HEMATOLOGY for Board Review

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PANCE/PANRE Review Course

Anemias
- Iron Deficiency
- Vitamin B12 Deficiency
- Folic Acid Deficiency
- G6PD Deficiency
- Hemolytic Anemia
- Sickle Cell
- Thalassemia

Thrombocytopenia
- Idiopathic Thrombocytopenia Purpura
- Thrombotic Thrombocytopenia Purpura

Coagulation Disorders
- Factor VIII
- Factor IX
- Factor XI
- Von Willebrand disorder
- FVIII mutation, Protein C&S
- Antithrombin III, Protein C&S

Malignancies
- Acute Myelogenous Leukemia
- Acute Lymphocytic Leukemia
- Chronic Myelogenous Leukemia
- Chronic Lymphocytic Leukemia
- Lymphoma
- Multiple Myeloma

Anemia General Principles
- Anemia is a sign, not a disease.
- Anemias are a dynamic process.
- Correct use of lab tests is paramount.
- Multifactorial causes of anemia are common.
- The diagnosis of iron deficiency anemia mandates further work-up to locate the etiology.
MORPHOLOGIC APPROACH TO ANEMIA

• Microcytic Anemia -> MCV < 80
  - Reduced iron availability — severe iron deficiency
  - Reduced heme synthesis — lead poisoning, congenital or acquired sideroblastic anemia
  - Reduced/disorderly globin production — thalassemias, sickle cell disorders

• Macrocytic Anemia -> MCV > 100
  - Megaloblastic anemias - Folic acid and Vitamin B12 deficiency
  - alcohol abuse, liver disease, and hypothyroidism
  - Myelodysplastic Syndrome

• Normocytic Anemia MCV 80-100
  - Anemia of chronic disease
  - Anemia of chronic renal failure
  - Multifactorial anemia

RBC Life Cycle

• Stem cell progenitor in BM influenced by epo to commit to alterations in rbc production
• Ideal balance of O2 transport and viscosity is a Hct 40-45% (rbc % of total blood volume)
• Normally only more mature RBC escape the marrow, reticulocytes.
• Destroyed after roughly 120 days.
  - Extravascular most common-spleen primarily, some in liver and lymph nodes as well
  - Intravascular-hemolysis

Reticulocyte Count

• Erythrocytes newly released from Marrow (1-2 days)
• Contain small amount of RNA (Polychromatophilic) seen with methylene blue dye
• Increase in response to erythropoietin (EPO)
• Can be used to evaluate marrow function
**KINETIC APPROACH TO ANEMIA**

- **Decreased Production (Low Retic count)**
  - Lack of nutrients...iron, Vitamin B12, Folate
  - Bone Marrow Suppression...Aplastic anemia
  - Low levels of trophic factors...chronic renal disease (low EPO), low thyroid, testosterone
  - Anemia of chronic disease (low sensitivity to EPO)

- **Increased destruction (High Retic count)**
  - Blood Loss-chronic
  - Hemolytic Anemias
    - Inherited...sickle cell, thalassemias
    - Acquired...autoimmune, drug-induced

**IRON METABOLISM**

- Serum iron is free
- Transferrin binds iron in circulation
  - TIBC is identical
  - % Saturation is serum iron/TIBC
- Ferritin stores iron in liver and Reticulo Endothelial System (RES). Contains Fe molecules for storage. Intracellular deposits (in precursors in BM) extruded prior to entry in periphery. Also in phagocytes.

**Iron Cycle**

- Red cell precursors get iron from Transferrin
- It gets incorporated into Heme
- The RBC’s phagocytized in the spleen, the Fe is freed from the heme and most is bound back to transferrin, while some remains in the phagocyte as ferritin
Signs of iron deficiency anemia

- Microcytic anemia
- spoon nails (koilonychia).
- Glossitis
- esophageal web formation (dysphagia due to Plummer-Vinson syndrome).
- Restless legs is often associated with anemia, check ferritin!
- Pica is unique to iron-deficiency syndrome.
- Hair Loss

Etiology of Iron deficiency Anemia

- Increased Requirements
  - Bleeding from some GI source
  - Menses
  - Blood donation (one unit= 250mg iron)
  - Growth periods, pregnancy, lactation
  - Infants fed cow’s milk suffer from reduced bioavailability iron and induced GI bleeding
- Inadequate supply
  - Intestinal malabsorption- iron absorbed in duodenum
  - Sprue, celiac, atrophic gastritis
  - Gastric surgery bypassing duodenum (Rx high doses)
  - Calcium inhibits GI absorption

