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

CBC	Monocytopenia vs. Pancytopenia
MCV, MCH MCHC	Microcytosis, Macrocytosis, Normocytic indexes
RDW	Anisocytosis (variability in size)
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:

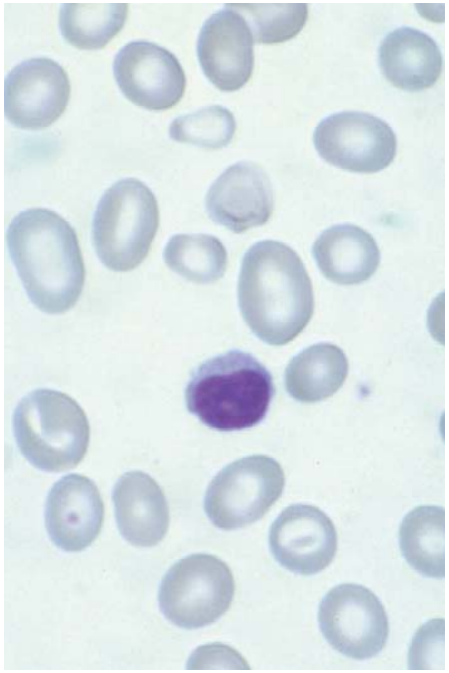
- Microcytic
- Macrocytic
- Normocytic

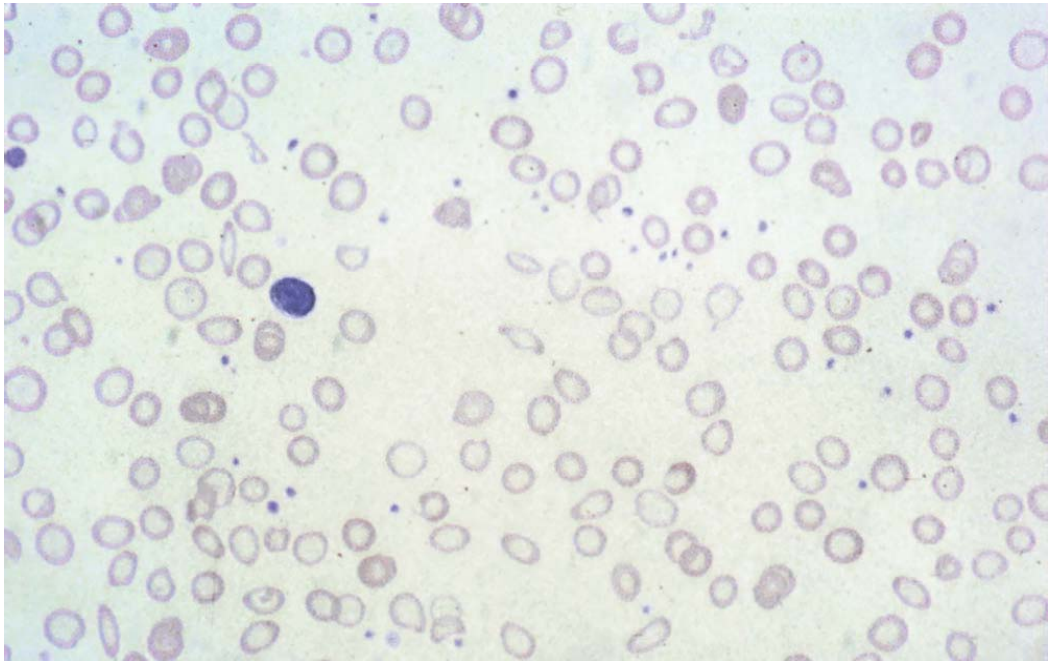
HYPOPROLIFERATIVE ANEMIA

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:

    Iron (mg) = (15 – patient's Hgb) x 2.3 x weight (kg) + 1,000 (for stores)
  - 20% develop abdominal pain, nausea, vomiting, diarrhea or constipation

