When the Plate is not Full

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Thrombocytopenia

- Mild 70 – 149K / Severe < 20K
- > 50 often asymptomatic
- 10 – 30K bleeding w/ minimal trauma
- < 10K spont bleeding risk (petechiae, bruising)
- < 5K HEMATOLOGIC EMERGENCY

4 Questions to Ask?

- Could it be pseudothrombocytopenia?
- What is most likely explanation?
- What is the severity of the thrombocytopenia?
- What are the risks posed by the causative disorder?
Hypersplenism

- Defined: Splenomegaly + anemia, leukopenia, or TP
  - Most pts w/ hypersplenism have splenomegaly
  - Many pts splenomegaly do not have hypersplenism
- Usually secondary to pathologic process
- Usually mild to severe ~ 50K
  - NOTE: IF < 20k SUSPECT ANOTHER CAUSE
- TP due to hypersplenism if:
  - Splenomegaly present
  - TP mild to mod
  - Moderately reduced neutrophil count and low NL Hgb
  - No impaired hematopoiesis on BM bx

Postsurgical

- Several processes at play:
  - Initial hemodilution
  - Increase consumption (1st 2-4 days)
  - Increased production (peaks 14 days)
  - Return to baseline
  - Can drop 30-70% after major surgery
  - Nadir usually POD#2

History

- Location and Severity of bleeding
- Acute/Chronic vs. relapsing bleeding
- Relationship w/ triggers (drugs, infections?)
- Symptoms of secondary illness
  - Neoplasm
  - Infection
  - Autoimmune (SLE, etc)

Other History

- Post-hemorrhagic E. Coli associated HUS
  - 1 week after prodromal diarrheal illness
- Fungemia associated
  - 1-3 weeks following complex illness w/ catheters and broad spectrum abx
- Insidious onset
  - Chronic liver ds or slow progressive BM disorder (myelodysplasia)

Drug induced

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<thead>
<tr>
<th>Table 13.25</th>
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<tbody>
<tr>
<td>List of Drugs Implicated in Drug-Induced Immune Thrombocytopenia</td>
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<td>Drugs Common to All Three Lists™</td>
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<td>Quinine, quinidine, rifampin, trimethoprim-sulfamethoxazole, vancomycin</td>
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Drug induced

- Acenocumarol
- Anticonvulsants
- Anticoagulants
- Antiretrovirals
- Cyclosporine
- Aminoglycosides
- Aprotinin
- Ethambutol
- Haloperidol
- Hydroxyurea
- Insulin
- Nifedipine
- Diltiazem
- Phenothiazines
- Phenytoin
d - Sulfonamides
- Terfenadine
- Heparin

Physical Exam

- Petechia / Purpura
  - Usually dependent or traumatized areas
  - “Wet Purpura” - more serious defect
    - Mucus membrane bleeding
    - GI bleed, epistaxis, etc.
- Abdomen (HSM)
- Lymph nodes
  - Malignancy, myeloproliferative d/o’s, HIV, EBV, etc
- Neuro exam (CNS hemorrhage)
  - Eyes (hemorrhage suggests CNS bleed)

LAB STUDIES

- Peripheral Smear
- Retic ct + Coombs test
  - Rule out Autoimmune Hemolytic Anemia
- Blood type (? AntiRh(D) therapy)
- HIV
- HCV Ab
- H. Pylori (not established in North America)
- Bone Marrow Bx if necessary
Factitious/Pseudo

- 1 in 1000 pts in general population
  - Naturally occurring GPIIb/IIIa autoAbs
  - Induces aggregation in presence of EDTA
- Repeat in Heparin or Na Citrate tube OR finger prick sample
  - Maintain 37 degrees (98.6) celsius attenuates clumping
- Confirm by peripheral smear
- Abciximab – similar process to EDTA
- If thrombocytopenia persistent - search for other cause

### Diagnosis Assays

- aPTT, PT (INR), thrombin time, fibrinogen, D-dimer assay
- LA assay (nonspecific inhibitor, anticoagulant and anti-GpIIb-IIIa-platelet I assays
- Serum protein electrophoresis, IgG, IgM, IgG levels
- HIV serologic studies

### Histological Assays

- HIV-associated thrombocytopenia
  - BM aspiration, biopsy
  - Assess megakaryocyte numbers and morphology, exclude primary BM disorder

### Laboratory Tests Used to Investigate a Patient With Thrombocytopenia

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### Specialized Tests

- GPI-specific platelet antibody assays (e.g., MAIPA)
- Relatively specific assay for primary and secondary ITP
- Drug-dependent increase in platelet-associated IgG
- Specific assay for D-ITP
- Drug-dependent platelet activation test (e.g., platelet serotonin release assay or PFA-4-heparin or PFA-4-polymers) ELISA
- Radionuclide platelet life span study with imaging (e.g., [125I]in platelet survival study)

**Chronic, “unclear” Thrombocytopenia**

Erlanger Baroness Hematology

- # 7257
  - They will prepare an extra peripheral smear for you to look at prior to read coming back from pathology
- No extra charge to patient
Viral Infections: EBV, CMV, etc.

