Most Common Hemostasis Consults: Thrombocytopenia

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- No relevant financial conflicts
- Genzyme: Consultancy
Objectives

• Discuss thrombocytopenia in hospitalized patients
  – Focus on thrombocytopenic emergencies

• Outline management strategies

• Highlight areas of uncertainty
Thrombocytopenia

- **Common hematologic finding in hospitalized patients (n=6,894 critically ill patients)**
  - On admission: 8-68%
  - During ICU: 13-44%

- **Impact on morbidity and mortality (N=8)**
  - 6 found an independent association with death
  - Relationship with change in platelet count over time
  - Increased survival with recovery

- **Identified risk factors**
  - Infection/sepsis, high illness severity score, organ dysfunction, renal failure, intravascular devices, cardiothoracic procedures

Hui et al. Chest 2011
### Thrombocytopenia Causes

<table>
<thead>
<tr>
<th>Causes</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis (all)</td>
<td>65 (47.8)</td>
</tr>
<tr>
<td>Sepsis with documented bacteremia</td>
<td>38 (27.9)</td>
</tr>
<tr>
<td>Other infection</td>
<td>15 (11.0)</td>
</tr>
<tr>
<td>Overt DIC</td>
<td>19 (14.0)</td>
</tr>
<tr>
<td>Primary hematologic disorder</td>
<td>12 (8.8)</td>
</tr>
<tr>
<td>Liver disease/hypersplenism</td>
<td>25 (18.4)</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>7 (5.1)</td>
</tr>
<tr>
<td>Massive transfusion</td>
<td>10 (7.4)</td>
</tr>
<tr>
<td>Cytostatic drugs</td>
<td>9 (6.6)</td>
</tr>
<tr>
<td>Other medications</td>
<td>12 (8.8)</td>
</tr>
<tr>
<td>Other causes</td>
<td>9 (6.6)</td>
</tr>
<tr>
<td>Unknown cause</td>
<td>19 (14.0)</td>
</tr>
<tr>
<td>More than one cause</td>
<td>35 (25.7)</td>
</tr>
</tbody>
</table>

DIC, diffuse intravascular coagulation.

In 35 patients, more than one cause was present, so the cumulative percentage adds up to \( \geq \) 100%.
Evaluation of Thrombocytopenia

- Exclude thrombocytopenic emergencies
- Examine the blood smear
- Assess the degree of thrombocytopenia
- Consider the clinical context and exposures
- Determine the timing of thrombocytopenia
- Evaluate for additional symptoms

Arnold et al. ASH-SAP, 2013
Thrombocytopenic Emergencies

• Immune Mediated
  – Drug-induced thrombocytopenia (DITP)
  – Heparin-induced thrombocytopenia (HIT)
  – Primary immune thrombocytopenia (ITP)
  – Post-transfusional purpura (PTP)

• Non-Immune Mediated
  – Thrombotic thrombocytopenic purpura (TTP)
  – Catastrophic antiphospholipid antibody syndrome (CAPS)
  – Disseminated intravascular coagulation (DIC)
Heparin Induced Thrombocytopenia

- 50% fall to a nadir $\geq 20 \times 10^9/l$
- Usually within 5-10 days of exposure
  \[ \leq 1 \text{ day with heparin exposure within the last 30 days} \]
- Thrombosis (50% of patients)
- Discontinue all heparin, use alternative anticoagulant, evaluate sites of possible thrombosis and DIC

<table>
<thead>
<tr>
<th>HIT Pretest Probability: The 4T’s</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombocytopenia</strong></td>
</tr>
<tr>
<td>&gt; 50% platelet count fall to nadir ≥ 20</td>
</tr>
<tr>
<td>30-50% platelet count fall to nadir 10-19</td>
</tr>
<tr>
<td>&lt;30% platelet count fall to nadir ≤ 10</td>
</tr>
<tr>
<td><strong>Timing of fall in platelet count or other sequelae</strong></td>
</tr>
<tr>
<td>Onset d 5-10 or &lt; 1 d (if heparin exposure within 30 d)</td>
</tr>
<tr>
<td>&gt; d 10, or timing unclear, or &lt; d 1 with recent heparin 31-100 d</td>
</tr>
<tr>
<td>Platelet count fall &lt; d 4 (without recent heparin exposure)</td>
</tr>
<tr>
<td><strong>Thrombosis or other sequelae</strong></td>
</tr>
<tr>
<td>New thrombosis; skin necrosis; post-heparin bolus acute systemic reaction</td>
</tr>
<tr>
<td>Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis – not confirmed</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td><strong>OTher cause for thrombocytopenia</strong></td>
</tr>
<tr>
<td>No other cause for platelet count fall is evident</td>
</tr>
<tr>
<td>Possible other cause is evident</td>
</tr>
<tr>
<td>Definite other cause is present</td>
</tr>
</tbody>
</table>
Heparin Induced Thrombocytopenia

- PROTECT study: 794
  - Low pre-test score: 86% (1.5% +SRA)
  - Moderate pre-test score: 12.4% (6.8% +SRA)
  - High pre-test score: 1% (12.5% had +SRA)
  - Slight agreement between real-time and adjudication (k=0.23)
  - Thrombosis without thrombocytopenia, information on prior heparin exposure, and “other causes” domain were areas needing improvement

- “HIT is frequently suspected and rarely confirmed”
- Refinement to the 4Ts is needed

Crowther et al. J Crit Care, 2014
Immune Thrombocytopenia (ITP)

- Acute onset of isolated thrombocytopenia in an otherwise healthy patient
- Mucosal bleeding
- Severe thrombocytopenia (usually < 20 x 10⁹/l)

Management:
- Adults: Bleeding and/or a platelet count < 30 x 10⁹/l
- Children: Based on bleeding symptoms
- First-line: Corticosteroids, IVIg, Anti-D immunoglobulin

Neunert et al. Blood 2011
ITP: Upfront Therapy?