IRON DEFICIENCY ANEMIA

- Parenteral iron therapy only for:
  - Patients with malabsortion
  - 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

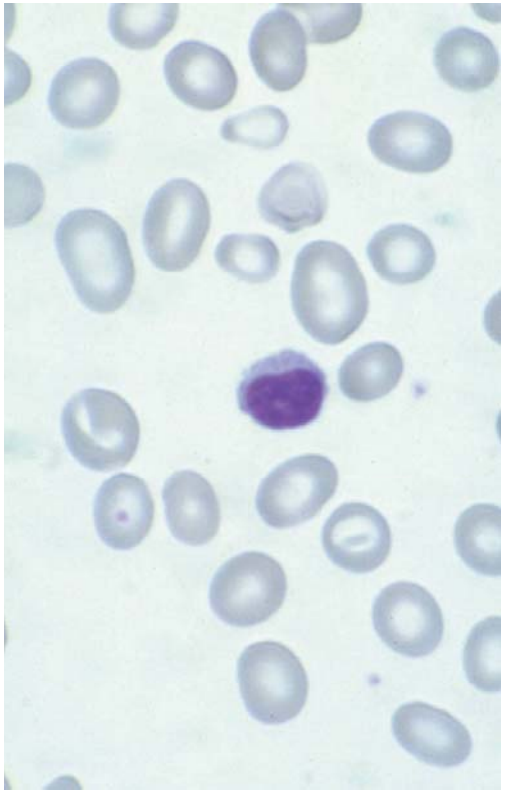
- Response to therapy:
  - Increase in reticulocyte count in 4-7 days, peaks in 10 days
  - Hemoglobin increases by 2 g/dl after 3 weeks of therapy
- Duration of therapy:
  - 4-6 months after anemia is corrected
  - Or ferritin levels is above 50 ng/mL

