Objectives

- Appreciate the incidence, clinical implications and most common causes of thrombocytopenia in the hospital setting
- Devise an approach to the diagnosis and initial management of acute serious causes of thrombocytopenia: DIC, TMA (TTP/HUS), HIT, ITP
  - Definitions and pathophysiology
  - Diagnosis
  - Key management strategies
- Recognize appropriate indications for platelet transfusion support, weighing the risks and benefits

Disclosures

- NONE
Thrombocytopenia: Definitions

- Reduction in the number of platelets
- Terminology varies, but generally:

<table>
<thead>
<tr>
<th>Platelet count ($10^9/L$)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-150</td>
<td>&quot;Mild&quot;</td>
</tr>
<tr>
<td>30-50</td>
<td>&quot;Moderate&quot;</td>
</tr>
<tr>
<td>10-10</td>
<td>&quot;Severe&quot;</td>
</tr>
<tr>
<td>&lt;10</td>
<td>&quot;Very Severe&quot;</td>
</tr>
</tbody>
</table>

- "Pseudothrombocytopenia" occurs in 1 in 1000 healthy individuals – check the smear!
- In vitro agglutination of platelets in EDTA (purple top)
- "Satellitism": adhesion of plts to PMNs

Veneti, Blood Transf 7:75, 2009

Thrombocytopenia: Incidence

- Most common coagulation issue in ICU patients
- 15-60%, depending on the definition used
  - Half present with low platelets, remainder develop it in ICU
  - 2-15% have platelets < 50K
  - Most common condition: sepsis
- More common in surgical and trauma patients than in medical 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


Thrombocytopenia: Implications

- Platelet counts of ≥10,000 well tolerated
  - Based on studies of chemotherapy (AML) patients
  - 3% of days complicated by any bleeding


- 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

Sekikawa, Clin Hem 1978

- 3 nonlethal major bleeding events over >18,000 pt-days in chronic severe aplastic anemia

Sagmeister, Blood 93:3124, 1999
Thrombocytopenia: Causes

- Basic reasons for a low platelet count
  - Diminished production: lifespan of 10 days, so relatively rapid changes
  - Produced but diluted out: massive transfusion
  - Produced but maldistributed: hepatic/splenic sequestration
  - Destroyed or consumed: exceeding production
- Most common etiology of thrombocytopenia in a hospitalized patient is MULTIFACTORIAL
  - Often a combination of compromised production and increased consumption/destruction

References:
- Rice, Chest 136:1622, 2009

Diminished Platelet Production: Drugs, Drugs, Drugs

- 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
- Classes of agents:
  - Antineoplastics
  - Antivirals
  - Thiazides
  - Daptomycin
  - Telbivudine
  - Linezolid
  - Amphotericin
  - Digoxin
  - Haloperidol
  - Nitrofurantoin
  - Meropenem

References:
- Rice, Chest 136:1622, 2009
- Priziola, Crit Care Med 38:S145, 2010
- Rice, Chest 136:1622, 2009
- Rice, Chest 136:1622, 2009
- Louie, J Viral Hep doi:10/j.1365-2893.2010.01366x

Diminished Platelet Production: Infections and Toxin Injury

- Viruses: possible with any, but most reported with certain infections, including:
  - HIV
  - Hepatitis C
  - Parvovirus
  - Epstein-Barr Virus
  - Varicella
- Toxin Injury
  - Ethanol (bone marrow suppression, liver disease)
  - Radiation therapy
  - Diminished thrombopoietin levels in liver disease
  - Chronic infection/toxic effect may prevent adequate compensatory production with acute dilution, consumption, or destruction

References:
- Rice, Chest 136:1622, 2009
- Louie, J Viral Hep doi:10/j.1365-2893.2010.01366x
Platelet Dilution and Maldistribution

- Massive transfusion
  - Greater than 20 units of RBCs for acute trauma
  - 75% develop platelet counts < 50,000
- High risk of dilutional thrombocytopenia if
  - Replacement of entire blood volume in 24 hours
  - Replacement of 50% of blood volume within 1-4 hours
- However, bleeding is likely multi-factorial due to hypothermia, acidosis, dilution of coagulation factors


