An Overview of the Anemias
Iron Deficiency, Megaloblastic, Hemolytic and Hemoglobinopathies
Deana Hallman, M.D.
ANEMIA

- Definition:
  - A reduction in the red blood cell mass

- Degree of anemia is measured by:
  - Volume of red cells expressed as a percentage of the blood volume - hematocrit (Hct)
  - Plasma concentration of hemoglobin (Hgb)
ANEMIA

- An important indicator of disease, its cause should always be sought.

- Symptoms & signs depend on:
  - Level of hematocrit
    - Mild to moderate anemia - asymptomatic
  - Rate at which anemia developed
    - Rapid onset causes more symptoms
  - Underlying cause
ANEMIA - Symptoms

○ Moderate:
  • Fatigue
  • Dyspnea
  • Palpitations
  • Poor exercise tolerance
  • Dizziness
  • Headaches
  • Tinnitus

○ Severe:
  • Anorexia
  • Indigestion
  • Irritability
  • Difficulty sleeping
  • Difficulty concentrating
  • Abnormal menstruations
  • Impotence, loss of libido
  • Chest pains, myocardial infarction
ANEMIA - Signs

- Pallor
  - Oral mucous membranes
  - Nail beds
  - Conjunctivae
  - Palm creases
- Tachycardia
- Hyperdynamic precordium
- Flow murmurs

- Jaundice
- Splenomegaly

Seen mainly in patients with hemolysis and hemoglobinopathies
# ANEMIA – Basic Lab Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Monocytopenia vs. Pancytopenia</td>
</tr>
<tr>
<td>MCV, MCH</td>
<td>Microcytosis, Macrocytosis, Normocytic indexes</td>
</tr>
<tr>
<td>MCHC</td>
<td></td>
</tr>
<tr>
<td>RDW</td>
<td>Anisocytosis (variability in size)</td>
</tr>
</tbody>
</table>
| Retic count| **↓** in primary failure of production
|            | **↑** in blood loss, hemolysis                                               |
| Blood smear| Morphology evaluation for abnormalities in shape, size and for presence of RBC inclusions |
ANEMIA - Etiologies

- Blood loss
- Accelerated RBC destruction (hemolysis, hemoglobinopathies)
- Primary failure of RBC production (diminished erythropoiesis or hypoproliferative)
HYPOPROLIFERATIVE ANEMIA

May be subdivided according to the size of the red blood cell:

- Microcytic
- Macrocytic
- Normocytic
HYPOPROLIFERATIVE ANEMIA

Microcytic

- Iron deficiency anemia
- Thalassemia
- Sideroblastic anemia
- Lead poisoning
- Anemia of chronic disease
IRON DEFICIENCY ANEMIA
IRON DEFICIENCY ANEMIA

- Most common anemia worldwide
  - Globally, 50% of anemia

- 841,000 deaths annually worldwide
  - Africa and parts of Asia – 71% of global mortality
  - North America – 1.4% of mortality
IRON DEFICIENCY ANEMIA

- Most frequent cause is BLOOD LOSS
  - Men & postmenopausal women
    - GI bleeding - seek malignancies
    - In 15% patients cause not found
  - Premenopausal women
    - Vaginal bleeding (menses)
    - Parturitional hemorrhage
  - Rare causes
    - hemoptysis, hematuria
IRON DEFICIENCY ANEMIA

○ Increased requirements:
  ● Rapid growth – premature infants, children, adolescents
  ● Pregnancy, lactation

○ Dietary lack

○ Impaired absorption:
  ● Gastric resection
  ● Pancreatic insufficiency
  ● Intestinal malabsorption syndromes
    ○ Tropical and nontropical sprue
    ○ Crohn’s disease of small bowel
    ○ Short bowel syndrome
IRON DEFICIENCY ANEMIA

Clinical features:
- Pica – starch, ice, clay
- Koilonychia – spooning of the nails
- Blue sclerae
- Glossitis – sore tongue
- Cheilosis – fissures at corners of mouth
- Angular stomatitis
- Esophageal webs
IRON DEFICIENCY ANEMIA

