Hematology Tools to aid in the Diagnosis and Management of Thrombocytopenia

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Objectives

- Discuss the importance of providing accurate platelet counts and the clinical value of the Immature Platelet Fraction.
- Review the mechanisms of thrombocytopenia and disease states that are often associated with thrombocytopenia as a secondary side effect.
- Explain the advantages and disadvantages of the traditional lab tests for the diagnosis and treatment of thrombocytopenia.
Definition of Thrombocytopenia

- Traditional lower limit of normal is $150 \times 10^9/L$
- Platelet Count < the 2.5th lower percentile of the platelet count distribution
- Platelet counts between $100 \times 10^9/L$ and $150 \times 10^9/L$ do not necessarily indicate disease if stable for 6 mths

Relevance of thrombocytopenia

- Is variable and depends on the clinical presentation.
- Platelets play an essential role in preserving vessel wall integrity, so it’s associated with a defect of primary hemostasis.
- Spontaneous bleeding does not usually occur until the platelet count is less than 10-20 × 10^9/L.

Relevance of thrombocytopenia

- Aggravate surgical or traumatic bleeding.
- Prevent the administration of effective treatment for several conditions.
- A low platelet count is the only initial manifestation of an underlying disorder that poses greater risks than thrombocytopenia itself.
- An important marker of disease activity (e.g., thrombotic microangiopathies).
Importance of Accurate Platelet Count

In the not so distance past
Today’s Hematology Analyzers

Impedance Platelet Counting
PLT-F Channel

PLT performance
• Impedance platelet analysis (size) has limitations in the identification and discrimination of platelets from interfering particles with the same size.
• Possible interferences
  – RBC fragments counted as platelets: falsely high
  – Microcytic RBCs counted as platelets: falsely high
  – Large platelets counted as RBC: falsely low

Optical Platelet Counts
• Dual Light Scatter
• Reduces some interferences
  – Microcytic RBC
  – RBC Fragments
• Captures giant platelets
PLT-F Channel

Reagent Reaction

RBC  PLT  IPF

PLT-F Channel

Reportable Parameters
PLT-F
IPF
Binding sites of Fluorocell PLT

Fluorocell PLT stains nucleic acid rich organelle
- Rough-surfaced endoplasmic reticulum (ribosomal RNA)
- Mitochondria (MtDNA)

PLT-F separates platelets from RBC fragment by the differences in staining

- CD41/CD61 positive = Platelets
- Staining by PLT-F dedicated reagent
  - Platelets - Strong, especially within the cell
  - RBC fragments - Weak, only cell membrane
Interference with Routine Impedance Count

β-Thalassemia Major with numerous fragmented red cells

**XE: PLT-I**
- Microcytic RBC

**XE: PLT-O**
- Microcytic RBC

**XN: PLT-F**
- Microcytic RBC

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Improved Performance of PLT-F

Acute Promyelocytic Leukemia / chemo: white blood cell fragments

**XE: PLT-O**
- WBC cytoplasm fragments

**XN: PLT-F**
- WBC cytoplasm fragments

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**Results:**
- **XE: PLT-I** PLT-I = 477*10^9/L, IPF% = 13.9%
- **XE: PLT-O** PLT-I = 514*10^9/L, IPF% = 12.9%
- **XN: PLT-F** PLT-I = 28*10^9/L, IPF% = 41.2%
- **WBC cytoplasm fragments**
Platelet Counting Today

• Multiple Robust Methods
  – Impedance
  – Optical
  – Fluorescent
• Better Accuracy & Precision
• Confidence in low end counts?

Establishing the Mechanism of Thrombocytopenia
Relevance of Thrombocytopenia

• Hospitalized patients
  – Thrombocytopenia appears frequently in the background of a multisystem disorder
  – May be determined by multiple mechanisms.

• Outpatients
  – Thrombocytopenia is often isolated and asymptomatic
  – Diagnosis of the specific cause is usually straightforward

Establishing the cause of thrombocytopenia

• Pregnancy
  – Possible consequences for the fetus
Establishing the cause of thrombocytopenia

Table 1. Clinical scenarios and most common causes of thrombocytopenia

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<th>Scenario</th>
<th>Inpatient</th>
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TTP/HUS indicates thrombotic thrombocytopenia purpura/hemolytic uremic syndrome; MAS, macrophage activation syndrome (including hemophagocytic syndrome); CIT, chemotherapy-induced thrombocytopenia; HELLP, hemolysis, elevated liver enzymes, and low platelets.


