Management of HIT in Cardiac Surgery Patients

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Learning Objectives:

- Incidence and significance of HIT in cardiac surgery patients
- Pathophysiology of HIT
- Diagnosis
  - HIT type II (immune mediated, clinically significant)
- Management of HIT patients
  1. Following cardiac surgery
  2. Ab positive before cardiac surgery
- Controversies and implications
Heparin: Mechanism and limitations

Heparin: mode of action

Indirect effect on thrombin via AT. Acts like a catalyst in an enzymatic reaction.
Heparin: Limitations

**Heparin’s limitations**

The heparin:AT complex inhibits only soluble thrombin... not fibrin-bound thrombin

- Heparin increases the affinity of thrombin for fibrin.

**Heparin’s limitations**

Heparin binds to plasma proteins and cells

- Heparin activates platelets directly.
- Heparin can induce an immune response in the form of HIT/HITT.
- Heparin exhibits a nonlinear dose-response.
Heparin: a natural but highly antigenic product

- Combine 5,000 lbs. intestines, 200 gallons water, 10 gallons apple cider vinegar, and 5 gallons toluene, and boil for 17 hours.

- Add 30 gallons acetic acid, 35 gallons ammonia, sodium hydroxide to adjust pH, and 235 gallons water. Bring to boil; then filter.

- Add 200 gallons hot water and allow to stand and skim off the fat.

- Keep pancreatic extract at 100°F for three days, then boil. Filter solids and assay for heparin content.
HIT and associated thrombosis occurs in the subset of patients with platelet-activating anti-PF4/H antibodies.

Adapted from Warkentin TE. Br J Haematol 2003, 121:535.
Incidence: “Iceberg Model”

- Thrombosis: 0.2%–1.0%
- Thrombocytopenia: 1%–3%
- Antibody formation: 3%–30%+
Pathophysiology

Epitome caused by conformational change of PF4

Aggregation

Thrombosis
Clinical Presentation

Classically platelet (rather than fibrin) rich “white” clot syndromes
## Risk Factors for HIT

<table>
<thead>
<tr>
<th>Heparin-associated factors</th>
<th>Patient-associated factors</th>
</tr>
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<tbody>
<tr>
<td>Type of heparin (UFH $&gt;$ LMWH)</td>
<td>Patient population</td>
</tr>
<tr>
<td>Source of UFH heparin (bovine lung $&gt;$ porcine intestinal mucosa)</td>
<td>Age</td>
</tr>
<tr>
<td>Duration of heparin exposure</td>
<td>Sex (female $&gt;$ male)</td>
</tr>
<tr>
<td></td>
<td>Genotype</td>
</tr>
</tbody>
</table>

LMWH, low molecular weight heparin; UFH, unfractionated heparin.

UFH (5.3 fold), Rx for more than 6 days (3-10 fold), surgical $>$ medical patients (3 fold, highest cardiac surgery), female (2.4 fold), elderly (2.4 fold)

Cuker A, Curr Opinions Hematology 2011
Definition and Timing of Thrombocytopenia

Definition of suspected HIT:

- >50% drop in platelet count from the highest post operative value
- occurs between day 5-14 after starting any heparin dose with or without thrombotic complication.

Timing:
- Typical Onset: between 5-10 days post CABG
- Early Onset: Day 1-4 post CABG --Previous exposure or HIT positive <100d
- Delay Onset: days or few weeks without any exposure of Heparin post CABG --High HIT antibodies titers that activate platelets
Diagnosis Often Missed

Curve: days requested, Bars: HIT Ab+
Early “negative” test may be misleading
Specific Testing for HIT

Activation assays (Functional antibodies)
- Serotonin Release Assay
- Platelet Aggregation Assay

Antigen assays (all antibodies)
- Enzyme-Linked Immunoassay (ELISA)
- PF4 Antibodies (GAM)

Less sensitive, more specific, technically demanding, not standardized

More sensitive, less specific, technically simple, standardized
Dx: Clinical Criteria and Laboratory Assays

<table>
<thead>
<tr>
<th>Feature</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnitude of platelet count fall</td>
<td>Measured from peak platelet count after heparin exposure. Characteristically ≥50%; 30–50% in 10% of cases.</td>
</tr>
<tr>
<td>Timing of platelet count fall</td>
<td>Characteristically 5–14 days after initial heparin exposure. Rapid-onset HIT within 24 h after heparin exposure may occur in patients with a previous recent heparin exposure, usually within the last 30 days.</td>
</tr>
<tr>
<td>Nadir platelet count</td>
<td>Characteristically ≥20 × 10⁹/l. May be lower in cases associated with DIC.</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>May be venous or arterial. Present in approximately half of cases at diagnosis.</td>
</tr>
<tr>
<td>Absence of hemorrhage</td>
<td>Significant bleeding is rare in HIT. Its presence may suggest an alternative diagnosis.</td>
</tr>
<tr>
<td>Absence of alternative causes of thrombocytopenia</td>
<td>Such as infection, other medications known to cause thrombocytopenia, and cardiopulmonary bypass within the previous 96 h.</td>
</tr>
</tbody>
</table>

DIC, disseminated intravascular coagulation; HIT, heparin-induced thrombocytopenia.