- Laboratory features:
  - ↓ MCV, MCH, MCHC
  - ↑ or normal Platelet levels
  - ↓ Serum iron levels
  - ↑ Serum transferrin levels (TIBC)
  - ↓ Serum transferrin saturation (%)
  - ↓ Serum ferritin levels
  - Absent bone marrow iron stores
IRON DEFICIENCY ANEMIA

○ Blood transfusions:
  ● Only if the patient has evidence of cardiac ischemia or failure
  ● Administer with caution in patients with long standing anemia
    ○ They have expanded plasma volumes
    ○ Further increase in intravascular volume triggers congestive heart failure, especially in the elderly
IRON DEFICIENCY ANEMIA

Treatment of choice is oral iron supplements:
- Iron salts vs. complex iron compounds (SR)
  - 150–300 mg elemental iron per day, divided into 3 or 4 doses
  - Total iron deficit estimated by:
    \[
    \text{Iron (mg)} = (15 - \text{patient’s Hgb}) \times 2.3 \times \text{weight (kg)} + 1,000 \text{ (for stores)}
    \]
- 20% develop abdominal pain, nausea, vomiting, diarrhea or constipation
IRON DEFICIENCY ANEMIA

- Parenteral iron therapy only for:
  - Patients with malabsorption
  - Truly intolerant to oral supplements
  - Demand not satisfied with oral supplements alone – chronic bleeding

- Risk of anaphylaxis is 1 %
  - More frequent in women with collagen vascular disease
  - May be fatal despite treatment
IRON DEFICIENCY ANEMIA

- Response to therapy:
  - Increase in reticulocyte count in 4-7 days, peaks in 10 days
  - Hemoglobin increases by 2 g/dl after 3 weeks of therapy

- Duration of therapy:
  - 4-6 months after anemia is corrected
  - Or ferritin levels is above 50 ng/mL
HYPOPROLIFERATIVE ANEMIA

Macrocytic

- Megaloblastic
  - Cobalamin ($B_{12}$) deficiency
  - Folate deficiency
  - Myelodysplasia
  - Drug-induced megaloblastic anemia
- Nonmegaloblastic macrocytic anemia
  - High reticulocyte count
  - Liver disease
  - Hypothyroidism
MEGALOBLASTIC ANEMIA
MEGALOBLASTIC ANEMIA

- Defect in DNA synthesis affecting rapidly dividing cells in the bone marrow
  - Cells are unable to complete cell division
- Megaloblastic process eventually lead to:
  - Pancytopenia
  - Gastrointestinal problems (weight loss, diarrhea and/or constipation)
- Most common conditions causing megaloblastosis:
  - Folic acid deficiency
  - Cobalamin (B₁₂) deficiency
FOLATE DEFICIENCY

- Poor dietary intake - most common
  - Alcoholics, addicts, elderly, poverty, invalids
- Increased demand or loss
  - Pregnancy, lactation, prematurity (weight <1500 g)
  - Chronic hemolysis, malignancy (of rapid growth)
  - Inflammatory diseases, exfoliative dermatitis
  - Long-term dialysis, liver disease
- Malabsorption
  - Sprue, nontropical sprue, gluten enteropathy
  - Crohn’s disease, short bowel syndrome, amyloidosis
- Antifolate drugs
  - Phenytoin, primidone, tetracycline, sulphasalazine
**COBALAMIN (B₁₂) DEFICIENCY**

- **Nutritional deficiency**
  - Strict vegetarian diet, poverty, psychiatric disease
- **Malabsorption**: Pernicious anemia - most common
- **Gastointestinal causes**
  - Congenital absence or functional abnormality of IF
  - Total or partial gastrectomy, ileal resection
  - Intestinal diverticulosis, fistula, stricture, blind loop
  - Crohn’s disease, sprue, gluten-enteropathy
  - Zollinger-Elllison, atrophic gastritis, gastric bypass
- **Other causes**
  - Pancreatic insufficiency, alcoholism, HIV infection
  - Radiotherapy to ileum
  - Proton pump inhibitors, colchicine, metformin
PERNICIOUS ANEMIA