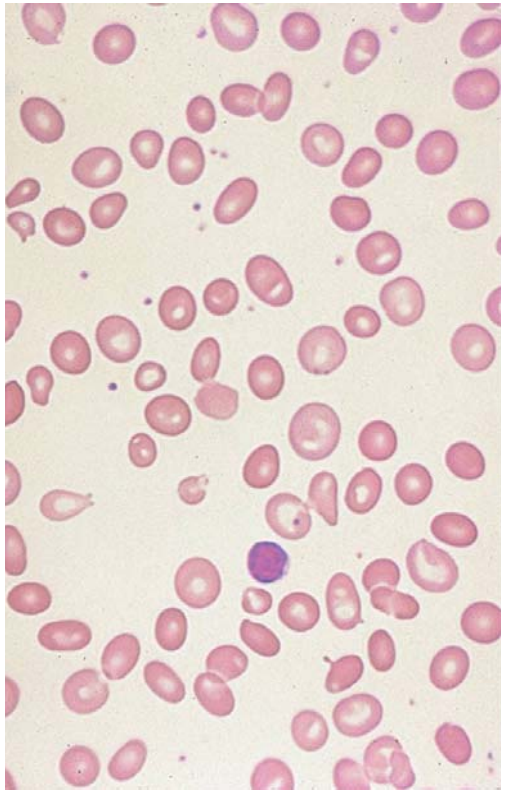
HYPOPROLIFERATIVE ANEMIA

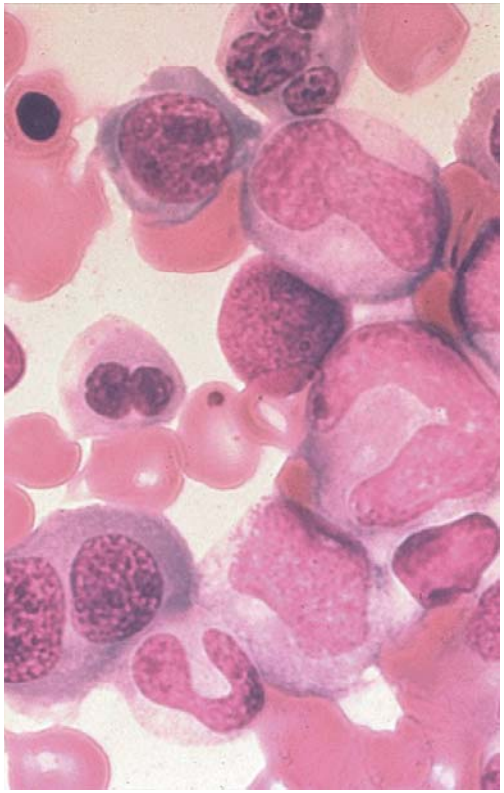
Macrocytic

- 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 (B_{12}) 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 (B_{12}) 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_{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

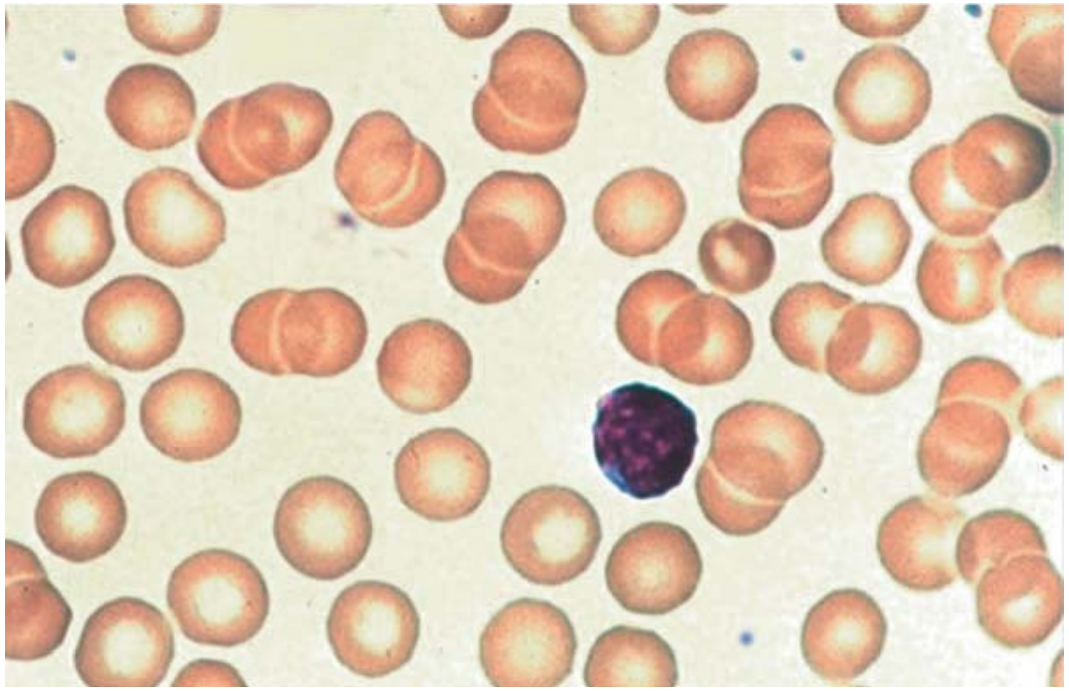
- Response to therapy:
  - Reticulocytes in 2-3 days, peaks in 8 days
  - Hemoglobin increases within a week
  - Anemia resolves in 2 months
- Watch out for:
  - Acute hypokalemia, hyperuricemia, hypophosphatemia
  - Development of iron deficiency
- Neurologic disease:
  - Not always reversible
  - Maximal improvement in 6-12 months

