### Anemias
- Vitamin B12 deficiency
- Folate deficiency
- Iron deficiency
- G6PD deficiency
- Hemolytic and aplastic anemia
- Sickle cell anemia
- Thalassemia

### Coagulation Disorders
- Factor VIII disorders
- Factor IX disorders
- Factor XI disorders

### Thrombocytopenia
- Idiopathic thrombocytopenic purpura
- Thrombotic thrombocytopenic purpura
- Von Willebrand's disease

### Malignancies
- Acute/chronic lymphocytic leukemia
- Acute/chronic myelogenous leukemia
- Lymphoma
- Multiple myeloma

### Anemia General Principles
- Anemia is a sign, not a disease.
- Anemia's are a dynamic process.
- It is never normal to be anemic.
- Correct use of lab tests is paramount.
- Concomitant causes of anemia are common.
- The diagnosis of iron deficiency anemia mandates further work-up.
### Morphologic Approach to Anemia

- **Microcytic Anemia**
  - MCV < 80
  - Reduced iron availability — severe iron deficiency, the anemia of chronic disease, copper deficiency
  - Reduced heme synthesis — lead poisoning, congenital or acquired sideroblastic anemia
  - Reduced globin production — thalassemic states, other hemoglobinopathies

- **Macrocytic Anemia**
  - MCV > 100
  - Megaloblastic anemias— Folic acid and Vitamin B12 deficiency
  - Alcohol abuse, liver disease, and hypothyroidism

- **Normocytic Anemia**
  - Anemia of chronic disease
  - Anemia of chronic renal failure

### RBC Destruction/ Life Cycle

- Normal life span about 120 days
- Destroyed by phagocytes
  - Spleen, liver, bone marrow, lymph nodes
  - Heme → biliverdin → unconjugated (indirect) bilirubin
  - Liver converts to conjugated (direct) bilirubin which enhances elimination from the body
  - Globin and iron → recycled
- RBC destruction in blood vessels → free Hb in urine (Hemoglobinuria vs. Hematuria which is whole red blood cells in urine due to kidney or tissue damage)

### Reticulocyte Count

- Erythrocytes newly released from Bone Marrow
- Contain small amount of RNA
- Stain with methylene blue
- Increase in response to erythropoietin (EPO)
**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

- **Increased destruction (High Retic count)**
  - Hemolytic Anemias
    - Inherited...sickle cell, thalassemias
    - Acquired...idiopathic, drug-induced, and myelodysplastic syndrome.

**Algorithm using Retic. count, WBC, Platelet**

- Low Retic count suggests poorly functioning bone marrow
  - Normal Platelets and WBC
    - Acute blood loss
    - Renal disease
    - Infections
    - Drugs
  - Low platelets and WBC
    - Leukemia
    - Aplastic anemia
    - Infection

**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)
Case One

- 76 yo female comes in c/o being “run down” for over a month
- Only med is daily ibuprofen for chronic LBP
- PMH unremarkable, no previous hosp.
- Denies extra stress, problems sleeping except for restless legs
- Recently has been craving ice to chew (Pagophagia)
- Physical exam unremarkable except angular stomatitis, glossitis, pale conjunctiva, 2/6 SEM at LUSB, and spoon nails as below

(From wikipedia commons)

Angular Stomatitis (Cheilosis) (from wikipedia commons)
LAB RESULTS

- Hgb 8.2 (12.3 – 15.3), Hct 27.4 (36 – 44)
- MCV 80.8 (80-100)
- RDW (12.7-14.5) 14.6- Anisocytosis
- Retic count (1.1-2.1) 1.6
- Serum ferritin 11.2 (40-200)
- Serum iron 28.6 (30-160)
- TIBC (transferrin level) 376 (230-400)
- Transferrin saturation 10.2 (9.6-29)

What is your next step?

1. Bone marrow
2. Rx with vitamin B12
3. Transfuse 2 units packed cells
4. GI work-up for occult bleeding
5. Treat with EPO
What is your next step?