- Severe lack of **Intrinsic Factor** due to gastric atrophy
- Common disease in north Europe
  - Associated with:
    - Premature graying, blue eyes, blood type A, HLA-3
    - HLA-B8, B12, BW15 in those with endocrine disease
  - Occurs with autoimmune disorders:
    - Graves’ disease, Hashimoto thyroiditis
    - Vitiligo, Addison’s disease, Hypoparathyroidism
    - Adult-onset hypogammaglobulinemia
  - Diagnosis:
    - Anti-parietal cell Ab in 90% patients, less specific
    - Anti-intrinsic factor Ab in 60%, most specific
    - Schilling test – cumbersome, not done lately
MEGALOBLASTIC ANEMIA

Clinical features:
- Glossitis – sore tongue
- Cheilosis - fissures at corners of the mouth
- Increased pigmentation of nail beds and skin creases
- Lemon-colored skin (jaundice + pallor)
- Mild splenomegaly (due to extramedullary erythropoiesis)
- Neurological manifestations (B\textsubscript{12} deficiency)
NEUROLOGICAL MANIFESTATIONS
In Cobalamin ($B_{12}$) deficiency

- May be present even without anemia:
  - Posterior column dysfunction
    - Loss of proprioception and vibration sense
    - Wide-based gait, difficulty walking
  - Pyramidal, spinocerebellar, and spinothalamic tract disease
    - Muscular weakness, spasticity, hyper-reflexia, scissor gait
  - Peripheral nerve damage
    - Loss of DT Reflexes, Cranial nerve palsies
  - Dementia, neuropsychiatric disease
MEGALOBLASTIC ANEMIA

- **Laboratory features:**
  - Increased MCV, macrocytosis
  - Leucopenia, thrombocytopenia
  - Low reticulocyte count
  - Low serum haptoglobin levels

- **Blood morphology:**
  - Oval macrocytes, anisocytosis, poikilocytosis
  - Hypersegmented neutrophils

- **Decreased serum levels:**
  - Folic acid
  - Vitamin $B_{12}$
MEGALOBLASTIC ANEMIA

- Treatment:
  - If pernicious anemia is suspected:
    - Vitamin B$_{12}$ (1000 μg) IM daily for 7 days, then monthly for maintenance (for life)
  - Patients with normal B$_{12}$ absorption:
    - may be given oral/sublingual supplements
  - Folic acid supplements:
    - Orally 1-5 mg daily
MEGALOBLASTIC ANEMIA

- **Response to therapy:**
  - Reticulocytes in 2-3 days, peaks in 8 days
  - Hemoglobin increases within a week
  - Anemia resolves in 2 months

- **Watch out for:**
  - Acute hypokalemia, hyperuricemia, hypophosphatemia
  - Development of iron deficiency

- **Neurologic disease:**
  - Not always reversible
  - Maximal improvement in 6-12 months
HYPOPROLIFERATIVE ANEMIA

Normocytic

- Bone marrow failure
  - Aplastic anemia
  - Pure red cell aplasia
- Myelophthisis – marrow infiltration
  - Solid tumors: breast, prostate, lung
- Endocrinopathies
- Early iron deficiency
- “Mixed” anemias
- Anemia of chronic disease
ANEMIA OF CHRONIC DISEASE
ANEMIA OF CHRONIC DISEASE

- Most common anemia in hospitalized patients
- Associated conditions:
  - Chronic infections
  - Chronic inflammatory conditions
  - Autoimmune disorders
  - Malignancy
  - Trauma, tissue injury
ANEMIA OF CHRONIC DISEASE

