Mechanisms of Thrombocytopenia

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Faculty/Presenter Disclosure

- **Faculty**: Donald M. Arnold

- **Relationships with commercial interests:**
  - None
  - **Other**: Employee of Hamilton Health Sciences, CBS Medical Consultant
Disclosure of Commercial Support

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• **Potential for conflict(s) of interest:**
  – None
Mitigating Potential Bias

- N/A
Objectives

1. How is the platelet count regulated?

2. Platelet diagnoses you don’t want to miss

3. When you should/ should not transfuse
1. Regulation of Platelet Number

Steady State

LOW platelets

HIGH platelets
Platelet count is stable over time

NHANES III (N=12,142). Mean platelet counts (95% CI), models controlled for nutrition and inflammation.

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic white</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>20–29</td>
<td>251 (245–257)</td>
<td>250 (244–256)</td>
<td>253 (247–258)</td>
<td>252 (246–257)</td>
</tr>
<tr>
<td>30–39</td>
<td>252 (245–258)</td>
<td>251 (244–257)</td>
<td>254 (247–261)</td>
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<td>40–49</td>
<td>249 (245–255)</td>
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<td>50–59</td>
<td>253 (245–260)</td>
<td>254 (247–261)</td>
<td>256 (250–263)</td>
<td>256 (249–262)</td>
</tr>
</tbody>
</table>

*Segal, Ann Epidemiol 2006*
Platelet-type bleeding
Thrombocytopenia in hospital

Very common

• 1 in 20 people attending for pre-op assessments
• 1 in 4 patients admitted to hospital
• 1 in 2 patients in ICU


Almost always secondary

• Inflammation, consumption, dilution, etc

Poor prognostic sign

• Morbidity is rarely from bleeding
• Underlying illness, omission of treatments
Mortality

N=3,746 critically ill patients from the PROTECT trial

Williamson DR et al, CHEST 2013
2. Approach to thrombocytopenia

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Life-threatening causes</td>
</tr>
<tr>
<td>2</td>
<td>Examine the blood film</td>
</tr>
<tr>
<td>3</td>
<td>Determine clinical context</td>
</tr>
<tr>
<td>4</td>
<td>Assess the severity</td>
</tr>
<tr>
<td>5</td>
<td>Assess timing of onset</td>
</tr>
<tr>
<td>6</td>
<td>Assess for bleeding signs</td>
</tr>
</tbody>
</table>

Diagnoses you don’t want to miss

1. Life-threatening causes
2. Examine the blood film
3. Determine clinical context
4. Assess the severity
5. Assess timing of onset
6. Assess for bleeding signs

- Acute leukemia (AML)
- Thrombotic thrombocytopenic purpura (TTP)
- Disseminated intravascular coagulation (DIC)
- Heparin - induced thrombocytopenia (HIT)
- Drug-induced immune thrombocytopenia (D-ITP)
1. Life-threatening causes
2. Examine the blood film
3. Determine clinical context
4. Assess the severity
5. Assess timing of onset
6. Assess for bleeding signs

## Thrombocytopenia

### Severe

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>Think about:</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLTs &lt; 30</td>
<td>ITP (primary or secondary)</td>
</tr>
<tr>
<td>PLTs 30 – 80</td>
<td>HIT</td>
</tr>
<tr>
<td>PLTs 80 – 130</td>
<td>Hypersplenism</td>
</tr>
</tbody>
</table>

### Timing

<table>
<thead>
<tr>
<th>TIMING</th>
<th>Think about:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – 2 days</td>
<td>Dilution (post-op)</td>
</tr>
<tr>
<td>5 – 10 days</td>
<td>Drug-induced ITP , HIT</td>
</tr>
<tr>
<td>Weeks - months</td>
<td>Bone marrow failure, other</td>
</tr>
</tbody>
</table>
3. Management

1. Hematology oncology

2. Cardiac surgery

3. Acute thrombocytopenic disorders
37F with AML. Admitted for consolidation chemotherapy. Baseline PLT = 110 x10⁹/L. Day 8 post chemo: PLT = 16 x10⁹/L. No bleeding.

