Critical Care Heme Update

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DISCLOSURE
Relevant Financial Relationship(s)
Speaker Bureau - None
Consultant – None
Grants - Alexion

What I will be Talking About

• Bad Platelets
• Bad Thrombosis
• Bad Blood

Heparin Induced Thrombocytopenia

• Frequent and major cause of heparin related complications
• Very common
• Very confusing

What is HIT?

• Heparin binds PF4
• Complex of PF4 and heparin form antibodies
• Antibodies bind to platelet Fc receptor and activate platelet and macrophages
• Drug induced platelet activation syndrome
HIT: Natural History
- Occurs with 1-5% of standard heparin
  - Much less with LMWH (~0.5%)
- Occurs >2 days after first exposure to heparin
- Mild to moderate thrombocytopenia (50-90k)
- Up to 50% of patients will have thrombosis
- Thrombosis rate is 10%/day

Incidence: Surgical Patients

<table>
<thead>
<tr>
<th>Population</th>
<th>Incidence of HIT%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>1%</td>
</tr>
<tr>
<td>UFH</td>
<td>0.1-1%</td>
</tr>
<tr>
<td>LMWH</td>
<td>0.6%</td>
</tr>
<tr>
<td>ICU</td>
<td>0.1-1</td>
</tr>
<tr>
<td>Heparin Flushes</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Obstetrics</td>
<td>&lt; 0.1</td>
</tr>
</tbody>
</table>

Incidence: Medical Patients

<table>
<thead>
<tr>
<th>Population</th>
<th>Incidence of HIT%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic UFH</td>
<td>1-5%</td>
</tr>
<tr>
<td>Therapeutic UFH</td>
<td>1-5%</td>
</tr>
<tr>
<td>Heparin Flushes</td>
<td>0.1-1</td>
</tr>
<tr>
<td>LMWH</td>
<td>0.1-1</td>
</tr>
<tr>
<td>Cardiac Surgery</td>
<td>1-3%</td>
</tr>
</tbody>
</table>

Monitoring for HIT
- Check platelets every 2-3 days from day 4 to 14 in patient who risk is > 1%
- Surgery
  - UFH prophylactic or therapeutic
  - Cardiac surgery
- Medical
  - Cancer patients
  - UFH prophylactic or therapeutic

HIT: Diagnosis I
- Clinical diagnosis supported by lab data
- Drop in platelet count by 50% from peak
  - Patients can have HIT with normal platelet counts
- Recurrent thrombosis on heparin
Drug Induced, ITP

Number of patients with HIT

Platelet count nadir $\times 10^9/L$

Median Nadir = 59,000
OHSU = 62,000

Heparin Induced Thrombocytopenia and Gender

- Review of 7 prospective HIT studies
- Women more likely to get HIT (OR 2.37)
- Especially with UFH
  - UFH vs LMWH M:1.83 F:9.22
- More likely to get HIT with surgery
  - 1.75 vs 14 (medical vs surgery)

Mimickers of HIT

- Clinical diagnosis can be hard in complex patients
  - Sepsis
    - Platelets drop by 50% day of + blood culture
  - Post-surgical
  - Large thrombosis

Mimickers of HIT

Surgery

1 2 3 4 5
Heparin

HIT: Diagnosis II

- Laboratory
  - Platelet aggregation
  - Anti PF4 antibodies

HIT: Diagnosis II

- Platelet aggregation: sensitive and specific if serotonin or similar technique used
  - Can be falsely negative in first 24 hours
  - Specificity and sensitivity > 90%
  - Technically demanding
### HIT: Diagnosis II

- **Anti-PF4 antibodies:** Very sensitive but low specificity in certain populations
  - Cardiac and vascular surgery +PF4 found in > 50% in all patients
  - Need to interpret with clinical likelihood of HIT

### HIT: The 4 T’s

- **Thrombocytopenia:** > 50% fall with nadir 50,000-100,000/ul
- **Timing:** 5-10 days after heparin
- **New Thrombosis or skin reaction**
- **No Other cause for thrombocytopenia**