- Characterized by:
  - Release of proinflammatory cytokines
  - Inadequate iron delivery to the marrow, despite normal or increased iron stores
  - Relatively low erythropoietin levels
  - Decreased marrow response to erythropoietin
  - Mildly shortened red cell survival

- This is a diagnosis of exclusion – all other possible causes of anemia must be ruled out
ANEMIA OF CHRONIC DISEASE

○ Laboratory features:
  ● CBC: 80% normocytic normochromic
    20% microcytic hypochromic
  ● ↑ Sed Rate
  ● ↓ Serum iron levels
  ● ↓ Serum transferrin levels (TIBC)
  ● ↑ Serum ferritin levels
  ● ↑ Bone marrow iron stores
ANEMIA OF CHRONIC DISEASE

- Manage, treat underlying disorder
- Transfusions only if < 8g/dl or physiologic compromise
- Recombinant EPO useful in:
  - Uremic anemia (50-150 U/kg TIW)
  - HIV infection
  - RA & other collagen diseases
  - Malignancies (300 U/kg TIW)
  - Multiple myeloma
ANEMIA - Etiologies

- Blood loss
- Primary failure of RBC production (diminished erythropoiesis or hypoproliferative)
- Accelerated RBC destruction (hemolysis, hemoglobinopathies)
HEMOLYTIC ANEMIA - Characteristics

- Shortening of the normal RBC life span
  - Premature destruction, survival <15 days
- Accumulation of Hgb catabolism products
  - Extravascular
    - Increased bilirubin production (jaundice)
    - Increased urinary and fecal urobilinogen
  - Intravascular
    - Decreased serum haptoglobin levels
    - Hemoglobin (Coca-cola), hemosiderin in urine
- Marked increase in BM erythropoiesis
HEMOLYSIS - Secondary Effects

- Reticulocytosis, red cell polychromasia
- Erythroid hyperplasia of the bone marrow
  - In chronic hemolysis
- Sequestration of cells in spleen
  - Work hypertrophy (SPLENOMEGALY)
- Increased folic acid requirements
  - May lead to megaloblastic anemia
- Increased uric acid production
  - May lead to uric acid nephropathy
HEMOLYSIS - Clinical Evaluation

- History of:
  - Rapid vs. gradual onset of symptoms
  - Fatigue, weakness, dark urine
  - Use of drugs: oxidative, immunogenic
  - Unexplained deep vein thrombosis
  - Anemia since childhood
  - Surgeries: splenectomy or cholecystectomy

- Family history of:
  - Anemia
  - Splenomegaly or splenectomies
  - Gallstones or cholecystectomies

- Examine for:
  - Pallor, jaundice
  - Splenomegaly, leg ulcers
# HEMOLYSIS - Laboratory Evaluation

<table>
<thead>
<tr>
<th>BASIC</th>
<th>SPECIFIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reticulocyte count</td>
<td>Osmotic fragility test</td>
</tr>
<tr>
<td>LDH</td>
<td>RBC protein analysis</td>
</tr>
<tr>
<td>Bilirubin total, indirect</td>
<td>G6PD assay</td>
</tr>
<tr>
<td>Haptoglobin levels</td>
<td>Sickle preparation</td>
</tr>
<tr>
<td>Urine hemosiderin</td>
<td>Hgb electrophoresis</td>
</tr>
<tr>
<td>Peripheral Blood Smear evaluation</td>
<td>Direct Coombs test</td>
</tr>
<tr>
<td></td>
<td>Cold agglutinins</td>
</tr>
<tr>
<td></td>
<td>Sugar water, Ham test</td>
</tr>
</tbody>
</table>
Hereditary Hemolytic Anemias

- **Membrane Defects**
  - Hereditary Spherocytosis
  - Hereditary Elliptocytosis
  - Hereditary Pyropoikilocytosis
  - Hereditary Stomatocytosis

- **Enzyme Defects**
  - Glucose-6-phosphatase dehydrogenase
  - Pyruvate kinase
  - Pyrimidine-5-nucleotidase
  - Triose phosphate isomerase

