Heparin Induced Thrombocytopenia (HIT)

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Goals of Presentation

• Identify patients at risk for developing HIT
• How to diagnose HIT
• Types of HIT
• Treatments of HIT
• Management of anticoagulation especially Coumadin in the setting of Argatroban
• Duration of anticoagulation
Case

• 70 year old African American patient was admitted to Baptist Beaches with leg swelling approximately 10 days after a hip surgery.
• He did receive heparin (DVT prophylactic doses) in his previous hospitalization and was found to have a DVT. His platelet count on admission was normal and was started on a heparin drip
• 4-5 days later his platelet count started dropping and his leg swelling got worse
• A HIT ELISA was ordered
Risk Factors

- Unfractionated Heparin vs. Low molecular weight Heparin - 2.6 % vs. 0.2 %
- Sex - females have a higher risk than men
- Age - the incidence rises with age. HIT is very rare in children and in patients under the age of 40
- Heparin dose - there is some data suggesting that higher dose especially for a longer duration increases the risk of HIT
- Surgery - the risk of HIT is higher in patients undergoing surgery especially cardiac surgery
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Risk</th>
<th>Clinical Population at Risk</th>
<th>Incidence of PF4–Heparin Antibodies*</th>
<th>Incidence of HIT</th>
<th>Platelet-Count Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin (new or remote [&gt;100 days] exposure)</td>
<td>High</td>
<td>Patients undergoing orthopedic surgery¹,⁷</td>
<td>14</td>
<td>3–5</td>
<td>At baseline and at least every other day from days 4 to 14 of heparin therapy or until heparin discontinued† ‡</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td>Adults undergoing cardiac surgery⁷</td>
<td>25–50</td>
<td>1–2</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td>Children undergoing cardiac surgery²⁰</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td>General medical patients⁶,¹¹</td>
<td>8–20</td>
<td>0.8–3.0</td>
<td></td>
</tr>
<tr>
<td>Low to rare</td>
<td></td>
<td>General pediatric patients²⁰</td>
<td>0–2.3</td>
<td>0–0.1</td>
<td>Not essential†</td>
</tr>
<tr>
<td>Low-molecular-weight heparin (new or remote [&gt;100 days] exposure)</td>
<td>Intermediate</td>
<td>Medical patients⁸,⁹</td>
<td>2–8</td>
<td>0–0.9</td>
<td>At baseline and every 2 to 4 days after days 4 through 14 of low-molecular weight heparin therapy or until therapy discontinued†</td>
</tr>
<tr>
<td>Rare</td>
<td></td>
<td>Pregnant women²⁶</td>
<td>Unknown</td>
<td>0–0.1</td>
<td>Routine monitoring not recommended†</td>
</tr>
<tr>
<td>Heparin or low-molecular-weight heparin (exposure within 100 days)</td>
<td>Unknown</td>
<td>All clinical populations¹⁰</td>
<td>Unknown</td>
<td>Unknown</td>
<td>At baseline, within 24 hr, and every other day from days 4 through 14 until heparin is discontinued† ‡</td>
</tr>
</tbody>
</table>
Pathophysiology

- Caused by autoantibodies to platelet factor 4 (PF4), complexed with heparin
- Major mechanism of thrombocytopenia is removal of IgG coated platelets by the macrophages and reticuloendothelial complexes
- Unlike other drug induced thrombocytopenia, the risk of thrombosis occurs probably because of platelet activation
Platelet removal by splenic macrophages

Platelet activation

Platelet release

Platelet aggregation

Thrombosis

Release of procoagulant microparticles
Types of HIT

• Type 1- is a mild transient drop in platelet count usually occurring 1-2 days of starting heparin. The platelet count usually nadirs around 100,000 and counts returns to normal with continued heparin exposure. Mechanism appears to be non immune mediated platelet aggregation

• Type 2- is the clinically significant syndrome caused by antibodies to PF4 and is associated with thrombosis

• Sub- Clinical HIT- refers to patients who have recovered from HIT and have detectable HIT antibodies. They are at a high risk of developing recurrent HIT
Clinical Manifestation

- Thrombocytopenia- occurs in 85-95% of cases. Usually nadirs around 60,000. Platelet counts less than 20,000 are very rare and other etiologies of thrombocytopenia should be investigated. The drop in platelet count is usually 50% of baseline.