Treatment

- Ferrous sulfate 325mg b.i.d.
  - Beware constipation
  - Recheck ferritin in 6-8 weeks
  - Continue oral iron until serum ferritin normalizes (up to 6 months)
  - Iron pills need to be given 2 hours before, or four hours after antacids
  - Vit C helps absorption
- IV Iron replacement
  - Non-constipating
  - 2-5 doses depending on concentration
  - Recheck ferritin in 3-4 weeks
<table>
<thead>
<tr>
<th>Normal</th>
<th>Fe deficiency without anemia</th>
<th>Fe deficiency with mild anemia</th>
<th>Severe Fe deficiency with severe anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow iron</td>
<td>2+ to 3+</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Serum iron</td>
<td>50 to 150</td>
<td>60 to 150</td>
<td>&lt;60</td>
</tr>
<tr>
<td>Iron binding capacity (transferrin)</td>
<td>300 to 360</td>
<td>300 to 360</td>
<td>350 to 400</td>
</tr>
<tr>
<td>Saturation (SI/TIBC, percent)</td>
<td>20 to 50</td>
<td>30</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Normal</td>
<td>Normal</td>
<td>8 to 12</td>
</tr>
<tr>
<td>Red cell morphology</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal or slight hypochromia</td>
</tr>
<tr>
<td>Plasma or serum ferritin</td>
<td>40 to 200</td>
<td>&lt;40</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Other tissue changes</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

### Hemoglobinopathies

- **Sickle Cell Disease** - Heterozygous (trait) HbS <50% and Homozygous (SC Anemia) HbS 90%

- **Thalassemias**
  - Alpha has 4 subtypes. Alpha2, Alpha1, HbH, Hydrops Fetalis.
  - Beta has 2 subtypes. Beta Minor, Beta Major

### Normal Adult Hemoglobins

<table>
<thead>
<tr>
<th>Name of Hemoglobin</th>
<th>Distribution</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>95%-98% of adult Hb</td>
<td>α₂β₂</td>
</tr>
<tr>
<td>A₂</td>
<td>1.5%-3.5% of Adult Hb</td>
<td>α₂Δ₂</td>
</tr>
<tr>
<td>F</td>
<td>Fetal, 0.5%-1.0% of adult Hb</td>
<td>α₂γ₂</td>
</tr>
</tbody>
</table>
Sickle Cell

- Autosomal recessive disease
- Substitution of the amino acid valine for glutamine to form $$\beta^S$$ globin, HbS
- 8% to 10% of African Americans carry gene
- Generally normocytic but polymorphic with target cells, sickled cells
- Diagnose with HbEP and the presence of HbS, higher levels of HbF

Pathophysiology of SCD

- On deoxygenation, hemoglobin S polymers form, causing cell sickling and damage to the membrane
- Vaso-occlusive episodes result from a combination of vascular adhesion of young sickle cells and consequent trapping of dense sickle cells
- Splenic infarction can occur with hypoxia (altitude) resulting in functional hypoplastic state (Howell-Jolly bodies, basophilic stippling and NRBC)
- Renal Hematuria is common

SICKLE CELL TRAIT

- Normally asymptomatic
- In high O2 demand/dehydration states can develop crisis
- Over years will accrue micro infarcts resulting in kidney damage and potentially cardiac damage
SICKLE CELL ANEMIA

- Chronic hemolysis of sickle cell disease is usually associated with:
  - a mild to moderate anemia (hematocrit 20 to 30 percent)
  - reticulocytosis of 3 to 15 percent (accounting for the high or high-normal mean corpuscular volume [MCV])
  - unconjugated hyperbilirubinemia
  - elevated serum lactate dehydrogenase
  - Gallstones are common

- Red cells are normochromic unless there is coexistent thalassemia or iron deficiency
- Cardiac symptoms from chronic overload (CHF) and microinfarcts/fibrosis

Clinical manifestations

- Infections: Strep pneumonia and H. Influenza
- Gallstones
- Renal failure due to papillary infarcts
  - painless hematuria is common
- Chronic leg ulcers
- *Aplastic crisis can result from Parvovirus 19 infect.
- Hand & foot syndrome (dactylitis)- painful crisis in hands/feet- common children under four
- Priapism needs to be treated within 4 to 6 hours
- Chronic osteomyelitis (salmonelli typhi)

Acute Pain Episodes

Sickle cell "crisis"

- Precipitated by dehydration, infection, stress
- Lasts 1-2 weeks
- Fever, WBC, no change in RBC usually
- Acute Chest Syndrome (infiltrate +/- infarct), CP, Wheeze
- Abd. Liver, Splenic (*SSS), Renal infarcts
- Bone infarcts, avascular necrosis, CVA
- Low risk of narcotic addiction
- Generate feelings of despair, depression

