Approach to Thrombocytopenia in the Inpatient Setting

Shweta Kurian, MD,
Medical Oncologist and Hematologist
MedStar Franklin Square and MedStar Bel Air
Incidence and Prevalence

- In a registry of over 64,000 patients admitted with non-ST elevation acute coronary syndromes:
  - 6.8% of patients had baseline thrombocytopenia
  - 13% developed over their stay

- A 2011 systematic review of 6,894 critically ill patients –
  - 8% to 68% of patients had thrombocytopenia on admission to the intensive care unit (ICU)
  - 13% to 44% of patients developed it during their ICU stay.
  - Thrombocytopenia correlated with high-severity illness, sepsis, and organ dysfunction.
Physiological conditions with the low normal platelet count,

- Platelet clumping in vitro (Pseudothrombocytopenia)
- Gestational thrombocytopenia, and
- Hemodilution

• Pseudothrombocytopenia is a laboratory artifact - platelet clumping
• Naturally occurring EDTA-dependent platelet antibodies.
• Confirmed by examining the peripheral smear for platelet clumps or Citrated Platelet count.
• No clinical significance in vivo.
• 5-10% of pregnant women will develop incidental (or gestational) thrombocytopenia accounting for approximately 75% of all thrombocytopenias presenting in pregnancy.

• Thrombocytopenia following massive transfusion due to hemodilution.

• Retrospective study (39 trauma patients), 4 patients received 20 or more red blood cell (RBC)-containing products 3 (75%) developed a platelet count < 50K compared to none who received fewer than 20 RBC units.

Major surgery is another common cause. After major surgery, platelet counts typically decline quickly - 1 to 4 days due to consumption and dilution.

In a study of 581 patients who underwent cardiac surgery with cardiopulmonary bypass, thrombocytopenia occurred in 56.3% of patients **within 10 days of surgery.**

Similar decreases in the platelet counts with other surgeries.

Causes of Thrombocytopenia in inpatient setting

- Pseudothrombocytopenia
- ITP
- DITP-Drug induced ITP
- Infections( HIV/HepC/ EBV/Sepsis)
- Hypersplenism due to Chronic Liver disease
- Alcohol
- Pregnancy- Preeclampsia/HELLP/DIC
- Multiorgan failure syndrome
- HIT

- TMA- TTP/HUS
- MDS
- DIC
- Marrow infiltration
- Autoimmune Disorders/ APS
- PNH
- Nutrient Deficiencies- B12 /Folate
Commonest Causes in ICU patients

Cohort of 329 medical and surgical ICU patients with New onset thrombocytopenia

- Sepsis (48 %)
- Sepsis with documented bacteremia (28 %)
- Liver disease/hypersplenism (18 %)
- Overt DIC (14 %)
- Unknown cause (14 %)
- Infection, other (11 %)
- Primary hematologic disorder (9 %)
- Medications, non-cytotoxic (9 %)
- Medications, cytotoxic (7 %)
- Massive transfusion (7 %)
- Other causes (7 %)
- Alcoholism (5 %)
• Adverse outcomes as severity of thrombocytopenia worsens.

Higher degree of thrombocytopenia correlated with the increased risk of bleeding in the PROTECT trial (adjusted hazard ratios for mild, moderate, and severe thrombocytopenia were 1.96, 3.52, and 3.54, respectively)

• Moderate and severe (but not mild) thrombocytopenia also correlated with an increased length of ICU stay and ICU death
• **Thrombocytopenia as a Predictor of Death**

• In almost all patient populations, thrombocytopenia - an ominous sign.

  - In critically ill patients, thrombocytopenia was an independent predictor of death in hospital (odds ratio [OR], 2.1–26.2) and in the ICU (OR, 3.1–4.2) across six observational studies (N 6,894).

  - In patients with acute coronary syndrome, thrombocytopenia, irrespective of the cause (HIT [0.3%], glycoproteinIIb/IIIa associated thrombocytopenia [0.6%] or other thrombocytopenia [0.7%])—was associated with higher risk of bleeding and in-hospital death.
• **Association Between Thrombocytopenia and Thrombosis**
  - Does not protect against thrombosis

• **May be associated with increased risk** antiphospholipid antibody syndrome (APS), HIT, and disseminated intravascular coagulation (DIC).
• Similar rates of venous and arterial thromboembolic events in APS patients with thrombocytopenia compared to patients with normal platelet counts.

• In a retrospective analysis of 408 patients with HIT, severity of thrombocytopenia correlated with an increased risk of thrombosis; over 90% decrease in platelet count had the highest risk (OR, 8.79 [95% CI, 2.26–34.17])

• DIC can present with bleeding and/or thrombotic manifestations despite moderate to severe thrombocytopenia.

