Assessing thrombocytopenia in the intensive care unit: The past, present, and future

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Objectives

1. Characterize the multiple mechanisms that can contribute to thrombocytopenia in the ICU

2. Evaluate the trajectory of the patient’s platelet count and apply this information to establish a diagnosis and inform prognosis

3. Transfuse platelets appropriately to prevent and manage bleeding in thrombocytopenic patients admitted to the ICU
Epidemiology of thrombocytopenia in ICU

• **Prevalence** at ICU admission ranges from 8% to 68%

• **Incidence** of developing thrombocytopenia in the ICU ranges from 14% to 44%

• Variability reflect variation in patient population, ICU characteristics, and the definition of thrombocytopenia
Epidemiology of thrombocytopenia in ICU

• PROTECT Trial (n = 3,639)
  – Prevalence of thrombocytopenia 26.2% (952 patients)
  
  – Incidence of Thrombocytopenia
    • Mild (100–149 × 10⁹/L) 15.3% (417 patients)
    • Moderate (50–99 × 10⁹/L) 5.1% (140 patients)
    • Severe (< 50 × 10⁹/L) 1.6% (44 patients)

Risk factors for thrombocytopenia in ICU

- **Risk factors** commonly associated with ICU-acquired thrombocytopenia (multivariate analyses)
  - Severity of illness
  - Organ dysfunction
  - Sepsis
  - Vasopressor use
  - Renal failure.

Consequences of thrombocytopenia in ICU

• **Bleeding and Transfusion**
  – **PROTECT**
    • Any thrombocytopenia associated with major hemorrhage and transfusion of RBCs, PLTs, FFP, or cryoprecipitate
  – **Observational studies**
    • Thrombocytopenia (incident or prevalent) is associated with bleeding and transfusion
Consequences of thrombocytopenia in ICU

• Mortality
  – PROTECT
    • Severe thrombocytopenia associated with increased ICU and hospital mortality (1.6% of patients)
  – Observational studies
    • 6/8 observational studies thrombocytopenia was found to independently predict mortality
Thrombocytopenia as a marker of illness

- Thrombocytopenia also associated with:
  - Increased ICU and hospital LOS
  - Need for organ support

- Blunted recovery predicts death
- Deaths are not typically due to bleeding
Causes

• Common

• Uncommon

• Rare
Causes

• **Common**
  – Sepsis
  – Disseminated intravascular coagulation
  – Consumption (eg major trauma, cardiopulmonary bypass)
  – Dilution (with massive transfusion)
  – Myelosuppressive chemotherapy
  – Mechanical circulatory support
Causes

• **Uncommon**
  – Heparin-induced thrombocytopenia
  – Hemophagocytic syndrome
Causes

• Rare
  – Drug-induced thrombocytopenia (other than heparin or cytotoxic chemotherapy)
  – Leukemia, myelodysplasia, aplastic anemia, etc, unless abnormalities were already present before ICU admission
  – Thrombotic thrombocytopenic purpura
  – Immune/idiopathic thrombocytopenia
  – Post-transfusion purpura
Mechanisms

• Poorly understood

• May have multiple possible causes

• Tools to distinguish between them are limited
Mechanisms

- **Decreased Production**
  - Note** Inflammatory cytokines stimulate thrombopoiesis
  - Unlikely to be the dominant factor
    - Exceptions include preexisting marrow disease or cytotoxic chemotherapy.

- **Sequestration**
  - Only if preexisting (eg, liver disease with portal hypertension)
  - May contribute to the severity of thrombocytopenia and reduce post-transfusion platelet increments
Mechanisms

• Destruction and/or Consumption
  – Explains the bulk of thrombocytopenia in the ICU
  – Thrombin
  – Antibodies
  – Hemophagocytosis
  – Histones
  – ADAMTS13 depletion
  – Complement activation
**Sepsis**

- 10% of ICU admissions
- 50% of TCP in ICU

- Thrombocytopenia may modify the host immune response to Infection

- Consideration mechanisms suggests directions for therapeutic trials.
Thrombocytopenia in Sepsis