- Management
  - Hydration +/- Bicarb
  - O2
  - Pain management
  - Seek source of infection-> Aggressively treat
### Health Care Maintenance

- Routine visits with primary provider
- Folic acid 1 mg daily
- Transcranial doppler exam
  - Detect patients that would benefit from regular transfusions to prevent CVA
- Retina exam to look for proliferative changes
- Strep pneumonia vaccine below age 5 both 7 and 23-valent, then 23-valent every 7 years
  - H. flu, meningococcal, influenza starting age 6 months
- Daily prophylactic oral penicillin until age 5

### ß-THALASSEMIAS

- Defect in ß chain synthesis and ß-α coupling
  - causing unmatched α-globin chains to accumulate and aggregate inside the RBC
  - Decrease or absent HbA, increase HbF and HbA2
- ß-Thalassemia minor (ß-thalassemia trait)
  - Heterozygous condition
- ß-Thalassemia major (Cooley anemia)
  - Homozygous condition
  - no ß chains are synthesized; only HbF and HbA2

### ß-THALASSEMIA TRAIT (HETEROZYGOUS CARRIER)

- Mild to moderate anemia
  - HGB 9-11 g/dL
  - Microcytic, Hypochromic
  - Mishapen cells, “pitted out” precipitates
- Generally asymptomatic but may have splenomegaly
- Often diagnosed on routine blood count
- Dx with HbEP, raised HbF & HbA2, however, HbA is still the most prevalent
- Treat: usually no treatment necessary
**β-THALASSEmia MAJOR (HOMOZYGOUS BETA)**

- Severe anemia
- Microcytic Polymorphic
  - pronounced variation in red cell size and shape (High RDW)
  - pale red cells, target cells, basophilic stippling (ribosomal precipitates), nucleated red cells, moderately raised retic count, elevated iron
- Infants well at birth but develop anemia in first few months when switch occurs from gamma (HbF) to beta globin chains
- Cardiac stress (CHF), hepatosplenomegaly, chipmunk facies
- Allogenic Bone Marrow transplantation Rx of choice, otherwise supportive care

**ΑLPHA THALASSEmia SYNDROMES**

- α-thalassemia-2 trait (silent)-Loss of 1/4 alpha globin genes
  - No abnormalities of MCV or Hb electropheresis
- α-thalassemia-1 trait (minor)- loss of 2/4 alpha globin genes
  - Mild anemia, MCV is often less than 80, but HbEP is normal
  - Clinically mimics β minor
- Hemoglobin H disease-Loss of ¾ alpha globin genes
  - Hemoglobin H, composed of four beta chains (beta4)
  - chronic hemolytic anemia, due to the formation of inclusion bodies in circulating red cells as Hb H precipitates (unstable)
  - See HbH on HbEP (HbA>HbH)
- Hydrops fetalis with Hb Barts
  - none of the four alpha globin loci is functional

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Genotypic Abnormality</th>
<th>Clinical Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Thalassemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalassemia major</td>
<td>Homozygous β0-thalassemia</td>
<td>Severe hemolysis, ineffective erythropoiesis, transfusion dependency, iron overload</td>
</tr>
<tr>
<td>Thalassemia intermedia</td>
<td>Compound heterozygous β+ and β-thalassemia</td>
<td>Moderate hemolysis, severe anemia, but not transfusion dependent; main life-threatening complication is iron overload</td>
</tr>
<tr>
<td>Thalassemia minor</td>
<td>Heterozygous β+ or β- thalassemia</td>
<td>Microcytosis, mild anemia</td>
</tr>
<tr>
<td>α-Thalassemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silent carrier</td>
<td>α-αααα</td>
<td>Normal complete blood count</td>
</tr>
<tr>
<td>α-Thalassemia trait</td>
<td>0αααα - (α-thalassemia 1) CR</td>
<td>Mild microcytic anemia</td>
</tr>
<tr>
<td></td>
<td>0αααα - (α-thalassemia 2)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin H</td>
<td>β+β+</td>
<td>Moderate Microcytic anemia, HSM, marrow expansion</td>
</tr>
<tr>
<td>Hydrops fetalis</td>
<td>αααα -</td>
<td>Severe anemia, intrauterine anemia from congestive heart failure; death in utero or at birth</td>
</tr>
</tbody>
</table>
NORMOCYTIC ANEMIAS

- Anemia of chronic renal insufficiency
- EPO is effective treatment
- **Acute blood loss (24-96h window)**
  - Orthostatic Symptoms predominate
  - resting tachycardia and hypotension
  - can take 24 hr. for Hct to fall
  - after 3-5 days reticulocytosis elevates MCV
- Anemia of liver disease (multifactorial):
  - remodeling of RBC membranes
  - hypersplenism
  - folate deficiency
  - co-existing iron deficiency

