Evaluation and Management of Thrombocytopenia

Kathryn Hassell, M.D.
Professor of Medicine, Division of Hematology
University of Colorado Denver

Disclosures

- No Financial Conflicts
- No Off-Label Discussion

Objectives

- Integrate the understanding of mechanisms of thrombocytopenia when deciding on evaluation and intervention
- Analyze available clinical and initial laboratory information to develop a differential diagnosis for thrombocytopenia
- Initiate and monitor therapy for severe thrombocytopenic syndromes, in collaboration with hematology consultation as needed
- Recognize situations for which platelet transfusion is beneficial or potentially harmful
Thrombocytopenia: Definitions

- Reduction in the number of platelets <100K
- Terminology varies, but generally:
  - Platelet count ($\times 10^9/L$)
  - Description
  - 50-100 (150): "Mild"
  - 30-50: "Moderate"
  - 10-30: "Severe"
  - <10: "Very Severe"
- "Pseudothrombocytopenia" occurs in 1 in 1000 healthy individuals – check the smear!
- In vitro agglutination of platelets in EDTA (purple top)
- "Satellitism": adhesion of plt to PMNs


Thrombocytopenia: Incidence

- Seen in ~1% of adult acute care hospital inpts
- <30% of these patients manifest with bleeding
- More common in surgical and trauma patients than in medical patients
- In ICU patients, associated with higher morbidity and mortality
  - Mortality increased 4-6X if thrombocytopenia sustained >4 days
  - Independent of bleeding events: marker of serious medical illness, failure to reverse underlying cause
  - More worrisome if it occurs after initial recovery


Thrombocytopenia in the ICU

- Most common coagulation issue in ICU patients
  - 15-68%, depending on the definition used, 2-15% have pls <50K
  - Half present with low pltets, remainder develop it in ICU
  - Most common medical condition: sepsis

Platelets and Thrombopoietin (TPO)

Liver disease (not just cirrhosis) → ↓ TPO

Dilution
Sequestration
Splen or liver
Destruction
thrombotic
microangiopathies
immune-mediated
Primary BM disease

Takes at least 3-4 days to see rise in plt after suppression alleviated

Thrombocytopenia: Causes

- Most common etiology of thrombocytopenia in a hospitalized patient is MULTIFACTORIAL
  - Often a combination of compromised production and increased consumption/destruction
- Drug-induced thrombocytopenia affects up to 25% of acutely ill patients
  - Can suppress bone marrow production of platelets
  - Platelet counts commonly <50,000, nadirs may be <20,000
  - Occurs over days to weeks
- Infections/toxins: similar pattern

Priziola, Crit Care Med 38:S145, 2010; Louie, J Viral Hep doi:10/j.1365-2893.2010.01366x

Thrombocytopenia: Causes

- Classes of agents:
  - Antineoplastics
  - Antivirals
  - Thiazides
  - Daptomycin
  - Tolbutamide
  - Linezolid
  - Antifungals
  - Digoxin
  - Haloperidol
  - Nitrofurantoin
  - Meropenem
  - Quinolones

- Viruses: possible with any, but most reported with certain infections, including:
  - HIV
  - Hepatitis C
  - Parvovirus
  - Epstein-Barr Virus
  - Varicella
  - CMV

- Toxic Injury
  - Ethanol (bone marrow suppression, liver disease)
  - Radiation therapy
Typical Hospital Thrombocytopenia

- Common in the acutely ill
  - Fever/SIRS
  - Medications, medications, medications
  - Co-morbidities (e.g., liver disease, history of chemos/XRT) create "vulnerability"
- Counts of 20-30,000 not uncommon
- Knowledge of baseline status useful
  - If counts normal within last days/weeks or on presentation, then unlikely a primary BM disorder
  - Significance of fall from low baseline less clear, e.g., from 60K to 40K in ESLD
- Patience: may take days to weeks to resolve, even when contributing factors have improved

How Many Platelets Do You Need? Not Many

- Platelet counts of ≥10,000 well-tolerated
  - Based on studies of chemotherapy (AML) patients
  - 3% of days complicated by any bleeding
    - Rebulla, NEJM 337:1870, 1997
- Platelet counts of ≥5,000 may be adequate
  - Based on studies in aplastic anemia
  - Loss of blood in stool increases at platelet count of <5,000
    - Schlichter, Clin Hem 1978
  - 3 nonlethal major bleeding events over >18,000 pt-days in chronic severe aplastic anemia
    - Sagmeister, Blood 93:1124, 1999