<table>
<thead>
<tr>
<th>T’s</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>Platelet count &gt; 50% and platelet peak 400</td>
<td>Platelet count &gt; 50% and platelet peak 400</td>
<td>Platelet count &gt; 50% and platelet peak 400</td>
</tr>
<tr>
<td>Timing of platelet count fall</td>
<td>One or more times 5-10 or platelet fall &gt; 15,000/ul 3 days after heparin exposure</td>
<td>Five or more times 5-10 or platelet fall &gt; 15,000/ul 3 days after heparin exposure</td>
<td>Five or more times 5-10 or platelet fall &gt; 15,000/ul 3 days after heparin exposure</td>
</tr>
<tr>
<td>Other causes for thrombocytopenia</td>
<td>None apparent</td>
<td>None apparent</td>
<td>None apparent</td>
</tr>
</tbody>
</table>

- Score 0 - 3: Unlikely to be HIT (<5%)
- Score 4 - 5: Possible HIT (10-30%)
- Score 6 – 8: Probable HIT (> 50%)

### HIT: Diagnosis III

- Score ≤ 3: No testing
- Score > 3
  - Stop all heparin
  - Obtain testing
    - If score 4-5:
      - Negative – HIT ruled out
      - Positive – need verification
    - If score > 6
      - Negative – reassess for HIT
      - Positive - HIT

### HIT: Argatroban

- Preferred in sick patients
- 2 ug/kg/min adjust aPTT to 2-3 times normal
  - ICU start at 1 ug/kg/min
  - Post-CABG start at 0.5-1 ug/kg/min
- Dose adjust in 0.5 ug/kg/min increments
  - Average patient needs only 3 dose adjustments
- Affect INR

### HIT: Other Drugs

- **Fondaparinux**
  - Long half-life
  - Does not appear to cross react
    - Does form PF4 complexes
  - Useful for
    - Long term therapy
    - Change over to warfarin
    - Warfarin refractory patient
    - Patient with history of HIT
**HIT: Other Drugs**

- **Lepirudin**
  - Very sensitive to renal function
  - Can go > 100 hours
  - No antidote if patient bleeds
  - Antibodies form in 50-70% of patients
  - Fatal anaphylaxis reported

- **Bivalirudin**
  - Data for use in cath lab and CABG

**New Agents**

- No data
- Should not cross react
- Roles
  - After acute HIT
  - Patients with history of HIT

**HIT: Anticoagulation Therapy**

- Who needs it?
  - Patients with thrombosis
  - Any patients with HIT
    - 30% thrombosis rate
    - Duration in no thrombosis patients
      - Until platelets return to normal
      - Consider 2-4 weeks in post-op HIT

**Frequency of Thrombosis after Heparin is Stopped**

**Warfarin**

- Contraindicated in acute HIT!
- Associated with limb loss
  - Drop in protein C and S
- If on warfarin need to reverse
- However, still best long term therapy

**Warfarin and HIT**

- Initiate with low doses (2.5 mg) when platelet count returns to normal
  1. Follow chromogenic X assay
  2. Follow INR and adjust for argatroban effect
  3. Use fondaparinux/new drugs
- Should have generous (72 hours) overlap
Past History of HIT

- Use alternative anticoagulants
- If need heparin
  - Antibodies disappear in 3 months
  - Can use brief exposure for surgery

Treatment of DVT/PE

- Thrombolytic Therapy
- Inferior Vena Cava Filter
- Outpatient PE therapy

Thrombolytic Therapy DVT

- Intravenous therapy
  - Multiple trials
  - Fell out of favor due to lack of long term effectiveness in preventing post-thrombotic syndrome

Thrombolytic: DVT

- Systemic Therapy – Cochrane
  - Increased early and late clot lysis
    - RR 4.14 and 2.71
  - Reduced PTS
    - 0.66 (0.47-0.94)
  - Reduced Ulcers
    - NS
  - Bleeding
    - RR 1.73

The New Era

- Catheter based thrombolytic therapy
  - Multiple case series
    - N = ~ 700
    - Patency 75-80%
  - High rate of anatomical “lesions”
Thrombolytic Therapy: DVT
- Selected patients with large very proximal DVT should get catheter directed thrombolytic therapy
  - Symptoms < 14 days
  - Good health status
  - Good candidate for thrombolytic therapy
- Venous lesions should be corrected by angioplasty or stents

Randomized Trial
- N = 209
- Open label
- Up to 21 days after thrombosis
- Catheter directed thrombolytic therapy vs standard of care

Catheter Directed Thrombolytic Therapy
- Large proximal venous thrombosis
- Good candidates for thrombolytic therapy
- Can “cool” off with heparin
- NIH RCT underway
  - OHSU Study Site

Lancet 379:31-8, 2012
Inferior Vena Cava Filters

There is absolutely positively no consensus on the proper use of inferior vena cava filters

- Only 1 RCT
- Prevents (early on) PE in anticoagulated patients but no influence on mortality
- ~1-2% fatal PE rate in IVC filters patients in ICU studies
- Increase incidence of DVT at insertion site
- Raises risk of future DVT (~2x)

Retrievable Filters: Panacea or Pandemic?