- Retrospective cohort study of septic shock (n = 980; APACHE II = 25)
- Prevalence of TCP at ICU admission: 17% (n = 165)
- Incident of TCP in ICU: 28% (n = 271)

- Median time to TCP (PLT < 100): 2 days (IQR 1 to 3)
- Median time from TCP to platelet recovery: 6 days (IQR 4 – 8)
- Average platelet nadir: 62 (SD 24.6) in survivors
Thrombocytopenia in Sepsis

In a propensity-matched cohort analysis

- TCP **not** associated with hospital mortality (OR 1.17; 95% CI 0.81-1.69)
- TCP is associated with:
  - ICU length of stay 9 vs. 6 days; p<0.01
  - Duration of mechanical ventilation 7 vs. 4 days; p<0.01
  - Duration of vasopressor use 4 vs. 3 days; p<0.01
  - Major bleeding events 41% vs 18%; p<0.01

Thrombocytopenia in Sepsis

• **Thrombin**
  - Sepsis is a well-recognized trigger of DIC
  - Driven by upregulation of tissue factor expression on monocytes
  - Several targeted anticoagulants (TFPI, AT, APC) have been evaluated in the treatment of sepsis...largely negative results

  - ACTIVE RESEARCH:
    • ‘Less targeted’ anticoagulants may be beneficial to reduce thrombin-mediated platelet activation and DIC
Heparin Anticoagulation to improve outcomes in septic shock

**HALO**

- Propensity Matched Cohort Study
- Meta-Analysis
- National Survey
- Pilot Randomized Feasibility Trial
- Exit survey
- Cytokine Analysis
- Activation of Coagulation
- Cell free DNA
- Phase II International RCT
- Phase III International RCT
Thrombocytopenia in Sepsis

- Hemophagocytosis (HPS)
  - Evolving knowledge base pertaining to the definition & diagnosis
  - Evidence to inform treatment is lacking
  - Current therapies target T cells (steroids, cyclosporine) and macrophages (etoposide)
  - IVIG may support defective humoral immunity and reduce systematic inflammation
  - RCTs suggest a survival benefit of IVIG
IntraVenous Immune Globulin In Severe Sepsis

InVIGIS

International Survey
• Utility, Utilization
• Barriers/facilitators
• Willingness to study

PS Matched Cohort
• Mortality
• Utilization
• Dosing

Modeled Economic Evaluation of IVIG in Sepsis

Population Cohort
• Long-term sepsis-mortality
• Health-care utilization

Integrated Economic Evaluation

Pilot RCT → 2B Adaptive RCT → Phase 3 International Multicentre RCT

Translational Biology
• **ADAMTS13 deficiency**
  – Possible contribution to thrombocytopenia and microvascular injury should lead to consideration of future trials evaluating plasma exchange or infusion of recombinant ADAMTS13
  – Meta-analysis of plasma exchange suggests benefit in adults
  – Considerable European interest in non-centrifugal plasma filtration
How I approach thrombocytopenia in the ICU

Past

Present

Future
Approaching thrombocytopenia in the ICU

• Past
  – What is the context of the patient’s ICU admission?
  – Is there evidence of a preexisting illness or the use of a drug known to cause thrombocytopenia?
  – Could the ICU admission have been precipitated by a catastrophic illness associated with thrombocytopenia, such as thrombotic thrombocytopenic purpura, hemophagocytic syndrome, or acute leukemia?
  – Was there major trauma or surgery that would consume platelets, or transfusion and fluid resuscitation that would cause dilution?
Approaching thrombocytopenia in the ICU

• Present
  • What is the trajectory of the platelet count, and how does it relate to the patient’s clinical course?
  • How low is the platelet count?
  • Is there thrombosis?
Trajectory #1: Present low...stay low

- Suggests an independent cause of thrombocytopenia
  - marrow failure
  - Hypersplenism
- Investigation could include assessment of spleen size, review of the peripheral blood film, and bone marrow examination
Trajectory #2: Falls immediate; recovers quickly