ANEMIA OF CHRONIC DISEASE (ACD)
(ANEMIA OF INFLAMMATION)

- Second most common anemia after Iron Deficiency
- Induced by inflammatory cytokines (IL-6) and Hepcidin
- Reduction in red blood cell (RBC) production by BM
- Trapping of iron in macrophages
- reduced plasma iron levels making iron relatively unavailable for new hemoglobin synthesis
- Erythroid precursors are impaired
- Interferons are potent inhibitors
- Blunted erythropoietin response/resistance

Diagnosis of Anemia of Chronic Disease is often complicated...

<table>
<thead>
<tr>
<th>Test</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Iron</td>
<td>Locked in storage ↓</td>
</tr>
<tr>
<td>TIBC</td>
<td>Iron stores high ↑</td>
</tr>
<tr>
<td>Iron Sat</td>
<td>Low availability ↓</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Acute phase ↑</td>
</tr>
<tr>
<td>Reticulocyte</td>
<td>↑</td>
</tr>
</tbody>
</table>
ACUTE VARIANT (ANEMIA OF CRITICAL ILLNESS)

- Acute event-related anemia
  - after surgery, major trauma, myocardial infarction, or sepsis
- Secondary to tissue damage and acute inflammatory changes
- Shares many of the features of ACD
  - low serum iron
  - high ferritin
  - blunted response to EPO

Underlying causes of ACD

- Acute and chronic infections
  - PNA, sepsis
  - chronic UTI, TB, cellulitis
- Malignancies
  - metastatic cancer
  - chronic leukemia or low grade lymphoma
- Chronic arthritic conditions - RA, UC, Crohn’s
- Thyroid disorders, DM
- Low Epo as IL suppress renal release

TREATMENT OF ACD

- Erythropoietin (EPO) is most effective therapy
- Oral iron of little benefit unless also iron deficient
- Transfusions only for short-term if Hb<8
- Who to treat with EPO?
  - Hemoglobin <10
  - Additional risk factors (pulmonary, CV, renal)
- What is goal of therapy?
  - Hb 11 to 12 generally accepted
HEMOLYTIC ANEMIA

- Caused by premature breakdown of RBCs
  - Intracorpuscular defects - RBC membrane defects
    - Hereditary Spherocytosis
  - Extracorpuscular defects -
    - Autoimmune Hemolytic Anemia
      - Positive coombs test
      - Rx prednisone high dose and taper slowly
      - G6PD Deficiency
      - Drug effect-chemotherapy
  - Severity of anemia related to rate RBC destruction and ability of bone marrow to produce reticulocytes

Typical case of hemolytic anemia

- Acute onset pallor from anemia - depends on severity and BM response
- Splenomegaly (extravascular)
- Jaundice with high indirect bilirubin - too much for the liver to keep up with
- Increased serum LDH
- Reduced serum haptoglobin
- Increased reticulocytes
- Positive coombs test if autoimmune etiology

HEREDITARY SPHEROCYTOSIS

- Forms spherocytic cells that are destroyed in spleen
- Present with jaundice and splenomegaly
- Elevated retic count
- Spherocytes on smear
- Splenectomy often required
  - major risk is bacterial sepsis: pneumococcus, H. Flu, meningococcus
  - especially in children younger than age 3
  - need to immunize prior to surgery
GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G-6-PD) Deficiency

- RBCs depend on anaerobic metabolism
- First enzyme in pentose phosphate shunt
  - catalyzes conversion NADP⁺→NADPH
- RBCs deficient if G-6-PD susceptible to hemolysis
- 10% of male blacks in the U.S. are affected
  - gene carried on X-chromosome
- Hemolysis occurs after exposure to a drug or substance that produces an oxidant stress
  - Bite cells and Heinz bodies
- Favism - ingestion of, or exposure to, fava beans may cause a devastating intravascular hemolysis

DRUG CAUSES of HEMOLYSIS in PATIENTS with G6PD DEFICIENCY

- Antimalarials
  - primiquine
  - pamaquine
- Analgesics
  - phenacetin
  - acetyl salicylic acid
- Others
  - sulfonamides
  - nalidixic acid
  - dapsone