1. Bone marrow
2. Rx with vitamin B12
3. Transfuse 2 units packed cells
4. GI work-up for occult bleeding
5. Treat with EPO

Signs of iron deficiency anemia

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

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 blood tests 6 weeks later
  - Continue oral iron until serum ferritin normalizes (up to 6 months)
- Iron salts not absorbed well if taken with food
- Iron pills need to be given 2 hours before, or four hours after antacids
- Vitamin C helps absorption

<table>
<thead>
<tr>
<th></th>
<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>
<td>None</td>
</tr>
<tr>
<td>Serum iron</td>
<td>60 to 150</td>
<td>60 to 150</td>
<td>&lt;60</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Iron binding capacity (transferrin)</td>
<td>300 to 350</td>
<td>100 to 150</td>
<td>150 to 400</td>
<td>&gt;110</td>
</tr>
<tr>
<td>Saturation (SI/TIBC), percent</td>
<td>20 to 50</td>
<td>30</td>
<td>&lt;15</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Normal</td>
<td>Normal</td>
<td>9 to 12</td>
<td>6 to 7</td>
</tr>
<tr>
<td>Red cell morphology</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal or slight hypochromia</td>
<td>Hypochromia and microcytosis</td>
</tr>
<tr>
<td>Plasma or serum ferritin</td>
<td>40 to 200</td>
<td>&lt;40</td>
<td>&lt;20</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Other tissue changes</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Nail and epithelial changes</td>
</tr>
</tbody>
</table>

Case Two

- 47 yo male with 10 year h/o type 2 comes for PE
- Currently taking max doses metformin & glyburide
- BP 148/92, retinal exam shows cotton wool exudates
- Diminished monofilament sensation on feet
- Diabetes poorly controlled with A1c=10.6%
- Microalbumin 300 (<20), creatinine 1.4
- CBC shows Hgb 9.1, MCV 85, normal platelets
- Stool guiac negative x 3
- Serum ferritin 170 (40-200), Retic count .5%
- Serum iron 65 (60-150), TIBC 320 (300-360)
What can cause elevated ferritin AND low serum iron

1. Chronic inflammation
2. Aplastic anemia
3. Hemolysis
4. Hemoglobinopathies
5. Acute leukemia

What is the best treatment for this patient?

1. EPO
2. Transfuse 2 units pc
3. Oral iron
4. Parenteral iron
What is the best treatment for this patient?

1. EPO
2. Transfuse 2 units pc
3. Oral iron
4. Parenteral iron

What is the best treatment for this patient?

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

- Second most common anemia after iron deficiency
- Induced by inflammatory cytokines (IL-6)
- 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

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

<table>
<thead>
<tr>
<th></th>
<th>Chronic Disease</th>
<th>Iron Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>TIBC (transferrin)</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Iron saturation</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>nL or ↑</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
  • TB
  • Endocarditis
  • Chronic UTI
• Malignancies
  • Metastatic cancer
  • Leukemia
  • Lymphoma
• Chronic arthritic conditions
• Chronic renal insufficiency
• Hypothyroidism
• ANY CHRONIC INFLAMMATORY CONDITION!

DIAGNOSIS OF ANEMIA CHRONIC DISEASE

• Generally mild/moderate anemia (Hb 8-10)
• Normochromic, normocytic (may be slightly low)
• Low to normal reticulocyte count
• Reduced serum iron and transferrin saturation
• Reduced or normal TIBC/transferrin levels
• Normal ferritin levels (acute phase reactant)
• Need to exclude chronic renal failure, hyperthyroidism, hypothyroidism
• May have concomitant iron deficiency anemia
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

HEMOGLOBINOPATHIES

- Sickle cell disease - homozygous
  - Autosomal recessive disease
  - Substitution of the amino acid valine for glutamine
  - 8% to 10% of African Americans carry gene
- Sickle cell trait - heterozygotes
  - Splenic infarction can occur with hypoxia (altitude)
  - Renal hematuria common
  - Beware bacteruria during pregnancy (pyelonephritis)
- Thalassemias - imbalanced synthesis of normal globin chains
  - Beta
  - Alpha

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>
Pathophysiology of SCD

- On deoxygenation, hemoglobin S polymers form, causing cell sickling and damage to the membrane.
- Vasocclusive episodes result from a combination of vascular adhesion of young sickle cells and consequent trapping of dense sickle cells.
- Functional asplenism.

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
- Red cells are normochromic unless there is coexistent thalassemia or iron deficiency.
- Hb electrophoresis high levels Hb F.