- Sequestration
  - Portal hypertension, hepatomegaly
  - Hypersplenism


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

DIC: Definition & Clinical Setting

- Disseminated Intravascular COAGULATION
- Clinical settings that stimulate diffuse thrombosis:
  - Sepsis/severe infection
  - Polytrauma or neurotrauma
  - Malignancy
    - Solid tumors, lymphoproliferative, myeloproliferative
  - Obstetric conditions
    - Amnion fluid embolism, Abruptio, Preeclampsia
  - Vascular abnormalities
    - Kasabach-Merritt syndrome, AAA, other malformations
  - Severe allergic/toxic reactions
  - Severe immunologic reactions
DIC: Pathophysiology

- Consumption of Platelets
  - "Thrombotic" phenotype
    - ↓ platelet count
    - ↓ Protein C, AT
    - ↓ Fibrinogen, ↑ FSP
  - "Fibrinolytic phenotype"
    - ↑ PT, aPTT, ↓ fibrinogen

- Consumption of Clotting Factors
  - ↑ PT, aPTT, ↓ fibrinogen
  - ↓ fibrinogen, ↑ FSP

- Consumption of Anticoagulants
  - ↓ Protein C, AT

Gando, Crit Care Med 38: S35, 2010

DIC: Diagnosis

- Overt DIC: score ≥5

<table>
<thead>
<tr>
<th></th>
<th>0 points</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>≥100</td>
<td>50-99</td>
<td>&lt;50</td>
<td>--</td>
</tr>
<tr>
<td>PT (INR)</td>
<td>&lt;1.2</td>
<td>1.3-1.8</td>
<td>&gt;1.9</td>
<td>--</td>
</tr>
<tr>
<td>D-dimer (mg/L)</td>
<td>≤2.0</td>
<td>--</td>
<td>2.1-4.0</td>
<td>&gt;4.0</td>
</tr>
<tr>
<td>Fibrinogen (mg/FL)</td>
<td>≥100</td>
<td>&lt;100</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

- 28-day mortality of 40-70% (vs. 15-29% without DIC)
  - Sivula, Intensive Care Medicine 31:1209, 2005

- Non-Overt DIC: score>5

<table>
<thead>
<tr>
<th></th>
<th>0 points</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>=100</td>
<td>&gt;100 = +1</td>
<td>&lt;100 = +1</td>
<td>--</td>
</tr>
<tr>
<td>PT</td>
<td>&lt;1.2</td>
<td>1.3-1.8</td>
<td>&gt;1.9</td>
<td>--</td>
</tr>
<tr>
<td>Antithrombin or Prot C</td>
<td>Stable = 0</td>
<td>Improving = +1</td>
<td>Worsening = +1</td>
<td>Normal = -1</td>
</tr>
</tbody>
</table>

- 28-day mortality of 77.8% (vs. 29% without DIC)
  - Tabil, Blood Coagul Fibrinolysis 16:69, 2005

DIC: Recognition

- Appropriate clinical setting
- Overt vs. non-overt: reflects degree of compensation
  - Impacted by underlying comorbidities (e.g. bone marrow suppression, hepatic dysfunction)
  - Some clinical states (e.g. hepatic failure) represent non-overt DIC
- Temporal changes over time
  - No single test or single time point "diagnostic" of DIC
  - Elevated D-dimer is not specific or diagnostic
  - Just an expensive way to measure fibrin split products

**DIC: Interventions**

- **Protein C, AT**
- **Fibrinogen, FSP**
- **PT, aPTT, fibrinogen**
- **Anticoagulants**
- **Platelets**
- **Clotting Factors**
- **Consumption**


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**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

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**TMA: Definitions**

- **Thrombotic Microangiopathy**: group of disorders characterized by
  - Microangiopathic hemolytic anemia (MAHA)
  - Thrombocytopenia
  - Organ dysfunction: target varies with condition
  - Thrombotic thrombocytopenia purpura (TTP)
    - MAHA, low platelets, low-grade fever, kidney, brain
  - Hemolytic Uremic Syndrome (HUS)
    - MAHA, low platelets, kidney
  - Hemolysis Elevated Liver Enzymes Low Plts
    - MAHA, low platelets, liver

TMA: Pathophysiology

- **TTP**
  - Deficiency of ADAMTS-13
  - Acquired: autoantibody
  - Congenital: mutations (90+ known)

- **HUS**
  - "Atypical" - increased C' activity
  - Familial: C'H mutations
  - other C' genes
  - Acquired: autoantibody to Factor H