- Timing- Typical onset occurs in 5-7 days of initial exposure. Cases of early onset of HIT may be seen in patients who have been exposed to heparin in the past and have circulating antibodies. The resolution of thrombocytopenia following withdrawal of heparin usually occurs within 7 days.
Clinical Manifestations Continued

- Thrombosis occurs in 50% of patients with HIT. Venous thrombosis is more common than arterial events, with the ratio being approximately 3:1. Pulmonary embolism is the most common life-threatening event.

- Common sites of venous thrombosis include lower extremities and pulmonary vasculature. In one series, upper extremity thrombosis only developed in the setting of a central catheter.

- Most patients who develop HIT have a higher-than-average risk of thrombosis at baseline.
Case Continued

• The patients HIT ELISA was positive with an optical density of 1.8
• His repeat Doppler's showed worsening of the lower extremity thrombus
• Heparin was stopped and the patient was started on Argatroban
Diagnosis of HIT

• 4 T score- very important to evaluate pretest probability of HIT. Online calculator available. If the score is high or intermediate a presumptive diagnosis of HIT should be made and treatment started. If the score is low, HIT antibody testing should not be generally pursued
  – Thrombocytopenia
  – Timing of Thrombocytopenia
  – Thrombosis
  – Other causes of thrombocytopenia
Thrombocytopenia

- Platelet count fall >50 percent and nadir ≥20,000/microL – 2 points
- Platelet count fall 30 to 50 percent or nadir 10 to 19,000/microL – 1 points
- Platelet count fall <30 percent or nadir <10,000/microL – 0 points

**Timing of platelet count fall**

- Clear onset between days 5 and 10 or platelet count fall at ≤1 day if prior heparin exposure within the last 30 days – 2 points
- Consistent with fall at 5 to 10 days but unclear (eg, missing platelet counts), onset after day 10, or fall ≤1 day with prior heparin exposure within 30 to 100 days – 1 point
- Platelet count fall at <4 days without recent exposure – 0 points

**Thrombosis or other sequelae**

- Confirmed new thrombosis, skin necrosis, or acute systemic reaction after intravenous unfractionated heparin bolus – 2 points
- Progressive or recurrent thrombosis, non-necrotizing (erythematous) skin lesions, or suspected thrombosis that has not been proven – 1 point
- None – 0 points

**Other causes for thrombocytopenia**

- None apparent – 2 points
- Possible – 1 point
- Definite – 0 points

**Interpretation** — A point value for each of the four categories is determined, and the sum of these values gives a total from 0 to 8. Pretest probabilities for HIT are as follows:

- 0 to 3 points – Low probability
- 4 to 5 points – Intermediate probability
- 6 to 8 points – High probability
Serological Testing

• HIT ELISA antibody- good screening, but not very specific. OD less than 0.4 argues against HIT. Some experts believe than an OD greater than 2 confirms the diagnosis

• SSRA – Serotonin release assay is very specific but not sensitive. It is time consuming and results are usually not back before 7-10 days
Imaging Studies

• Venous Dopplers of the upper and lower extremity are routinely recommended even if there is no clinical signs of thrombosis

• Other imaging tests including but not limited to CT angiography, arterial dopplers, angiogram depend on the clinical situation
Case Continued

- SSRA was ordered and the patient was on Argatroban
- His platelet count which nadired at 65,000 started to improve and reached over 100,000 after 3 days
- Coumadin was started once the platelet count was over 100,000
- Daily PT/INR were ordered and followed
Treatment of HIT

• Immediate discontinuation of heparin- this is the most important step

• It is imperative that the patient receives no heparin, including on dialysis, heparin flushes or heplocks. Certain central catheters are coated with heparin and they should be removed