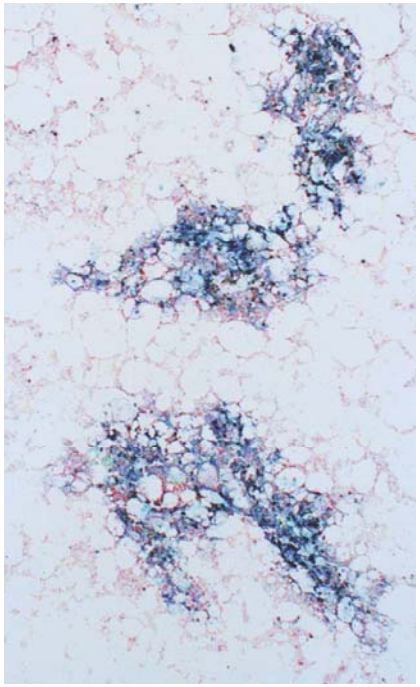
HYPOPROLIFERATIVE ANEMIA

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

BASIC :

- Reticulocyte count
- LDH
- Bilirubin total, indirect
- Haptoglobin levels
- Urine hemosiderin
- Peripheral Blood Smear evaluation

SPECIFIC:

- Osmotic fragility test
- RBC protein analysis
- G6PD assay
- Sickle preparation
- Hgb electrophoresis
- Direct Coombs test
- Cold agglutinins
- Sugar water, Ham test

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)

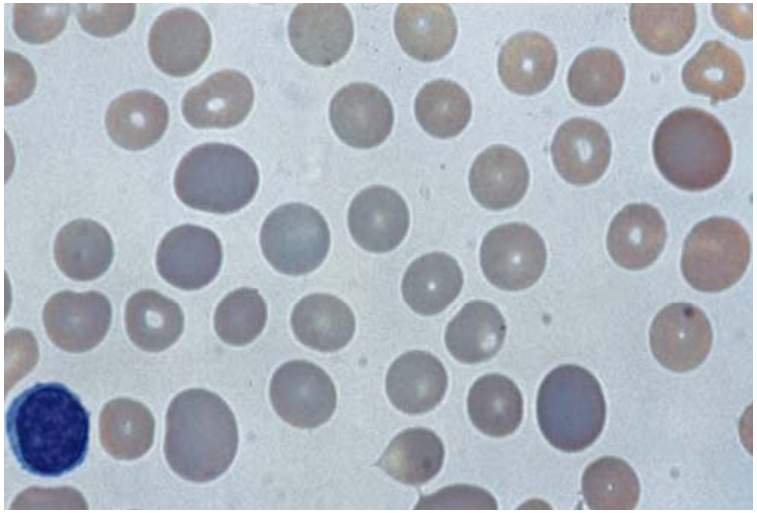
CLINICAL FEATURES

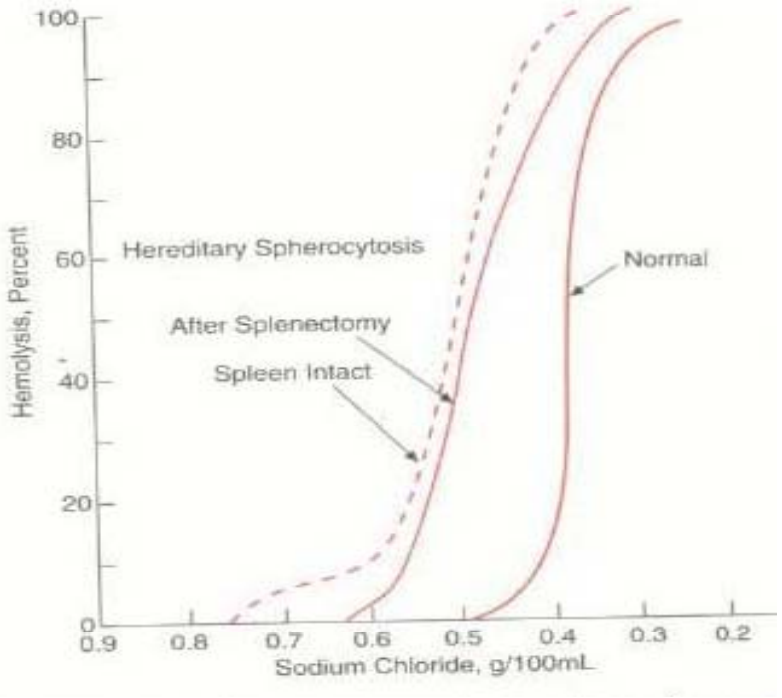
- Prevalence 1/5000 (of North Europe ancestry)
- Autosomal dominant (75%)
- Autosomal recessive (more severe disease)