  "Diarrheal" - Shiga toxin injury to glomerular endothelial cells

TMA: Diagnosis

- **MAHA**
  - Falling hemoglobin despite elevated reticulocyte count
  - Release of RBC enzymes
    - AST, LDH, indirect bilirubin
  - Schistocytes on peripheral smear
  - Thrombocytopenia: moderate-severe
  - Distinguishing HUS from TTP
    - Creatinine higher in HUS
    - Evidence of E. coli O157:H7 infection
    - ADAMTS-13 assay
    - Poor response to plasmapheresis
  - Normal aPTT, PT, thrombin time, fibrinogen

Testing options

- ADAMTS-13 activity and antigen
- Detection of anti-ADAMTS-13 antibodies
- Genetic characterization of ADAMTS-13 gene

Congenital TTP

- Severe deficiency (usually undetectable, may be 5-6%) without antibodies during remission

Acquired TTP

- Highly variable activity levels
- Values of <10% more common in idiopathic, relapsing
- Severe deficiencies in other TMAis (consumption?)
- 15% typical HUS, 16% in overt DIC

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

- Congenital TTP
  - Severe deficiency (usually undetectable, may be 5-6%) without antibodies during remission

- Acquired TTP
  - Highly variable activity levels
  - Values of <10% more common in idiopathic, relapsing
  - Severe deficiencies in other TMAis (consumption?)
  - 15% typical HUS, 16% in overt DIC

**TMA: Initial Management**

- **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 superior to infusion
    - Return of donor plasma; cryo-poor preferred
  - Immunosuppressive therapy: assumes antibodies present, no randomized trials
    - Usually steroids (e.g. methylprednisolone 1-2 mg/kg)


- **HUS**
  - Plasma therapy: no proven benefit in diarrheal or atypical HUS
  - Some subset might benefit e.g. Factor H deficiency, autoantibodies, hyperfunctional complement mutations
  - However, often done early in the course - watch for lack of response
  - Supportive care, "anti-complement" therapy?
  - Daily monitoring (just before TPE) to look for:
    - Improving Hb with falling reticulocyte count
    - Normalization of hemolytic markers (LDH, bili)
    - Normalization of creatinine
  - Continue until "in remission" x 2 days


**HIT: Definitions and Clinical Settings**

- **Heparin-Induced Thrombocytopenia**
  - Historically called "Type II" or "immune" type
    - "Type I" refers to non-immune mild decrease in platelet count seen in first 1-3 days of (unfractionated) heparin tx
  - At-risk populations
    - General medical patients
    - Surgical and orthopedic patients
    - Females>males
  - Low-risk populations (low frequency)
    - LMWH, subcutaneous route, short duration
    - Obstetrical patients
    - Pediatric patients
    - Chronic dialysis

  Arepally, Ann Int Med 61: 77, 2010
**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) BEGIN to occur 4-5 days after antigen exposure
  - presence of antibody is not sufficient to create clinical HIT

**HIT: Diagnosis**

- Clinical Criteria: the "4 Ts" score

<table>
<thead>
<tr>
<th>Points (0, 1, or 2), Maximum = 8</th>
<th>2</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadir (x10^9/L)</td>
<td>20-100</td>
<td>10-19</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Fall</td>
<td>&gt;50%</td>
<td>30-50%</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>Timing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent heparin</td>
<td>≤1 dy</td>
<td>≤1 dy</td>
<td></td>
</tr>
<tr>
<td>No prev heparin</td>
<td>5-10 dys</td>
<td>Unclear or &gt;10 dys</td>
<td>≤4 days</td>
</tr>
<tr>
<td>Thrombosis, AR, skin lesions</td>
<td>New event after heparin</td>
<td>Progressive or new thrombosis/event</td>
<td>None</td>
</tr>
<tr>
<td>Other cause for ↓ plt</td>
<td>None</td>
<td>Possible</td>
<td>Definite</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
**HIT: Diagnosis**

- Positive HIT ELISA does not mean the patient has HIT; antibodies without clinical HIT common:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Rate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult by-pass</td>
<td>50%</td>
<td>Blood 96:1703</td>
</tr>
<tr>
<td>Pediatric by-pass</td>
<td>1.7-16%</td>
<td>Anesth Analg 107:371</td>
</tr>
<tr>
<td>Ortho prophylaxis (UFH)</td>
<td>15%</td>
<td>Blood 96:1703</td>
</tr>
<tr>
<td>Ortho prophylaxis (LWMH)</td>
<td>8%</td>
<td>Blood 96:1703</td>
</tr>
<tr>
<td>Med prophylaxis (UFH)</td>
<td>3%</td>
<td>Blood 101:2955, 2003</td>
</tr>
<tr>
<td>Neurology prophylaxis (UFH)</td>
<td>20%</td>
<td>Neurology 62:657, 2004</td>
</tr>
<tr>
<td>PCI (cath-UFH)</td>
<td>12%</td>
<td>Thromb Res 115:475, 2005</td>
</tr>
<tr>
<td>Chronic hemodialysis</td>
<td>12%</td>
<td>Kidney Int 73:713, 2008</td>
</tr>
<tr>
<td>Vascular surgery</td>
<td>32%</td>
<td>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%</td>
<td>Am J Emer Med 25:279</td>
</tr>
</tbody>
</table>