APLASTIC ANEMIA

- Pancytopenia
  - Present with recurrent infections (due to profound neutropenia)
- Mucosal hemorrhage due to thrombocytopenia
- Anemia fatigue and dyspnea, lack of reticulocytes
- Marrow is profoundly hypocellular with a decrease in all elements
- Rx options:
  - Hematopoietic cell transplantation if HLA compatible sibling
  - Immunosuppressive regimens (cyclosporine)
  - Supportive management GCSF, IVIG
  - Antithymocyte globulin (ATG)- selectively destroys T-cells
  - Antiserum from animals immunized against human thymocytes
### Causes of Acquired Aplastic Anemia

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
</tr>
<tr>
<td>Cytotoxic drugs and Radiation</td>
</tr>
<tr>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Gold</td>
</tr>
<tr>
<td>NSAID - phenylbutazone, indomethacin</td>
</tr>
<tr>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Antineoplastic drugs - felbamate</td>
</tr>
<tr>
<td>Arsenicals</td>
</tr>
<tr>
<td>Benzene</td>
</tr>
<tr>
<td>Lindane</td>
</tr>
<tr>
<td>Glue vapors</td>
</tr>
<tr>
<td>Non-A, non-B, non-C hepatitis</td>
</tr>
<tr>
<td>HIV infection</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Graft versus host disease</td>
</tr>
</tbody>
</table>

### Main Causes of MEGALOBLASTIC ANEMIAS

- **Alcoholism** frequently causes elevated MCV
  - Vitamin B12 (cobalamin) deficiency due to:
    - Inadequate absorption due to **Pernicious Anemia**
    - Gastric Disease/Removal of terminal ileum
    - **Strict Vegan**
  - Folic Acid deficiency due to inadequate diet, EtOH or increased demand
  - Chemotherapeutic drugs can cause megaloblastic anemia
  - **Myelodysplastic Syndrome**

### Diagnostic Work-up of B12 Deficiency

- Neurologic symptoms are related to lack of Cobalamin
- Neuro symptoms often unrelated to degree of anemia
- Up to 50% have normal MCV and no anemia
- If you treat with folate, only anemia improves
- B12 Serum levels are helpful if **low**, but can be normal
- **Schilling Test** rarely needed - measure absorption radioactive B12
- Methylmalonic Acid high with cobalamin deficiency
- Homocysteine elevated in both B12 and folate deficiency
- Use tests for follow-up to confirm successful therapy
PERNICIOUS ANEMIA

- Autoimmune gastritis
- Autoimmune attack on gastric intrinsic factor (IF)
- 70% have elevated anti-IF antibodies
- Increased risk gastric cancer
  - Gastric carcinoid tumors
- 25% have autoimmune thyroid disorders
- Lab: RBC show macrocytosis (MCV>100)
  - Hypersegmented neutrophils

CLINICAL MANIFESTATIONS

- Dementia or depression can be major symptom
- 12% present with neuropathy but not anemia
- Stomatitis, glossitis
- Ataxia, broad-based gait, rhomberg, slow reflexes
- Loss of position sense, vibration, reduced skin sensation
- Treatment:
  - Option 1: Daily 1000mcg x7, then weekly x7 then monthly for lifetime
  - Option 2: Daily high dose 1-2mg daily. At least 2% is absorbed and results look superior to parenteral route

FOLIC ACID DEFICIENCY

- Most common cause is nutritional
- Connected to alcohol abuse, malnutrition
- Clinical syndrome similar to pernicious anemia
- Diagnose with serum folic acid level
- Treat with 1mg daily supplement
- Homocysteine level is best way to monitor progress
- Pregnancy increases demand for folic acid
  - Helps to prevent fetal neural tube defects
  - All women of child-bearing age daily .4 mg
  - Prescription Prenatal vitamins have 1 mg***
Platelet Abnormalities
- Thrombocytopenia due to decreased production
  - Aplastic anemia, drug reaction, leukemia
- Idiopathic Thrombocytopenic Purpura (ITP)
- Thrombotic Thrombocytopenic Purpura (TTP)
- Hemolytic Uremic Syndrome (HUS)
- Drugs: sulfonamides, heparin (3-5%) - HIT syndrome
- Infections: Sepsis, HIV, Mono-EBV
- Sequestration in enlarged spleen (most common)
- Common in advanced liver disease

Idiopathic Thrombocytopenic Purpura (ITP)
- Idiopathic with Autoimmune features
  - Petechial hemorrhage, mucosal bleeding, and thrombocytopenia, with counts often lower than 20,000/mcL
  - Diagnosis of exclusion by evaluating for other sources of Plt. Test for antibody not really used
  - Make sure it is not a lab error (EDTA tube) with clumping of plt. Check manual smear.
  - ITP of pregnancy usually transient, but check infant plt count x48h post delivery