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^{Med} Variant:

- Neonatal jaundice
- Favism
  - Reaction to fava beans
- Chronic continuous hemolysis
  - Congenital nonspherocytic hemolytic anemia

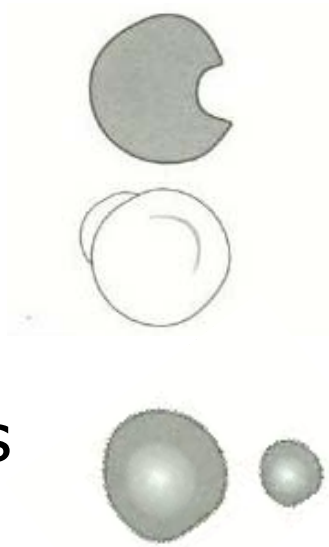
OXIDANT DRUGS

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

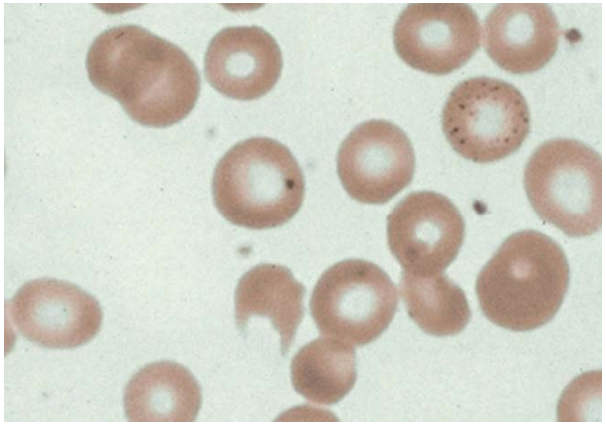
G6PD DEFICIENCY

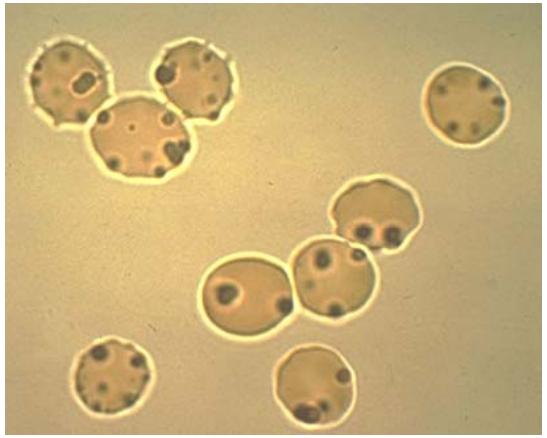
BLOOD MORPHOLOGY

