How to Approach the Inpatient with Low Platelet Counts

Steven Fein, MD, MPH
What I’m going to tell you

• Hospital-based hematology
• Inpatients with low platelet counts
  – Nonmalignant, not HIT
  – HIT
  – APL leukemia
• What to do about low platelet counts
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Hematology

• Clotting
  – DVT/PE/stroke, "unusual site" clotting
  – Antiphospholipid syndrome
  – Heparin-induced thrombosis (HIT)

• Bleeding
  – Hemophilia, bleeding tendency, anticoagulants

• Abnormal blood counts
  – Myeloproliferative disorder, ITP, Anemia

• Blood cancers
  – Leukemia, lymphoma, multiple myeloma
Hematology interfaces with all specialties
Why hematology?

• Non-malignant hematology
  – Interesting
  – Variety of disorders, all ages
  – Save lives
  – Cutting edge

• Malignant hematology
  – Cure some people with cancer

• Related to the other people doing it
Why do heme and onc go together?

- Historically hematology was focused on bleeding disorders and transfusions
- Blood cancers were the first to be treated successfully
- Oncology was born out of hematology
- Hematology was reinvented with new treatments including immunotherapy, anticoagulants and IV iron infusion
Hospital-based hematology

• Hematology is a fundamental inpatient hospital specialty
• Many patients present with blood conditions
• Many life-threatening conditions require hematology experts
  • Severe bleeding with coagulopathy
    • inherited or acquired hemophilia
    • intracranial hemorrhage
    • pregnancy/postpartum bleeding
  • DVT/PE, HIT, stroke, ”unusual site” clotting
  • Low platelet counts, ITP, APL leukemia
  • High blood counts, stroke related to MPD
  • TTP, HUS, HLH, rare hematology conditions
What I’m going to tell you

• Hospital-based hematology

• Inpatients with low platelet counts
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  – HIT
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• What to do about low platelet counts
What does low plt count mean?

• Platelet count is a snapshot in a complex physiologic process of making and using plts
• Plt count =

  production – (destruction or consumption)

• Usual platelet lifespan 3-5 days

• Low platelet count not necessarily a bleeding tendency because “healthy” platelets being made
• At some low level spontaneous bleeding risk occurs, but it is much lower than you may think
Platelet clumping

Antibodies bind plts in EDTA
No clinical significance, but
Can affect decisions about
treatment/interventions

Can have low plt with clumps
but uncommon

Citrate count not worth it

“Low count confirmed” means
no clumping seen by lab tech
Bleeding and Coagulopathies in Critical Care

Sepsis (especially consider)
  Human immunodeficiency virus (HIV) infection
  Disseminated intravascular coagulation
Major blood loss and hemodilution
Mechanical fragmentation
  Post-cardiopulmonary bypass
  Intraaortic balloon pump
  Renal dialysis
  Extracorporeal membrane oxygenation

Immune-mediated disorder
  Immune thrombocytopenic purpura
  Antiphospholipid syndrome
  Post-transfusion purpura
Microangiopathic hemolytic anemia
  Disseminated intravascular coagulation
  Thrombotic thrombocytopenic purpura
  Hemolytic–uremic syndrome
Hypersplenism
Other disorder
  Myelodysplastic syndrome
  Cancer
  Hereditary thrombocytopenia
Hematologist’s perspective on low plts

- Low platelet count is a clue for other diagnoses
- If it’s chronic, then assume ITP or hypersplenism
- If it’s subacute, then r/o heme malignancy & APL
- If it’s acute then r/o HIT, or assume meds/infection
Low platelet count case

86yo woman
HCV antibody pos
Chronic low plt

<table>
<thead>
<tr>
<th>Date</th>
<th>Platelet Count</th>
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<tbody>
<tr>
<td>02/06/20</td>
<td>14.5</td>
</tr>
<tr>
<td>12/31/20</td>
<td>14.5</td>
</tr>
<tr>
<td>12/30/20</td>
<td>14.9</td>
</tr>
<tr>
<td>12/29/20</td>
<td>16.0 (H)</td>
</tr>
<tr>
<td>12/28/20</td>
<td>43.3</td>
</tr>
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<td>42.9</td>
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<td>12/26/20</td>
<td>45.3 (H)</td>
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<td>12/25/20</td>
<td>48.7 (H)</td>
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<td>6.48</td>
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<tr>
<td>12/21/20</td>
<td>7.28</td>
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<tr>
<td>12/20/20</td>
<td>16 * (L)</td>
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<tr>
<td>12/19/20</td>
<td>55 (L)</td>
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<td>12/18/20</td>
<td>40 (L)</td>
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<tr>
<td>12/17/20</td>
<td>47 (L)</td>
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**IMPRESSION:**
1. Liver showing mild coarsening of the echotexture and some surface irregularity consistent with hepatic cirrhosis. No focal masses are seen.
2. Small right pleural effusion.