Thrombocytopenia: Treat Patients, Not Numbers

- In the absence of bleeding symptoms and interventions, platelet counts of 5-10,000 may be well-tolerated
  - Especially true for ITP
  - Need to weigh confounding factors e.g., other coagulation system changes, platelet dysfunction
- Only data for prophylaxis are in chemotherapy-induced thrombocytopenia
  - Typically maintain platelets ≥10,000
- NO proven benefit for ANY transfusion threshold in other settings
Reason to Care: Thrombocytopenia as an Indication of a Bigger Problem

Specific Severe Conditions Marked by Thrombocytopenia

- Characterized by increased consumption or destruction of platelets
- Platelets may be (initially) innocent bystanders
- Recognition of the specific condition necessary to provide appropriate management
- Treatment is based on reversing the underlying pathophysiology
  - Correcting the platelet count is not the goal: harm often comes from the underlying condition NOT the thrombocytopenia
  - Correcting the platelet count (e.g. transfusion) does not improve the condition and may create harm

Important Thrombocytopenic Syndromes

- Associated with microangiopathy
- Disseminated intravascular coagulation (DIC)
- Thrombotic microangiopathies (TMAs)
  - Thrombotic thrombocytopenia purpura (TTP)
  - Complement-mediated TMA (HUS)
  - Hemolytic elevated liver enzymes low platelets (HELLP)
- Associated with immune destruction
  - Immune thrombocytopenia purpura (ITP)
- Associated with heparin (HIT)
Sorting It Out: Key Clinical/Laboratory Parameters

- **Platelet count**: severity, rate of decrease
- **Medication reconciliation**: type of drug, timing
- **Evidence of hemolysis**: microangiopathy
  - Elevated reticulocyte count
  - Falling Hb, especially if retic count is not high
  - AST, LDH, Indirect bilirubin
  - Schistocytes (mechanical) or spherocytes (immune)
- **Basic coagulation parameters**: PT/INR, (aPTT)
- **Markers of fibrinogenolysis**: FSPs/D-dimer
- **Creatinine**: severity of increase

Hemolysis: Laboratory Clues

- ↑ LDH
- ↑ Reticulocytes
- ↑ AST (SGOT)
- ↑ Indirect Bilirubin
- Hemoglobinuria not RBCS
- ↑ Urobilinogen in Urine

ALT (SGPT) and direct bilirubin should be normal

Functional Evidence of RBC Loss (Hemolysis)

<table>
<thead>
<tr>
<th></th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient #1</td>
<td>Evidence of hemolysis (partially compensated)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>8.9</td>
<td>8.1</td>
<td>7.9</td>
</tr>
<tr>
<td>Retic</td>
<td>15%</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>Patient #2</td>
<td>Evidence of hemolysis (compensated)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>8.9</td>
<td>8.8</td>
<td>9.0</td>
</tr>
<tr>
<td>Retic</td>
<td>&gt;23%</td>
<td>&gt;23%</td>
<td>&gt;23%</td>
</tr>
<tr>
<td>Patient #1</td>
<td>Active RBC destruction unlikely; Hb stable without increased retic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>8.9</td>
<td>8.8</td>
<td>9.0</td>
</tr>
<tr>
<td>Retic</td>
<td>2%</td>
<td>1.8%</td>
<td>3%</td>
</tr>
</tbody>
</table>
How many are too many?
- Everyone may have scattered schistocytes (0-0.2%)
- Can be seen in metastatic cancer, sepsis, chronic renal failure, infection, preterm infants, pre-clampsia, acute renal failure without TMA

Attempts to standardize assessment:
- Should be the main finding and >1%
- Recommend counting 1000 cells (microscopy)
- Smaller than normal RBC, sharp edges, various shapes

Schistocytes: Not So Easy

Single site clinical lab study:
- Review of 282 smears, estimated % schistocytes

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>0-1%</th>
<th>1-3%</th>
<th>3-6%</th>
<th>6-12%</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIC</td>
<td>21</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>TTP/HUS</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HELLP</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Autoimmune HA</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Metastatic cancer</td>
<td>53</td>
<td>21</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Acute renal failure*</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Not TMA