Should you transfuse platelets?
Answers for Question #1

1. YES

2. NO

(Correct answer: 2)
PLT transfusion strategies: Heme-Onc (n=2331 participants)

- **High vs. low PLT count threshold** \((N=3)\)
  - No difference in bleeding \((RR 1.35; 95\% CI 0.95 to 1.9)\)

- **High vs. low platelet dose** \((n=6)\)
  - No different in bleeding

- **Prophylactic vs. therapeutic-only** \((N=3)\)
  - No difference in bleeding \((RR= 1.66; 95\% CI 0.9 to 3.04)\)

*Estcourt L et al. Cochrane Database Syst Rev. 2012*
TOPPS trial
(Stanworth et al, *NEJM* 2013)

Multicenter, non-inferiority RCT (N=600): therapeutic (no prophylaxis) vs. prophylactic PLT transfusions for PLT <10 x10^9/L.

- **Bleeding events (WHO Grade 2, 3, or 4):**
  - 50% vs 43% (P=0.06 for non-inferiority)

- A ‘no-prophylaxis’ strategy was not non-inferior to a prophylaxis strategy (e.g. it might be worse).
Time to Bleeding

Proportion of Patients with Bleeding

Hazard ratio, 1.30 (95% CI, 1.04–1.64)
P = 0.02

Days since Randomization

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Prophylaxis</th>
<th>No prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>298</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>188</td>
<td>152</td>
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<td></td>
<td>170</td>
<td>140</td>
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<tr>
<td></td>
<td>165</td>
<td>139</td>
</tr>
</tbody>
</table>

Wandt et al (Lancet 2012)

Multicenter, RCT N=391 patients therapeutic (e.g. wait until bleeding occurs) vs. prophylactic PLT transfusion strategy (for PLT ≤ 10 x10⁹/L)

- Increased risk of bleeding in patients with AML
- No increased risk of major bleeding in autologous transplantation.
Proportion with Bleeding
*(Wandt, Lancet 2012)*

<table>
<thead>
<tr>
<th>Time to onset (days)</th>
<th>Therapeutic strategy</th>
<th>Prophylactic strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>0</td>
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<tr>
<td>15</td>
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<tr>
<td>20</td>
<td>30</td>
<td>10</td>
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<tr>
<td>25</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>60</td>
<td></td>
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</tbody>
</table>

Number at risk:
- Therapeutic: 197, 188, 151, 54, 28, 3, 0
- Prophylactic: 194, 192, 175, 84, 40, 10, 0
Question #2:  
*Cardiac surgery*

76M, diabetes. Platelet count at baseline 175 x10⁹/L. He underwent coronary artery bypass graft surgery (prolonged bypass). Uncomplicated post operative course. On day 8, the PLT count is = 70 x 10⁹/L.

What is the most likely diagnosis?
Answers for Question #2

1. Post operative dilutional thrombocytopenia
2. Heparin-induced thrombocytopenia
3. Sepsis
4. Myelodysplastic syndrome

(correct answer: 2)
Natural History of Postoperative Thrombocytopenia

HIT

Clinical Presentation:
• 50% drop in PLT
• 5 – 10 after heparin
• High risk of thrombosis (50%), limb loss, death (5 – 10%)

Treatment:
• Anticoagulation (non-heparin): argatroban, fondaparinux
• IVIG?

Warkentin, Ann Int Med 1997
Warkentin, Theodore E.
Heparin-induced thrombocytopenia: pathogenesis and management.
British Journal of Haematology 121 (4), 535-555.
Question #3: *Immune thrombocytopenia (ITP)*

28F presents to the Emergency Department with a 1-week of bruising and 1-day of diffuse petechial rash. She has blood blisters in her mouth.

What is the best treatment?
Answers for Question #3

1. Intravenous immune globulin (IVIG)
2. Platelet transfusion
3. IVIG and corticosteroids
4. Careful observation

(correct answer: 3)
Emergency Management of ITP

Arnold, Hematology 2015;2015:237-242

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Take home messages

1. Thrombocytopenia is a poor prognostic indicator.

2. PLT $< 10 \times 10^9/L$ for transfusion for chemotherapy.

3. Think about HIT (surgical $>$ medical).

4. For acute ITP, IVIG and corticosteroids are first-line.
“Sometimes we doctors, despite all our years of training and experience, can only marvel at how little we really know.”

–Jeff Brown
Thank you.