**IMPRESSION:**
Heterogeneous activity within the liver consistent with a cirrhotic liver seen on previous imaging. There is splenomegaly with mild diffuse increased uptake consistent with colloid shift suggesting portal hypertension.
What causes low platelet counts?

<table>
<thead>
<tr>
<th>Large platelets</th>
<th>ACUTE/SUBACUTE</th>
<th>CHRONIC</th>
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</thead>
<tbody>
<tr>
<td>High MPV</td>
<td>Acute ITP</td>
<td>Chronic ITP</td>
</tr>
<tr>
<td></td>
<td>“consumption”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thrombosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bleeding/hematoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DIC, HIT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemodilution/IVF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heme malignancy/APL</td>
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</table>

<table>
<thead>
<tr>
<th>Small platelets</th>
<th>BM suppression</th>
<th>BM dysfunction</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Infection</td>
<td>Aplastic anemia</td>
</tr>
<tr>
<td></td>
<td>Medications</td>
<td>MDS/heme malignancy</td>
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<tr>
<td></td>
<td>Chemotherapy</td>
<td>AIDS</td>
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</table>
When to suspect chronic ITP

- Usually patients not ill, not bleeding
- *Incidental* finding on CBC- only low plt count
- Rule out MDS/AA
- Hypersplenism is the same guess as ITP
- Platelets usually large (high MPV)
- ITP patients usually do not bleed unless plts<20, but cirrhosis pts have bleeding
What to do about **chronic** low plts

- **ITP or hypersplenism** (usually platelet count $>30$)
  - Decide whether bleeding or procedure planned
  - Consider IVIG for planned procedures
  - Transfusions for visible bleeding or procedure
  - Determine safety/appropriateness of anticoagulants

- **Bone marrow dysfunction**-chronic (MDS/AA)
  - Determine heme malignancy diagnosis and interventions
  - Transfusions for plt $<10$ or visible bleeding or procedures
Diagnosing **acute** ITP exacerbation

- NOT incidental → usually bruised/bleeding
- Low platelets with normal HCT and WBC
- No culprit drug causing BM suppression
- Vancomycin causes ITP (not BM suppression)
- **Minimal response to platelet transfusion**
These are not ITP
These are not ITP

Microangiopathic hemolytic anemia

Platelet clumping

APL leukemia
Classic ITP experiment by William Harrington

- Blood from patients with chronic ITP injected into himself and 9 other subjects with normal platelet counts
- Thrombocytopenia immediately observed in 8 subjects
- An antiplatelet “factor” in the globulin fraction of plasma, not the albumin fraction, was responsible

How ITP treatments work

ITP treatments
steroids
IVIG
Rituximab
Eltrombopag
Avatrombopag
Romiplostim
Fostamatinib
Who to hospitalize for acute ITP

- Very low platelet count (<20,000/µL)
- Mucocutaneous bleeding (mouth, nose)
- Significant patient comorbidity or age > 70
- Outpatient management not possible
Management of acute ITP

Steroid pulse
Consider IVIg

Rituximab and/or
Romiplostim/Eltrombopag
Vancomycin-Induced Immune Thrombocytopenia


Figure 1. Clinical Course of a Patient with Vancomycin-Induced Thrombocytopenia.
Drug-induced low platelets