- **Hemoglobin Defects**
  - Hemoglobin S
  - Hemoglobin C, D, E
  - Unstable Hgb variants

- **Thalassemia Syndromes**
  - Alpha thalassemia
  - Beta thalassemia
HEREDITARY SPHEROCYTOSIS

MOLECULAR DEFECTS
- Ankyrin gene mutations causing spectrin and ankyrin deficiency (most common)
- Band 3 gene mutations (20% cases)
- α-spectrin gene mutations (autosomal recessive)

CLINICAL FEATURES
- Prevalence 1/5000 (of North Europe ancestry)
- Autosomal dominant (75%)
- Autosomal recessive (more severe disease)
HEREDITARY SPHEROCYTOSIS

DIAGNOSIS
- Family history
- Clinical findings
- Blood Morphology:
  SPHEROCYTES

Specific test:
Osmotic fragility test
HEREDITARY SPHEROCYTOSIS

CLINICAL PRESENTATION
- Anemia, splenomegaly
- Intermittent jaundice
- Hemolysis after infections
- Gallstones (43-85%)
- Asymptomatic (20-30%)

TREATMENT
- Splenectomy: >10 years old
- Vaccines: pneumococcal, meningococcal, influenza
- Folic acid supplementation
G6PD DEFICIENCY

GENETIC VARIANTS
- G6PD A-: 10% of American blacks
  - RBC’s have 10-60% enzyme, decay in older cells
- Mediterranean: populations of Middle East
  - RBC’s have <10% enzyme activity

CLINICAL FEATURES (G6PD A- Variant)
- X-linked inheritance
- No anemia in steady state
- Acute hemolysis occur 2-3 days after insult
- Hemolysis is self-limited
  - Recovery due to reticulocytosis
G6PD DEFICIENCY

G6PD A- Variant:
- Acute hemolysis occur with:
  - Infections
  - Diabetic coma
  - Liver, renal disease
  - Use of oxidant drugs

G6PD<sup>Med</sup> Variant:
- Neonatal jaundice
- Favism
  - Reaction to fava beans
- Chronic continuous hemolysis
  - Congenital nonspherocytic hemolytic anemia

OXIDANT DRUGS
- Sulfonamides
- Nitrofurantoin
- Nalidixic Acid
- Dapsone
- Chloramphenicol
- Doxorubicin
- Antimalarials
- Aminosalicylic Acid
- Phenacetin
- Probenecid
- Procainamide
- Vitamin C and K
- High-dose Aspirin
G6PD DEFICIENCY

BLOOD MORPHOLOGY

- Bite cells
- Blister cells
- Spherocytes
- Reticulocytes
  - New methylene blue stain
- Heinz bodies
  - Crystal violet stain
G6PD DEFICIENCY

DIAGNOSIS:
- Screening test:
  - Supravital stain (methylene blue)
- Definitive test:
  - G6PD Assay

TREATMENT:
- Treat underlying infections or diseases
- Avoid oxidant drugs
- Splenectomy
  - for those with chronic hemolysis
SICKLE CELL ANEMIA

MOLECULAR DEFECT
- Point mutation:
  - valine $\rightarrow$ glutamic acid at $\beta$ globin chain
- Resultant hemoglobin (Hb S) has abnormal physiochemical properties

CLINICAL FEATURES
- SICKLE CELL TRAIT:
  - Heterozygous $\rightarrow$ 40% is HbS
  - Patient is basically asymptomatic
- SICKLE CELL ANEMIA:
  - Homozygous $\rightarrow$ Almost all is HbS
  - Patient has full clinical syndrome
SICKLE CELL ANEMIA

Major Clinical Problems

Chronic Hemolysis
- Severe anemia
- Reticulocytosis
- Leukocytosis
- Thrombocytosis

Chronic Hyperbilirubinemia
- Jaundice
- Gallstones
- Liver disease

Vaso-occlusive Complications
- Ischemia (painful crisis)
- Infarctions
- Asplenia
**SICKLE CELL ANEMIA**