Idiopathic Thrombocytopenic Purpura (cont.)
- Chronic in adults: Treat <30K or symptoms
  - Steroids first choice x 4 weeks
  - Intravenous Immunoglobulin (IVIG)
  - Splenectomy causes remission in 60%
  - Immunosuppressive agents- Rituxan
  - Romiplostim injections (Thrombopoietin activator in hematopoietic cells)
  - Generally less bleeding than would expect for plt counts that low in other circumstances
THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

- Rare disease-cause often unknown, HIV, cancer, Mitomycin C, Cyclosporin, Plavix
- FAT-RN
  - Fever
  - Hemolytic Anemia with schistocytes and helmet cells
  - Thrombocytopenia
  - Renal impairment (generally mild Cr <3)
  - Neurologic abnormalities-seizures, AMS
- Coagulation tests usually normal
- Rx large-volume plasmapheresis, in some instances immunosuppressive agents (Rituximab, Cyclophosphamide)

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Platelet Defect vs. Clotting Factor Deficiency

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Platelet defect</th>
<th>Clotting factor deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of bleeding</td>
<td>Skin, mucus membranes (gingivae, nares, GI and genitourinary tracts)</td>
<td>Deep in soft tissues (joints, muscles)</td>
</tr>
<tr>
<td>Bleeding after minor cuts</td>
<td>Yes</td>
<td>Not usually</td>
</tr>
<tr>
<td>Petechiae</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Ecchymoses</td>
<td>Small, superficial</td>
<td>Large, palpable</td>
</tr>
<tr>
<td>Hemarthroses, muscle hematomas</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Bleeding after surgery</td>
<td>Immediate, mild</td>
<td>Delayed, severe</td>
</tr>
</tbody>
</table>

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The coagulation cascade
Coagulation Tests

For your own reference/refresh:

- PT/INR: tissue factor like reagent, so measures VII. Up in VitK def, Coumadin, Liver Dz, DIC
  - PT/INR and PTT also BOTH measure the common pathway
- PTT Mixing Studies: looks for factor deficiency vs Inhibitor
- BT: clinical observation of plt function, usually prolonged in vWD and thrombocytopenia.
- Platelet Aggregation: adds plt to aggregates in test tube to look for defects (vWD)

Coagulation Tests Cont.

- D-Dimer: specific to plasmin degradation of fibrin. So picks up presence of clots. Up in DIC, pulmonary embolus, DVT
- TT: measures only fibrinogen to fibrin
- Fibrinogen: depleted quickly in DIC

VON WILLEBRAND DISEASE (VWD)

- Most common bleeding disorder (1-3% population)
  - Majority asymptomatic
  - Platelet type: Heavy menses, mucosal bleeds, cuts prolong
  - Factor type: deep joint and post op bleeds
- Autosomal dominant inheritance
- Von Willebrand factor (vWF) is defective/deficient
  - Large multimetric protein made from megakaryocytes & endothelial cells
  - Forms adhesive bridge between platelets and endothelium
  - Carrier molecule for Factor VIII
- Lab mostly normal:
  - PTT and BT slightly elevated. Corrects with mixing study.
  - vWF levels are low in 1&3, normal in type 2
  - platelet aggregation test abnormal
### TREATMENT OF VWD

<table>
<thead>
<tr>
<th>Treatment Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDAVP (desmopressin)</td>
<td>- Increases plasma VWF levels by stimulating secretion from endothelium&lt;br&gt;- Duration of response is variable&lt;br&gt;- IV an hour before surgery or major bleed, Nasal spray for small bleeds as outpatient management</td>
</tr>
<tr>
<td>Cryoprecipitate (rare cases)</td>
<td>- Contains both VWF and VIII</td>
</tr>
<tr>
<td>Platelet transfusion</td>
<td>- Has platelet vWF which can assist</td>
</tr>
<tr>
<td>Factor VIII concentrate</td>
<td>- Contains large amount vWF</td>
</tr>
</tbody>
</table>

### HEMOPHILIAS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex-linked recessive (30% spontaneous mutation)</td>
<td>- Genes on long arm of X chromosome</td>
</tr>
<tr>
<td>Hemophilia A</td>
<td>- Affects one in 10,000 males&lt;br&gt;- Deficient or defective clotting factor VIII&lt;br&gt;- PTT prolonged; PT/INR, Ptt count, BT normal&lt;br&gt;- Dx with quant/qual Factor VIII test&lt;br&gt;- Tx mild with DDAVP, major sx with IV Factor VIII</td>
</tr>
<tr>
<td>Hemophilia B - Christmas Tree Disease</td>
<td>Factor IX Deficiency&lt;br&gt;- Dx with quantitative IX test&lt;br&gt;- Tx recombinant IX concentrate</td>
</tr>
</tbody>
</table>