A Rational Approach to the Diagnosis and Management of Thrombocytopenia in the Hospitalized Patient, Donald M. Arnolda,b and Wendy Lima Semin Hematol 48:251–258

1. Consider life threatening conditions
   - Drug-induced immune thrombocytopenia (DITP)
   - Heparin-induced thrombocytopenia (HIT)
   - Thrombotic thrombocytopenic purpura (TTP)
   - Post transfusion purpura (PTP)
   - Disseminated intravascular coagulation (DIC)
   - Primary ITP with bleeding
   - Acute leukemia

2. Examine the blood film
   - Platelet clumping: pseudothrombocytopenia
   - Schistocytic erythrocytes: TTP, DIC
   - Large platelets: inherited thrombocytopenia
   - Small platelets: Wiskott-Aldrich syndrome
   - Grey platelets: grey platelet syndrome
   - Granulocytic Döhle bodies: May-Hegglin anomaly

3. Determine the clinical context
   - Post-operative patients: dilutional, HIT
   - ICU: sepsis, drugs, DIC, etc
   - Neonates: consider neonatal alloimmune thrombocytopenia, HIT is uncommon
   - Cancer patients: DIC, TTP

4. Assess the severity of thrombocytopenia
   - Below 20 x 10⁹/L: Primary or secondary ITP (including DITP)
   - 20 – 100 x 10⁹/L: HIT (typical nadir is 70 x 10⁹/L)
   - 100 x 10⁹/L: splenomegaly/ hypersplenism

5. Assess timing of thrombocytopenia in relation to exposures
   - Within 5 – 7 days: classic HIT, classic DITP, PTP
   - Within hours of drug exposure: acute-onset HIT, or DITP from tirofiban, epifibatide or abciximab

6. Assess for signs of bleeding
   - Bleeding: DITP, PTP, DIC
   - Lack of bleeding: HIT, TTP, APS, DIC
1. Consider life threatening conditions

- Drug-induced immune thrombocytopenia (DITP)
- Heparin-induced thrombocytopenia (HIT)
- Thrombotic thrombocytopenic purpura (TTP)
- Post transfusion purpura (PTP)
- Disseminated intravascular coagulation (DIC)
- Primary ITP with bleeding
- Acute leukemia
2. Examine the blood film

- Platelet clumping: pseudothrombocytopenia
- Schistocytic erythrocytes: TTP, DIC
- Large platelets: inherited thrombocytopenia
- Small platelets: Wiskott-Aldrich syndrome
- Grey platelets: grey platelet syndrome
- Granulocytic Döhle bodies: May-Hegglin anomaly
Schistocytes
Gray Platelet

Normal Platelet
Black arrow- Inclusion body in Neutrophil
May- Hegglin anomaly

Red arrow- Giant platelets
3. Determine the clinical context

- Post-operative patients: dilutional, HIT
- ICU: sepsis, drugs, DIC, etc
- Neonates: consider neonatal alloimmune thrombocytopenia, HIT is uncommon
- Cancer patients: DIC, TTP
4. Assess the severity of thrombocytopenia

- Below $20 \times 10^9$/L: Primary or secondary ITP (including DITP)
- $20 - 100 \times 10^9$/L: HIT (typical nadir is $70 \times 10^9$/L)
- $100 \times 10^9$/L: splenomegaly/ hypersplenism
5. Assess timing of thrombocytopenia in relation to exposures

- Within 5 – 7 days: classic HIT, classic DITP, PTP
- Within hours of drug exposure: Acute-onset HIT, or DITP from tirofiban, eptifibatide or abciximab
6. Assess for signs of bleeding

- Bleeding: DITP, PTP, DIC
- Lack of bleeding: HIT, TTP, APS, DIC
• LABORATORY TESTING —
• CBC and peripheral blood smear
• B12, Folate
• CMP
• Hepatitis C, HIV
• R/o Infection- Bacterial/Viral
Anemia + thrombocytopenia
- longstanding bleeding (gastrointestinal).
- systemic disorders.
  • Sepsis with disseminated intravascular coagulation (DIC)
  • TTP, HUS, or DITMA
  • Autoimmune disorders (Felty's syndrome)
  • Nutrient deficiencies (folate, vitamin B12, copper)
  • Infections
  • Bone marrow disorders (myelodysplastic syndromes, leukemia, bone marrow infiltration by malignancy)
Leukocytosis + thrombocytopenia
-infection,
-chronic inflammation, and malignancy.