Mechanisms of Thrombocytopenia

- Decreased Production in the Bone Marrow
  - Aplastic anemia
  - Myelodysplastic syndromes
  - Chemotherapy-induced thrombocytopenia

- Increased Destruction / Consumption
  - DIC
  - Thrombotic microangiopathies
Mechanisms of Thrombocytopenia

• Platelet sequestration
  – Seen in congestive splenomegaly due to portal hypertension
  – Characterized by redistribution of platelets from the circulating pool to the splenic pool

• Hemodilution
  – Patients who have suffered a massive hemorrhage
  – Received colloids, crystalloids, and platelet-poor blood products

Mechanisms of Thrombocytopenia

• Multiple Mechanisms
  – Primary ITP
  – Hepatitis C virus infection
History & Physical Exam

• New onset, chronic, or relapsing
• Family History
  – Autoimmune disorders, infections, or malignancies; pregnancy status in premenopausal woman; recent medications and vaccinations; recent travels (eg, malaria, rickettsiosis, dengue fever); recent transfusions; recent organ transplantation; ingestion of alcohol and quinine-containing beverages; dietary habits; and risk factors for retroviral infections and viral hepatitis

History & Physical Exam

• Bleeding history
  – Does not help in diagnosing the nature of the thrombocytopenia
  – Gives important clues about its duration and defines its clinical phenotype.
The Laboratory’s Role

• Accurate Platelet Count
• Peripheral Smear Review
  – Still the most important diagnostic approach
• All 3 Blood Lineages should be examined
  – Thrombotic microangiopathy (Fragments)
  – Acute Leukemia (Blasts)
Platelets

- Platelet Clumping
  - EDTA Clumpers (1 in 1000 normal adults)
- Platelet size and granularity
  - Hereditary disease
    - Macrothrombocytopenia
    - Gray platelet syndrome
    - Platelet destruction – large and normal size
    - Platelet production – normal
    - Myleodysplastic syndromes – variable size, frequently hypogranular

WBC

- Leukemia and Lymphomas
- WBC Inclusions
- Neutrophilia, Lymphocytosis, Leukopenia
- Pelger Huet Anomaly
- Toxic Granulation associated with sepsis
RBC

- Schistocytes
  - Thrombotic microangiopathy (TTP/HUS)
  - DIC
- Microspherocytes
- Macrocytosis (with hypersegmented neuts)
- Dacrocytes (teardrops)
- NRBC
  - Hemolytic anemia
  - Myelofibrosis
  - Infiltration of the bone marrow

Algorithm Based on observation of the peripheral blood film

- Thrombocytopenia
  - Platelet clumping
  - Artificial thrombocytopenia
- Examine peripheral blood smear
  - True thrombocytopenia
- Hereditary thrombocytopenia
  - Giant platelets w/WBC inclusions
- TTP/HUS DIC
- LDH, bilirubin, Haptoglobin, PT, aPTT, D-dimers, Fibrinogen
- Blasts Neutrophilic RBCs Pelger-Huet Dacrocytes Etc.
- Consider Evans syndrome
- Lymphocytosis Aplastic anemia Neutropenia Toxic granulation Etc.
- DAT Reticulocytes LDH, bilirubin
- Consider infection
- ESR, CRP, CXR, Virology, blood cultures, etc.
- Investigations based on clinical assessment

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There is no single hematologic or biochemical test that is conclusive for a given mechanism of thrombocytopenia.

**Other testing information**

- Liver function and Renal panels
- Clotting testing + D-dimer
- Lactate dehydrogenase

Bone Marrow Biopsy
New Platelet Parameters

MPV

• MPV – Mean Platelet Volume
  – Measures the average size of the platelet (similar to MCV for RBCs)
  – Calculated or derived parameter
  – May be used as an indicator of thrombopoiesis
**MPV**

- Limitations
  - Not all large platelets are young platelets
  - MPV is derived or calculated from the platelet histogram
    - What do you do if you don’t have a good histogram?

