Heparin & HIT: State of the Art

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Objectives

- Acknowledge Heparin (almighty)
- HIT? Why care?
- Is it HIT?
- It is HIT. Now what?

Heparin

1916
McClean: 2nd year medical student at Johns Hopkins working under Dr. Howell
- canine liver cells, anticoagulant
  - "hepar" or "ήπαρ" is Greek for "liver"

1933-1935: Univ Toronto, Karolinska Institute
1935: first human trials
1937: "safe"
Heparin
(UFH: unfractionated heparin)

- Pharmaceutical grade: Bovine & Porcine
- Also:
  - Turkey
  - Whale
  - Dromedary camel
  - Mouse
  - Lobster
  - Fresh water mussel
  - Clam
  - Shrimp
  - Mangrove crab
  - Sand dollar

Recombinant technology... $$$

Heparin

- MI, A-fib, DVT/PE, hypercoag
- CABG, Vascular Surgery, Cardiology
- Catheters, grafts
- IV flushes, dialysis, blood collection
- Naturally occurring:
  - Basophils and mast cells; endothelial cells
  - Not dissolve thrombus

Binds to anti-thrombin III (ATIII)
- Inhibits factors Ixa, Xa, Xla, and kallikren

Heparin

the most powerful anticoagulant of the Twentieth Century
saving uncountable lives and limbs
also produces the most extreme hypercoagulable disorder
costing thousands yearly their lives and limbs.
Heparin

- 1 trillion units of heparin used yearly
- 12 million Americans get heparin (33% of patients hospitalized)
- 8% develop antibody to heparin (bovine, porcine, synthetic)
- 1% get severe antibody reaction

8280

*Shuster, JVS, 2003

Thrombocytopenia = Low platelets

Net bleed...

CLOTTING!!!

Thrombotic storm

Aster, AJW 1995, 20:132; 1374-76
Differential Diagnosis of Acquired Thrombocytopenia

- **Drugs**
  - Heparin
  - Procainamide
  - Diuretics (furosemide)
  - Angiotensin-converting enzyme inhibitors
  - Thrombolytic therapy
  - GP IIb/IIIa antagonists

- **Devices**
  - Membrane oxygenator
  - Intra-aortic balloon pump

- **Pseudothrombocytopenia**
  - Platelet clumping
  - Hemodilution

- **Associated disorders**
  - Hypoplasemia
  - Infections/epis
  - Hypertension and subsequent disseminated intravascular coagulation

- **Other causes**
  - Chronic iatrogenic thrombocytopenia with thrombocytopenia purpura with occlusion
  - Antiphospholipid antibody syndrome
  - Postoperative fluid shifts
  - Graft placement

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**HIT is rare: Myth**

- Unfractionated heparin (UFH): 3 to 5% HIT
- SQ LMWH, flush, coated cath: 0.5% HIT
- Fondaparinux: rare but reported

- UFH > LMWH > heparinoids >> fondaparinux

*Studies JVL, 2003*
Iceberg Model

- Multiple thromboses: 0.01-0.1%
- Isolated thrombosis: 30%
- Asymptomatic thrombocytopenia: 50%
- HIT IgG seroconversion: 10%

LaMuraglia et al. JVS 2012

Warkentin TE, et al. 1994;75-127
HIT? Why care?

Heparin-induced thrombocytopenia
- **Typical**
  - 70% of patients with HIT
  - Platelet drop 5-14 days after heparin tx
  - No thromboses
- **Rapid-onset**
  - 25% of patients with HIT
  - Prior treatment (<100 days)
  - Platelet drop and thromboses ≤24hrs after heparin tx
- **Delayed-onset**
  - 5% of patients with HIT
  - Platelet drop with thromboses
  - days to 3 weeks after heparin discontinued

HIT? Why care?

- **Heparin-induced thrombocytopenia**
  - Pro-thrombotic
  - **Venous** and/or **Arterial**
    - 50% develop both, mostly venous
    - No thrombus... YET!
    - 33% in next 10 days

C= PF4 Ab
B= PF4 Ab + HIT but no thromboses
A= PF4 Ab + HIT + thromboses

LaMuraglia et al. JVS 2012

HIT? Why care?

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HIT? Why care?