**CLINICAL MANIFESTATIONS**

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>ACUTE</th>
<th>CHRONIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary</strong></td>
<td>Acute chest syndrome</td>
<td>Chronic hypoxemia</td>
</tr>
<tr>
<td><strong>Genito-urinary</strong></td>
<td>Hematuria, Papillary necrosis</td>
<td>Hyposthenuria, Tubular defects</td>
</tr>
<tr>
<td><strong>Hepatobiliary</strong></td>
<td>RUQ syndrome, Viral hepatitis</td>
<td>Cholelithiasis, Sickle hepatopathy</td>
</tr>
<tr>
<td><strong>Cardio-vascular</strong></td>
<td>Angina, Ischemic infarcts</td>
<td>Cardiomegaly, Heart failure</td>
</tr>
</tbody>
</table>
SICKLE CELL ANEMIA

CLINICAL MANIFESTATIONS

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<th>ACUTE</th>
<th>CHRONIC</th>
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</thead>
<tbody>
<tr>
<td>Ocular</td>
<td>Retinal ischemia, hemorrhage, detachment</td>
<td>Proliferative retinopathy</td>
</tr>
<tr>
<td>Neurologic</td>
<td>TIA’s, Thrombotic &amp; hemorrhagic strokes, Seizures</td>
<td>Spinal disease Neo-vascularization Aneurysm formation</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td>Skin ulcers</td>
</tr>
<tr>
<td>Skeletal</td>
<td>Osteomyelitis (Salmonella) Bony infarcts</td>
<td>Avascular necrosis X-ray abnormalities (fishmouth deformity)</td>
</tr>
</tbody>
</table>
SICKLE CELL ANEMIA

DIAGNOSIS

- Screening test
  - Sickle cell preparation
  - Solubility test
- Definitive test
  - Hgb electrophoresis
- Prenatal diagnosis
  - Mst II Southern blot
  - PCR

MORPHOLOGY

- Sickle cells
- Polychromasia
- Reticulocytes
- Howell-Jolly bodies
SICKLE CELL ANEMIA

SUPPORTIVE THERAPY

- Painful Crisis
  - Analgesia, hydration, oxygen
  - Treat infections
- Hemolytic Crisis
  - Blood transfusions
  - Iron chelation therapy
  - Treat infections
  - Folic Acid – chronic use
- Life-threatening Vasoocclusion
  - Exchange transfusions
- Prophylaxis
  - Penicillin
  - Vaccines

TREATMENT

- BM transplantation
- Hydroxyurea (Hydrea)
  - Induces HbF
  - Retards HbS polymerization
  - Reduces number and severity of painful crisis
THALASSEMAIA SYNDROMES

- Heterogenous group of inherited anemias
- Defective synthesis of the alpha or beta globin chains:
  - Alpha thalassemia
  - Beta thalassemia
- Most common in Mediterranean area, Arabia, India and Southeast Asia
**ALPHA THALASSEMIA**

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>GENETIC DEFECT</th>
<th>CLINICAL FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silent carrier</td>
<td>$\alpha^{-}/\alpha \alpha$</td>
<td>None</td>
</tr>
<tr>
<td>Trait</td>
<td>$\alpha^-/\alpha^- \quad \alpha^-/\alpha \alpha$</td>
<td>Mild microcytic anemia</td>
</tr>
<tr>
<td>Hemoglobin H</td>
<td>$\alpha^-/\alpha^- \quad \alpha^-/\alpha \alpha$</td>
<td>Mild anemia, hemolysis, not transfusion dependent</td>
</tr>
<tr>
<td>Hydrops fetalis</td>
<td>$\alpha^-/\alpha^- \quad \alpha^-/\alpha \alpha$</td>
<td>Severe anemia, anasarca, death in utero</td>
</tr>
</tbody>
</table>
## Beta Thalassemia

