for a rapid and confident exclusion of Heparin Induced Thrombocytopenia

Jamal Barsheed
Outline

What is HIT ?
- description
- diagnosis
- treatment
- clinicians and labs needs

STic Expert® HIT
- product overview
- handling
- kit description

Evaluation results
- clinical validation

Conclusion
What is HIT?
Description of HIT

- **Heparin Induced Thrombocytopenia**
- **Adverse effect of heparin**
- **Antibody-mediated**
- **Main symptom: thrombocytopenia**
  - platelet count drop > 50% from the baseline
  - occurs 5-14 days after the start of heparin treatment
- **May affect up to 5 % of patients on UFH and 0.5- 1% of patients on LMWH**
- **Strong association with venous and arterial thrombosis**
  - High morbidity risks

**HIT suspicion: huge stress for clinician/lab**
HIT pathophysiology

- Platelet removal by splenic macrophages
- Thrombocytopenia
- Platelet activation
- Platelet aggregation
- Release of procoagulant microparticles
- Thrombosis
- Release of IgG
- Immune Complex
- Fc Receptor
- Platelet
- Heparin
- PF4
Clinical interest

The type of heparin given to the patient determines the overall size of the iceberg.

Kelton J G, Warkentin T E Blood 2008;112:2607-2616

HIT incidence in clinical context

Cardiac surgery - UFH
Orthopedic - UFH
Orthopedic - LMWH
Medecine - UFH
Medecine - LMWH
Diagnosis

Combination of clinical and biological criteria

- pre-test scoring (4T's)
- biological assays

**Pre-test scoring: 4 T's**

- **Thrombocytopenia**
  - level of platelet fall
- **Timing**
  - time after heparin exposure
- **Thrombosis**
  - occurrence after heparin exposure
- **Other cause of thrombocytopenia**
  - need to be reliably excluded

**Identification of 3 levels of risks**

- 0-3: low
- 4-5: intermediate
- 6-8: high
## How to calculate the 4T score?

<table>
<thead>
<tr>
<th>points</th>
<th>2</th>
<th>1</th>
<th>0</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>- Platelet count fall &gt; 50% and nadir ≥ 20 G/L</td>
<td>- Platelet count fall 30 à 50% or nadir between 10 and 19 G/L</td>
<td>- Platelet count fall &lt; 30% or nadir&lt; 10 G/L</td>
<td>/2</td>
</tr>
<tr>
<td><strong>Timing of platelet count fall</strong></td>
<td>- Clear onset between days 5 to 10 after the start of treatment or at day 1 (if prior heparin exposure within -30 days)</td>
<td>- Thrombocytopenia after day 10 of the start of treatment at day 1 (if prior heparin exposure within -30-100 days ago) on day 10.</td>
<td>- Platelet count fall &lt; 4 days without recent exposure</td>
<td>/2</td>
</tr>
<tr>
<td><strong>Thrombosis or other sequelea</strong></td>
<td>- New thrombosis - Skin necrosis (injection point) - Acute systemic reaction after bolus IV</td>
<td>- Progressive or recurrent thrombosis - thrombosis suspicion - skin necrosis at the point of injection</td>
<td>- None</td>
<td>/2</td>
</tr>
<tr>
<td><strong>oTHER causes of thrombocytopenia</strong> (drugs etc...)</td>
<td>- None apparent</td>
<td>Possible</td>
<td>Definite other causes - Infections - Chemo / radiotherapy - DIC</td>
<td>/2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Probability:**
- High: Score 6 to 8
- Medium: Score 4 to 5
- Low: Score 0 to 3
Diagnosis

**Combination of clinical and biological criteria**
- pre-test scoring (4T's)
- biological assays

- **Functional assays**
  - (SRA, HIPA, PA)
  - = detect platelets activating antibodies
  - 😊 highest sensitivity/specificity
  - 😞 complex, expensive, time consuming
  - 😞 not standardised
  - 😞 not widespread use

