HIT and urgent open heart surgery: a sticky situation

Hematology Grand Rounds
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Case presentation

57 year old man w/ ischemic cardiomyopathy and decompensated CHF undergoing evaluation for LVAD as destination therapy.

- Presented 6/11 in AK with acute decompensated CHF due to ischemia.
  - **LHC 6/13: 100% LAD occlusion d/t in-stent restenosis.** Left circ w/ 50-75% pre and in-stent restenosis.
  - Course c/b AKI on CKD and RLL PNA.

- Transferred to UWMC on 6/14 → required initiation of dobutamine. TTE showed a dilated LV and EF of 25% → evaluated by CT Surgery for LVAD placement as destination tx.


**PMH:** Afib, CHF (NYHA class III-IV, EF 10-15% 5/2014) with multiple admissions in last year, CAD s/p MI on 2010 and 2012 with PCI to LAD and circ, HLD, anemia, OSA

**SH:** Lives in AK with brother, remote tobacco, remote occasional alcohol, medical cannabis

**FH:** CAD, DM, breast ca
Case presentation

- Platelet count
- Hematology consulted
- Plts 332, UFH starts
- Plts 173, UFH stops, bival starts

Graph showing platelet count from 6/14/14 to 6/30/14.
UW Anticoagulation Website

- http://depts.washington.edu/anticoag/home/
HIT Probability Scoring

- 4T Score:
  - Thrombocytopenia (degree of platelet fall)
  - Timing of platelet fall
  - Thrombosis (or other sequelae)
  - oTher causes of thrombocytopenia
- 0-2 points per parameter
- \( \leq 3 \) low probability, 4-5 intermediate probability, \( \geq 6 \) high probability
- Helps guides management including lab assays.

Our patient: 4T score 6 = high probability
Anti-PF-4 ELISA OD 1.966
SRA pending (eventually positive)
Team following treatment guidelines on the AC website

The problems in this case:

1. The patient needs urgent cardiac surgery.

2. Intraoperative exposure to large amount of heparin is necessary.

3. When exposed to heparin, his pre-existing anti-heparin/PF4 Abs may activate platelets and put him at very high risk of thrombosis.
HIT: brief review

IgG recognizes PF4 bound to heparin

HIT Ab also activate endothelial cells and monos

FcyIIa receptors cluster

Procoagulant platelet-derived microparticles

Platelet activation

Anti-PF-4 IgG transient—clears after 50-80 days.
Options for managing HIT and open heart surgery

1. Wait it out
2. Avoid the problem (non-heparin anticoagulant)
3. Block platelet activation/aggregation*
4. Remove activating antibody (plasma exchange)*

(*either not recommended or not even mentioned in the 9th edition ACCP Guidelines)
Options for managing HIT and open heart surgery

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2. Avoid the problem (non-heparin anticoagulant)
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Options for managing HIT and open heart surgery #1: Wait.

- Patients with hx HIT w/ but negative PF-4 Abs (by EIA) are **not** at increased risk of HIT with heparin re-exposure.

- Sensitization does not occur with <4 days of re-exposure to heparin if activating Abs are absent.

- PF-4 Abs are transient, so patients >100 days from HIT diagnosis safe for re-exposure even without repeat titer.

Linkins et al., *Chest*, 2012.
Options for managing HIT and open heart surgery #1: Wait.

Retrospective review of 20 pts with HIT re-exposed to heparin
- 18 with clinical dx + Ab + SRA; 2 with clinical + Ab but no SRA

Looked at pre and post re-exposure Ab (EIA) and SRA
- 12 pts seroconverted (↑ titer by EIA and/or +SRA)
  - 7 with detectable Ab before re-exposure (no +SRA)
    - 5 with EIA and SRA
    - 2 with EIA only
  - 3 patients w/ undetectable Ab before re-exposure ➔ both EIA and SRA
  - Only 1 pt developed clinical HIT (undetectable pre)
- 2 pts with detectable Ab before re-exposure did not seroconvert

Take home: Likely safe to re-expose patients to heparin even with positive Abs, if Abs are not activating (ie, SRA is negative).

Options for managing HIT and open heart surgery #1: Wait.