- 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

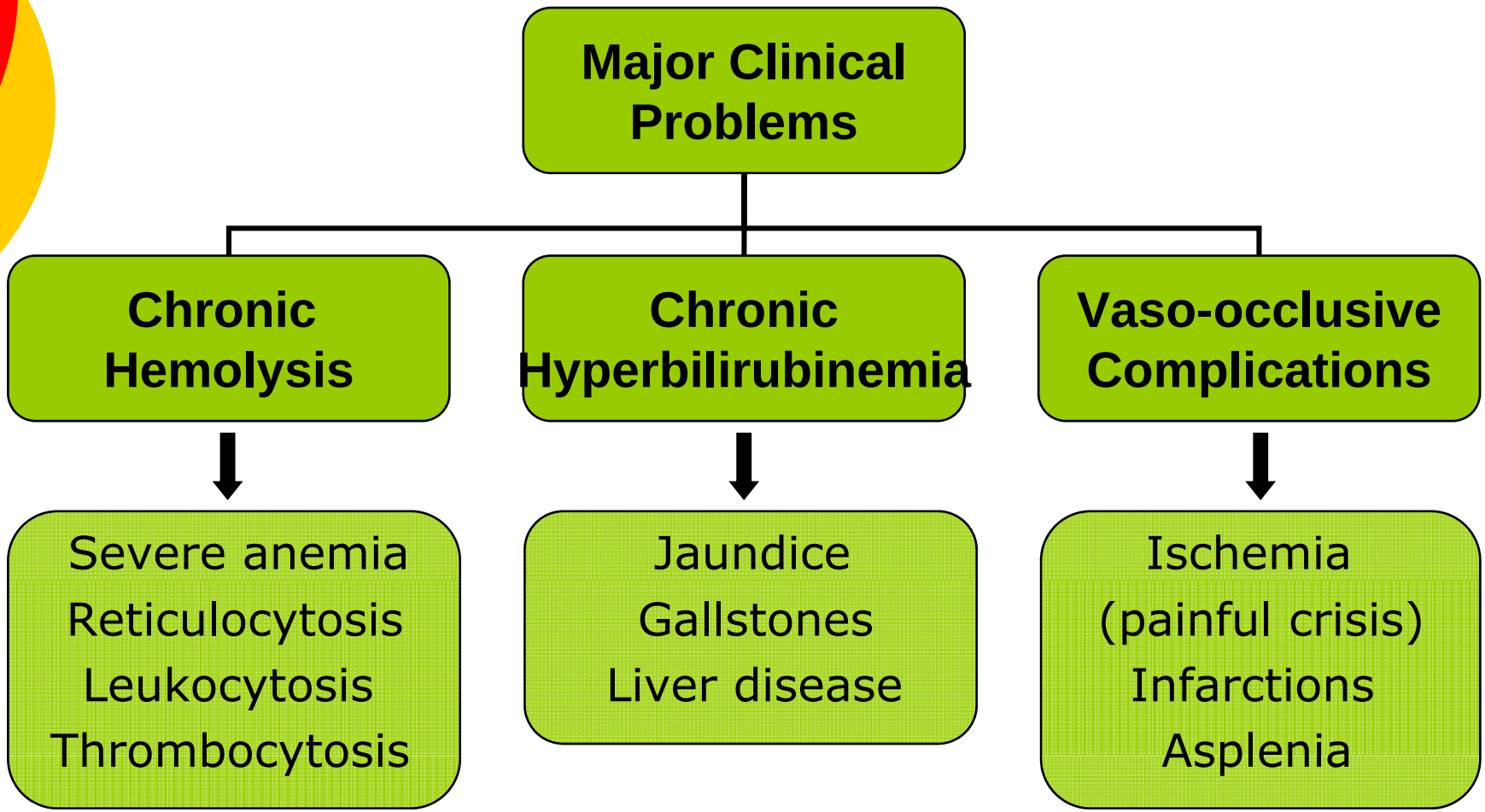
MOLECULAR DEFECT

- Point mutation:
  - valine ⇨ glutamic acid at β globin chain
- Resultant hemoglobin (**Hb S**) has abnormal physiochemical properties

CLINICAL FEATURES

- SICKLE CELL TRAIT :
  - Heterozygous ⇨ 40% is HbS
  - Patient is basically asymptomatic
- SICKLE CELL ANEMIA :
  - Homozygous ⇨ Almost <u>all</u> is HbS
  - Patient has full clinical syndrome