- Median in DIC 0.70%, TTP 2.45%, HUS, 2.90
- Inter-rater confidence: 0.856

Next Step: Coagulation Parameters

Classical findings
- Normal in TTP/HUS, ITP, [HIT]
- Abnormal in DIC

Not always so easy – confounding factors
- Vitamin K deficiency (antibiotics, NPO/poor nutrition): PT, when severe also aPTT
- Antiphospholipid antibody syndrome: aPTT
- Anticoagulation: aPTT, PT
- Heparinized lines: aPTT
- Liver disease: aPTT, PT, fibrinogen, FSP, D-dimer
- D-dimer is non-specific ≠ active clot, DIC
Disseminated Intravascular Coagulation: Definition & Concepts

- Acquired syndrome of coagulation with loss of localization arising from different causes
- Can originate from and cause damage to the microvasculature; if severe, causes organ damage
- Characterized by the generation of fibrin-related products (e.g. FSP, D-dimer) and acquired inflammatory and non-inflammatory vessel injury
- Two general types:
  - Overt, often decompensated
  - Non-overt, more often compensated


DIC: Most Common Settings

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>DIC/PreDIC Cases</th>
<th>Total Cases</th>
<th>Frequency of DIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious disease</td>
<td>77</td>
<td>219</td>
<td>35.1%</td>
</tr>
<tr>
<td>Solid cancer</td>
<td>61</td>
<td>142</td>
<td>42.9%</td>
</tr>
<tr>
<td>Hematopoietic cancer</td>
<td>60</td>
<td>114</td>
<td>52.6%</td>
</tr>
<tr>
<td>Aneurysm (e.g. aortic)</td>
<td>15</td>
<td>29</td>
<td>51.7%</td>
</tr>
<tr>
<td>Obstetrics disease</td>
<td>6</td>
<td>10</td>
<td>60.0%</td>
</tr>
<tr>
<td>Trauma</td>
<td>10</td>
<td>26</td>
<td>38.4%</td>
</tr>
<tr>
<td>Digestive disease</td>
<td>5</td>
<td>18</td>
<td>27.7%</td>
</tr>
<tr>
<td>Collagen vascular disease</td>
<td>1</td>
<td>10</td>
<td>10.0%</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>45</td>
<td>22.2%</td>
</tr>
</tbody>
</table>


DIC: Pathophysiology

Gando, Crit Care Med 38:S35, 2010
DIC: Clinical Manifestations

DIC: Recognition—Intervention(?)

- Temporal changes over time
  - No single test or single time point “diagnostic” of DIC: dynamic complex process
  - Elevated D-dimer is not specific or diagnostic
    - Just an expensive way to measure fibrin split products
  - Morbidity, mortality associated with microvascular occlusion, organ damage
    - Ideally, introduce anticoagulation in non-overt stage
    - Prophylactic dosing preferred over treatment doses unless overt VTE
  - Efforts to control of thrombin (mixed results to date)
    - Soluble thrombomodulin, antithrombin concentrates

If Intervention is Attempted:

Table 3 Treatment of DIC in four types of DIC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Non-symptomatic type</th>
<th>Organ failure type</th>
<th>Bleeding type</th>
<th>Massive bleeding type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underlying conditions</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>R</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Anti-FXa</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Synthetic protease inhibitor*</td>
<td>R</td>
<td>NR</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Natural protease inhibitor*</td>
<td>R</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Antifibrinolytic treatment</td>
<td>NR</td>
<td>NR</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

*Not available in the US

References:
- Gando, Crit Care Med 38:S35, 2010
- Thromb Haemost 266, 2013
Mainstay of Treatment of DIC

- Treat the underlying cause
- Reverse the underlying cause
- Eliminate the underlying cause
- Get rid of the underlying cause
- Fix the underlying cause
- Stop the underlying cause
- Eradicate the underlying cause

Monitor coag panel (plts, PT, fibrinogen) for stability, improvement

Primary Thrombotic Microangiopathy (TMA)

- Microangiopathy and thrombocytopenia but normal coagulation studies
- Oklahoma registry: systemic infection (bacterial, viral, fungal) ultimately accounted for symptoms thought to be TTP (n=31 of 415)
  - All had MAHA and low platelets
  - 87% neuro changes (63% "major"), 90% AKI, 68% fever
  - Classic pentad (and coma) more common in systemic infection than in apparent TTP cases
  - 56% had low ADAMTS13 activity (levels 12-47%)  
  - 4 had levels <10%, 2 with inhibitors