“6.1 Patients With a History of HIT Who Require Cardiac Surgery

• Although the evidence is very limited, the combination of the unique properties of HIT antibodies...and the serious difficulties that may be encountered using nonheparin anticoagulants...lead us to conclude that the risk of short-term re-exposure may be justified in specific circumstances [CPB, e.g.]”

• “...use of heparin should be restricted to...surgery, and [otherwise] scrupulously avoided.”

Linkins et al., Chest, 2012.
Options for managing HIT and open heart surgery

1. Wait it out
2. Avoid the problem (non-heparin anticoagulant)
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Options for managing HIT and open heart surgery #2: Avoid the problem.

Non-heparin anticoagulants:

• Bivalirudin:
  – 20 amino-acid synthetic peptide modeled after hirudin
  – Reversible inhibitor of thrombin
    • Inactivated by cleavage by plasma enzymes including thrombin
  – $T_{1/2}$ is 25 minutes

Warkentin and Greinacher Ann Thorac Surg 2003

Hirudo medicinalis
Options for managing HIT and open heart surgery #2: Bivalirudin.

- EVOLUTION-ON (*no HIT*): Bival vs UFH + protamine for OHS on CPB (2:1 randomized; 98 bival, 52 UFH), multicenter RCT
  - 1° endpoint (procedural success): same
  - 2° endpoints:
    - Transfusion need: 58% (B) and 60% (H)
    - Major bleeding: 6% in bivalirudin, 2% in UFH (*p* = 0.67)
      - ICH, RP bleed, GI bleed, re-exploration

- CHOOSE-ON: HIT or suspected HIT (*n* = 49, 42 HIT Ab+), on CPB, prospective multicenter cohort
  - Procedural success 94%, no major bleeding, no MIs, 1 CVA, 1 death.

- Dyke et al 2007: HIT or suspected HIT (*n* = 51, 35 HIT Ab+), *off-pump*, prospective multicenter cohort
  - Procedural success 92%, no major bleeding, 3 MIs, 1 CVA, no deaths.

Options for managing HIT and open heart surgery #2: Bivalirudin.

- “5.1.1. Patients with acute or subacute HIT…who require urgent cardiac surgery, we suggest the use of bivalirudin over other approaches (Grade 2C).”

But…

- Requires certain adaptations in technique.
  - Avoid blood stasis or pooling to avoid bivalirudin inactivation.
  - Ecarin clotting time preferred (but can use ACT).

- No reversal agent if bleeding occurs.


Linkins et al., Chest, 2012.
Options for managing HIT and open heart surgery #2: Not bivalirudin?

**NOT** recommended:
1. Argatroban  \[Excess bleeding\]
2. Lepirudin
3. Aspirin  \[Excess clotting\]

4. Ancrod:
   - Fibrinogenolytic derived from Malayan pit viper
   - En vogue (briefly) in 1990s
   - Ask Dr. Gernsheimer about this drug...

Calloselasma rhodostoma
Options for managing HIT and open heart surgery

1. Wait it out
2. Avoid the problem (non-heparin anticoagulant)
3. Block platelet activation/aggregation
4. Remove activating antibody (plasma exchange)
Options for managing HIT and open heart surgery #3: Block platelet function

1. Give prostacyclin (or analogue)
   – Produced by normal intact endothelium
   – Stimulate plt adenylate cyclase $\rightarrow$ increase intracellular AMP levels $\rightarrow$ block platelet activation

2. Block glycoprotein IIb IIIa
   – GPIIb IIIa binds vWF, fibrinogen, exposed collagen $\rightarrow$ platelet adhesion and aggregation

Both must be used with heparin.
Options for managing HIT and open heart surgery #3: Block platelet function

Prostacyclin or analogue (case reports)

• Iloprost:
  – Addonizio VP et al Surgery 1987 (n = 3)
  – Antoniou et al Heart Surg Forum 2002 (n = 22)

• Epoprostenol:

Pitfalls: Vasodilation and hypotension (may be profound), no reliable real-time monitoring (at least at UWMC)
Options for managing HIT and open heart surgery #3: Block platelet function