Leukopenia, anemia, and thrombocytopenia (Pancytopenia) – MDS/ Leukemia
• Symptoms or findings of systemic autoimmune disorders
  - ANA/ LPA
• Thrombosis – Rule out DIC, heparin-induced thrombocytopenia (HIT), and APS.
  - PT/aPTT/D dimer/Fibrinogen/Fibrin Split products/ HIT antibody and Serotonin Release Assay.
• Schistocytes on the peripheral smear should prompt coagulation testing (eg, PT, aPTT, fibrinogen), LDH and renal function to evaluate for DIC, TTP, or HUS
• Hematology Referral:
• Especially for emergencies-
  - Suspected TTP/HUS, HIT, Hematologic malignancies-
    Acute leukemia/Aplastic anemia.

- Bone marrow evaluation:
- helpful in some patients if the cause is unclear, or if a
  primary hematologic disorder is suspected.
Thrombocytopenia does NOT protect against venous or arterial thrombosis.

Appropriate use of thromboprophylaxis or anticoagulants – for patients with mild to moderate thrombocytopenia (>50K) if indicated.

For patients with more severe thrombocytopenia, decisions weighing in the risks of bleeding and benefits of anticoagulation.
• Isolated Thrombocytopenia
• May present with Bleeding
• Caused by antibody-mediated platelet destruction.

Management:
1. IV IG
2. Glucocorticoids
3. Splenectomy
4. Rituximab
5. Eltrombopag/Romiplostim- Thrombopoietic Growth factors
Disseminated intravascular coagulation (DIC)

- A systemic process
- Massive activation of Coagulation and fibrinolysis
- Consumption of clotting factors and platelets,
- Identifying the cause helps manage and halt this process

- Microangiopathic hemolytic anemia with schistocytes on the blood smear.
- Prolonged PT/aPTT
- Low fibrinogen
- Elevated D Dimer/ Fibrin split products
Platelet microthrombi in small vessels leading to organ damage.

- Thrombotic thrombocytopenic purpura (TTP),
- Complement-mediated TMA (C-TMA), and
- Shiga toxin-mediated Hemolytic Uremic Syndrome (HUS).
Clinical features

- Microangiopathic hemolytic anemia (MAHA), Schistocytes on the peripheral blood smear
- Thrombocytopenia, which can be severe
- Acute kidney injury
- Neurologic symptoms ranging from mild headache to seizures and transient focal abnormalities.
- Fever.
Challenges with TMAs

- Overlapping clinical presentations,

- But differing pathophysiology and

• So need for different treatments.

• Potentially life-threatening
Thrombotic Thrombocytopenic Purpura (TTP)

- Severely reduced activity of ADAMTS13, a protease that cleaves very large von Willebrand factor (VWF) multimers on endothelial cells.
- Acquired, autoimmune TTP - neutralizing autoantibody – more likely in a patient without a family history of TTP.
- Hereditary TTP inherited mutation in the ADAMTS13 gene
- ADAMTS13 activity <10 percent.
- Results of ADAMTS13 activity testing often are not immediately available.
• Urgent plasma exchange (PEX) therapy,
• Removes the autoantibody to ADAMTS13 and supplies functional ADAMTS13
• For patients known to have hereditary TTP, plasma infusion is sufficient
• Platelet transfusion should be reserved for treatment of severe bleeding in a patient with TTP due to the potential increased risk of thrombosis,
• Platelets should not be withheld in a bleeding patient due to concerns about this risk.
Complement-mediated TMA - (C-TMA)
(Complement-mediated HUS or "atypical HUS)

- Increased activation of complement on endothelial cells.
- Develop microthrombi in small vessels
- Kidney is often affected- increasing serum creatinine.
- Neutralizing autoantibody or an inherited mutation
- ADAMTS13 activity is ≥10 percent
- Stool studies are negative or Shiga toxin-producing organisms.

- Anti-complement therapy Eculizumab.
Shiga toxin-mediated hemolytic uremic syndrome (ST-HUS)

- Enteric infection with an organism that produces the toxin (eg, enterohemorrhagic *Escherichia coli, Shigella*)
- Severe abdominal pain and Bloody diarrhea
- Stool testing for Shiga toxin-secreting bacteria

*E. coli* 0157:H7, *Shigella dysenteriae* and for *Shiga toxin*

- Management involves supportive care
Heparin Induced Thrombocytopenia (HIT)

Complication of heparin therapy.

Two types

- **Type 1 HIT**
  develops within the first 2 days after heparin exposure, Platelet count normalizes with continued heparin therapy.
  Nonimmune disorder that results from the direct effect of heparin on platelet activation.

- **Type 2 HIT**
  Immune-mediated
  develops 4-10 days after heparin exposure
  life and limb-threatening thrombotic complications
Heparin Exposure

- Drop in platelet count, particularly if over 50% of the baseline count, *even if the platelet count nadir remains above 150 x 10^9/L.*

- Venous thromboembolism - most common complication.