The elongated and crescent-shaped red blood cells seen on this smear represent circulating irreversibly sickled cells. Target cells and a nucleated red blood cell are also seen. (Licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license.)
### Acute Pain Episodes

**Sickle cell “crisis”**

- Precipitated by weather, infection, stress
- Lasts 2 to 7 days
- Often undertreated!
- Low risk of narcotic addiction
- Generate feelings of despair, depression

**Management**

- Hydration
- Pain management
- Seek source of infection -> Antibiotics?
- Hydroxyurea has promise -> raises HbF levels

### Clinical manifestations of SCD

- Hand & foot syndrome (dactylitis) - painful crisis in hands/feet - common children under four
- *Aplastic crisis can result from Parvovirus 19* infect.
- Splenic sequestration with enlarging spleen
- *Acute chest syndrome - major cause of death - Fever, wheezing, chest pain, new pulmonary infiltrate
- *CVA risk increased if transcranial doppler slow (*Exchange transfusion indicated)*

### Clinical manifestations (cont.)

- Infections: *Strep pneumonia* and *H. Influenza*
- Gallstones
- Renal failure due to papillary infarcts
  - painless hematuria is common
- Chronic leg ulcers
- Priapism needs to be treated within 4 to 6 hours
- Aseptic necrosis in femoral and humeral heads
- Chronic osteomyelitis (*salmonelli typhi*)
### 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

### β-Thalassemias

- Diminished production of β-globin chains
  - causing unmatched α-globin chains to accumulate and aggregate

#### β-Thalassemia minor (β-thalassemia trait)
- Heterozygous condition

#### β-Thalassemia major (Cooley anemia)
- no β chains are synthesized; only HbF and HbA₂
- severe anemia that appears in the first year

### β-Thalassemia Major

- severe anemia
- blood film
  - 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
- infants well at birth but develop anemia in first few months when switch occurs from gamma (HbF) to beta globin chains
- progressive splenomegaly; iron loading; prone to infection
- Allogenic Bone Marrow transplantation Rx of choice
### B-THALASSEMIA TRAIT (HETEROZYGOUS CARRIER)

- mild hypochromic microcytic anemia
  - HGB 9-11 g/dL
  - MCV 50-70 fl
  - MCH 20-22 pg
- no clinical features, patients asymptomatic
- often diagnosed on routine blood count
- raised HbA2 level

### ALPHA THALASSEMIA SYNDROMES

- α-thalassemia-2 trait (minima)
  - Loss of one of the four alpha globin genes
  - No abnormalities of blood testing
- α-thalassemia-1 trait (minor)
  - Loss of two of the four alpha globin genes
  - MCV is often less than 80, but Hb electrophoresis is normal
- Hemoglobin H disease
  - Hemoglobin H, composed of four beta chains (beta4)
  - Three of the four alpha globin loci are nonfunctional
  - Chronic hemolytic anemia, due to the formation of inclusion bodies in circulating red cells as Hb H precipitates
- Hydrops fetalis with Hb Barts
  - None of the four alpha globin loci is functional

### Disorder | Genotypic Abnormality | Clinical Phenotype
--- | --- | ---
β-Thalassemia | | 
Thalassemia major (Cooley's anemia) | Homozygous β- thalassemia | Severe hemolysis, ineffective erythropoiesis, transfusion dependency, iron overload
Thalassemia intermedia | Compound heterozygous β- and β+ thalassemia | Moderate hemolysis, severe anemia, but not transfusion dependent; main life-threatening complication is iron overload
Thalassemia minor | Heterozygous β- or β+- thalassemia | Microcytosis, mild anemia
α-Thalassemia | | 
Silent carrier | α-/αα | Normal complete blood count
α-Thalassemia trait | αα- / (α-thalassemia 1) OR Mild microcytic anemia
αα- / (α-thalassemia 2) | | 
Hemoglobin H | α-/αα | Chronic anemia and mild hemolysis; not transfusion dependent
Hydrops fetalis | αα- / | Severe anemia, intrauterine anemia, congenital heart failure; death in utero or at birth
NORMOCYTIC ANEMIAS

- Anemia of Chronic renal Insufficiency
  - EPO is effective treatment
- Acute blood loss
  - Orthostatic Symptoms predominate
  - Resting tachycardia and hypotension
  - Can take 24 hr. for Hct to fall
  - 3-5 days reticulocytosis elevates MCV
- Anemia of liver disease multifactorial:
  - Remodeling of RBC membranes
  - Folate deficiency
  - Co-existing iron deficiency