### Factor XI Deficiency

<table>
<thead>
<tr>
<th>Description</th>
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<tbody>
<tr>
<td>Ashkenazi Jewish population</td>
<td></td>
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<tr>
<td>Bleeding after trauma</td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Treat with recombinant Factor XI</td>
<td></td>
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</table>
### Thrombophilia/Hypercoaguable

- **FVLeiden Mutation**: FV resistant to aPC causing unopposed coagulation pathway. Hetero (4-8x). No treat if no thrombosis. 1st x6-12mos, 2nd lifelong, Homo (80x) lifelong AC. Most common genetic thrombophilia.
- **ATIII deficiency**: Blocks II, also IX, XI, XII and less VII. Acts as protease inactivator so deficiency allows unchecked coagulation. No treat if no thrombosis. Treat after 1st 6mos if other transient factor, if unprovoked then lifelong.
- **Protein C&S Deficiency**: Block V, VIII. Deficiency allows more rapid thrombin formation. (5-10x) No treat if no other risk. Treat if high risk or if thrombosis occurred- lifelong
- **Prothrombin Gene Mutation**: Increases prothrombin levels. (2-3x) Treat hetero 1st x6-12mos, Homo or 2nd lifelong.

### Disseminated Intravascular Coagulation (DIC)

- Systemic disorder producing both:
  - Thrombosis
  - Hemorrhage
- Complicates about 1% hospital admissions
- DIC results from:
  - Tissue/endothelial damage on large scale (large TF exposure): burns, G- bacterial sepsis, vasculitis, trauma
  - Procoagulant in blood: cancer, placental abruption
  - Severe allergic reaction

### DIC (cont.)

- Coagulation factors consumed faster than liver can produce new factors
- Platelets are consumed faster than BM can cope
- Fulminant form is often severe (sepsis)
- Will see the bleeding symptoms more frequently
- Insidious form associated with malignancies especially pancreatic
  - Thrombotic complications (Trousseau syndrome-migratory thrombophlebitis)
  - If slow enough BM and Liver can keep up with the demand for Plt and Factors
Common manifestations of acute DIC

- Bleeding-IV sites, petechiae, GI/Lung
- Renal dysfunction- Oliguria, ARF
- Respiratory dysfunction- Dyspnea
- Shock- hemodynamic instability
- Thromboembolism-DVT/PE, CVA
- Central nervous system-Seizures, Coma
- PT/INR, PTT, TT, Fibrinogen all effected
- FDP increased, Plt count depleted
- Schistocytes (MAHA)

DIC Treatment Options

- Treatment of underlying disorder

Supportive:
- Platelet +/- PRBC transfusions
- Fresh frozen plasma - contains factors
- Cryoprecipitate - contains fibrinogen

Acute Leukemias

- Acute Lymphocytic Leukemia (ALL) T or B
  - Peak incidence age 3-5
  - 20% adult leukemia, most childhood cases
  - Philadelphia chromosome 25% to 30% of all adult cases (higher risk patients)
  - RF: Radiation, prior chemo, Organic solvents, Downs
  - Sx: BM failure, infections, bleeding, HSM, LAD

- Acute Myeloid Leukemia (AML)
  - Peak incidence age 60
  - >30% Blasts in peripheral blood
  - Auer Rods formed by the aggregation of myeloid granules
  - Sx specific: M3 DIC, M4/M5 high WBC
  - Tissue infiltrate- chloroma, skin- leukemia cutis
Chronic Leukemia

- Chronic Lymphocytic Leukemia
  - most common form of leukemia in adults in Western countries
  - median age at diagnosis is 62 years
  - therapy should be initiated only when indicated by one or more disease-related symptoms, hepatosplenomegaly, or recurrent infections
- Chronic Myelogenous Leukemia
  - Chromosome 22 translocation mutation causing BCR/Abl (Philadelphia Chromosome)
  - Can remain in chronic phase average 3-4yr

CML Natural History

- Chronic Phase
  - Asymptomatic with high WBC (20K-100K), splenomegaly, wt loss
- Accelerated phase with increasing symptoms
  - 10 to 20% blast cells on peripheral smear
  - Increased basophils, low plt, low Hb
- Blast crisis >20% blasts
  - Evolves to acute leukemia (2/3 AML, 1/3 ALL)
  - Death occurs within weeks to months
  
Gleevec (imatinib) is new treatment
  - 80-85% go into remission
  - Lifelong Rx needed