- Arterial thrombosis (eg, myocardial infarction) may occur. sometimes termed Heparin-induced thrombocytopenia and thrombosis (HITT).
• HIT is a *Clinicopathologic* diagnosis
• Needs clinical feature + lab work for Diagnosis
• Caused by antibodies to complexes of platelet factor 4 (PF4) and heparin
• The antibodies bind to the PF4-heparin complexes on the platelet surface and *induce platelet activation* by cross-linking FcγIIA receptors.
• Incidence 0.2% in all heparin exposed patients.
• Greater than 50% risk of developing new thromboembolic events.

• The mortality rate is approximately 20%, and approximately 10% of patients require amputations or suffer other major morbidity
**Diagnostic tests**

**Immunoassays** – HIT antibody testing

- Identify antibodies against heparin/platelet factor 4 (PF4) complexes.
- Rapid turnaround time and high sensitivity (> 99%).
- Poor specificity (30%-70%) because they also detect non pathogenic antibodies.
- The specificity enhanced by optical density (OD) of the result.
- Higher absolute OD values correlate with a clinical diagnosis of HIT.
- OD of 0.4 to <1.00 indicated a 5% or lower probability of a strongly positive result on functional testing with the serotonin release assay (SRA),
- OD of 2.0 or more resulted in an approximately 90% probability of a strong SRA result.
Functional assays - SRA/HIPA

• Measure the platelet-activating capacity of PF4/heparin-antibody complexes.

• Functional assays have greater specificity than immunoassays but are time-consuming

• Based on HIT antibodies causing platelets to aggregate and release serotonin. Sensitivity 69% to 94%, and specificity may be as high as 100%
Treatment

- Discontinue heparin
- Direct thrombin Inhibitor
  - Argatroban
  - Bivalirudin (patients – PCI)
  - Fondaparinux (Indirect factor Xa inhibitor)- pregnant women.
Safe platelet count for invasive procedures

• Most platelet count thresholds for invasive procedures are based on weak observational evidence.
• Procedures with a greater risk of bleeding are performed at higher platelet counts.
• Raising the platelet count for an invasive procedure depend on the underlying condition (Steroids or IVIG for ITP; platelet transfusion for myelodysplastic syndromes)
• Individuals with impaired platelet function may require platelet transfusions despite adequate platelet counts
• Correct coagulation abnormalities if present.
### Table 2. Summary of Platelet Transfusion Triggers From Published Guidelines

<table>
<thead>
<tr>
<th>Indication</th>
<th>Platelet Transfusion Trigger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical patients</td>
<td>$50 \times 10^9/L$</td>
</tr>
<tr>
<td>Cardiac surgery with CPB</td>
<td>$50 \times 10^9/L$ or reserved for bleeding</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>$50 \times 10^9/L$</td>
</tr>
<tr>
<td>Surgical and obstetric patients with microvascular bleeding</td>
<td>$50 \times 10^9/L$</td>
</tr>
<tr>
<td>Surgery with a low risk of bleeding</td>
<td>$50 \times 10^9/L$</td>
</tr>
<tr>
<td>HELLP syndrome requiring cesarean section</td>
<td>$50 \times 10^9/L$</td>
</tr>
<tr>
<td>HELLP syndrome requiring vaginal delivery</td>
<td>$30 \times 10^9/L$</td>
</tr>
<tr>
<td>Spinal anesthesia</td>
<td>$50 \times 10^9/L$</td>
</tr>
<tr>
<td>Epidural anesthesia</td>
<td>$80 \times 10^9/L$</td>
</tr>
<tr>
<td>Ophthalmologic and CNS surgery</td>
<td>$100 \times 10^9/L$</td>
</tr>
<tr>
<td>Massive transfusion</td>
<td>$50 \times 10^9/L$</td>
</tr>
<tr>
<td>Multiple trauma or CNS injury</td>
<td>$100 \times 10^9/L$</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>$50 \times 10^9/L$ or reserved for bleeding</td>
</tr>
<tr>
<td>Autoimmune thrombocytopenia</td>
<td>Reserved for serious bleeding</td>
</tr>
</tbody>
</table>

Abbreviations: CPB, cardiopulmonary bypass; HELLP, hemolysis elevated liver enzymes low platelets; CNS, central nervous system.
Summary

Thrombocytopenia in inpatient setting – very common

Life-threatening causes should be considered initially

Examination of the Peripheral smear

Temporal relation to drop in platelet count with respect to drug exposure or RBC transfusion, the severity of thrombocytopenia, and the presence or absence of Bleeding, symptoms provide clues to the underlying cause.

Platelet transfusions for serious bleeding and

Thrombocytopenia alone is not a contraindication to antithrombotic therapy

weigh risks vs benefits
References


Uptodate: Approach to the adult with unexplained thrombocytopenia
Thank You!