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>GENETIC DEFECT</th>
<th>CLINICAL FEATURES</th>
</tr>
</thead>
</table>
| Minor    | $\beta^o / \beta$  
          | $\beta^+ / \beta$ | Mild microcytic anemia |
| Intermedia | $\beta^o / \beta$  
               | $\beta^+ / \beta^+$ | Anemia, not transfusion dependent, iron overload |
| Major    | $\beta^o / \beta^o$  
          | $\beta^+ / \beta^+$ | “Cooley’s anemia”  
                      | Severe anemia, transfusion dependent, iron overload |
THALASSEMIA MAJOR

CLINICAL FEATURES

- Severe anemia
  - ineffective erythropoiesis
  - extravascular hemolysis
- Marked marrow expansion
  - skeletal deformities
  - “chipmunk” facies
- Extramedullary hematopoiesis
  - Hepatosplenomegaly
- Systemic iron overload

MANAGEMENT

- Blood transfusions
- Iron chelation
- Splenectomy (>5 yrs)
- BM Transplant
- Prenatal diagnosis
  - DNA analysis
β THALASSEMIA TRAIT

CLINICAL FEATURES:
- Mild anemia, asymptomatic
- CBC: ↓ MCV
  ↓ MCH
  ↑ RBC number
- Dx: ↑ HbA2
  ↑ HbF
- Diff Dx: iron deficiency

MORPHOLOGY:
- Hypochromia
- Microcytosis
- Target cells
- Teardrops
- Basophilic stippling
Acquired Hemolytic Anemias

- Immune Hemolytic Anemias
  - IgG-induced (Warm antibody)
  - IgM-induced (Cold hemagglutinins)
  - Drug-induced

- Chronic Intravascular Hemolysis
  - Paroxysmal Nocturnal Hemoglobinemia
  - Mechanical Hemolysis
    - Heart valve hemolysis
    - March hemoglobinuria
    - Microangiopathic Hemolytic Anemia
AUTOIMMUNE HEMOLYTIC ANEMIA

- Most common: **IgG** - directed against RBC Ag (“Rh”)
- Ab reactive at body temperature (warm)
- IgG-coated RBC’s are recognized by Fc receptors of macrophages and trigger erythrophagocytosis
  - In **spleen**, liver, bone marrow
  - Hemolysis is mostly extravascular
  - RBC’s also coated with C$_3$B (by complement activation) have an accelerated clearance

- Manifests anemia, jaundice & splenomegaly
- Associated to autoimmune disorders (SLE) and lymphoproliferative disorders (CLL, NHL)
IgG - IMMUNE HEMOLYTIC ANEMIA

TREATMENT

- Prednisone (40-120 mg/day)
  - 80% response, 25% sustained
- Splenectomy
  - 50-70% response
- Immunosuppressiessive therapy
  - Azathioprine, cyclosporine
  - Cyclophosphamide, Vinca
  - 50% response, long-term
- High dose gammaglobulin
  - 50-60% response, expensive
- Anti-CD20 Ab (Rituximab)

DIAGNOSIS

- Morphology: spherocytes
- Positive antiglobulin test (direct Coombs)
IgM - IMMUNE HEMOLYTIC ANEMIA

- IgM - directed against RBC Ag ("I", "i", "Pr")
- Ab reactive at low temperatures (cold)
- Ag-Ab complex on surface of RBC activates classical complement pathway (C-dependent hemolysis)
  - Coats RBC with C_3b, cleared by liver (extravascular)
  - RBC destroyed directly (intravascular)

COLD AGGLUTININ DISEASE

- Monoclonal IgM κ against "I", very high titers (>1:1000)
- Usually affects the elderly, related to Waldenstrom
- Manifests acrocyanosis of ears, nose tip, toes and fingers
- Skin color is dusky blue tone that blanches
IgM - IMMUNE HEMOLYTIC ANEMIA

Cold agglutinins associated to other diseases

- To Mycoplasma pneumonia
  - IgM polyclonal Ab against “I”
  - Splenomegaly in most, acrocyanosis in unusual
  - Disease is self-resolving in 2 to 3 weeks