- Rapid acceptance of retrievable filters
- Caveats
  - 10-20% cannot be removed
  - > 50% aren’t removed
  - Limited clinical studies
  - Limited long term follow-up

Filters

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Bard Recovery Vena Cava Filter


Retrievable Filters
- Need system in place to retrieve
- Reports of retrieval many months out
- Can retrieve while anticoagulated
- Uncertain if patients need to be monitored for strut breakage

IVC Filters
- Still should be used with caution
- Indications
  - Large DVT and temporary contraindication to anticoagulation
  - Large DVT and poor cardiopulmonary status
  - NOT indicated for PE prophylaxis
- Patients must be warned that "retrievable" filter may be permanent
- Will RAISE the risk of DVT!
- Need to anticoagulate as soon as feasible

Reasons NOT to Put in a Filter
- Pulmonary embolism:
  - 1st week of anticoagulation
  - despite warfarin
- Deep Venous Thrombosis:
  - With free floating thrombus
  - Extension of DVT
  - Despite warfarin
  - In cancer patients

Thrombolytic Therapy: PE
There is no clinical utility in thrombolytic therapy for the vast majority of patients with pulmonary embolism

Curr Opin Hem 2009 Sep;16(5):402-6

Two studies show doubling risk of death with thrombolytic therapy when used in normotensive patients.

Thrombolytic Therapy: PE

- Does not offer clinical benefit in almost all PE patients
- Use should be restricted to patient with refractory hypotension
  - Can consider in “high-risk” normotensive patients (2B)
- Screen carefully for bleeding risks
- Do not start heparin until at least 4 hours after therapy when aPTT ≤2x nl

The Future

- Large 1000 patient RCT of heparin vs thrombolytic for “high-risk” patients underway in Europe
  - + Troponin
  - + R heart strain
  - Normal BP

Can PE be Treated as Outpatients?

- Increasing incidence of “mild” PE
- Systems in place for home therapy of DVT

Aujezky Trial

- N = 344
- PESI < 85
- No difference in death, bleeding, or recurrent thrombosis

Pulmonary embolism severity index (PESI)

- Points are assigned as follows:
  - 1 for each year of age
  - 10 for male sex
  - 20 for HR>110 beats/min
  - 10 for heart failure
  - 30 for malignancy
  - 10 for chronic lung disease
  - 30 for SBP<100
  - 20 for RR>30
  - 20 for temp <36 degrees C
  - 60 for AMS
  - 20 for PaO2<90%

The future RCT: heparin vs thrombolytic for “high-risk” patients underway in Europe.

Doubled risk of death with thrombolytic therapy in normotensive patients.

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**PESI score**
- Class I < 65
- Class II 66-85
- Class III 86-105
- Class IV 106-125
- Class V > 125
- 30 day mortality increases with each class
- Class V has a 25 fold higher risk of post-discharge death than Class I

**Outpatient Therapy**
- PESI < 85
  - No hypoxia, SBP < 100, recent bleeding, plts < 70,000, comorbidities or recurrent DVT
- Good social support
- Expected to be compliant

**Why Do We Give Blood?**
- To improve oxygen carrying capacity!
- \( \text{DO}_2 = \text{Hemoglobin} \times \text{Cardiac Output} \)
- What level of anemia does hemoglobin become the limiting factor?

**How Low Can You Go?**
- Studies in healthy patients have shown no impairment of oxygen delivery with hemoglobins down to 4-5 g/dL

**Hemoglobin Level and Symptoms**

<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.0-11.0</td>
<td>Little to no dysfunction</td>
</tr>
<tr>
<td>7.5</td>
<td>Exertional dyspnea</td>
</tr>
<tr>
<td>6.0</td>
<td>Some weakness</td>
</tr>
<tr>
<td>3.0</td>
<td>Dyspnea at rest</td>
</tr>
<tr>
<td>2.0-2.5</td>
<td>Cardiac failure</td>
</tr>
</tbody>
</table>


**How Low Can You Go?**
- Extensive studies of Jehovah Witnesses
- Risk factors for death
  - Amount of blood loss
  - Coronary artery disease
Do Transfusions Help?