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Drugs Implicated in Five or More Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparins</td>
<td>Unfractionated heparin, low-molecular-weight heparin</td>
</tr>
<tr>
<td>Cinchona alkaloids</td>
<td>Quinine, quinidine</td>
</tr>
<tr>
<td>Platelet inhibitors</td>
<td>Abciximab, eptifibatide, tirofiban</td>
</tr>
<tr>
<td>Antirheumatic agents</td>
<td>Gold salts</td>
</tr>
<tr>
<td>Antimicrobial agents</td>
<td>Linezolid, rifampin, sulfonamides, vancomycin</td>
</tr>
<tr>
<td>Sedatives and anticonvulsant agents</td>
<td>Carbamazepine, phenytoin, valproic acid</td>
</tr>
<tr>
<td>Histamine-receptor antagonists</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Analgesic agents</td>
<td>Acetaminophen, diclofenac, naproxen</td>
</tr>
<tr>
<td>Diuretic agents</td>
<td>Chlorothiazide</td>
</tr>
<tr>
<td>Chemotherapeutic and immunosuppressant agents</td>
<td>Fludarabine, oxaliplatin</td>
</tr>
</tbody>
</table>
Low platelets during pregnancy

• Immune thrombocytopenia purpura (ITP)
  – New diagnosis or exacerbation of underlying ITP
  – Autoimmune, counts low (e.g. 20k)

• *Gestational* thrombocytopenia (ITP variant)
  – “dilution” and autoimmune, 7% of all pregnancies

• Preeclampsia and HELLP Syndrome

• Thrombotic thrombocytopenia purpura (TTP)
ITP during pregnancy

- May be exacerbation of “underlying” non-preg ITP
- May persist after pregnancy
- Peripartum bleeding is uncommon
- Usually treatments more toxic than condition
- Count too low for spinal anesthesia (need plt>80)
- Count too low for safe parturition (need plt>50)
- Neonatal thrombocytopenia
ITP during pregnancy

- Try to minimize steroids-prefer IVIG
- Don’t treat numbers until ready for procedures
- May need weekly IVIG for parturition
- C-section not required, but Ob may recommend it
- Epidural needs plt>80
- 5% of babies will have plt<20→they may need IVIG
- Mother needs hematology f/u
Preeclampsia

• Common (6%) and unpredictable
  – Age < 20 or age > 30
  – Obesity
  – HTN before pregnancy
  – Diabetes a risk factor
• BP > 140/90 and proteinuria (>0.3 g/day)
• Platelets low sometimes, but not usually
• Treatment is delivery, Mg to prevent seizure
Pathophysiology of Preeclampsia
HELLP syndrome

- Same pathophysiology as Preeclampsia
  - 10% or preeclampsia patients
  
  **Hemolysis**
  
  **Elevated Liver enzymes**
  
  **Low Platelets**

- Nausea, abdominal pain, risk for eclampsia

- Treatment is delivery, Mg to prevent seizure
Preeclampsia and HELLP

- Probably thrombotic disorders
- Hepatic infarct → hematoma
- Can lead to DIC, including low fibrinogen
- Consider steroid pulse
- Platelet transfusion if platelet<20

- Risk of recurrence in future pregnancies
Thrombotic Thrombocytopenic Purpura (TTP)

- Low platelets and clotting/microthrombosis
- Usually young women (autoimmune)
- Occasionally associated with pregnancy
- *Microangiopathic hemolytic anemia*
- Need at least two of pentad:
  - Anemia, thrombocytopenia
  - Fever, Acute renal failure
  - Neurologic signs or symptoms
ANTIBODIES TO VON WILLEBRAND FACTOR–CLEAVING PROTEASE IN ACUTE THROMBOTIC THROMBOCYTOPENIC PURPURA

HAN-MOU TSAI, M.D., AND ERIC CHUN-YET LIAN, M.D.
TTP diagnosis and treatment

- 1925 Moschcowitz: 16yo girl with stroke and MI
- 1980’s Plasma exchange (plasmapheresis)
- 1990’s Rituximab and chemotherapy
- 2020’s Anti-VWF Antibody
What I’m going to tell you

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  – HIT
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• What to do about low platelet counts
HIT Complicating Orthopedic Surgery

- Patients with HIT (n=9)
- Unilateral lower-limb DVT
- Bilateral lower-limb DVT
- Arterial clot
- Pulmonary embolism

Normal Postoperative Platelet Counts (mean ± 2 SD)

Platelet Count x 10^9 /L

Pre 1 2 3 4 5 6 7 8 9 10 11 12 13 14

Postoperative Day

## Frequency of HIT (Platelet Fall >50%)

<table>
<thead>
<tr>
<th></th>
<th>UFH</th>
<th>LMWH*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIT</td>
<td>16/332 (4.8%)</td>
<td>2/333 (0.6%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HIT-IgG</td>
<td>29/205 (14.1%)</td>
<td>11/182 (6.0%)</td>
<td>=0.01</td>
</tr>
</tbody>
</table>