Primary Thrombotic Microangiopathy (TMA)

- Acquired TTP more common in adults (2.9 per 1 million)
- Hereditary TMA, HUS more common in children

Clinical considerations

- Diarrheal illness, AKI: Shiga-toxin HUS (outbreaks)
- Sudden onset severe systemic symptoms and anuric AKI, drug exposure to quinine, gemcitabine, quetiapine: drug-induced immune TMA
- Gradual onset of renal failure over wks/mos, CyA or tacrolimus: drug-induced toxic TMA

Primary Thrombotic Microangiopathy (TMA)

Endotheliosis with intraluminal and vessel wall fibrin

TMA: Pathophysiology

- TTP
  - Deficiency of ADAMTS-13
    - Acquired: autoantibody
    - Congenital: mutations (90+ known), <5% of cases
  - Complement-mediated

- Increased C' activity
  - Familial: C3, CFH mutations, other C' genes
  - Acquired: autoantibody to Factor H

TMA: Role of ADAMTS-13 Testing

- Testing options
  - ADAMTS-13 activity and antigen
  - Detection of anti-ADAMTS-13 antibodies
  - Genetic characterization of ADAMTS-13 gene
- Hereditary TTP
  - Severe deficiency (usually undetectable, may be 5-6%) without antibodies during remission
- Acquired TTP
  - Highly variable activity levels, usually not severely low
  - Values of <10% more common in idiopathic, relapsing
  - Severe deficiencies in other TMAs (consumption?)
    - 18% in C'-mediated TMA (HUS), 16% in overt DIC

TMA: Additional Diagnostic Labs

<table>
<thead>
<tr>
<th>Shiga toxin (STEC)</th>
<th>ADAMTS13 deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool culture for E. coli</td>
<td>ADAMTS13 activity</td>
</tr>
<tr>
<td>Toxinsology for shiga toxin or PCR of shiga toxin gene</td>
<td>ADAMTS13 autoantibodies</td>
</tr>
<tr>
<td>Urine culture for E. coli</td>
<td>ADAMTS13 gene mutation</td>
</tr>
</tbody>
</table>

Complement dysregulation

- Plasma/serum C3, factor H, factor I, factor B
- MCP (CD46) expression on PMCs
- Factor H autoantibodies
- Specific mutations

- S. Pneumoniae
- T antigen expression on RBC
- PCR of blood and/or secretions
- Blood culture

Other Associations

- Pregnancy test
- Liver and pancreatic enzymes
- B27: human leukocyte antigen, MMA
- HIV and other viral serologies (e.g. varicella, echovirus, coxsackie A&B)
- ANA, antiphospholipid Ab testing
- PCR for influenza A
- Evaluate for C. Diff.

Barbour, Srgd. 36th Symposium 27:2673, 2012;
Barbour, Thor Apher Dial 15:10, 2010

TTP: Initial Management

- Hereditary/Acquired TTP
  - Fresh frozen plasma therapy: replacement of ADAMTS-13, removal of antibodies
    - Infusion therapy (25 mg/kg total daily) has benefit
      - 52% complete remission, 57% overall survival
    - Therapeutic plasma exchange (TPE) preferred and (probably) superior to infusion
      - Return of donor plasma; cryo-poor preferred
      - 80% complete remission, 85% overall survival
    - Immunosuppressive therapy: assumes antibodies present, no randomized trials
      - Usually steroids (e.g. methylprednisolone 1-2 mg/kg)

Clark, Sem Dialysis 25:214, 2012

TTP: Initial Management

- Daily monitoring (just before TPE) to look for:
  - Improving Hb with falling reticulocyte count
  - Normalization of hemolytic markers (LDH, bilirubin)
  - Normalization of creatinine
  - Continue until "in remission" x 2 days; no data to support "5 days of exchange?"
    - Might be considered a minimum; if still worsening, reconsider the diagnosis (e.g. type of TMA)
    - Why stop if they’re still getting better but not yet stabilized?
    - Some require exchanges for weeks to attain stability and eventual recovery