GPIIb IIIa inhibitor

• Tirofiban (case reports/series)
  – Koster et al Anesthesiol 2001. (n = 10)
  – Durand et al Eur J Cardiothorac Surg 2008 (n = 1)
  – Neuray et al Ann Thorac Surg 2012 (n = 1, peds)  
    \[\text{Excess bleeding noted!}\]

• Pitfalls: Can cause severe bleeding refractory to plt transfusions, drug-induced thrombocytopenia, clearance, monitoring (?)
Options for managing HIT and open heart surgery

1. Wait it out
2. Avoid the problem (non-heparin anticoagulant)
3. Block platelet activation/aggregation
4. Remove activating antibody (plasma exchange)
Options for managing HIT and open heart surgery #4: Remove antibody

Plasma exchange:

- Ab removed by PLEX, although IgG removal inefficient as IgG is intra and extra-vascular → re-equilibrates after PLEX.
  
- However, complete Ab removal likely not necessary and EIA lags SRA response.

Options for managing HIT and open heart surgery #4: Remove antibody

Other data for PLEX for HIT and urgent cardiac surgery?

- 9 patients with (sub)acute HIT (dx w/in 9 wks); 2 with hx HIT and positive PF-4 Abs.
  - Clinical dx and positive anti-PF-4 Abs
  - Functional testing w/ heparin-induced plt aggregation (all pts neg)
  - SRA not done.
- PLEX performed intra-op—if stable, before UFH started; if unstable, UFH and CPB started, then PLEX.
- Practical consideration: PLEX removes heparin too.

Options for managing HIT and open heart surgery #4: Remove antibody

No post-op PLEX even in pts who did not clear Abs.

Options for managing HIT and open heart surgery #4: Remove antibody

Options for managing HIT and open heart surgery #4: Remove antibody

Lingering questions:
• When is the right time for PLEX?
• Functional assay?

Single patient case reports of pre-op PLEX:
  – Voeller et al J Thorac Cardiovasc Surg 2010: Ab+ and SRA+ patient. PLEX pre-op x7 until Ab-, then destination LVAD.
  – Kajitani J Card Surg. 2001: Ab+ patient, no SRA. PLEX pre-op x3 until Ab-, then CABG. Also ASA, clopidogrel, steroids.
• Both got CPB with UFH, no post-op PLEX, no complications

Case presentation revisited

Recommendations:
• Evidence for PLEX was not strong enough to recommend.
• Platelet inhibition too unpredictable/risky.
• If urgent surgery needed, use bivalirudin.
• If possible, wait 3 months for Ab to clear then use UFH.

However...
• Patient actually improved enough for discharge home without LVAD.
• Repeat SRA 7 days after initial was negative! (Initial was borderline positive.)
• LVAD placed 8/2014 uneventfully.
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HIT: brief review

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<tr>
<th>Patient Population (Minimum of 4-d Exposure)</th>
<th>Incidence of HIT, %</th>
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<tbody>
<tr>
<td>Postoperative patients</td>
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<tr>
<td>Heparin, prophylactic dose[^3,4,14,25]</td>
<td>1-5</td>
</tr>
<tr>
<td>Heparin, therapeutic dose[^26]</td>
<td>1-5</td>
</tr>
<tr>
<td>Heparin, flushes[^a]</td>
<td>0.1-1</td>
</tr>
<tr>
<td>LMWH, prophylactic or therapeutic dose[^14,25]</td>
<td>0.1-1</td>
</tr>
<tr>
<td>Cardiac surgery patients[^14,27,28,29]</td>
<td>1-3</td>
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<tr>
<td>Medical</td>
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<tr>
<td>Patients with cancer[^24,30,31]</td>
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<tr>
<td>Heparin, prophylactic or therapeutic dose[^24]</td>
<td>0.1-1</td>
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<tr>
<td>LMWH, prophylactic or therapeutic dose[^26,30]</td>
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<tr>
<td>Intensive care patients[^32]</td>
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<tr>
<td>Heparin, flushes[^33]</td>
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<tr>
<td>Obstetrics patients[^21,22,34,35]</td>
<td>&lt;0.1</td>
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[^a] Case reports only.

See Table 1 legend for expansion of abbreviations.