SICKLE CELL ANEMIA



SICKLE CELL ANEMIA

CLINICAL MANIFESTATIONS

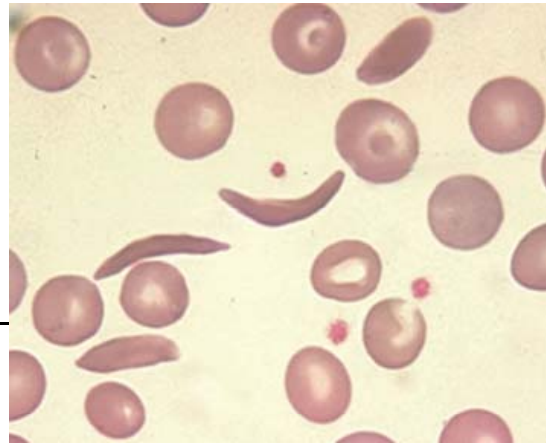
ORGAN	ACUTE	CHRONIC
Pulmonary	Acute chest syndrome	Chronic hypoxemia
Genito-urinary	Hematuria Papillary necrosis	Hyposthenuria Tubular defects
Hepato-biliary	RUQ syndrome Viral hepatitis	Cholelithiasis Sickle hepatopathy
Cardio-vascular	Angina Ischemic infarcts	Cardiomegaly Heart failure

SICKLE CELL ANEMIA

CLINICAL MANIFESTATIONS

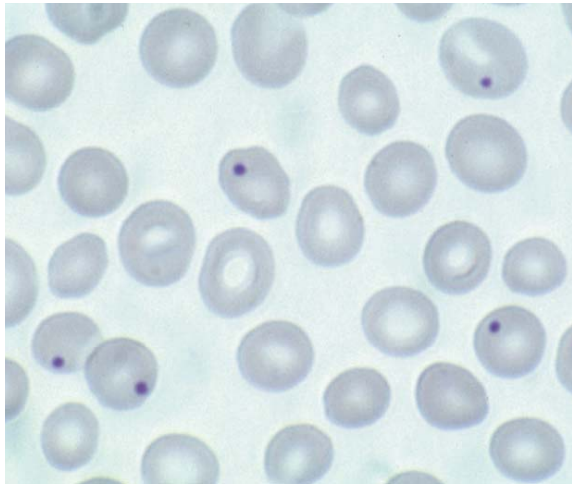
ORGAN	ACUTE	CHRONIC
Ocular	Retinal ischemia, hemorrhage, detachment	Proliferative retinopathy
Neurologic	TIA's, Thrombotic & hemorrhagic strokes, Seizures	Spinal disease Neo-vascularization Aneurysm formation
Skin		Skin ulcers
Skeletal	Osteomyelitis (Salmonella) Bony infarcts	Avascular necrosis X-ray abnormalities (fishmouth deformity)

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 transplantion
- Hydroxyurea (Hydrea)
  - Induces HbF
  - Retards HbS polymerization
  - Reduces number and severity of painful crisis

THALASSEMIA 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

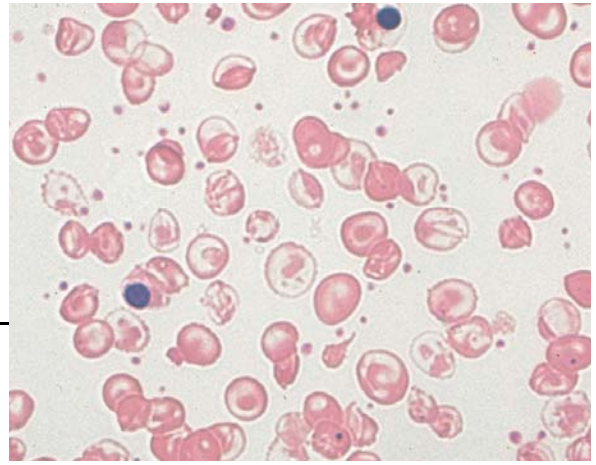
ALPHA THALASSEMIA

SYNDROME	GENETIC DEFECT	CLINICAL FEATURES
Silent carrier	$\alpha - / \alpha\ \alpha$	None
Trait	$\alpha - / \alpha -$ $- - / \alpha\ \alpha$	Mild microcytic anemia
Hemoglobin H	$- - / \alpha -$	Mild anemia, hemolysis, not transfusion dependent
Hydrops fetalis	$- - / - -$	Severe anemia, anasarca, death in utero

