Heparin induced thrombocytopenia

Canadian Critical Care Forum

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Ryan Zarychanski MD MSc. FRCPC
Department of Internal Medicine,
Sections of Critical care and Hematology
University of Manitoba, Winnipeg, MB
Disclosures

Research support: Pfizer
Objectives

1. Epidemiology of HIT in critical illness
2. Pathogenesis of HIT
3. Diagnosing and treating HIT
4. Preventing HIT in the ICU
Frequency of thrombocytopenia in ICU
Hui P, Cook DJ, Arnold. Chest 2011

- Systematic Review:
- 24 Studies (12 prospective)  N = 6894
- Medical, surgical, mixed or trauma ICUs

Prevalence:  8% to 68%
Incidence:  13% to 44%

Risk of bleeding – poorly reported
Increased mortality in 6 of 8 studies
Etiology of thrombocytopenia in the ICU

Lot of reasons!

Sepsis / DIC
Hemophagocytic syndrome
Drugs
Cancer and chemotherapy
Massive Transfusion
Cardiopulmonary bypass / ECMO
TTP
HIT
Heparin-induced thrombocytopenia (HIT)

Diagnosis

SRA+ = platelet-activating antibodies

EIA-IgG/A/M result (OD units): ≤0.4  0.4-1.0  1.0-1.5  1.5-2.0  >2.0
Probability of SRA+ status: ~0%  ~5%  ~25%  ~50%  ~90%
Probability of thrombosis: ------  ~15%  ~20%  ~30%  ~50%
Incidence of HIT/HITT in the ICU

**Dalteparin versus Unfractionated Heparin in Critically Ill Patients**

The PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group


N = 3746
### Incidence of HIT/HITT in the ICU

<table>
<thead>
<tr>
<th></th>
<th>Dalteparin</th>
<th>Unfractionated heparin</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 (0.3%)</td>
<td>12 (0.6%)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

**Per Protocol Analysis**

|           | 3 (0.2%)   | 12 (0.8%)              | 0.046  |

- Increased risk in surgical patients and females


Heparin (re)Exposure

Rapid-onset HIT (hours–days)

Typical HIT Mean Day 9 (4–14 days)

Delayed-onset HIT (9–40 days)

Day 1  Day 4  Day 14  Day 30

THROMBOCYTOPENIA (± THROMBOSIS)

Dr. A IMahameed. Cleveland Clinic, OH.
Diagnosing HIT: The 4T score

<table>
<thead>
<tr>
<th>Thrombocytopenia</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count fall &gt;50 percent AND nadir $\geq$ 20,000/microL</td>
<td>2</td>
</tr>
<tr>
<td>Platelet count fall 30 to 50 percent OR nadir 10,000 to 19,000/microL</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count fall &lt;30 percent OR nadir &lt;10,000/microL</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Timing of platelet count fall</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear onset between days 5 and 10 of heparin exposure, OR platelet count fall at</td>
<td>2</td>
</tr>
<tr>
<td>≤1 day if prior heparin exposure within the last 30 days</td>
<td></td>
</tr>
<tr>
<td>Consistent with fall in platelet count at 5 to 10 days, but unclear, OR onset after</td>
<td>1</td>
</tr>
<tr>
<td>day 10, OR fall ≤1 day with prior heparin exposure within 30 to 100 days</td>
<td></td>
</tr>
<tr>
<td>Platelet count fall at &lt;4 days without recent heparin exposure</td>
<td>0</td>
</tr>
</tbody>
</table>
## Diagnosing HIT: The 4T score

<table>
<thead>
<tr>
<th>Thrombosis or other sequelae</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed new thrombosis, skin necrosis, or acute systemic reaction after intravenous unfractionated heparin bolus</td>
<td>2</td>
</tr>
<tr>
<td>Progressive or recurrent thrombosis, non-necrotizing (erythematous) skin lesions, or suspected thrombosis that has not been proven</td>
<td>1</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other causes for thrombocytopenia present</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None apparent</td>
<td>2</td>
</tr>
<tr>
<td>Possible</td>
<td>1</td>
</tr>
<tr>
<td>Definite</td>
<td>0</td>
</tr>
</tbody>
</table>
### Interpreting the 4T score

<table>
<thead>
<tr>
<th>Pre-test probability of HIT</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low probability</td>
<td>0 to 3</td>
</tr>
<tr>
<td>Intermediate probability</td>
<td>4 to 5</td>
</tr>
<tr>
<td>High probability</td>
<td>6 to 8</td>
</tr>
</tbody>
</table>

- Low pre-test probability = no further testing indicated

Cuker A, Gimotty PA, Crowther MA. Blood. 2012;120:4160
4 T score in the ICU

- RCT of 3746 med/surg ICU patients
- 794 enrolled in HIT sub study
  - 474 had laboratory HIT testing

Patients investigated for HIT if:
- Platelet count decreased to less than 50 x10^9/L
- Unexplained platelet count decrease to less than 50% of baseline ICU admission count
- Developed VTE
- HIT was otherwise clinically suspected

Cook DJ. PROTECT. NEJM 2011;364:1305
4T score in the ICU

Low PTP (3 or lower) 1.5% positive SRA

Intermediate PTP (score of 4-5) 6.8% positive SRA

High PTP (score of ≥6) 12.5% positive SRA

• Real-time 4Ts scoring by research coordinators at the time of testing for HIT was not consistent with 4Ts scores obtained by central adjudicators