Basophilic Stippling: Thalassemia, Chronic Ethn
Lead/Metal Poisoning

Basophilic Stippling: Thalassemia, Chronic Ethn
Lead/Metal Poisoning

Cryoglobulin: Cryoglobulinemia, Mycoplasma,
MM, some autoimmune disorders

Giant Platelets: Congenital, ITP

Megakaryocyte Fragments: Myelofibrosis

Hemolysis, Myelofibrosis
Oval Macrocytosis: B12/Folate Deficiency

Round Macrocytosis: Myelodysplastic syndrome, myelofibrosis, chronic liver disease

Schistocytes: TTP, HUS, DIC, Defective Prosthetic Heart Valve

Target Cells: Chronic Liver Ds, Hemoglobinopathies

Platelet Agglutination: Pseudothrombocytopenia

Emergent Thrombocytopenia
- Immune (idiopathic) Thrombocytopenic Purpura
- NOW: Immune Thrombocytopenia (i.e., ITP)
- Heparin-Induced Thrombocytopenia
- Thrombotic Thrombocytopenic Purpura
- Pre-eclampsia/HELLP Syndrome
- DIC: Sepsis, Trauma, Burns, Malignancy
- Other: Aplastic Anemia, Chemotherapy, Radiation, Acute Leukemias, Myelodysplastic disorders
Nonemergent Thrombocytopenia

- Drug-Induced Thrombocytopenia
- Infections
- Liver Ds
- Gestational Thrombocytopenia

ITP - Definitions

- PRIMARY - <100k + no other cause
- SECONDARY – other than primary
  - SLE
  - Hep C
  - Lymphoproliferative
- NEWLY DIAGNOSED – within 3 months
- PERSISTENT – 3-12 months
- CHRONIC - >12 months

ITP - Definitions

- SEVERE – bleeding at presentation or new bleeding under therapy
- REFRACTORY – no response after splenectomy or relapsed after surgery
  - Poses risk of bleeding and requires additional therapy

ITP - Mechanisms

- IMMUNE TOLERANCE DEFECTS
  - loss of tolerance to glycoproteins on platelets and Megakaryocytes
    - Peripheral (plt specific – amenable, less likely to recur)
    - Differentiation blocks (altered B-cell lines)
    - Central (during development/bone marrow – recurrence rate higher)

ITP

- SECONDARY
  - Peripheral Defects
    - ITP of Childhood
      - 2/3 post viral; 80% spontaneous remission
    - Vaccination
      - MMR (1 in 40,000 incidence)
    - Infections
      - Hepatitis C (present in 20% of ITP cases)
      - HIV (responds to HAART)
      - H. Pylori, CMV, VZV

- SECONDARY
  - Differentiation blockade defects
    - Chronic Lymphocytic Leukemia (CLL)
    - Other Lymphomas, Leukemia (<1%)
  - Central tolerance defects
    - Autoimmune Lymphoproliferative Syndromes
    - Evans Syndrome
    - Antiphospholipid Ab Synd (40% ITP pts +)
    - SLE
    - Post-transplantation
Primary ITP

- **Mechanisms**
  - Ab-coated plt removed by splenic macrophages
  - Alternatives at play as splenectomy fails in 1/3 cases
  - Complement mediated lysis
  - HIV pts – peroxide mediated lysis (complement independent)

ITP

- **Mechanism**
  - Platelet production normal or decreased
  - T-cell mediated plt destruction

ITP – Clinical Features

- Given propensity for secondary mechanisms
  - Rash, arthralgias and serositis – SLE
  - Hepatomegaly, elev transaminases – Hep C
  - Fever, lymphadenopathy – Infxn, Lymphoid malignancy
- Primary – bleeding primary manifestation
  - Mucocutaneous – Purpura
    - Gingival, epistaxis, menorrhagia
    - GI tract
  - Bleeding uncommon if plt ct > 30K
    - NOT universal truth

ITP Prognosis/Txment

- **Children**
  - 80% spontaneously recover within 6 months
  - 1/200 Severe hemorrhage (Newly diagnosed)
  - < 1/500 ICH (usually w/in 1st mo diagnosis)
    - Corticosteroids, IVIg, or Anti-D (Rh+ pts)
  - Other 20% - persistent Thrombocytopenia
    - Rituximab (22% remission rate)
    - Romiplostim (83-88% response rate in Chronic ITP) – long term safety not established
ITP Prognosis/Txment

**Children**
- **Splenectomy** – severe, persistent t-penia + bleeding – 75% response rates
- Attempt to wait until age 5 for splenectomy due to risk of sepsis
- Immunizations PRIOR to splenectomy
  - S. pneumoniae, N. meningitidis, H. influenza
  - Penicillin prophylaxis until adulthood