Other TMA: Initial Management

- Shiga-toxin mediated TMA: supportive
- Drug-mediated TMA
  - Immune (quinine): supportive, discontinue drug
  - Toxic (CyA, tacrolimus): supportive, dose reduction may be sufficient
- Complement-mediated TMA:
  - Immune suppression if antibody-mediated (anti-Factor H)
  - Anti-complement therapy (eculizumab)
  - But at the start can be difficult to discern so often plasma exchange and steroids are initiated

Anti-complement Therapy: Eculizumab

- Inhibitor of C5 activation, used for PNH
- Successful use in Shiga-toxin HUS and complement-mediated TMA
- Considered when initial response to TPE is lost or initially poor
- Initial dosing (600 mg/wk x 4), 900 mg week 5, then every 2 weeks maintenance
- May see results within first week
- Meningococcal vaccine needed 2 weeks before first dose: significant inhibition of ability of complement to clear meningococci

ITP: Definitions and Clinical Settings

- Immune Thrombocytopenia Purpura
  - No longer "idiopathic" when using the term
  - Characterized by duration
  - Acute: <3 months; severe, often abrupt, profound
  - Persistent: 3-12 months
  - Chronic: >12 months; more often moderate
- Secondary – “primary” a diagnosis of exclusion
  - Autoimmune disorders (e.g. SLE, RA, APS, SJögrens)
  - Infections (e.g. Hepatitis C, HIV, H. pylori)
  - Lymphoproliferative disorders (often CLL, rarely NHL)
  - Recent vaccination (e.g. MMR)
  - Drugs, drugs, drugs
ITP: Drug-Induced

- Up to 25% of acutely ill have drug-induced thrombocytopenia (immune + non-immune)
- Multiple mechanisms, multiple drugs

<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hapten-dependent</td>
<td>Penicillin, Cephalosporins, Fluoroquinolones</td>
</tr>
<tr>
<td>Drug-GP complex</td>
<td>Quinine, NSAIDs, Quinidine, Sulfonamides, Rifampin, Ranitidine</td>
</tr>
<tr>
<td>Ligand-induced binding</td>
<td>Epifibatide, Ticlopidine</td>
</tr>
<tr>
<td>Drug-specific antibody</td>
<td>Abciximab</td>
</tr>
<tr>
<td>Antibody-dependent</td>
<td>Gold, Procainamide, Enamcept, Eculizumab</td>
</tr>
<tr>
<td>Immune complex</td>
<td>Heparin</td>
</tr>
</tbody>
</table>


ITP: Pathophysiology

- Immune-mediated
  - IgG Ab often directed at specific GP receptors
  - Platelet destruction
    - RE system
    - Spleen
  - Damage to megakaryocytes
  - Diminished TPO
  - Inappropriately low response, plt production

ITP: Diagnosis

- Clinical characteristics
  - Very severe, onset over days (vs. weeks/months)
  - Associated risk factors, e.g. autoimmune disease, infections, drugs
  - NO splenomegaly (primary ITP)
  - Isolated thrombocytopenia, large platelets
- Testing: BM bx not recommended if typical
  - Basic evaluation: HIV, Hep C, H pylori, quantitative immunoglobulins (CVID), Direct Coombs, Rh
  - Potential utility: specific GP antibodies, ANA, APS testing, anti-thyroid Ab, other viral infections e.g. CMV
  - No proven benefit: TPO level, bleeding time, platelet antibodies, serum complement, platelet survival
**ITP: Initial Management**

- Risk of fatal events: 0.0162 – 0.0389 cases per adult patient-year at risk
  - Thought more likely if <5-20K plt, bleeding sx
  - If secondary, fix the underlying cause if possible (e.g. stop the drug)
- Initial therapy: immune modulation may take 5+ days
  - Corticosteroid therapy
    - Prednisone: 0.5-2 mg/kg daily
    - Dexamethsone: 40 mg/day x 4 days, repeat every 14 days
  - IVIG or IV anti-D (if Rh+)
- Typical next step: splenectomy vs. rituxan


---

**Refractory ITP: TPO-Receptor Agonists**

- Stimulation of platelet production
  - Romiplostim (Nplate): s.q weekly
  - Eltrombopag (Promacta): oral once daily
- Most often used third-line, or as a bridge while awaiting effect of rituximab or other immune-modulating therapy
- Immediate side effects include HA, nausea and vomiting
- May cause marrow fibrosis
- Of interest in Hep C-related thrombocytopenia to permit full-dose, full-duration anti-viral therapy