- Heparin-induced thrombocytopenia
  ***No diagnosis = no treatment***
  - Limb amps 10-20%
  - Death 20-30%
  - Residual effects (stroke, MI, PE)

HIT is rare: Myth

- ICU
- Vascular Surgery
- Orthopedic
- Cardiothoracic
- Medicine/Cardiology

Equal risks...NOT

- Major > Minor
  = Sites of vascular injury
- Develop Ab or Develop thrombosis
  - Ortho + UFH + Ab = high risk thrombosis
  - Bovine > Porcine
  - IV > SQ
  - Women > Men
  - Old > young
  - >=4 days of therapy
HIT is rare: Myth

- Lack of awareness
  - Platelet monitoring is key

BEFORE heparin tx
DURING heparin tx
AFTER heparin tx

Platelet Count Drops PRIOR to Thromboses

Clinical Suspicion must be HIGH

<table>
<thead>
<tr>
<th>Level</th>
<th>Points</th>
</tr>
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<tbody>
<tr>
<td>High</td>
<td>6-8</td>
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<tr>
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<td>4-5</td>
</tr>
<tr>
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<td>0-3</td>
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</tbody>
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Warkentin et al, NEJM 1995;332:1330

*Thrombotic episode

LaMuraglia et al JVS 2012

Table 3: Clinical suspicion to diagnose of heparin induced thrombocytopenia*
4T scoring system

- Study in 111 patients:
  - Low score = 0.9% HIT
  - Intermediate score = 11.4% HIT
  - High score = 34% HIT

<table>
<thead>
<tr>
<th>THROMBOCYTOPENIA</th>
<th>TIMING</th>
<th>THROMBOSIS</th>
<th>OTHER</th>
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Just stop the Heparin: NO!

1. Remove the trigger: ALL heparin
   - Just heparin cessation can exacerbate new thrombi (up to 50%)
   ---5% fatal

2. Stop warfarin!

3. Treat the "thrombotic storm": Thrombin inhibitor

4. Don’t give platelets! Don’t place IVC filter!

4. CLINICAL DIAGNOSIS....don’t wait for tests!!
   New complications: 6% per day

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*Rice, Arch Int Med 164: 2004
Do bother the Hematologist!

- **Etiology**
  - Sepsis, drugs, post-pump, graft material, hemodilution, microangiopathies, pseudothrombocytopenia...

- **Interpret confirmatory lab tests**
  - Immunoassays-ELISA (specific)
  - HIPA & SRA (functional, sensitive)

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**Do bother the Hematologist**

- **Management of thrombin inhibitors**
  - Bivalirudin
  - Lepirudin (kidney clearance)
  - Argatroban (liver clearance)

  - When/how begin warfarin dosing:
    
    ----when platelets $\geq 150K$
Do bother the Hematologist

- Access other tx options
  - IgG
  - platelet infusion if bleeding issues
  - Plasmapheresis

- Can patient ever have heparin again?

Can’t prevent HIT: FALSE

- Medical history positive for heparin use?
- Limit heparin to <4 days
- Avoid “routine” heparin flushes
- Use warfarin early (in non-HIT pts)
  -----Initiate oral anticoag at start of heparin tx-----
- Use LMWH if possible as first heparin

"As a surgeon, I can handle bleeding...
...it’s the clot I despise!"

—Unknown
Objectives

- **HIT? Why care?**
  - It’s not rare
  - Think of prevention

- **Is it HIT?**
  - Assess platelet count
  - Assess for thromboses
  - 4T scoring

- **It is HIT. Now what?**
  - Stop heparin
  - Don’t start warfarin
  - Don’t give platelets or IVCF
  - Start thrombin inhibitor (with help of hematologist)
  - Send labs back

What is the incidence of HIT in patients exposed to heparin more than 4 days?

1. **10-20%**
2. **5-10%**
3. **3-5%**
4. **0.3-3%**
5. **0.05-0.1%**
What is the incidence of HIT in patients exposed to heparin more than 4 days?

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5. 0.05-0.1%

What is most suggestive of HIT?

1. Platelet count = 180 x 10^3/mm³
2. Platelet count = 60 x 10^3/mm³
3. Drop of platelet count <30%
4. Drop in platelet count <50%
5. Rise in platelet count >50%
Which manifestation of HIT leads to the most frequent complications in HIT?

1. Arterial thrombosis
2. Venous thrombosis
3. Thrombocytopenia
4. Heparin-induced skin lesions
5. Acute system reactions (fever, chills, tachycardia)

In addition to immediate cessation of all UFH products, what is the next appropriate step in treating HIT?

1. LMWH
2. Aspirin
3. Warfarin
4. Platelet infusion
5. Argatroban
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Questions?

References
- Warkentin, TE. Chest 2004, 125; 511-529.
- Aster, NEJM 1995, 332: 1374-76