**Adults**
- RR 2.3 (95% CI: 1.8-3.0) of morbidity and mortality
- Death from bleeding + sepsis equal
- Most cases evolve into Chronic Disease
- Risk of bleeding greater than children
- Goal of therapy – hemostatic plt ct > 20-30K
- Txment rarely required if plt ct > 50K

**Corticosteroids**
- 80% initially respond; most relapse
- Dexamethasone 40 mg qd x 4 days;
  - 50% responders maintained >50K at 6 mos
- Dexamethasone cycles (4-6 at 2 wk intervals)
  - 80-90% relapse free survival at 15 mos
- Rituximab + Dexamethasone
  - Higher response rates over Dexameth alone at 6 mos
  - Gains lost over time

**IVlg**
- Used w/ steroids for faster rise of plt ct
- Also used to sustain plt ct once steroids tapered
  - Response rate 60-80% within few days
    - Duration of 1-3 wks
  - 1 gm/kg/day for 1-2 days
- Mech of action: modulation of receptor expression/activity; inhibit killer T-cell activation, complement neutralization, cytokine modulation, megakaryocyte apoptosis

**IVlg**
- Toxicities
  - Aseptic meningitis
  - Fluid overload
  - Nephrotoxicity
  - Thrombosis
  - Severe Hemolytic Anemia (rare)
**ITP Prognosis/Txment**

- **Anti-Rh (D)**
  - Clears Ab coated RBCs; prevents clearance of opsonized platelets
  - Modulation of receptor sites/ decr cytokines
  - ONLY Rh(D) + patients w/ spleen

- **Toxicities**
  - Drops Hgb 0.5 – 2 gm/dL
  - DIC, AKI, death (rare)

- **Approved dosing:** 50 ug/kg – 70% response rate
  - Higher dosing – higher response rates

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**2nd Line Txment**

- **Rituximab**
  - Infusion rxns, serum sickness, dysrhythmia
  - Fatal reactivation Hep B (contraindicated)
  - Reactivation John Cunningham (JC) virus – multifocal leukoencephalopathy

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**2nd Line Txment**

- **Splenectomy – “gold standard”**
    - 66% response rate; median duration of f/u 28 mos
  - SR 1223 pts – 5yr success rate 72%
    - Most relapses within first 2 yrs
  - Infxn risk greatest 1st 90 days post op
    - RR 2.6 (95% CI 1.3 – 5.1) 0-90 days
    - RR 1.0 91-365 days
    - RR 1.4 (95% CI 1.0-2.0) > 365 days
  - Pre-immunize – 2 weeks prior
    - Pneumococcal, Meningococcal, H. Flu
    - Booster Pneumococcal/Meningococcal at 5 yrs

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**2nd Line Txment**

- **American Society of Hematology Guidelines**
  - Splenectomy (Grade 1b)
  - Rituximab (Grade 2c)

- **Thrombopoietin Receptor Antagonists** (Romiplostim, Eltrombopag)

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**SPECIAL SITUATIONS**

- **Emergent (severe t-penia)**
  - Hospitalize – Corticosteroids, IVIg
  - Platelet transfusion (w/ IVIg)
  - Splenectomy
SPECIAL SITUATIONS
• Pregnancy
  • 4-8% w/ Gestational Thrombocytopenia
    o Usu b/w 75 – 150K
    o Epidural safe > 75K

  • Think Pre-E / HELPP in 2nd and 3rd Trimester

  • ITP #1 cause isolated t-penia 1st trim

  • 1st/2nd Trim, no bleeding, >20K ct
    o No treatment

SPECIAL SITUATIONS
• Pregnancy - Approaching Term
  • Goal of 50-70K (epidural anesthesia)
    o Corticosteroids (risk of Preg Induced HTN)
    o IV Ig 2gm/kg

  • Splenectomy 2nd trimester optimal

  • Rituximab (delays neonatal B cell maturation)

SPECIAL SITUATIONS
• Pregnancy - Approaching Term
  • 10-15% offspring ITP moms – plt ct < 50K
  • 1-5% < 20K
    o 50% have bleeding during delivery

    o < 1% ICH

    o C-section not protective
      • (normal maternal indications govern decision)

ITP SUMMARY
• Present at plt ct < 100k (no other cause)
• Secondary assoc Autoimmune, Lymphoproliferative disorder or chronic infections
• Children 80% spont resolution; Adults 80% chronic
• Bleeding most common elderly
• 1st line therapy: Corticosteroids + IV Ig or anti-Rh(D)
• 2nd line: Splenectomy, Rituximab, TRAs
• Splenectomy best data for long term remission
• Immunize prior to splenectomy;
• Treat febrile illness aggressively post-splenectomy

Thrombocytopenia Summary
• Rule out Pseudothrombocytopenia
• Look for secondary cause – peripheral smear
• Stop offending agent if found
• Life threatening bleeding – Prophylactic plt tfusion
  o Rarely needed – trauma, major surgery
• DO NOT Txfuse HIT/TTP/HUS
  o Exacerbate plt mediated thrombotic complications
• Thoracentesis/Paracentesis/Liver Bx usu ok if >50K

References