**Reticulated Platelets**

- Newly released platelets, contain RNA and are *larger than* mature platelets
- They are the platelet analogue of red cell reticulocytes
- Are more reactive than mature platelets
- Reflect the rate of thrombopoiesis
- Platelet RNA content correlates with megakaryocytic activity
Reticulated Platelets

- Distinction between causes of thrombocytopenia:
  - Marrow failure (low reticulated platelet count)
  - Increased marrow production secondary to peripheral platelet destruction/consumption (high reticulated platelet count)
- The RNA can be stained using supravital or fluorescent dyes
- Can potentially be quantitated by microscopy and flow cytometry
- Needs fluorescent label with nucleic acid affinity

Immature Platelet Fraction

- % of total platelets that are immature
- Measures platelets newly released from the bone marrow
- Indicator of thrombopoiesis
PLT-F Channel

Scattergram - Normal Pattern

Low PLT + Low IPF
Consistent with disorder of production

Normal

Low PLT+ High IPF
Destruction consistent with autoimmune or other destruction mechanism (ITP, TTP, DIC)

Differentiate Physiological Mechanisms
Briggs, C.
British Journal of Hematology

Immune Thrombocytopenia purpura

- ITP is a diagnosis by exclusion
  - Other causes of thrombocytopenia
  - Other causes of immune thrombocytopenia, i.e. secondary thrombocytopenia

- ITP is complicated
  - Not necessarily just a platelet destructive or consumptive mechanism
Immune Thrombocytopenia purpura

• Clinical Diagnosis - 3 key criteria
  – Isolated thrombocytopenia an otherwise normal peripheral complete blood count and smear
  – Absence of hepatosplenomegaly and lymphadenopathy on physical examination
  – Ideally, a substantial platelet response to ITP-specific therapy, such as intravenous immunoglobulin (IVIg), IV anti-D immunoglobulin, or steroids

ITP Resources

Chronic Hepatitis C

Possible Mechanisms of Thrombocytopenia in Hepatitis C

• Peripheral platelet destruction
  – Immune-mediated
  – Hypersplenism

• Decreased platelet production
  – Reduced Thrombopoietin (TPO) synthesis
  – Viral effects on megakaryocytes
  – Interferon therapy
Study Design

- 47 patients with chronic hepatitis C
  - 29 with thrombocytopenia
  - 18 without thrombocytopenia
  - 6 in each group were taking interferon
- Clinical data
  - Cirrhosis, portal hypertension, splenomegaly
  - Medications
  - Results of lab tests (within 3 months) – albumin, INR, LFT’s, hepatitis C viral load

Summary of Findings in 29 Thrombocytopenic Patients

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<tr>
<th>Splenomegaly</th>
<th>IPF Increased</th>
<th>IPF Normal</th>
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<td>Splenomegaly</td>
<td>Platelet sequestration in spleen (n=11, 38%)</td>
<td>Hypersplenism plus failure of thrombopoiesis to compensate (n=8, 27%)</td>
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<tr>
<td>No Splenomegaly</td>
<td>Immunologic destruction of platelets (n=6, 21%)</td>
<td>Decreased platelet production (n=4, 14%)</td>
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Possible Clinical Application

- Major mechanism of thrombocytopenia
  - Peripheral platelet destruction
  - But defect in platelet production may contribute in some cases, especially where IPF is normal
- Further testing may be warranted in the subgroup with normal IPF
  - Bone marrow to rule out bone marrow defect which may be associated with hepatitis C (e.g., lymphoproliferative disorder)

Summary

- Peripheral sequestration or destruction of platelets is the major mechanism for thrombocytopenia in chronic hepatitis C; hypersplenism is the most notable cause
- Failure of thrombopoiesis to compensate is most likely a contributory mechanism
Other Potential Uses of IPF

Drug Induced Thrombocytopenia

- Usually by accelerating PLT destruction via drug-dependent anti-platelet antibodies
- Drug binds to platelet surface glycoproteins (GPIb-IX, GPIIb-IIIa) causing conformational change and exposing neoepitope that serves as target for antibodies
- Drug-dependent anti-platelet antibodies are very specific and usually do not cross react with other drugs of the same class
Drug Induced Thrombocytopenia