• Initiation of a non heparin anticoagulant
Non Heparin Anticoagulant

• Rationale is that patients with HIT have a 50% risk of developing thrombosis at 30 days.
• Non heparin anticoagulant does not treat HIT. It reduces the risk of thrombotic complications.
Argatroban

- Most commonly used
- Direct thrombin inhibitor
- Half life of 30 minutes
- Steady state of anticoagulation is reached 2-3 hours after starting Argatroban.
- PTT should return to normal within 2 hours of stopping Argatroban
- There is a dose dependent rise in PT/INR with Argatroban and the INR can be as high as 2 on it
- Dose needs to be adjusted in patients with elevated LFT
Lepirudin

- Currently not available
- Higher rates of reaction
- Data showed it only to reduce risk of thrombosis in patients with HIT
Bivalirudin

- Brand name Angiomax
- Direct Thrombin Inhibitor and Hirudin analogue
- Shorter half life
- Reduced doses can be safely used in patients with both liver and renal dysfunction
- Used in the cath lab
Arixtra

- It is chemically synthesized version of the active pentasaccharide subunit of heparin that does not interact with platelet factor 4 and therefore has a theoretical role in treatment and/or prevention of HIT
- 2012 ACCP guidelines mentions the use of Arixtra in HIT
- The role of it has been debated between various experts
- Advantages include sub q administration, no monitoring required and ease of use
- Disadvantages include rare reports of antibodies which cross react with PF4, longer half life and no antidote
New Oral Anticoagulants

• No data exists
• Very few and rare case reports
• Theoretically they all should work
• Practically they are never used unless more solid data emerges
Case Continued

- 2 days after starting Coumadin, the patient's INR was 2.4. The Argatroban was discontinued.
- Few days later the platelet count started to drop and the patient showed signs of arterial thrombosis and skin necrosis and he was transferred to Baptist Medical Center Downtown.
- His Argatroban was restarted, but unfortunately the patient developed arterial thrombotic events and needed lower extremity amputations and had a prolonged stay in the hospital.
Managing Anticoagulation

- Managing anticoagulation with Argatroban and Coumadin can be tricky
- Argatroban raises the INR by itself
- There are different physicians/nurses/pharmacists on the case and sometimes it is discontinued before the full therapeutic effect is in place
- Coumadin should only be started after the platelet counts are over 100,000/150,000 for a few days
- Don’t stop Argatroban until the INR is over 4
- At least 5 days of overlap between Argatroban and Coumadin
- Check INR 2 hours after stopping Argatroban and if the INR is less than 2, restart Argatroban
- Follow INR closely upon discontinuation of Argatroban
HIT With Bleeding

• HIT with bleeding is rare since platelet counts are usually over 20,000. If there is clinical bleeding platelet transfusions can be given
HIT and Cardiopulmonary Bypass

• Unfractionated heparin can be safely used provided the HIT ELISA is negative. It usually takes 60-90 days for the antibody to disappear.

• Unfractionated heparin should be used only during surgery and a different anticoagulant should be used in the post operative setting.
CPB During an Acute or Sub Acute Episode of HIT (HIT Antibodies Present)

- Difficult situation
- Case by case basis
- Case reports of using heparin for heart transplants
- ACCP recommendations
  - Urgent cardiac surgery- Angiomax
  - Urgent PTCA- Angiomax or Argatroban
  - If heparin has to be used, consider intraoperative plasma exchange to remove the antibody
Duration of Anticoagulation

• HIT alone with no thrombosis - at least 30 days
• HIT with thrombosis- the duration depends on type and severity of thrombosis.
• Can be 3 months for an upper extremity clot to up to 1 year for a PE
Prevention

• Avoid heparin exposure. DVT prophylaxis to be determined based on risk and ACCP guidelines (which can be vague)
• Use low molecular weight heparin compared to unfractionated heparin
• Decrease hospital stay and thus decrease duration of exposure to heparin
Questions?