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunologic</td>
<td>1. Polytypic ELISA</td>
<td>&gt;95%</td>
<td>50–89%</td>
<td>Magnitude of a positive result correlates with clinical probability of HIT</td>
</tr>
<tr>
<td></td>
<td>2. IgG-specific ELISA</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>3. PGIA</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Functional</td>
<td>1. SRA</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
<td>Only available at select centers; may require referral to a reference laboratory</td>
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<tr>
<td></td>
<td>2. HIPA</td>
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PGIA particle gel immunoassay, SRA serotonin release assay, HIPA heparin-induced platelet activation assay

Clinical pathological diagnosis
Cuker A J Thromb Thrombolysis 2001
Treatment Algorithm

Immediate cessation of heparin?  Additional therapy?

Cuker A J Thromb Thrombolysis 2001
Management of HIT after cardiac surgery

- Formally document heparin “allergy” in PMR
- Immediately stop all heparin (low dose heparin, low molecular weight heparin, flushes etc.). Delays increase thrombosis risk
- Initiate non-heparin anticoagulation to prevent or to treat possible thrombosis *
- Avoid prophylactic platelet transfusions (increase risk of thrombosis). Only used to Rx bleeding
- Additional Rx of complications: limb amputation if threatening arterial thrombosis occurs
Non Heparin Anticoagulants

Direct Thrombin Inhibitors (DTIs):

1. **Lepirudin (Refludan®) Recombinant Hirudin**
   MOA: irreversible inhibition exosite 1 and catalytic site

2. **Bivalirudin (Angiomax®) 20-amino acid peptide**
   MOA: reversible inhibition of exosite 1 and catalytic site (once peptide bond is cleaved by plasma enzymes and thrombin itself, reverse inhibition)

3. **Argatroban**
   MOA: reversible inhibition of catalytic sites
Direct Thrombin Inhibitors
# Pharmacological Therapy: HIT

<table>
<thead>
<tr>
<th>Agent</th>
<th>Initial dosing</th>
<th>Monitoring</th>
<th>Clearance (half-life)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argatroban</td>
<td>Bolus: None</td>
<td>Adjust to APTT of 1.5–3.0 times patient baseline</td>
<td>Hepatobiliary (40–50 min)</td>
</tr>
<tr>
<td></td>
<td>Continuous infusion:</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Normal organ function $\rightarrow$ 2 $\mu$g/kg/min</td>
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<td></td>
<td>Liver dysfunction (total serum bilirubin $&gt;1.5$ mg/dl), heart failure, postcardiac surgery, anasarca $\rightarrow$ 0.5–1.2 $\mu$g/kg/min</td>
<td></td>
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</tr>
<tr>
<td>Lepirudin</td>
<td>Bolus: 0.2 mg/kg (only if life-threatening or limb-threatening thrombosis)</td>
<td>Adjust to APTT of 1.5–2.0 times patient baseline</td>
<td>Renal (80 min)</td>
</tr>
<tr>
<td></td>
<td>Continuous infusion:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$Cr &lt;1.0$ mg/dl $\rightarrow$ 0.10 mg/kg/h</td>
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<tr>
<td></td>
<td>$Cr 1.0–1.6$ mg/dl $\rightarrow$ 0.05 mg/kg/h</td>
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<tr>
<td></td>
<td>$Cr 1.6–4.5$ mg/dl $\rightarrow$ 0.01 mg/kg/h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$Cr &gt;4.5$ mg/dl $\rightarrow$ 0.005 mg/kg/h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Bolus: None</td>
<td>Adjust to APTT of 1.5–2.5 times patient baseline</td>
<td>Enzymatic and renal (25 min)</td>
</tr>
<tr>
<td></td>
<td>Continuous infusion:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal organ function $\rightarrow$ 0.15 mg/kg/h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal or hepatic dysfunction $\rightarrow$ dose reduction may be necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desirudin</td>
<td>15 mg or 30 mg subcutaneous Q12h♥</td>
<td>Probably not necessary; plasma levels of drug correlate with APTT</td>
<td>Renal (2 h)</td>
</tr>
<tr>
<td>Danaparoid</td>
<td>Bolus: $&lt;60$ kg $\rightarrow$ 1500 U $60–75$ kg $\rightarrow$ 2250 U $75–90$ kg $\rightarrow$ 3000 U $&gt;90$ kg $\rightarrow$ 3750 U Accelerated initial infusion: 400 U/h $\times$ 4 h, then 300 U $\times$ 4 h Maintenance infusion: Normal renal function $\rightarrow$ 200 U/h Renal insufficiency $\rightarrow$ 150 U/h</td>
<td>Adjust to anti-Xa level of 0.5–0.8 U/ml (if assay is available)</td>
<td>Renal (24 h)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>5 mg subcutaneous daily $&lt;50$ kg $\rightarrow$ 5 mg subcutaneous daily $50–100$ kg $\rightarrow$ 7.5 mg subcutaneous daily $&gt;100$ kg $\rightarrow$ 10 mg subcutaneous daily</td>
<td>None</td>
<td>Renal (17–20 h)</td>
</tr>
<tr>
<td></td>
<td>$Cl_{Cr}$, 30–50 ml/min $\rightarrow$ use caution $Cl_{Cr}$, $&lt;30$ ml/min $\rightarrow$ contraindicated</td>
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</tr>
</tbody>
</table>
Thrombosis events with DTIs