• Diagnosis is made when thrombocytopenia resolves after the suspected drug is discontinued
• Median for PLT count recovery after discontinuation of drug is 5-7 days
• Assays for drug-dependent antiplatelet antibodies not readily available
• If PLT is less than 10,000 /μL or bleeding occurs, treat with steroids as well as transfusion incase of ITP

Drug Induced Thrombocytopenia

• The mostly likely culprits include
  – Quinine
  – Quinidine
  – Valproic acid
  – Ranitidine
  – Rifampin
  – Trimethoprim-sulfamethoxazole
  – GPIIbIIIa inhibitors
  – Heparin
• Some of the others…
### Drugs Causing Thrombocytopenia Supported by One or More Case Reports With Level I (Definitive) Evidence or Two or More Case Reports With Level II Evidence*1

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*1 The full list of articles reviewed and the database established by this review are available at [http://www.sheehan.edu/george](http://www.sheehan.edu/george).
Heparin-Induced Thrombocytopenia

- **Type I**
  - A relatively mild fall in PLT count within first 2 days of heparin initiation; PLT count often remains in the normal range
  - PLT count often returns to normal with continued heparin administration
  - Non-immune mediated
  - No clinical consequence
Heparin-Induced Thrombocytopenia

- Incidence of immune mediated HIT occurs in 0.3-3% of patients exposed to heparin for more than 3 days
- Pathophysiology
  - Heparin binds platelet factor 4 (PF4) and a conformational change occurs which forms an epitope recognized by most HIT antibodies (IgG and IgM)
  - Heparin-PF4-antibody complex leads to platelet activation which leads to further release of PF4
  - Activated PLT aggregate and leads to thrombosis as well as thrombocytopenia

Heparin-Induced Thrombocytopenia

- Spontaneous bleeding is rare
- Rapid onset: anamnestic response – heparin exposure within 100d
- Delayed or late onset HIT: within 30 days of heparin exposure, but no very recent heparin
- Mechanism is unclear
Heparin-Induced Thrombocytopenia

- Clinical diagnosis
- Laboratory tests
  - Platelet count <150,000 or 50% decrease from baseline
  - Mean platelet count 60,000; 10% <20,000
  - IPF probably increased

- Lab MUST demonstrate presence of heparin dependent antibodies
- Diagnostic tests
  - 14 C serotonin release assay
    - 100% sensitivity, 97% specificity
    - Very expensive and technically difficult
  - Heparin-induced PLT aggregation assay
    - Less than 80% sensitivity, 90% specificity
  - Solid phase immunoassay (ELISA immunoassay to detect presence of heparin dependent antibodies)
    - 91% sensitivity, very low specificity
Heparin-Induced Thrombocytopenia

- **Treatment**
  - Cessation of all heparin exposure
  - Use of lepirudin/bivalirudin or argatroban (direct thrombin inhibitor) for anticoagulation until PLT count has recovered
  - Initiate warfarin after a patient is stably anticoagulated
  - Other agents
    - Fondaparinux
    - Danaparoid

- Patients with a history of HIT who require cardiopulmonary bypass who are antibody negative at the time of surgery do not generally develop complications with the brief heparin exposure

Challenges in the Diagnosis and Management of HIT

- HIT can be a devastating prothrombotic disease
- Diagnosis should be suspected based on clinical findings
- Lab test are useful, but have limitations
- There are other causes of thrombocytopenia (eg, sepsis, DIC, primary bone marrow disorders etc…)
- HIT is overdiagnosed if EIAs alone are used
### Potential IPF Applications

- TPO monitoring
- Bone Marrow recovery after Peripheral Blood Stem Cell transplant
- Cardiology

### IN SUMMARY

- Healthy bone marrows respond to decreased circulating platelets by releasing young platelets
- Thrombopoiesis is a dynamic process which has varying physiologic responses in different clinical conditions
- It is essential to determine the pathophysiologic cause of thrombocytopenia
- Young platelets can be recognized by both their size, and by their nucleic acid content
IN SUMMARY

• The Lab’s role in aiding the physician in the diagnosis and treatment of thrombocytopenia is essential
• Accurate and Precise Platelet count are critical
• Peripheral Blood smear review is of upmost importance
• The fully automated Immature Platelet Fraction is a helpful tool to the physician in the diagnosis and treatment of thrombocytopenia

Questions?