- **Immunnoassays**
  - = detect antibodies against [Heparin/PF4]
  - 😊 better standardization
  - 😊 easier to use
  - 😞 lower specificity

→ No perfect test, room for improvement
Treatment of HIT

HIT: SEVERE clinical impacts
Suspicion of HIT = stress for clinician/lab

Clinician does not wait for lab results
→ switch to alternative anticoagulant

Alternative anticoagulants
→ high risk of bleeding (no antidote)
→ much more expensive

Real frequency of HIT
6~12% of patients investigated for HIT have really HIT*
88~94% of patients suspected of HIT don't have HIT

Heparin-induced thrombocytopenia (HIT) is a clinical-pathologic syndrome (i.e., disease) that depends on both clinical and pathologic criteria being present [1]. The clinical criteria include the presence of thrombocytopenia and/or thrombosis, which may be transient or permanent, occurring occasionally in HIT patients [2]. The pathologic criteria consist of the detectability of HIT antibodies in the patient’s serum/plasma. HIT antibodies are directed against heparin-dependent platelet-activating antibodies that are present at a high frequency in patients with HIT [3].

Heparin-induced thrombocytopenia (HIT) is a clinical-pathologic syndrome (i.e., disease) that depends on both clinical and pathologic criteria being present [1]. The clinical criteria include the presence of thrombocytopenia and/or thrombosis, which may be transient or permanent, occurring occasionally in HIT patients [2]. The pathologic criteria consist of the detectability of HIT antibodies in the patient’s serum/plasma. HIT antibodies are directed against heparin-dependent platelet-activating antibodies that are present at a high frequency in patients with HIT [3].

Heparin-induced thrombocytopenia (HIT) is a clinical-pathologic syndrome (i.e., disease) that depends on both clinical and pathologic criteria being present [1]. The clinical criteria include the presence of thrombocytopenia and/or thrombosis, which may be transient or permanent, occurring occasionally in HIT patients [2]. The pathologic criteria consist of the detectability of HIT antibodies in the patient’s serum/plasma. HIT antibodies are directed against heparin-dependent platelet-activating antibodies that are present at a high frequency in patients with HIT [3].

Heparin-induced thrombocytopenia (HIT) is a clinical-pathologic syndrome (i.e., disease) that depends on both clinical and pathologic criteria being present [1]. The clinical criteria include the presence of thrombocytopenia and/or thrombosis, which may be transient or permanent, occurring occasionally in HIT patients [2]. The pathologic criteria consist of the detectability of HIT antibodies in the patient’s serum/plasma. HIT antibodies are directed against heparin-dependent platelet-activating antibodies that are present at a high frequency in patients with HIT [3].
Clinicians and labs needs?
Clinicians and labs needs

Clinician

Huge interest to quickly RULE-OUT HIT

→ avoid alternative treatment, maintain heparin
  • less bleeding risks
  • costs savings
    ✓ treatment
    ✓ less additional expensive testing, labor cost

From the lab perspective

Unitary test
Rapid
Easy to use
24/7, STAT adapted
Negative Predictive Value 100%
High specificity
STic Expert® HIT
Product overview

STic Expert HIT 5, Cat. Nr. 01058
STic Expert HIT 20, Cat. Nr. 01059

- Intended use: qualitative detection of IgG antibodies against PF4/polyanion complexes
- Test principle: immunochromatography / lateral flow
- Unitary test, extremely simple handling
- Results in 10 min
- Validated with PLASMA and serum
Handling: simple and quick

1. 5 µl serum
2. 2 drops of buffer
3. Visual inspection endpoint after 10 min
Lateral-flow immunoassay principle (LFI-HIT) is based on the capillary action which induces a flow of the test sample along a solid phase (test strip).

The test strip contains a conjugate which is a gold nanoparticle coated with an anti-ligand.

To the sample pad, 5 μl of the patient’s serum/Plasma and two drops of a reagent are added.