- Seen in major surgery (esp. CPB) or massive transfusion.
Trajectory #3: Falls in first few days; recovers with improvement of the clinical condition

- Seen in sepsis, pancreatitis, burns, multi-organ dysfunction
Trajectory #4: Fall and stay low in a patient whose clinical course is otherwise recovering

- Consider iatrogenic causes
  - HIT, other drugs, (post-transfusion purpura)
Trajectory #5: Falls in first few days; stays low in a patient with persistent multi-organ failure

- Observed in the sickest of patients who have the worst prognosis.
  - Sepsis, DIC, HPS, and shock are possible.
- It is not clear to what extent the thrombocytopenia contributes to poor outcomes.
Approaching thrombocytopenia in the ICU

• Present
  • What is the trajectory of the platelet count, and how does it relate to the patient’s clinical course?
  • How low is the platelet count?
  • Is there thrombosis?
Approaching thrombocytopenia in the ICU

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  • What is the trajectory of the platelet count, and how does it relate to the patient’s clinical course?
  • How low is the platelet count?
  • Is there thrombosis?
Approaching thrombocytopenia in the ICU

• Future
  – Is the platelet count following the expected trajectory, given your analysis of the cause?
Management of thrombocytopenia in ICU

• Treat the underlying cause!

• Manage expectations
  – Sepsis: improvement not expected until 2 days after discontinuation of pressors
  – ECMO/VAD: likely to persist until device removal
Management of thrombocytopenia in ICU

• **Platelet transfusion**
  – Risk:Benefit of platelet transfusion is unknown
  – Effectiveness of platelet transfusion to stop bleeding, reduce transfusion, or improve clinical outcomes is uncertain
  – Harms associated with PLT transfusion are well documented
    – Nosocomial infection, thrombosis, acute lung injury

  – High quality trials are warranted
<table>
<thead>
<tr>
<th>Indication</th>
<th>Platelet threshold‡</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe bleeding</td>
<td>Maintain PLT &gt; 50 x10⁹/L; consider using an MTP</td>
<td>Strong</td>
<td>Low</td>
</tr>
<tr>
<td>Prophylaxis in adults</td>
<td>10 x10⁹/L</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Prior to elective central venous catheter</td>
<td>20 x10⁹/L§</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Prior to chest tube insertion or thoracentesis</td>
<td>50 x10⁹/L</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Prior to bronchoscopy with lavage</td>
<td>20 x10⁹/L</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Prior to paracentesis</td>
<td>Not routinely required</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Prior to bone marrow biopsy</td>
<td>Not routinely required</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Prior to elective diagnostic lumbar puncture</td>
<td>50 x10⁹/L</td>
<td>Weak</td>
<td>Very low</td>
</tr>
<tr>
<td>Prior to urgent diagnostic lumbar puncture</td>
<td>20 x10⁹/L</td>
<td>Weak</td>
<td>Very low</td>
</tr>
<tr>
<td>Prior to major elective surgery (excluding neurosurgery)</td>
<td>50 x10⁹/L</td>
<td>Weak</td>
<td>Very low</td>
</tr>
<tr>
<td>Prior to neurosurgery</td>
<td>100 x10⁹/L</td>
<td>Weak</td>
<td>Very low</td>
</tr>
<tr>
<td>Traumatic brain injury, Intracranial hemorrhage</td>
<td>100 x10⁹/L</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Prior to insertion of an intraventricular drain (EVD)</td>
<td>100 x10⁹/L</td>
<td>Weak</td>
<td>Very Low</td>
</tr>
</tbody>
</table>
Conclusions

• Thrombocytopenia in the ICU is common and correlates with an adverse prognosis

• Multiple mechanisms may contribute to thrombocytopenia; Differentiating the pertinent cause (or causes) in individual patients is challenging

• Looking back at the patient’s medical history and presenting illness, while observing the platelet trajectory and the clinical course, offers clues to the diagnosis and prognosis.

• Optimal platelet transfusion strategies to prevent or treat bleeding in thrombocytopenic ICU patients remain to be defined
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