**Possible HIT: Initial Management**

- Document clinical assessment (4Ts or equivalent)
- If moderate or high pre-test probability send ELISA
- If ELISA, O.D. >1.2 (>2.0), then likely to be HIT
- Negative ELISA, highly unlikely 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


**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” = diagnosis of exclusion
    - Autoimmune disorders (e.g. SLE, RA, APS, Sjogren's)
    - Infections (e.g. Hepatitis C, HIV, H. pylori)
    - Lymphoproliferative disorders (often CLL, rarely NHL)
    - Recent vaccination (e.g. MMR)
    - Drugs, drugs, drugs

**ITP: Pathophysiology**

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

*Arnold, Exp Opin Invest Drug 18:805, 2009

**ITP: Drug-Induced**

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

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drugs/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>Eptifibatide, Tirofiban</td>
</tr>
<tr>
<td>Drug-specific antibody</td>
<td>Abciximab</td>
</tr>
<tr>
<td>Autoantibody</td>
<td>Gold, Procainamide</td>
</tr>
<tr>
<td>Immune complex</td>
<td>Heparin</td>
</tr>
</tbody>
</table>


**ITP: Diagnosis**

- Clinical characteristics
  - 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-thromboid Abs, other viral infections e.g. CMV
  - **No proven benefit:** TPO level, bleeding time, platelet antibodies, serum complement, platelet survival

*Provan, Blood 115:168, 2010*
**ITP: Initial Management**

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

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**Thrombocytopenia: To Transfuse or Not To Transfuse**

- Treating the patient, not a number
- In the absence of bleeding symptoms and interventions, platelet counts of 5-10,000 may be well-tolerated
  - Especially true for ITP, HIT
  - 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 ≥210,000
- NO proven benefit for ANY transfusion threshold in other settings

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**Potential Benefits and Harms of Platelet Transfusion**

- Expect 40-60,000 ↑ 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
- Potential harms of platelet transfusion:
  - Transfusion-related acute lung injury (TRALI)
  - Controversially, increased risk of arterial>venous thrombosis, adverse outcomes, mortality
  - Further immune stimulation (ITP)
  - Promotion of further thrombosis (DIC)

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Provan, Blood 115:168, 2010

Platelet Transfusion in TTP and HIT

- Limited evidence about harm from platelet transfusion in TTP
  - Dogma driven by case reports
  - Systematic review: 9/34 reported adverse outcome
    - Largest case series (Oklahoma registry data, n=54) noted no impact of platelet transfusion on death, fatal hemorrhage or severe neurologic events
    - Swisher, Transfusion 49:873, 2009
- Limited evidence about harm from platelet transfusion in HIT
  - Dogma driven by case reports in the 1970s
  - Case series of 17 patients with + HIT ELISA received platelets
    - no thrombotic events
    - Refaai, J Thromb Haemost 8:1419, 2010

Indications for Platelet Transfusion: Bleeding and Invasive Procedures

- No data to support ANY specific platelet count to control bleeding or for procedures
- MANY dogma: usually 50,000-100,000
- Single administration of 6-8 U platelets (or single donor unit) provides adequate hemostasis for individuals with inherited platelet dysfunction
  - Tosetto, Thromb Res 124:e13, 2009
- In other settings, usually multiple factors contribute to bleeding despite adequate platelet count
- Spinal procedures: actual experience, case series
  - Lumbar puncture: 20-40,000
  - Epidural/spinal anesthesia: 50-80,000
  - van Wees, J Anaesth 148:15, 2009

Summary

- Thrombocytopenia is common in hospitalized patients
  - Frequently multifactorial
  - Often stimulated by infections, medications
  - Baseline may be compromised by underlying conditions (e.g. liver disease, chronic infection)
- Severe disorders – DIC/TMA/HIT/ITP - 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