HEMOLYTIC ANEMIA

- Caused by premature breakdown of RBCs
  - Intracorpuscular Defects - RBC membrane defects
    - Hereditary Spherocytosis & Elliptocytosis
  - Extracorpuscular Defects -
    - Autoimmune Hemolytic Anemia
      - Positive coombs test
      - Rx prednisone high dose and taper slowly
      - G6PD Deficiency
- Severity of anemia related to rate RBC destruction and ability of bone marrow to produce reticulocytes
  - Free hemoglobin binds to haptoglobin
  - Removed by RES unless exceeds capacity (low haptoglobin)
  - Excess filtered through kidney -> dark urine

Typical case of Hemolytic anemia

- Acute onset pallor from anemia
- Jaundice with high indirect bilirubin
- Increased serum LDH
- Reduced (or absent) 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
  - FAVISM: Ingestion of, or exposure to, fava beans may cause a devastating intravascular hemolysis

**DRUGS CAUSES HEMOLYSIS IN PATIENTS WITH G6PD DEFICIENCY**
- Antimalarials
  - Primquine
  - Pamaquine
- Analgesics
  - Phenacetin
  - Acetyl salicylic acid
- Others
  - Sulfonamides
  - Nalidixic acid
  - Dapsone
APLASTIC ANEMIA

- Present with recurrent infections (due to profound neutropenia)
  - Mucosal hemorrhage due to thrombocytopenia
  - Fatigue and dyspnea
  - Pancytopenia, 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)
  - Antithymocyte globulin (ATG)- selectively destroys T-cells
  - Antiserum from animals immunized against human thymocytes

Causes of Acquired Aplastic Anemia

<table>
<thead>
<tr>
<th>Idiopathic</th>
</tr>
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<tbody>
<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>Antiepileptic drugs - felbamate</td>
</tr>
<tr>
<td>Antiretroviral</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 and/or alcoholism
  - Chemotherapeutic drugs can cause megaloblastic anemia
**DIAGNOSTIC WORK-UP of B12 deficiency**
- Neurologic symptoms are related to lack of Cobalmin
- 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 cobalmin deficiency
- Homocysteine elevated in both B12 and folate deficiency
- Use tests for follow-up to confirm successful therapy

**PERNOCIOUS 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
- Progressive cases develop peripheral neuropathy
- Ataxia, broad-based gait, rhomberg, slow reflexes
- Loss of position sense, vibration, reduced skin sensation
- Treatment:
  - Old Rx: weekly 1000 micrograms cobalmin x 6 then monthly for lifetime
  - New Rx: 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, faddism
• 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***

HEMORRHAGIC DISORDERS
• Platelet Abnormalities
  • Thrombocytopenia due to decreased production
  • Aplastic anemia, drug reaction
  • Idiopathic Thrombocytopenic Purpura (ITP)
  • Thrombotic Thrombocytopenic Purpura (TTP)
  • Drugs (heparin 3-5%), Viruses, SLE
  • Sequestration in enlarged spleen
  • Common in advanced liver disease
• Coagulation Factor Deficiencies

Idiopathic Thrombocytopenia Purpura (ITP)
• Self-limited in children (post virus) in 70%
• Petechial hemorrhage, mucosal bleeding, and thrombocytopenia, with counts often lower than 20,000/mcL
• Antiplatelet antibody test—Useful (many false +)
• Most clinicians prefer to treat children with steroids or intravenous immunoglobulin (IVIG) if platelet counts < 10,000
Idiopathic Thrombocytopenic Purpura (cont.)

- Chronic in **adults**: treat if platelet count <10,000-20,000
- Steroids first choice x 4 weeks
- Intravenous Immunoglobulin (IVIG)
- Splenectomy causes remission in 60%
- Immunosuppressive agents

<table>
<thead>
<tr>
<th>Features</th>
<th>Acute ITP</th>
<th>Chronic ITP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak age</td>
<td>Children (2-6 yrs)</td>
<td>Adults (20-40 yrs)</td>
</tr>
<tr>
<td>Female:Male</td>
<td>1:1</td>
<td>3:1</td>
</tr>
<tr>
<td>Antecedent infection</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Onset of symptoms</td>
<td>Abrupt</td>
<td>Abrupt-indolent</td>
</tr>
<tr>
<td>Platelet count at presentation</td>
<td>&lt;20,000</td>
<td>&lt;50,000</td>
</tr>
<tr>
<td>Duration</td>
<td>2-6 weeks</td>
<td>Long-term</td>
</tr>
<tr>
<td>Spontaneous remission</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

