (HIT treatment)

Negative ELISA
- HIT excluded; no further testing; modify clinical actions as appropriate; may consider SRA in rare cases when negative ELISA is significantly discordant from clinical impression

Positive ELISA
- HIT possible or probable; order SRA

Negative SRA
- HIT very unlikely; modify clinical actions as appropriate

Positive SRA
- HIT confirmed; continue HIT treatment
References

Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- Employment by the University of Utah Department of Pathology and ARUP Laboratories
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