ANEMIA

- Hemoglobin <13 grams or
- Hematocrit <39%
ANEMIA

MCV

RETICULOCYTE COUNT

Corrected retic ct :

>2%: blood loss or hemolysis

<2%: hypoproliferative process
ANEMIA

- MICROCYTIC
- Obtain and interpret iron studies
- Serum iron
- Total iron binding capacity (TIBC)
- Transferrin saturation
- Ferritin—correlates with total iron stores
  - can be nml or inc if co-existent inflammation
IRON DEFICIENCY

- Most common nutritional problem in the world
- Absorbed in small bowel, enhanced by gastric acid
- Absorption inhibited by inflammation, phytates (bran) & tannins (tea)
CAUSES OF IRON DEFICIENCY

- Blood loss – most common etiology
- Decreased intake
- Increased utilization - EPO therapy, chronic hemolysis
- Malabsorption – gastrectomy, sprue
CLINICAL MANIFESTATIONS OF IRON DEFICIENCY

- Impaired psychomotor development
- Fatigue, Irritability
- PICA
- Koilonychiae, Glossitis, Angular stomatitis
- Dysphagia
IRON DEFICIENCY LAB FINDINGS

- Low serum iron, increased TIBC
- % sat <20
MANAGEMENT OF IRON DEFICIENCY

- MUST LOOK FOR SOURCE OF BLEED:  ie: GI, GU, Regular blood donor

- Replacement:
  1. Oral: Ferrous sulfate 325 mg TID until serum iron, % sat, and ferritin mid-range normal, 6-12 months
  2. IV
SIDEROBLASTIC ANEMIAS

Diverse group of disorders of RBC production characterized by:

1. Defect involving incorporation of iron into heme molecule
2. Ringed sideroblasts in bone marrow
CLASSIFICATION OF SIDEROBLASTIC ANEMIA

- ACQUIRED IDIOPATHIC – now considered one of the MDS categories
- REVERSIBLE – alcohol, INH, chloramphenicol
- LEAD POISONING – autonomic & motor neuropathy, abdominal pain
THERAPY OF SIDEROBLASTIC ANEMIA

- SUPPORTIVE
- PYRIDOXINE
- ALLO BMT
- EPO
THALASSEMIA

- Perhaps man’s most common genetic disorder

- Beta Thal – decreased synthesis of beta globin chain mostly caused by point mutations, resulting in relative excess of alpha globin chains, dx-Hg electropheresis

- Alpha Thal – decreased synthesis of alpha globin chains mostly caused by gene deletion resulting in relative excess of beta globin chains, dx-Alpha thal gene probe
THALASSEMIA
CLINICAL CLASSIFICATION OF B-THALASSEMIA

- B-Thalassemia trait (B-thalassemia minor): uncomplicated heterozygous B-Thal
- B-Thalassemia intermedia: many different genotypes
- B-Thalassemia major (Cooley’s anemia): homozygous or compound heterozygous B-thal
- genotype-phenotype correlations often difficult to make: 100s of mutations, frequent interactions, role of other modifying genes and environment
CLINICAL DIAGNOSIS OF B-THALASSEMIA

- **B-Thalassemia trait**
  - microcytosis, hypochromia, +/- mild anemia
  - elevated level of HbA2 (>3.5%)

- **B-Thalassemia intermedia**
  - microcytic anemia, may need treatment
  - many different genotypes, high Hb F
  - bone disease, iron overload, splenomegaly, pulm hypertension
CLINICAL DIAGNOSIS OF B-THALASSEMIA

- B-Thalassemia major
  - transfusion-dependent microcytic anemia
  - very high Hb F (approaching 100%)
  - bone disease, iron overload, splenomegaly, pulmonary hypertension
BETA THALASSEMIA: COMPLICATIONS

If transfusion dependent, best if managed in thalassemia center

- Pulmonary hypertension
- Thromboembolism
- Heart Disease
- Endocrinopathies
- Bone Disease
- Liver Disease
- Growth Retardation/Skeletal changes
ALPHA THALASSEMIA

- Silent carrier: heterozygous a+ thal; 3 of 4 alpha genes present and functional; +/- mild microcytic anemia

- Trait: 2 of 4 alpha genes present and functional; +/- mild microcytic anemia; Hb Barts (gamma 4) in 2-10% newborns

- Hemoglobin H Disease: genotype a-/- -; 20-40% Hb Barts in newborns; 5-40% Hg H(Beta 4) in adults
ALPHA THALASSEMIA

- Hemoglobin H Disease: hemolysis of varying degrees, microcytosis, splenomegaly ineffective erythrocytosis, iron overload

- Hemoglobin Bart’s Hydrops Fetalis: Homozygous alpha 0 (-/- -); no functional alpha globulin genes: Hb Barts, eclampsia in mother, stillbirth, erythroblastosis in infant
ALPHA THALASSEMIA TRAIT

- 2 of 4 alpha genes present and functional
- +/- mild anemia
- MCV <80
- Usually diagnosis of exclusion
ALPHA THALASSEMIA

- SCREENING: in populations at high risk for Hb Bart’s or hydrops fetalis
- Hg H Disease: Regular medical follow-up
- Diagnosis of the very mild alpha thalassemias, carrier & trait is important only for counseling and avoiding misguided treatments like iron
- Diagnosed by Alpha Thal gene probe
THALASSEMIA