* enoxaparin

** PF4/heparin-ELISA

HIT case

50yo man
Right side weakness
Large bleeding stroke

Rehabilitation 2 weeks
Subq heparin to prevent DVT/PE
HIT case

Two weeks later
pulmonary embolus
When to suspect HIT
HIT causes clotting
B. Resting Platelet

C. Activated Platelet

Procoagulant, platelet-derived microparticles

TIMELINE OF HIT

HIT-IgG detectable

Venous
- DVT/PE
- Venous gangrene
- Adrenal infarction
- Cerebral sinus thrombosis

Arterial
- Lower limb thrombosis
- Stroke
- MI
- Other

Skin lesions at heparin injection sites

Acute systemic reaction (ASR) post-heparin bolus

Unfractionated Heparin (UFH)

Typical-onset HIT

Rapid-onset HIT

Rapid-onset HIT can occur if heparin given and HIT-IgG still present (usually within 100 days)

Warkentin & Greinacher. Heparin-Induced Thrombocytopenia (3rd ed). New York, Marcel Dekker, 2004
Who gets HIT?

• ACS/cardiac cath patients
• Cardiac surgery second heparin exposure
• Heparin/LMWH used to be used for DVT/Afib
• Heparin/LMWH for DVT prev post-op
• Heparin/LMWH for DVT prev non-surgical
• Autoimmune HIT (no heparin exposure)
• Vaccine-induced thrombosis (VIT)
Vaccine-induced thrombosis

Autoimmune HIT (aHIT) (with proximate heparin) (anti-PF4/heparin & anti-PF4)
- Delayed-onset HIT
- Persisting (refractory) HIT
- Heparin “flush” HIT
- Fondaparinux-associated HIT

aHIT Syndromes (without proximate heparin) (anti-PF4)
- Spontaneous HIT syndrome
- Post-total knee arthroplasty
- Medical variant (e.g., post-viral/bacterial infection)
- Vaccine-induced immune thrombocytopenia

Risk of Blood Clot

- Vaccine
  - 4 cases in 1,000,000 vaccines: 0.0004%
- Birth Control Pill
  - 500 – 1200 cases in 1,000,000 women: 0.05% to 0.12%
- Smoking
  - 1763 cases in 1,000,000 smokers: 0.18%
- COVID-19 Infection
  - 165,000 cases in 1,000,000 cases: 16.5%
HIT clinical spectrum

• Subclinical
• Low platelets without obvious clot
• Superficial venous thrombosis
• DVT/PE
• Arterial thrombosis and stroke
• Venous limb gangrene and distal infarction
• Adrenal infarction and retroperitoneal hem
Iceberg Model of HIT

HIT-associated Thrombosis

Thrombocytopenia

Activation assay

Antigen assay

Defining clinical HIT

Old definition:
• Platelets <150
• Platelet decrease 50%
• 5-7 days after 1st heparin/LMWH

New definition:
• Thrombosis or unusual bleeding during/after receiving heparin/LMWH
• Unexplained clinical deterioration/hypotension
• Skin nodules or blisters
• Timing of heparin/LMWH unimportant
• Platelet decrease not necessary

4 T criteria for HIT testing:
Thrombocytopenia
Thrombosis
Timing
No other cause
When to suspect HIT

• Clotting after receiving heparin or LMWH
• Unexplained clinical deterioration
  – Hypotension, dyspnea, hypoxia
• Decreasing platelet count
• Re-admitted cardiac or post-op patient
• Recent cardiac catheterization
• “Coumadin failure”
• Dark spots at heparin injection sites
Why HIT is so controversial

• Heparin is a standard, widely accepted medication that is usually beneficial

• HIT presentation is variable
  – Not always a large thrombus or low platelets
  – Probably a spectrum of HIT severity