- Four prospective randomized trials
- Considerable observational studies

**TRICC Trial**

- 2 strategies in critical care patients
  - Liberal: Txn < 10, goal 10-12
  - Conservative: Txn < 7, goal 7-9
- N = 838
- Overall mortality – No difference
- Younger patients and less sick did better with less blood
- 55% less transfusions in conservative group
- "Pulmonary edema" more common in liberal group (10 vs 5%)


**Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS)**

- Trial of transfusion strategy in elderly hip replacement
- NEJM 2011;365:2453-62

**The Trial**

- Patients > age 80
  - < 3 days post hip-fx repair
- N = 2016
- RCT
  - Goal Hgb > 10
  - Symptomatic transfusion
- Endpoints
  - Death, MI, QOL, unstable angina
Results

- Mean age 81.6
  - 76% female
  - 82% hypertension
  - 40% CAD
  - 25% diabetes
- Starting Hgb = 9.0 g/dL

Results

<table>
<thead>
<tr>
<th>Txn at Hgb of 30</th>
<th>Txn for symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb before TX</td>
<td>9.2</td>
</tr>
<tr>
<td>Median Units</td>
<td>2</td>
</tr>
<tr>
<td>Dead/Unable to Walk</td>
<td>35%</td>
</tr>
<tr>
<td>Dead at 60 Days</td>
<td>7.6%</td>
</tr>
</tbody>
</table>

Marik & Corwin Review

ICU Patients

- CCM 36:2667, 2008
- 45 studies with 272,566 patients
- 42/45 studies risk > benefits
- 2 studies risk neutral
- 1 benefit (subgroup)
  - Elderly with MI and Hct < 30%

Transfusion and Cardiovascular Disease

- Complex interactions
  - Improved oxygen carrying capacity
  - Increased viscosity
  - Decreased oxygen delivery
  - Fluid overload
  - Microthrombosis

Transfusions and Cardiovascular Disease

- 9 studies of transfusion for IHD
  - 3 positive*, 8 negative outcomes
  + all with different thresholds
- 14 studies of transfusion in CABG
  - 1 neutral, 13 negative outcomes
- 9 studies in PCI
  - 1 neutral 8 negative
The CRIT Trial
- Pilot study in heart disease
- Liberal arm
  - Hct -30% - 36% bad outcomes
- Conservative arm
  - Hct 24% - 14% bad outcomes

Hajjar Trial
- RCT in CABG
- Goal of trigger of 24% vs 30%
- N = 502
- JAMA. 2010;304(14):1559-1567

Hajjar Trial
- % Patients Transfused
  - 30: 78%  24: 47%
- Endpoint:
  - 30:10%  24:11% (ns)
- Number of RBC units transfused increase risk of death or complications 1.2/each unit

VA Evidence Base Review
- Transfusion no benefit and may be harmful with hgb > 10
- Outcomes do not improve in NSTEMI patients with transfusions with hgb 8-9
- Mortality higher in PCI transfused hgb 8-9
  - Higher in nonbleeding patients

Do Blood Transfusion Help?
- No real data that in a non-exsanguinating patient red cell transfusions are of benefit

Prospective Trials
- No benefit of transfusions in either ICU, elderly surgery patients, or in patients undergoing CABG
Do Transfusion Harm?

Risk

• Infections
  – Babesiosis, Chagas, vCJD, ....
• Reactions
• Lung damage
• Immunosuppression
  – Increased wound infections
  – Increased cancer recurrence
• Fluid overload
• MOSF

Marik & Corwin Review

• 17/18 studies RBC transfusions independent predictor of death
  – OR – 1.7
• Complications
  – Infections OR – 1.8
  – MOF
  – ARDS – 2.5
The Balance
• Abundant data for harm
• Minimal data for benefit

Prudent Strategy for Elective RBC transfusions
• Almost always if Hgb < 6 and never if Hbg > 10
• “Clinicians can accept Hbg > 7 g/dl in most patients with self-limited anemia”
  – ACP 1992
• Transfusion should be guide by symptoms not habit

Bottom Line
• Transfusion trigger for non-bleeding critical care patient
  – Hgb < 7 (Goal is 7-9)
• Exceptions
  – ACS Hct < 25%
  – Early sepsis Hbg < 10 (Goal is 10)

The Last Word
• “Unless your patient is actively bleeding to death, it is simply best not to transfuse any blood products”
  – John Holcomb, MD