### 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>
Differential diagnosis of ITP

- Falsely low platelet counts
  - In vitro platelet clumping caused by EDTA-dependent agglutinins or giant platelets
- Common causes of thrombocytopenia
  - Pregnancy
  - Gestational thrombocytopenia
  - Preeclampsia
  - Drug-induced thrombocytopenia: Heparin, Quinidine, Quinine, Sulfonamides, Gold
  - Viral infections: HIV, infectious mononucleosis, Hepatitis
  - Hypersplenism due to chronic liver disease

LAB TESTS IN HEMORRHAGIC DISORDERS

- Bleeding Time (BT): measures platelet function
- Platelet count: normal 150,000-300,000
- Prothrombin Time (PT): test of extrinsic system (INR)
- Partial Thromboplastin time (aPTT): intrinsic system
- Thrombin Time (TT): tests fibrinogen-> fibrin
- Fibrinogen Level: ↓ DIC
- D-Dimer: specific to plasmin degradation seen in DIC, pulmonary embolus
VON WILLEBRAND DISEASE (VWD)

- Most common bleeding disorder (1-3% population)
- Majority asymptomatic
- Autosomal dominant inheritance
- Von Willebrand factor (vWF) is defective/deficient
- Large multimeric protein from chromosome 12
- Forms adhesive bridge between platelets and endothelium
- Carrier molecule for Factor VIII
- Lab mostly normal:
  - aPTT and bleeding time slightly elevated
  - vWF levels are low
  - Ristocetin-induced platelet aggregation test

TREATMENT OF VWD

- DDAVP (deamino-8-arginine vasopressin)
  - ↑ plasma VWF levels by stimulating secretion from endothelium
  - Duration of response is variable
  - Dosage 0.3 µg/kg q 12 hr IV an hour before surgery
- Factor VIII concentrate
  - Contains large amount vWF

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

- Rare disease of unknown cause
- Severe thrombocytopenia
- Hemolytic anemia with schistocytes and helmet cells
- Neurologic abnormalities
- Seizures
- Clouded sensorium
- Fever
- Mild renal disease with creatinine <3.0
- Minimal changes in coagulation tests
- Rx large-volume plasmapheresis
Case Three

- 26 yo female had a normal spontaneous vaginal delivery an hour ago
- Following the delivery the obstetrician had difficulty removing the entire placenta
- Patient now mildly hypotensive and confused
- Oozing around IV site, increased bloody discharge from vagina
- Lab showed Hb 10.3, prolonged PT, aPTT, Thrombin Time (TT) and high levels of D-dimer

What is the best treatment?

1. Heparin IV
2. Warfarin po
3. Transfuse 2 units packed cells
4. DDAVP
5. Vitamin K subQ

What is the best treatment?

✓1. Heparin IV
2. Warfarin po
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Disseminated Intravascular Coagulation (DIC)

- Systemic disorder producing both:
  - Thrombosis
  - Hemorrhage
- Complicates about 1% hospital admissions
- Acute DIC results from:
  - Blood exposed to large amounts of tissue factor
  - Massive generation of thrombin
  - Coagulation triggered in overwhelming fashion
- Chronic DIC is low grade disorder

DIC (cont.)

- Procoagulant substances trigger systemic activation of coagulation system
- Coagulation factors consumed faster than liver can produce new factors
- Platelets are consumed faster than BM can cope
- Acute form is often severe
- Chronic form associated with malignancies especially pancreatic
  - Thrombotic complications (Trousseau syndrome - migratory thrombophlebitis)

Common manifestations of acute DIC

- Bleeding (64 percent)
- Renal dysfunction (25 percent)
- Hepatic dysfunction (19 percent)
- Respiratory dysfunction (16 percent)
- Shock (14 percent)
- Thromboembolism (7 percent)
- Central nervous system involvement (2 percent)
Causes of DIC

Activation of both coagulation and fibrinolysis
Triggers by:

- Sepsis
  - Meningococcemia
  - Gram + or -
- Trauma
  - Head injury
  - Fat embolism
- Malignancy
  - Solid cancers (pancreas)
  - Trousseau Syndrome
  - Migratory thrombophebitis
- Obstetrical complications
  - Amniotic fluid embolism
  - Abruptio placenta

DIC Treatment Options

- Treatment of underlying disorder
- Anticoagulation with heparin
- Platelet transfusion
- Fresh frozen plasma
- Coagulation inhibitor concentrate (ATIII)