• Hep/PF4 antibody not always detrimental
  – “False positive” or clinically insignificant HIT
### Table 1. 4T Scoring System for Evaluating the Pretest Probability of Heparin-Induced Thrombocytopenia.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
<th>Score</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Acute thrombocytopenia</td>
<td>Platelet count decrease of &gt;50% and nadir ≥20,000/mm³</td>
<td>Platelet count decrease of 30–50% or nadir 10,000–19,000/mm³</td>
<td>Platelet count decrease of &lt;30% or nadir ≤10,000/mm³</td>
</tr>
<tr>
<td>Timing of onset</td>
<td>Day 5–10, or day 1 if recent heparin exposure</td>
<td>&gt;Day 10 or unclear exposure</td>
<td>≤Day 4 with no recent heparin exposure</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>New thrombosis or anaphylactoid reaction after heparin bolus</td>
<td>Progressive or recurrent thrombosis</td>
<td>None</td>
</tr>
<tr>
<td>Other cause of thrombocytopenia</td>
<td>None</td>
<td>Possible</td>
<td>Definite</td>
</tr>
<tr>
<td>Total score</td>
<td>6–8, indicating high score</td>
<td>4 or 5, indicating intermediate score</td>
<td>0–3, indicating low score</td>
</tr>
</tbody>
</table>
Who should be tested for HIT?

- Recent heparin or LMWH plus
- Two of 4T criteria:
  - Thrombocytopenia
  - Thrombosis
  - Timing appropriate
  - No other explanation for low plt
- Thrombosis during or after heparin/LMWH
Who should be treated for HIT?

• Clinical/pathologic HIT plus clotting or clinical deterioration: argatroban
• HIT without clotting: consider fondaparinux
• Heparin antibody without clinical HIT: avoid heparin/enoxaparin
• Clinical HIT without PF-4 correlate: consider argatroban and repeat PF-4 Ab
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• What to do about low platelet counts
Acute Promyelocytic Leukemia
Acute Promyelocytic Leukemia (APL)

APL Cells: Morphology

FAB M3

FAB M3 Variant (25%)

APL Chromosomal Changes

$t(15;17)(q22;q11-22)$

PML = promyelocytic leukemia
RAR = retinoic acid receptor

PML

15

RARα

17

Der(15)

Der(17)

PML/RARα

RARα/PML


Capillari Oncology
Acute promyelocytic leukemia (APL)
Acute promyelocytic leukemia (APL)

Figure 1.

Log-rank $P < .0001$

Survival Probability

Months From Diagnosis

Don’t miss an APL patient

- Deadly if missed
- Most APL patients are young
- Need high suspicion for APL
  - Bleeding out of proportion to low plt count
  - Plt count increases after plt transfusion
  - “spontaneous” intracranial bleeding
  - Abnormal WBC differential
  - Low fibrinogen
What to do for a new APL patient

• Challenging to explain APL to patients and families
  – The patient may die while waiting for treatment to take effect
  – The patient may die despite the best effort to prevent ICH
  – If bleeding is avoided, the disease may be curable (>90%)

• Start cryo and platelet transfusions around the clock (not prn)
• Bone marrow biopsy is not urgent- you can test blood FISH and flow
• Consider tretinoin before diagnosis is confirmed, but cryo more impt
• Transfer to leukemia center
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What to do about acute low plts

• Determine likelihood of HIT, consider testing
• Determine likelihood of heme malignancy
• Consider stopping linezolid or pip/tazo if possible

• Focus on whether patient is bleeding or clotting
• Consider safety/appropriateness of anticoag
• Transfusions only for count <10-20 or visible bleeding or invasive procedure planned
When to consider platelet transfusions

- Low plt count <10-15
- Visible bleeding <50
- Invasive procedure <50
- Ob C-section <50
- CNS procedure <80
- Ob spinal <80
THE THRESHOLD FOR PROPHYLACTIC PLATELET TRANSFUSIONS IN ADULTS WITH ACUTE MYELOID LEUKEMIA

Transfusion at 10k vs. 20k

No transfusion vs. 10k
How to think about LMWH in patients with low plt counts

• The reason to avoid LMWH for plt 30-100 is concern for HIT, not concern for bleeding risk

• If HIT is not suspected, then OK for LMWH
My anticoag recommendations for patients with low plt counts

• Risk/benefit decision based on presumed or established diagnosis (i.e., is it ITP?)
  
  AND assessment of bleeding tendency

• If plt>30 and no bleeding seen then LMWH OK
• If bleeding seen or presumed, avoid anticoagulants
• If plt<30 then avoid anticoagulants
What we have discussed

- Low plt count diagnosis: acute vs. chronic
- Acute low plt count diagnosis: non-HIT vs. HIT
- Low plt count does not usually pose risk for bleeding tendency until about plt<20
- Low plt count that looks like HIT should prompt testing and possible intervention
- Anticoagulants are OK for patients with low platelets after assessing risk/benefit profile