Clinical Guideline
HEPARIN INDUCED THROMBOCYTOPENIA (HIT) – DIAGNOSIS AND MANAGEMENT IN CHILDREN AND NEONATES

SETTING
Bristol Royal Hospital For Children

FOR STAFF
Medical Staff

PATIENTS
Paediatric patients receiving heparin therapy

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1. Introduction

Heparin induced thrombocytopenia (HIT) and Heparin induced thrombocytopenia and thrombosis (HITT) are drug induced immune thrombocytopenias where antibodies form against the heparin-platelet factor 4 complex. These antibodies both activate platelets and clear them from the circulation resulting in a clinical picture of thrombosis and low platelets.

Classic findings of HIT are moderate thrombocytopenia and thrombosis developing 5-10 days after heparin exposure (it can occur more quickly if previous heparin exposure within 100 days). It can lead to life and limb threatening complications in patients receiving heparin therapy.

Thrombocytopenia is very commonly seen in sick paediatric patients on heparins but this is usually not due to HIT. Alternatives to consider are sepsis, disseminated intravascular coagulation (DIC), medications, extracorporeal membrane oxygenation (ECMO), congenital heart disease and bypass surgery.

Management of HIT requires prompt diagnosis, discontinuation of heparin and treatment with an alternative anticoagulant such as a direct thrombin inhibitor (DTI) or indirect Xa inhibitors. First line at UHBristol is currently Argatroban (a short-acting DTI).

HIT is rare in paediatrics, particularly in the non-PICU setting. The incidence of HIT in adults is approximately 1% for unfractionated heparin (UFH) and 0.5% for low molecular weight heparin (LMWH). The incidence in children is believed to be substantially less.
Diagnosis is based on clinical suspicion (falling platelet count, evidence of thrombosis or skin lesions) plus laboratory findings.

2. Monitoring in patients receiving heparin therapy

- platelet count prior to starting UFH
- daily platelet counts on day 4-14 for any patient receiving IV unfractionated heparin
- twice weekly FBC for the first two weeks for any child on LMWH
- if exposure to UFH within preceding 100 days, repeat platelet count at 24 hours post starting treatment

3. Management of suspected HIT

- If platelet count of patient receiving heparin falls by >30% from baseline, consider HIT
- Calculate pre-test probability of HIT (see table 1 below)
- If strong suspicion of HIT (pre-test probability 6-8)
  1. Send blood sample for HIT assay* (antibody screen – see below)
  2. Discontinue all heparin (including flushes) whilst awaiting HIT assay results
  3. Commence alternative anticoagulant – assess bleeding/thrombotic risk of patient
  4. Platelet transfusion is contra-indicated in HIT
  5. Consider USS of upper/ lower limbs to assess for thrombosis
- If intermediate pre-test probability (score 4-5)
  1. Send blood sample for HIT assay*
  2. Consider discontinuing all heparin (including flushes) whilst awaiting HIT assay results
  3. Consider commencing alternative anticoagulant – assess bleeding/thrombotic risk of patient
  4. Platelet transfusion is contra-indicated in HIT
  5. Consider USS of upper/ lower limbs to assess for thrombosis
- If low pre-test probability
  1. HIT assay not required
  2. Heparin may be continued if platelet count is adequate
  3. Investigate for other causes of thrombocytopenia
3.1. Table 1: HIT 4Ts score: Thrombocytopenia, Timing, Thrombosis, other cause – note, not validated in children

<table>
<thead>
<tr>
<th>Points</th>
<th>2</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>&gt;50% fall and platelet nadir ≥20 × 10⁹/l</td>
<td>30–50% fall or platelet nadir 10–19 × 10⁹/l</td>
<td>Fall &lt;30% or platelet nadir &lt;10 × 10⁹/l</td>
</tr>
<tr>
<td>Timing</td>
<td>Clear onset between days 5 and 10; or ≤1 d (if heparin exposure within past 30 d)</td>
<td>Consistent with immunization but not clear (e.g. missing platelet counts) or onset of thrombocytopenia after day 10; or fall ≤1d (if heparin exposure 30–100 d ago)</td>
<td>Platelet count fall ≤4 d (without recent heparin exposure)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>New thrombosis; skin necrosis; post-heparin bolus acute systemic reaction</td>
<td>Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis not yet proven</td>
<td>None</td>
</tr>
<tr>
<td>Other cause for thrombocytopenia</td>
<td>No other cause 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

First day of immunizing heparin exposure considered day 0; the day the platelet count begins to fall is considered the day of onset of thrombocytopenia (it generally takes 1–3 days more until an arbitrary threshold that defines thrombocytopenia is passed).

3.2. HIT assay* - need to discuss with Consultant Haematologist and Coagulation Laboratory

Samples are run in the coagulation lab and are requested on ICE under the Special Coag tab, left hand column. All requests should be discussed with a Consultant Paediatric Haematologist during working hours.

The test is an ELISA (enzyme-linked immunosorbent assay) which looks for antibodies to the heparin-platelet factor 4 complex and interpretation of results is based on clinical probability score and optical density.

The test has a high negative predictive value and a negative result excludes a diagnosis of HIT.
If the test result is positive, the likelihood of HIT is proportional to the optical density – false positive results do occur especially after cardiac surgery.