BETA THALASSEMIA

SYNDROME	GENETIC DEFECT	CLINICAL FEATURES
Minor	β^o / β β^+ / β	Mild microcytic anemia
Intermedia	β^o / β β^+ / β^+	Anemia, not transfusion dependent, iron overload
Major	β^o / β^o β^+ / β^+	"Cooley's anemia" Severe anemia, transfusion dependent, iron overload

THALASSEMIA MAJOR



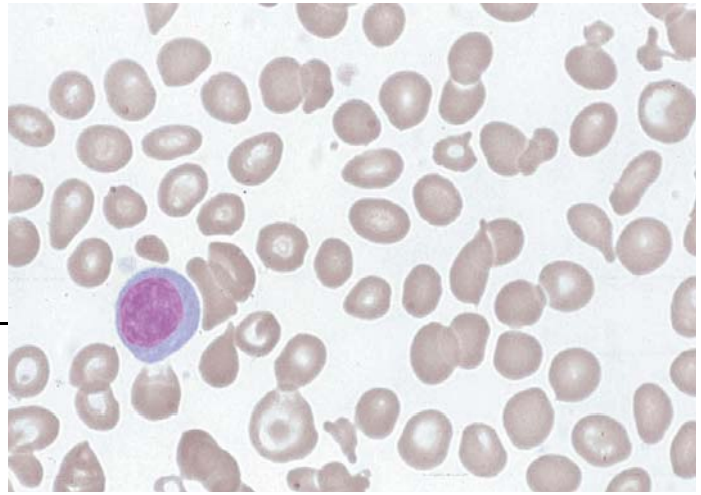
CLINICAL FEATURES

- 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:

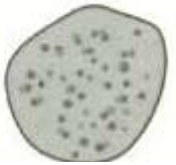
- Mild anemia, asymptomatic
- CBC: ⇩ MCV
  ⇩ MCH
  ⇧ RBC number
- Dx: ⇧ HbA2
  ⇧ HbF
- Diff Dx: iron deficiency

MORPHOLOGY:

- Hypochromia
- Microcytosis
- Target cells

- Teardrops

- Basophilic stippling



Acquired Hemolytic Anemias

- Immune Hemolytic Anemias
  - IgG-induced (Warm antibody)
  - IgM-induced (Cold hemaglutinins)
  - 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_3b (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

DIAGNOSIS

- Morphology: spherocytes
- Positive antiglobulin test (direct Coombs)

TREATMENT

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

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

DIAGNOSIS:

- Morphology:
  RBC agglutination
- Cold agglutinins
  (Anti-I or Anti-i)
- Coombs test
  (+ for complement)

TREATMENT:

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

DRUG - INDUCED HEMOLYTIC ANEMIA

DIAGNOSIS

- Morphology: spherocytes
- (+) Coombs

  [drug incubated donor RBC's]

TREATMENT

- D/C drug
- Steroids

- Hapten type
  - With high-dose penicillin
  - IgG +/- C_3b coats RBC
- Quinidine type (inocent bystander)
  - Ab against drug bound to protein
  - Activates C, C_3b 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 Cephalothin, rare hemolysis

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^o iron deficiency)
- Chronic intravascular hemolysis (most common)
- Paroxysmal hemolysis, nocturnal hemoglobinuria (<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, Danazole

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, microspherocytes
- 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