Patients with thrombosis complicating HIT

Composite endpoint: all-cause mortality, limb amputation, new thrombosis

- Controls, n=46
- Argatroban, n=144
- Controls, n=75
- Lepirudin, n=113

Marked reduction in endpoints *
Treatment of HIT (cont’d)

- Warfarin Rx recommended for 3-4 months
- Consider Warfarin after recovery of platelets (>150K)
- Avoid early warfarin without DTI Rx:
  Increase risk of limb necrosis during acute HIT caused by depletion of protein C
  - Occur in 5-10% of patients with HIT-associated DVT receiving anticoagulant
- 5-day overlap of non-heparin anticoagulant
  - Start with low dose warfarin
- Assays may be required to manage transition
  - DTI may impact PT
  - Chromogenic factor Xa assay
Heparin antibody formation after cardiac surgery: common

<table>
<thead>
<tr>
<th>Study</th>
<th>Frequency</th>
</tr>
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<tbody>
<tr>
<td>Visentin et al. (1996)</td>
<td>39%</td>
</tr>
<tr>
<td>Trossaert et al. (1998)</td>
<td>27%</td>
</tr>
<tr>
<td>Pouplard et al. (1999)</td>
<td>25%</td>
</tr>
<tr>
<td>Warkentin et al. (1999)</td>
<td>50%</td>
</tr>
<tr>
<td>Francis et al (2002)</td>
<td>42%</td>
</tr>
</tbody>
</table>
GUSTO IV Substudy Results

- **AB Pos (n=23)**
- **AB Neg (n=195)**

**Death or MI**
- AB Pos: 22%
- AB Neg: 6%
- p=0.008

**Death**
- AB Pos: 13%
- AB Neg: 6%
- p=0.217

**MI**
- AB Pos: 11%
- AB Neg: 6%
- p=0.012

3-4 fold increased risk

Heparin exposure in patients with ‘asymptomatic’ antibodies

466 patients undergoing CABG:
- 59 (12.7%) patients HIPA positive pre-op
- Odds Ratio for complications = 2.15 (1.15-4.04; P=0.017)

What are the treatment options for patients who have HIT and must undergo cardiac surgery?
## Heparin re-exposure with history of HIT

<table>
<thead>
<tr>
<th>Clinical picture</th>
<th>Laboratory profile</th>
<th>Recommended intraoperative anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immunologic assay</td>
<td>Functional assay</td>
</tr>
<tr>
<td>Remote HIT</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Subacute HIT</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Acute HIT</td>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>
Cardiac Surgery: Patients with acute or subacute HIT

Options:
1. Postpone cardiac surgery for several months, then may use heparin
2. Bivalirudin
3. Lepirudin
4. Epoprostenol + Heparin
5. Tirofiban + heparin
6. Danaparoid (withdrawn from the US market)
7. Off-pump technique using bivalirudin, lepirudin, or danaparoid if subacute HIT
Bivalirudin: EVOLUTION-ON study
J Thoracic and Cardiovascular Surgery 2006