- To Infectious mononucleosis
  - IgM polyclonal Ab against “i”
  - Hepatosplenomegaly in most, hemolysis in 3%
  - Disease duration from 1 to 2 months

- To Lymphoproliferative / Autoimmune disorders (CLL, NHL, SLE)
  - IgM κ monoclonal Ab against “I” or “i”
IgM - IMMUNE HEMOLYTIC ANEMIA

TREATMENT:
- Keep patient warm
- Alkylating agents (Cytoxan, Leukeran)
  - 50-60% response rate
- Plasmapheresis
  - Effective, short-term, expensive
- Steroids, short-term
  - For Infectious mononucleosis
- Tetracycllin or Erythromycin
  - For Mycoplasma pneumonia

DIAGNOSIS:
- Morphology: RBC agglutination
- Cold agglutinins (Anti-I or Anti-i)
- Coombs test (+ for complement)
DRUG - INDUCED HEMOLYTIC ANEMIA

**DIAGNOSIS**
- Hapten type
  - With high-dose penicillin
  - IgG +/- C₃b coats RBC
- Quinidine type (inocent bystander)
  - Ab against drug bound to protein
  - Activates C, C₃b coats RBC
- Alpha-methyldopa type (Aldomet)
  - Ab against Rh Ag
  - 25% develop (+) Coombs test
  - <1% hemolyze
- Nonspecific coating
  - Drug binds to RBC’s, proteins coat
  - With Cephlothin, rare hemolysis

**TREATMENT**
- D/C drug
- Steroids
PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Clonal BM disorder affecting stem cells
- Deficiency of protective membrane proteins (CD59, CD55)
- PNH cells are very sensitive to activated complement

CLINICAL FEATURES

- Anemia, reticulocytopenia, leukopenia, thrombocytopenia
- Spherocytes, microcytosis, hypochromia (2° iron deficiency)
- Chronic intravascular hemolysis (most common)
- Paroxysmal hemolysis, nocturnal hemoglobinurinia (<25%)
- Episodic severe abdominal, back & musculoskeletal pain
- Venous thrombosis of major vessels (50% mortality)
- Evolves to aplastic anemia or acute leukemia (5-10%)
PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

DIAGNOSIS
- Sugar water, acidified serum (Ham) tests
- Flow cytometry: Bimodal distribution, CD59- CD55-

SUPPORTIVE THERAPY
- Transfusion of filtered PRBC (removal of WBC)
- Folic acid, iron supplements
- Narcotics, hydration
- +/- Prednisone, Danazol

TREATMENT
- Bone marrow transplant
- Antithymocytic globulin
- Monoclonal Ab against C5 (Eculizumab) q 2 wk IV
MECHANICAL HEMOLYSIS

Heart valve hemolysis, March hemoglobinuria
Microangiopathic Hemolytic Anemia

- **Pathogenesis:**
  - Direct trauma to RBC’s

- **Blood morphology:**
  - Schistocytes, helmet cells, microspherocytosis

- **Diagnostic tests:**
  - Plasma hemoglobin - positive
  - Urine hemoglobin - positive
  - Urine hemosiderin - positive
  - Haptoglobin - decreased
MICROANGIOPATHIC HEMOLYTIC ANEMIA

- Fibrin deposits in small blood vessels cause fragmentation and deformation of the RBC’s
- Often are also thrombocytopenic
- Associated with several syndromes

TTP, HUS, DIC
- malignant hypertension
- pulmonary hypertension
- preeclampsia, eclampsia
- acute glomerulonephritis
- acute renal failure
- renal allograft rejection
- collagen vascular diseases
- SLE, scleroderma
- Wegener’s granulomatosis
- periarteritis nodosa
- carcinomatosis, hemangiomas
- Kasabach-Meritt syndrome
- viral (HIV), bacterial infections
- toxic effect of mitomycin C