Cook DJ. PROTECT. NEJM 2011;364:1305
Laboratory diagnosis HIT

1. **Enzyme linked immunoassay (EIA)**
   - Overly sensitive (especially the polyspecific assays)
   - PPV of EIA is only 10-20% in the ICU
   - Excellent NPV (almost 100%)
   - OD > 2.0 are are highly associated with HIT (>90%)

2. **Gel agglutination assay** (Dia-Med PF4)
   - Positive or negative (excellent NPV)
   - Rapid turn around

3. **Serotonin release assay** (SRA)
   - Gold standard
   - High sensitivity and specificity
   - Technically demanding
Clinical consequences of HIT

- New thrombosis ~50% (arterial or venous)
- Amputation: ~20%
- Death ~30%

Less well-known occurrences:
- Adrenal hemorrhagic infarction
- Heparin-induced skin lesions
- Anaphylaxis

Warkentin TE, Kelton JG. Am J Med. 1996;101
HIT as a ‘cause’ for ICU admission

- **Pulmonary embolus**
- **Adrenal failure**
  - Consider steroids if hypotensive, thrombocytopenic, and where HIT is possible
- **Acute anaphylactoid reaction**
  - 10-30 min after IV or 30-90 min after S/Q administration
  - Abrupt drop in platelet count
  - Fever, chills, tachycardia, hypertension, flushing, headache, chest pain, dyspnea, nausea, vomiting, large-volume diarrhea
Early-onset, but persistent TCP in ICU: HIT or not HIT??

- Two cardiac surgery cohorts
- Frequency of heparin-PF4 antibodies were similar to the ‘background’ rate of antibody formation in non-TCP post-op cardiac surgery patients

- Bottom line: Usually not HIT
  1% chance (higher if thrombosis)

Selleng S et al. J Thromb Haemst. 2010;8:30
Treatment principles of HIT: an ICU perspective

1. Stop and avoid all heparin
2. Give a non-heparin alternative anticoagulant
3. Avoid/postpone warfarin if HIT is suspected/diagnosed
4. Avoid IVC filters
5. Image for (lower-limb) DVT
6. Avoid prophylactic platelet transfusions
7. Confirm suspicion with the Serotonin Release Assay (SRA)
What do to if HIT is suspected?

Low likelihood of HIT

• Give heparin if T4 score is 3 or less

Intermediate likelihood of HIT

• Consider low-dose non-heparin alternatives
  • Danaparoid 750 IU S/Q TID
  • Fondaparinux 2.5 mg S/Q OD
  • Low intensity bilvalirudin (post surgical? / bleed risk)

High likelihood of HIT – Full treatment doses are suggested

• 1st choice: Danaparoid
• 2nd choice: Bilvalirudin, Argatroban
• 3rd choice: fondaparinux
Treatment principles of HIT: an ICU perspective

Direct thrombin inhibitors
- Argatroban
- Bivalirudin

Xa inhibitors
- Danaparoid
- Rivaroxaban

- Approved doses are too high
- ICU coagulopathies confound aPTT monitoring
- Effect on INR makes transition to warfarin challenging
- Hepatic metabolism
- Can be monitored by anti-Xa assay (not confounded by aPTT)
Treating HIT with full dose non-heparin anticoagulants in the ICU

• Approved doses are generally WAY to high

• **Argatroban** (2 mcg/kg/min): consider 0.2 mcg/kg/min  
  • Titrate to aPTT 1.5-2.5x baseline (60 to 99 ish)

• **Bivalirudin** (0.15 mg/kg/hr): consider 0.08 mg/kg/hr  
  • Titrate to aPTT 1.5-2.5x baseline (60 to 99 ish)
Treating HIT with full dose non-heparin anticoagulants in the ICU

- **Danaparoid**
  - IV bolus of 2250 units (according to wt.), followed by:
    - 400 units/hour for four hours
    - 300 units/hour for the next four hours
    - 200 units/hour thereafter.
    - Target anti-factor Xa levels of 0.5 to 0.8 units/mL
  - Long half life; no antidote
Is there evidence for any of this??

Argatroban versus Lepirudin in critically ill patients (ALicia): a randomized controlled trial (Critical Care 2014, 18:588)

- 66 critically ill patients with suspected HIT
- Less bleeding with argatroban
- Comparative filter times for 42% on CRRT

RCT of rivaroxaban is current enrolling
When should I start warfarin?

- Only when platelet count has substantially recovered (>150 x10^9/L)
- Start at low dose (5 mg of less per day)
- Overlap with the non-heparin anticoagulant for a minimum of 5 days
- Don’t be in a hurry to cause warfarin-induced skin necrosis?
Preventing HIT in the ICU

PROTECT trial: Incidence of HIT

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<td>Number of events</td>
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<td>p-value</td>
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<td>p = 0.046</td>
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Also

- Less HIT testing
- 73% relative risk reduction in HIT
- 50% relative risk reduction in PE
- Dalteparin superior cost/benefit profile

Cook DJ. PROTECT. NEJM 2011;364:1305
In Summary

- Most thrombocytopenia in ICU is not HIT (0.5% incidence)
- Pretest probability will help define a low risk population in which HIT can be excluded
- All patients with intermediate or high PTP should receive treatment for HIT (low or ‘full’ dose depending on risk suspicion and risk of bleeding)
- Danaparoid is the preferred drug for treating HIT (but is generally unavailable)
- Trials of NOACs are coming
Objectives

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Questions...?