---

**Other ITP Scenarios**

- *H pylori (+):* antibodies cross react with plt glycoproteins
  - Platelet response to antibiotic therapy 40-50% if successfully eradicate infection
- HIV-associated: in the HAART era
  - <50K in 1-5% of HIV-infected; <150K in 10-30%
  - Respond to usual therapy, with or without HAART
    - Ambiker, Adv in Hem 1, 2012
- Coronary disease and ITP (case series): low platelets not protective
  - PCI and CABG performed at plt counts as low as 5K
  - 46% discharged on ASA and clopidogrel
    - Brown, Inter J Cardiac Thorac Surg 151, 2011
A Hematologist’s Plea:
Stop “HIT-ting” People!

- Heparin-induced thrombocytopenia is a clinical syndrome
  - Most common in those receiving UFH
  - Rare in OB, peds, dialysis, uncommon with LMWH
  - Many humans make antibodies to heparin(s), including fondaparinux: this doesn’t mean they have HIT
  - The diagnosis cannot be made by laboratory testing: must have appropriate clinical criteria


HIT: Not Just an Antibody

- Antibodies without clinical HIT are common:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Antibody Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult cardiac by-pass*</td>
<td>50% Blood 96:1703</td>
</tr>
<tr>
<td>Pediatric by-pass</td>
<td>1.7-16% Anesth Analg 107:371</td>
</tr>
<tr>
<td>Ortho prophylaxis (UFH)</td>
<td>15% Blood 96:1703</td>
</tr>
<tr>
<td>Ortho prophylaxis (LWMH)</td>
<td>8% Blood 96:1703</td>
</tr>
<tr>
<td>Med prophylaxis (UFH)</td>
<td>3% Blood 101:2655, 2003</td>
</tr>
<tr>
<td>Neurology prophylaxis (UFH)</td>
<td>20% Neurology 62:857, 2004</td>
</tr>
<tr>
<td>PCI (cath-UFH)</td>
<td>12% Thromb Res 115:475, 2005</td>
</tr>
<tr>
<td>Chronic hemodialysis</td>
<td>12% Kidney Int 73:713, 2008</td>
</tr>
<tr>
<td>Vascular surgery</td>
<td>32% J Vasc Surg 48:377</td>
</tr>
<tr>
<td>ED for chest pain/VTE (in hosp in last 6 months)</td>
<td>6.9/9.2% Am J Emer Med 25:279</td>
</tr>
</tbody>
</table>

*including positive SRA in 10%

HIT: Pathophysiology

- IgG antibody to platelet factor 4 (PF4) neoantigen exposed after binding to heparin

- Takes 4-5 days to make IgG antibodies
- Manifestations (↓ plts)
- Begins to occur 4-5 days after antigen exposure
- Presence of antibody is not sufficient to create clinical HIT

Arepally, Ann Rev Med 61:77
**HIT: Diagnosis**

- **Clinical Criteria:** the "4 Ts" score

<table>
<thead>
<tr>
<th>Points (0, 1, or 2), Maximum = 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>20-100</td>
</tr>
<tr>
<td>10-19</td>
</tr>
<tr>
<td>&lt;10</td>
</tr>
<tr>
<td>Timing</td>
</tr>
<tr>
<td>≤ 1 dy</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Thrombosis, ASR, skin lesions</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Other cause for ↓ plt</td>
</tr>
</tbody>
</table>

**Probability of HIT:** High: 6-8  Moderate: 4-5  Low: 0-3


---

**Time Course for HIT**

- **Classic HIT**
- **HIT with Reexposure**
- **Unlikely HIT**

---

**Possible HIT: Initial Management**

- Document clinical assessment (4Ts or equivalent)
- If moderate or high pre-test probably send ELISA
  - Negative ELISA, highly unlikely to be HIT
  - ELISA O.D. >1.2 (>2.0), then more likely to be HIT
  - If ELISA is positive, send serotonin release assay
- While awaiting testing:
  - Stop heparin (all forms)
  - Start alternative therapy
  - Direct thrombin inhibitors: argatroban, lepirudin, bivalirudin
  - Fondaparinux may be acceptable, though HIT antibodies occur at same rate as LMWH, case reports of clinical HIT