### 3.3. Alternative anticoagulation in patients with suspected HIT

There are three main agents for consideration in patients with suspected or proven HIT. All have different properties and drawbacks.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Metabolism</th>
<th>Half-life</th>
<th>Dosing</th>
<th>Monitoring</th>
<th>Reversal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argatroban</td>
<td>Liver</td>
<td>45 minutes</td>
<td>0.75 micrograms/kg/min IV</td>
<td>1.5 - 3 x baseline APTT</td>
<td>Stop (Novo7)</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>80% proteolysis 20% renal</td>
<td>25 minutes</td>
<td>0.125mg/kg bolus 0.125mg/kg/h IV</td>
<td>1.5 - 2.5 x baseline APTT</td>
<td>Stop (Novo7)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Renal</td>
<td>18 hours</td>
<td>0.1mg/kg sc od</td>
<td>Anti Xa level 0.5–1 iu/ml (4 hours post dose)</td>
<td>Stop (Novo7)</td>
</tr>
</tbody>
</table>

### 3.3.1. Argatroban

Argatroban is a short-acting DTI which is cleared hepatically. It is contra-indicated in severe hepatic impairment or major bleeding (care should be taken if administered together with anti-platelet agents, urokinase, thrombolytics and other anticoagulants).

It is given as an intravenous infusion at a starting dose of 0.75 micrograms/kg/min. The starting dose is reduced to 0.2 micrograms/kg/min in hepatic impairment. A reduced dose may be advisable for the critically ill child or post cardiac surgery.

Argatroban is the only agent which has been prospectively trialled in the context of paediatric HIT – adverse outcomes occurred in 7 of 18 patients. Adverse events included two intracranial bleeds (one during and one after argatroban treatment); and thrombosis in five patients (two during and three after argatroban treatment). Given the poor baseline characteristics of the children in the study and the high risk of thrombosis in HIT (~50%), argatroban arguably showed good efficacy in this context.

**Argatroban dosing**

- Starting dose 0.75 micrograms/kg/min.
- Check full blood count, coagulation screen and fibrinogen at baseline and at 4 hours after starting infusion.
### 3.3.2. Bivalirudin

Bivalirudin is a short-acting DTI which is cleared renally. It is given by continuous infusion and has been used with success in the context of paediatric ECMO and ventricular assist devices (VAD). Bivalirudin has been prospectively studied in the treatment of venous and arterial thrombosis in infants less than 6 months of age. Out of 16 patients, two suffered significant haematuria (in both cases the APTT ratio was high) which settled after dose reduction. Efficacy appeared to be as good as or better than that expected with heparins.

**Bivalirudin dosing**

- **Starting dose** 0.125mg/kg/h
- **Check** full blood count, coagulation screen and fibrinogen at baseline and at 4 hours after starting infusion (2 hours in high risk patients)
- **Consider bolus** of 0.125mg/kg

<table>
<thead>
<tr>
<th>APTT ratio (of baseline)</th>
<th>Infusion rate change</th>
<th>Next APTT ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.5</td>
<td>Increase by 0.02 mg/kg/h</td>
<td>4 hours</td>
</tr>
<tr>
<td>1.5-2.5</td>
<td>No change</td>
<td>4 hours</td>
</tr>
<tr>
<td>(APTT &lt;100s)</td>
<td></td>
<td>After 2 consecutive APTT ratio within target range check 6-12hrly</td>
</tr>
<tr>
<td>&gt;2.5</td>
<td>Decrease by 0.02mg/kg/h</td>
<td>2 hours</td>
</tr>
<tr>
<td>&gt;3</td>
<td>Decrease by 0.04mg/kg/h (consider hold)</td>
<td>2 hours</td>
</tr>
</tbody>
</table>

- If PT/INR rises without APTT discuss with haematology
Fondaparinux (indirect Xa inhibitor) has also been studied in the paediatric setting though not in HIT. Fondaparinux is renally excreted and long-acting and thus may not be a good option for PICU patients. Fondaparinux may be used as an alternative to warfarin after the acute period.

3.4. Ongoing management of confirmed HIT

- The platelet count usually recovers 2-3 days after discontinuing heparin.
- Once argatroban/bivalirudin has been used for at least 5 days and platelet count has normalised, warfarin therapy can be commenced. Fondaparinux may be considered as an alternative.
- Argatroban and bivalirudin also prolong the INR and patients should have an INR >4 for 2 days before discontinuing the DTI infusion in the transition to warfarin.
- In patients with isolated thrombocytopenia (no thrombosis), warfarin should continue for 1-3 months. If thrombosis is present, 3-6 months of warfarin therapy is appropriate.
- Patients who have been diagnosed with HIT will receive an “Antibody card”.
- They should avoid all forms of heparin if possible.
- Any non-urgent surgery should be delayed for 3 months.
- Patients with a diagnosis of HIT requiring Cardiac or Vascular surgery should be discussed with a Haematologist.
- All confirmed HIT cases should be referred to haematology for follow up.
### Table A

Pediatric Thrombotic Disorders 2015 Edited by Goldenberg NA & Manco-Johnson MJ |
| RELATED DOCUMENTS AND PAGES | Anticoagulation On Picu And Dolphin Ward For Cardiac Patients  
Antithrombin Monitoring and Supplementation on PICU  
Low Molecular Weight Heparin Therapy in Children and Neonates  
Unfractionated Heparin Therapy in Non-cardiac Children and Neonates  
Heparin induced thrombocytopenia – UH Bristol Adult Guideline |
| AUTHORISING BODY | Paediatric Haematology, Oncology and Bone Marrow Transplant Quality Assurance Forum (Quaf) |
| SAFETY | N/A |
| QUERIES AND CONTACT | In Emergency contact on call Paediatric Intensive Care Consultant (ext. 28018) or Haematology Consultant via switchboard |