Lab findings in CML at diagnosis

- Raised WBC count (30-400 X 10^9/L)
- Differential
  - granulocytes at all stages of development
  - increased numbers of basophils and eosinophils
  - blast (primitive) cells
- Hgb concentration may be reduced
- RBC morphology usually unremarkable
- Nucleated RBC may be present
- Leukocyte alkaline phosphatase reduced
Multiple Myeloma

- Accumulation of plasma cells in Bone Marrow or visceral/soft tissue
- Symptoms: CRAB
  - Calcium-elevated from osteolytic bone destruction
  - Renal-Insufficiency from damage of protein deposition
  - Anemia- BM suppression
  - Bone-Lytic bone lesions
- Often found after eval for anemia, back pain, renal insufficiency, large protein/albumin variance

Diagnostic Criteria

MGUS: <10% plasma clonal cells in marrow. Mspike <3gm/100mL. No CRAB
Smoldering Myeloma: 10-60% plasma clonal cells in marrow or Mspike >3gm/100mL/Bence Jones in urine. But no CRAB.
Multiple Myeloma:
At least 1 of: 60% plasma cells in marrow without CRAB, FLC ratio 100 or greater (involved LC >100), focal lesion 5mm in size.
Plasmacytoma with >10% plasma clonal marrow involvement.
Or: Mspike >3gm/100mL/BJ Protein (>30% Plasma cell clone in nonsecretory) with CRAB.
Or >10% plasma cells in marrow with CRAB.
Plasmacytoma: Solitary lesions with <10% marrow plasma cell clone

Treatment MM

- Incurable disease
- Stem cell transplant is the treatment of choice if clinically stable
- Corticosteroids for immunomodulation
- Chemotherapy
- Always monitor closely for infections, diminished immune response
Lymphomas

**NHL:**
- 6th most common cancer in US (rates doubled in the past 20yr)
- 85% of lymphomas
- Several subtypes: (DLBCL, MCL, MZL, BL, TCL, MALT)
- Prognosis and Rx varies by type

**Hodgkins:** One of most curable malignancies.
- 15% of lymphomas

**NHL**
- Risk Factors: male, increasing age
  - Chronic immunosuppresion
  - Disruption in normal cell proliferation (Chemo/RT)
  - Chronic autoimmune disorders (SLE, RA)
  - Chronic infections (EBV, Mono, HIV, HHV, Hpylori)
- Presentation: weight loss, painless lymph nodes, night sweats, fevers (night), pruritis, chest +/or abdominal pain

**NHL (continue)**
- Diagnose:
  - Clinical - painless lymph nodes
  - Labs - ?WBC, ?LDH
  - Diagnostics - CT, PET, LN Biopsy
- Staging: stages I-IV, based on extent and location of LN distribution and involvement of extralymphatic organs, marrow, A/B symptom
- Rx: Chemo/RT, Rituximab if CD20+
  - If refractory, role for Stem Cell Transplant
  - 5 year survival 50-80% based on staging/type
Hodgkin’s Disease

- Risk Factors: male, bimodal age (15-30, >55), EBV, HIV, Family Hx (HLA link)
- Presentation: painless lymph node enlargement (85% are head & neck), (B sx) night sweats, pruritis, weight loss, hepatosplenomegaly, pain to LN after alcohol
- Diagnose: clinical-painless LN, biopsy with Reed Sternberg cells (multinucleated), oLDH
- Imaging - bulky LAD, orderly spread, most have mediastinal involvement

HD (cont.)

- 4 Histological types: nodular sclerosing, mixed cellularity, lymphocyte predominant, lymphocyte depleted
- Staging: I-IV, same as NHL, B symptoms
- Rx: Chemo, RT (very radiosensitive), stem cell for refractory disease
- Prognosis: very good prognosis, 75% curable

Clinical Features Hodgkins vs. NHL

<table>
<thead>
<tr>
<th></th>
<th>Hodgkins Disease</th>
<th>Non-Hodgkins Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>Unchanged</td>
<td>increasing</td>
</tr>
<tr>
<td>Age</td>
<td>Median 29 years</td>
<td>incidence increases</td>
</tr>
<tr>
<td></td>
<td>with age</td>
<td>g</td>
</tr>
<tr>
<td>Sites</td>
<td>Mostly nodal:</td>
<td>Supradiaphragmatic</td>
</tr>
<tr>
<td></td>
<td>Supradiaphragmatic</td>
<td></td>
</tr>
<tr>
<td>Clinical Features</td>
<td>Mediastinal mass</td>
<td>Nothing specific</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>Alcohol induces pain</td>
</tr>
<tr>
<td>Prognosis</td>
<td>70—80% cure</td>
<td>Most incurable but very variable</td>
</tr>
</tbody>
</table>
Thank you and good luck!