- **Corticosteroid**
  - Prednisone or high dose dexamethasone (HDD)
  - Dose versus duration

- **Additional upfront therapy**
  - Rituximab with or without HDD
    - Higher response rates at 6 months
      - 63% vs 36%, p = 0.004 (n=103)
      - 58% vs 37%, p = 0.02 (n=133)
    - Higher rates of adverse events in the combination arm
  - Eltrombopag and HDD (n=12)
    - Platelets $\geq 30 \times 10^9$/l at 6 months: 75%

Post-Transfusion Purpura

- Rare but important
  - Mortality of 10-20%
- Middle-aged women with history of pregnancy
- Severe thrombocytopenia and hemorrhagic complications
  - Fever, chills, and bronchospasm
- 2-14 days following transfusion

Management
- IVIg with or without corticosteroids
- Plasma exchange
- Avoid platelet transfusions or use HPA-compatible
Thrombocytopenic Emergencies

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  - Disseminated intravascular coagulation (DIC)
• Microangiopathic hemolytic anemia and thrombocytopenia without an identifiable cause
  – Neurological findings
  – Renal manifestations
  – Fever

• Reduced plasma levels of a disintegrin and metalloprotease with eight thrombospondin type-1 motifs (ADAMTS13) with or without any associated antibody
80% mortality without therapy

Management
- Immediate Plasmapheresis/plasma exchange
- Start corticosteroids

High relapse rate (20-30%)

Upfront role of Rituximab
- Scully et al. 2011 (n= 40)
  - Reduced length of stay (7 days)
  - Reduced relapse rate (11% vs 55%, p=0.001)
- We suggest rituximab be considered for upfront use (Grade 2C)

Catastrophic Antiphospholipid Antibody Syndrome

- Rare variant of antiphospholipid antibody syndrome
- Catastrophic onset of multiple small vessel events
- Often a trigger
  - Infection, medication, surgical procedure, or anticoagulation withdrawal
  - Prior diagnosis of APS or systemic lupus erythematosus
- Management
  - Not standardized
  - Anticoagulation, corticosteroids, and plasma exchange, IVIg
  - Additional immunosuppression: Rituximab
Thrombocytopenic Emergencies

- Immune Mediated: DITP, HIT, ITP, PTP
  - Suspect based on clinical history and exposures
  - Usually isolated thrombocytopenia

- Non-Immune Mediated: TTP, CAPS, DIC
  - Presence of microangiopathic hemolytic anemia
  - Additional laboratory evaluation such as LDH, PT, PTT, fibrinogen, and d-dimer can help guide differential

Management usually proceeds conclusive test results
## Platelet Sequestration and Dilution

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet sequestration</td>
<td>Portal hypertension</td>
</tr>
<tr>
<td>or hypersplenism</td>
<td>Storage diseases</td>
</tr>
<tr>
<td></td>
<td>Hematologic disorders</td>
</tr>
<tr>
<td></td>
<td>Infiltrative diseases</td>
</tr>
<tr>
<td>Platelet loss or dilution</td>
<td>Massive transfusion</td>
</tr>
<tr>
<td></td>
<td>Exchange transfusion</td>
</tr>
</tbody>
</table>

Usually a mild thrombocytopenia
## Diminished Platelet Production

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow infiltration</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Marrow injury or failure</td>
<td>Cytotoxic chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Infection (Viral)</td>
</tr>
<tr>
<td></td>
<td>Aplastic anemia</td>
</tr>
<tr>
<td>Ineffective Thrombopoiesis</td>
<td>Hereditary</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Nutritional deficiency</td>
</tr>
<tr>
<td></td>
<td>- Iron, folate, B12</td>
</tr>
<tr>
<td></td>
<td>Cyanotic heart disease</td>
</tr>
</tbody>
</table>

Additional findings on peripheral blood smear, physical examination, and indices
Management Strategy

• Identify and treat the underlying cause of thrombocytopenia

• Platelet transfusions in critically ill patients
  – Sustained response to a platelet count > 100 x 10⁹/l is rarely seen
  – No study has reported on bleeding symptoms
  – No improved survival
  – There remains insufficient evidence to support a specific platelet threshold for transfusion

Platelet transfusions in chemotherapy-induced thrombocytopenia

- Prophylactic versus therapeutic
  - Two major randomized studies
    - TOPPS trial (n=396) and German Study (n=600)
    - Reduction in high grade bleeding with prophylactic strategy
- Platelet Threshold
  - No increased bleeding, 30 day mortality, or time to first bleeding event with a threshold of $10 \times 10^9/l$ compared to a higher threshold
  - Lower threshold reduced number of platelet transfusions

Thrombocytopenia is common in hospitalized patients
  – Often related to underlying disease state

Isolated thrombocytopenic emergencies are rare but are associated with high morbidity and mortality

Additional research is needed to optimize and standardize diagnosis and management
  – Platelet thresholds and transfusion practices
  – Upfront management of thrombocytopenic emergencies