Practical Considerations
*Bad* Thrombocytopenia Syndromes

- Overt DIC vs. Liver Disease
  - If the parameters are stable, then the DIC compensated or it's "just" the liver disease
- Regarding MAHA in these syndromes
  - If the retic count is low and the Hb is stable, then it's not MAHA or any form of significant RBC destruction
  - If there are spherocytes it may be a really bad case of SLE or other autoimmune condition, not MAHA
- The TTP "pentad" is more common in non-TTP
- The only thing that makes the platelet count <10, in the absence of an obviously fulminant condition, is autoimmune destruction

Platelets and Hemostasis

- Adhesion and aggregation of platelets to area of vessel injury
  - Control is local: minimum number of functional platelets needed at the vessel wall may not be assessed by CBC

How Many Platelets Are Enough?

- Cochrane analysis of prophylaxis in chemotherapy/stem cell transplantation
  - No evidence prophylaxis prevents bleeding
    - Major bleeding the same (RR 1.66, 0.9-3.04)
    - Longer time to first bleeding with prophylaxis
  - If threshold is used, current evidence supports use of 10K vs. 20K
    - Significant bleeding similar (RR 1.15, 0.95-1.9)
    - More days with bleeding (RR 1.72, 1.33-2.22)
    - Low plt utilization with lower/no threshold (50%)

Estcourt, The Cochran Library 5, 2012
PLADO – Effects of Prophylactic Platelet Dose on Transfusion Outcomes

- Increased bleeding at/below 5K in 1102 adult and pediatric heme/onc patients

How Many Platelets Are Enough?

- TOPPS: No prophylaxis is NOT non-inferior
  - 600 chemo/SCT patients: "prn" vs 10K

  Without prophylaxis:
  - shorter time to first bleed
  - more days with Grade 2 bleeding (1.7 vs. 1.2)

But My Patients Aren’t on Chemo

- No data to address threshold for prophylactic platelet transfusion in hospitalized patients (borrow from oncology)
- No data to support ANY specific platelet count to control bleeding or for procedures
  - Single administration of 6-8 U platelets (or single donor unit) provides adequate hemostasis for individuals with inherited platelet dysfunction
  - In other settings, usually multiple factors contribute to bleeding despite adequate platelet count
Platelet Count Needed For Interventions

- **Dogma:** >50K (>100K for CNS, heart surgery)
- **However:**
  - Actual experience: Lumbar puncture 20-40K; Epidural/spinal 50-80K
  - 6-8 U platelets (or single donor unit) provides adequate hemostasis for inherited platelet dysfunctions
  - No increased bleeding with central line placement at 20K
  - Surgery/procedures for autoBMT pts at 20K
  - Thoracentesis: no correlation with bleeding even at plt <20K

Potential Benefits of Platelet Transfusion

- Expect 20-60,000 ↑ in plt count from a “4 pack” of random donor platelets or single donor unit
- Assumes no sequestration, activation/consumption or immune destruction
- Failure to increase suggests these processes are present
- No increase in up to 50% of critically ill patients

Increased Numbers May Not Equate with Outcomes

- May get local hemostatic effect without improving the circulating number measured by CBC
- No benefit (mortality, function) when plt given for ICH associated with antiplatelet therapy
- Platelet transfusion associated with worse outcomes if used traumatic brain injury patients with 50-107K
Potential Harms of Platelet Transfusion

- Transfusion-related acute lung injury (TRALI)  
  Spiess, Ann Int Med 144:65, 2010

- Potentiation of thrombosis: dataset analysis  
- 96,000 admissions for TTP/HIT/ITP (2007-2011)  
- Platelet transfusions for 10%/7%/25%  
- Associated in TTP and HIT with  
  - Arterial thrombosis: OR 5.8 and 3.4, respectively  
  - Mortality: OR 2.0 and 5.2, respectively  
- No association with ITP  
  Goel, Blood 125:1470, 2015

- Further immune stimulation (ITP)  

Summary

- Thrombocytopenia is common in hospitalized patients  
- Frequently multi-factorial  
- Often stimulated by infections, medications  
- Baseline may be compromised by underlying conditions (e.g. liver disease, chronic infection)

- Severe disorders - DIC/TMA/ITP/HIT - are marked by thrombocytopenia  
- Recognition is necessary to institute specific management to correct underlying process  
- Specific "platelet" therapy may not be needed  
- Most thrombocytopenia is well-tolerated and will not require platelet transfusion

Thank you!
Questions?