- Objectives: To evaluate the safety and efficacy of bivalirudin vs. heparin/protamine
- Methods: randomized, open-label, multicenter trial
  patients: CABG on-pump
  1. Bivalirudin: 101 patients
     (1mg/kg IV bolus then 2.5 mg/kg/h) Goal 2.5xbasline ACT
  2. Heparin: 49 patients
- Exclusion criteria: recent use of gp2b/3a antagonist, ADP antagonist, LMWH, thrombolytics
- Results:
  - Rapid and sustained increase in ACT.
  - No difference in % procedural success in 7 days, 30 days, 12 weeks
    * procedural success defined as freedom from death, Q wave MI, stroke or revascularization.
  - Higher blood loss in postop 2 hours in bivalirudin, no difference after 24 hours. No difference in intracranial, GI, intraocular, or retroperitoneal bleed.
Bivalirudin: EVOLUTION-OFF study
J Thoracic and Cardiovascular Surgery 2006

- Objectives: To evaluate the safety and efficacy of bivalirudin vs. heparin/protamine in off-pump CABG
- Methods: randomized, open-label, multicenter trial
  1. Bivalirudin: 105 patients
  2. Heparin: 52 patients
- Exclusion criteria: with HIT, previous sternotomy, on dialysis, stroke within 6 months, receive warfarin, clopidogrel, lepirudin, or agatroban, allergy with study drugs
- Results:
  - No difference in death, Q wave MI, repeat coronary revascularization and stroke at day 7/discharge.
  - At 30 days, higher number of stroke in heparin group than bivalirudin.
  - All-cause mortality was low (2%) at 30 days and 12 weeks.
  - More blood products transfused require for bivalirudin group despite similar rate of transfusion compared with heparin/protamine.
Bivalirudin: Plasma Levels

Plasma concentrations versus time

- Bolus 1mg/kg
- Bolus 0.75 mg/kg
- Infusion 2.5 mg/kg/h
- Infusion 1.75 mg/kg/h

- 25 minute half-life
- Shown to reduce risk of ischemia in PCI (6.5 mcg/mL)

Monitoring still required, ACT indicates drug presence
Surgical (Intra-Op) Considerations

• Eliminate all heparin (lines, SG, cannulas, OR and ICU)

• Anticoagulation and monitoring
  – Initial delivery (loading)
  – Continued (uninterrupted) drug infusion
    • route/location (make sure drug is delivered)

• Avoid stagnation
Surgical Considerations
Avoid Stagnation I

- Stagnation = thrombin
- Large bore, soft flow cannulas (minimize shear and turbulence)
- Closed systems (minimize blood air interface)
Avoid Stagnation II

• Cardioplegia
  – crystalloid vs. blood
  – flush blood cardioplegia unto field between doses
• All field (pericardial) suction directed to cell saver
• Thoughtful use of cardiac vents (intra cardiac blood)
  – Continuous vs. intermittent use
• Careful management of cardiotomy suction
  – Monitor carefully for thrombosis
  – Either re circulate continuously or send to cell saver
Special Considerations

• Excess volume (cardiotomy)
  – Cannot use UF during CPB

• Circulatory arrest
  – Unknown (extreme re warming, stagnation)

• Renal failure or insufficiency
  – MUF vs. patience and time
MUF: Parallel Circuits

Aortic vent/plegia

Keep circuits separate, use cardioplegia lines and roller pump for MUF circuit

Retrograde
Into RA

UF

CPB
Post Operative Care

- No heparin in any flushes
- Discontinue deep lines early (nidus for thrombus formation)
- Coumadin anticoagulation as needed
- Bivalirudin for AF, early mechanical valve Rx
- Consider routine DTI

OR

- Vigilance: test any potential post-op (heparin Rx) patients for potential HIT and treat as needed
Summary

• About 35-65% of the patients on CPB will be HIT Ab positive, but only a small percentage of those patients experience clinical HITT syndrome.

• Recognizing post op HIT/HITT is important. If HIT is highly suspected, initiate DTI anti-coagulation therapy immediately to prevent thrombotic events.

• Many anticoagulants are available for treatment of HIT, select agent based on patient’s profile and institutional experience.

• Test suspected patients for HIT/HITT pre operatively

• Delay surgery if possible. Heparin induced antibodies (IgG) usually become undetectable by 100 days (median=50 days).
Summary

- Heparin can be used in patients with previous HIT for cardiopulmonary bypass (CPB), provided weakly positive by Ab assay but negative washed platelet activation (functional) assay.
- Bivalirudin and lepirudin are commonly used during CPB in patients with acute or subacute HIT.
  - Requires planning (protocols) and training
- Ab positive patients (no clinical HIT) still carry a higher TE risk during CV interventions
Thank you for your attention
Questions ?
References:

References:

Pathophysiology