The buffer contains biotynilated human PF4/polyanion (PA) complex.
Figure

- At the same time, anti-PF4/PA human antibodies (if present) bind to the PF4/PA complexes.
- When the fluid passes the location of the test line on the strip, complexes containing biotinylated PF4/PA, anti-biotin coated gold nanoparticle(s) and human antibodies are retained by an immobilised goat antibody.
- This goat antibody was chosen to allow specific immobilisation of human IgG antibodies (which serves as the capture antibody printed onto the membrane).
- A positive reaction becomes visible as an intensively coloured line can be read visually (test line).
- The test strip also includes a second line (control line). At this location an antibody, which binds specifically to the biotin within the conjugate, is coated onto the test strip. The presence of the control line confirms that the test has performed properly.
Result interpretation

Compare the test line to the evaluation card

- intensity of the test line ≥ evaluation card → positive
- intensity of the test line ≤ evaluation card → negative

Positive result  Low positive result  Negative result
Evaluation results
Clinical validation

Institute for Clinical Immunology and Transfusion Medicine
- University of Giessen, Germany

- 452 surgical and medical patients suspected of HIT (prospective)
- Clinical pretest probability
  - 4T score
- Immunoassays
  - IgG ELISA (GTI & Hyphen)
  - PaGIA Biorad/Diamed
  - STic Expert® HIT
- Functional assay
  - HIPA
# Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Negative results</th>
<th>Positive results</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>true</td>
<td>false</td>
<td>true</td>
<td>false</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STIC Expert</td>
<td>389</td>
<td>0</td>
<td>34</td>
<td>29</td>
<td>1</td>
<td>0.93</td>
</tr>
<tr>
<td>GTI-IgG ELISA</td>
<td>373</td>
<td>0</td>
<td>34</td>
<td>45</td>
<td>1</td>
<td>0.892</td>
</tr>
<tr>
<td>Hyphen-IgG ELISA</td>
<td>365</td>
<td>0</td>
<td>34</td>
<td>53</td>
<td>1</td>
<td>0.873</td>
</tr>
<tr>
<td>PaGIA</td>
<td>361</td>
<td>3</td>
<td>31</td>
<td>55</td>
<td>0.912</td>
<td>0.868</td>
</tr>
<tr>
<td>HIPA</td>
<td>418</td>
<td>34</td>
<td>34</td>
<td>34</td>
<td>34</td>
<td>34</td>
</tr>
</tbody>
</table>

**STic Expert® HIT showed the best performances**

- NPV: 100%
- higher specificity (93%)
Conclusion of the study

**With STic Expert® HIT***

- negative individuals do not require additional laboratory testing in order to exclude the diagnosis of HIT
- enhanced specificity may help to avoid unnecessary confirmatory testing in referral laboratories

Key features summary
Key features

- Unitary test
- Rapid
- Easy to use
- 24/7, STAT
- adapted
- NPV 100%

Suitable for any hospital/lab size

Results in 10 minutes

No long training needed

Easy interpretation

Allows running the test before deciding to stop or continue heparin

Full exclusion of HIT

Avoids unnecessary changes of heparin

Lower risk of bleeding

Costs savings (treatment, add. tests)

Less false positive

Reduces over-diagnosis

High specificity
Conclusion

6~12% of patients investigated for HIT really have HIT

Ruling-out HIT quickly avoids unnecessary changes of heparin

- ~90% of suspected patients
- reduce bleedings risks
- reduce costs

Stago offers a comprehensive range

- STic Expert® HIT
- Asserachrom® HPIA-IgG
Webinar

Save the date

Friday January 31st 2014 at 4:00 p.m.
CET (Central European Time)

How to diagnose and manage Heparin-Induced Thrombocytopenia (HIT)?

Pr Yves Giruel
Professor of Hematology,
Trousseau Hospital and University Francois Rabelais, Tours (France)
This document is Diagnostica Stago's sole property. Consequently, any disclosure, reproduction and/or copy to any third party is strictly forbidden, unless prior written approval given by Diagnostica Stago. No contractual photos. This document contains information on products which is targeted to a wide range of audiences and could contain product details or information otherwise not accessible or valid in your country.