HEMOPHILIAS

- Sex-linked recessive
- Genes on long arm of X chromosome
- Hemophilia A affects one in 10,000 males
  - deficient or defective clotting factor VIII
- Hemophilia B - Factor IX Deficiency
- Factor XI Deficiency - Ashkenazi Jews
- Replacement therapy
  - Recombinant forms now available ($100,000/yr)
  - Cryoprecipitate effective but risky
### Acute Leukemias

- **Acute Lymphocytic Leukemia (ALL)**
  - Peak incidence age 3-5
  - 20% adult leukemia, most childhood cases
  - Philadelphia chromosome 25% to 30% of all adult cases
- **Acute Myeloid Leukemia (AML)**
  - Peak incidence age 60
  - **Auer Rods** formed by the aggregation of myeloid granules

### 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**
  - Caused by the transforming capability of the protein products resulting from the Philadelphia translocation (Ph Chromosome)
  - Average survival 5 years (until new therapies)

### CML Natural History

- Chronic phase lasts 3 to 5 years
  - Asymptomatic with high WBC counts
- Accelerated phase with increasing symptoms
  - 10 to 20% blast cells on peripheral smear
- Blast crisis
  - Evolves to acute leukemia (2/3 AML, 1/3 ALL)
  - Death occurs within weeks to months

Gleevec (imatinib) is new treatment
- 80% go into remission
- Lifelong Rx needed
**Clinical features of CML**
- fatigue
- weight loss
- sweating
- anemia
- easy bruising
- splenomegaly with or without hepatomegaly

**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 (maximum 0%)
    - never present in blood of normal people
  - Hgb concentration may be reduced
  - RBC morphology usually unremarkable
  - nucleated RBC may be present
  - platelet count may be raised (300-600 x 10^9/L)

**Multiple Myeloma**
- Accumulation of plasma cells in the bone marrow and, less often, soft tissues or visceral organs
- Lytic bone lesions are most typical
- Anemia, hypercalcemia, renal insufficiency
- Increased risk for life-threatening bacterial infections
  - Encapsulated organisms like Strep. Pneum., H. Flu
### Diagnostic criteria for myeloma

- >10% plasma cells in Bone Marrow or plasmacytoma on biopsy
- Clinical features of myeloma
  - Bone pain, often in low back
- Plus at least one of:
  - Serum paraprotein spike (IgG > 30 g/L; IgA > 20 g/L)
  - Seen on serum electrophoresis (SPEP)
  - Urine paraprotein (*Bence Jones* proteinuria)
  - Osteolytic lesions on skeletal survey; often cause hypercalcemia

### Lymphomas

- Lymphoma is the sixth most common type of cancer in the United States
- **15%** Hodgkin’s Lymphomas
- **85%** Non-Hodgkins lymphomas

### Hodgkin’s Disease

- Higher incidence in men than in women
- Occurs in a bimodal age distribution
  - Greatest peak in the third decade
  - Lesser peak in the seventh decade
- Increased incidence of Hodgkin lymphoma in persons with a history of infectious mononucleosis
- Neoplastic cell of Hodgkin lymphoma is almost always a B cell
  - Either the *Reed-Sternberg cell* or one of its mononuclear variants
### Hodgkins Clinical Features

- Most common presenting feature is painless lymph node enlargement
- Mediastinal lymphadenopathy is common at presentation.
- Orderly spread from one lymph node region to contiguous nodal sites.
- The spleen and the lymph nodes in the celiac axis are often the first sites of subdiaphragmatic disease

### Systemic Symptoms (B symptoms)

- Drenching sweats at night, fever, and unexplained weight loss.
  - Pel-Ebstein fevers are intermittent episodes of evening fevers that last for several days and alternate with afebrile periods.
- Total body pruritus
- A unique feature is pain at sites of lymphadenopathy immediately after ingestion of alcohol.

### Clinical Features Hodgkins vs. NHL

<table>
<thead>
<tr>
<th></th>
<th>Hodgkins Disease</th>
<th>Non-Hodgkins Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td>Unchanged</td>
<td>Increasing</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Median 29 years</td>
<td>Incidence increases with age</td>
</tr>
<tr>
<td><strong>Sites</strong></td>
<td>Mostly nodal:</td>
<td>No predictable pattern</td>
</tr>
<tr>
<td></td>
<td>Supradiaphragmic</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Features</strong></td>
<td>Medastinal mass.</td>
<td>Nothing specific</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
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<tr>
<td></td>
<td>Alcohol induces pain</td>
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</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>70—80% cure</td>
<td>Most incurable but very variable</td>
</tr>
</tbody>
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THANKS!

IT’S LUNCHTIME