BIGGEST MISTAKE:
Treated with iron without benefit of iron studies
NORMOCHROMIC NORMOCYCTIC ANEMIA

ANEMIA OF CHRONIC DISEASE

Hypoproliferative anemia

- Decreased red cell survival
- Impaired EPO production
- Impaired marrow response to EPO
- Impaired mobilization of iron
- Inflammatory response to underlying disorder
ANEMIA OF CHRONIC DISEASE

- Chronic nonhematologic conditions:
  - Infectious
  - Malignant
  - Inflammatory
  - Traumatic
ANEMIA OF CHRONIC DISEASE: DIAGNOSIS

- Exclude other etiologies of anemia
- Confirm hypoproliferative anemia
- Low serum iron despite increased iron stores in bone marrow & macrophages
ANEMIA OF CHRONIC DISEASE: THERAPY

› Most are self-limiting and need no specific treatment
› Treat the underlying disorder
› Correct any coexistent deficiency
› Selected patients may benefit from EPO
MACROCYTIC ANEMIA

- Characterized by abnormal nuclear maturation of red cell precursors
- B12 Deficiency
- Folic Acid Deficiency
- Chemotherapy
- MDS
- Monoclonal protein
B12 ABSORPTION

- **STOMACH**: Acid, pepsin
  - Parietal cells
  - Intrinsic factor
- **DUODENUM**
- **TERMINAL ILEUM**
CAUSES OF B12 DEFICIENCY

- Dietary lack
- Inadequate proteolysis of B12
  - H2 Blockers, PPIs
- Deficiency of intrinsic factor
  - Gastrectomy, H2 Blockers
  - Pernicious Anemia
- Associated autoimmune disorders: hypothyroidism, Hashimoto’s, vitiligo, diabetes, Addison’s disease
CAUSES OF B12 DEFICIENCY

- Metformin
- Infections: HIV, H. pylori
- Blind loop
- Diphyllobothrium latum
- Intestinal malabsorption
- Congenital disorders
- Nitrous Oxide inhalation
- Pancreatic insufficiency
SYMPTOMS OF B12 DEFICIENCY

- Brain and cranial nerves-dementia, personality changes, psychiatric disorders, disturbances in taste & smell, optic nerve abnormalities

- Peripheral neuropathy-paresthesias, sensory disturbances, diminished vibration and position sense

- Myelopathy affecting:
  - posterior columns: acroparesthesias, sensory disturbances, incoordination, ataxia, diminished vibration, position
  - lateral columns: weakness, spasticity
Neuropsych symptoms can predate hematological changes.

Serum B12 level <300 is standard diagnostic test but may not accurately reflect tissue levels.

Hyperlobated WBCs
B 12 DEFICIENCY

- Methylmalonic acid and homocysteine levels elevated
- Antibody testing to diagnose PA:
  - anti-parietal cell ab
  - anti-intrinsic factor ab
TREATMENT

・ Oral- becoming the replacement mode of choice; includes SL
・ IM or SQ
・ Nasal, expensive
・ Prophylactic for gastric or ileal resection
CAUSES OF FOLATE DEFICIENCY

- Dietary deficiency, can evolve in months
- Increased requirements
- Intestinal malabsorption
- Drugs that interfere with folate metabolism
DIAGNOSIS OF FOLATE DEFICIENCY

- **SERUM FOLATE**
  - May normalize after 1 meal
  - May be low normal with true folate deficiency

- **RBC FOLATE**
  - Normal or borderline in 60% pregnant pts and 30% alcoholics with true folate deficiency
TREATMENT

- Folic acid 1 mg po daily is usually adequate
- Maintenance Rx: depends on underlying disorder
- Prophylactic Rx: Pregnancy, prematurity, hemolysis, dialysis
HEMOLYTIC ANEMIA

PREMATURE DESTRUCTION OF RBC’S

Occurs by 2 different mechanisms

- Extra vascular hemolysis: RBCs prematurely removed from circulation by liver or spleen
- Intravascular hemolysis: RBCs lyse in the circulation
HEMOLYTIC ANEMIA

2 MAIN CAUSES

- Intrinsic RBC defects (inherited)
- Extra-corpuscular causes (acquired)
HEMOLYTIC ANEMIA

HEREDITARY HEMOLYTIC DISORDERS

- RBC Enzyme Defects
- RBC Membrane Defects
- Hemoglobinopathies
- Thalassemias
HEMOLYTIC ANEMIAS

- ACQUIRED HEMOLYTIC DISORDERS
- Immune Hemolytic Anemias
- Splenomegaly
- Microangiopathic Hemolytic Anemia
- PNH
- Direct toxic effect (malaria, clostridia)
- Spur Cell Anemia
DIAGNOSIS OF HEMOLYTIC ANEMIA

- Corrected Retic ct >2%
- Elevated indirect bilirubin
- Elevated LDH
- Haptoglobin low or absent
- Urine hemosiderin: present in intravascular hemolysis only
- Urine hemoglobin: present in severe intravascular hemolysis - urine dipstick positive for blood but no RBCs seen on micro
AUTOIMMUNE HEMOLYTIC ANEMIA
DIAGNOSIS: DIRECT ANTIGLOBULIN TEST-Coombs

- Useful in diagnosing immune hemolytic anemia where there is antibody coating a patients red blood cells
- Done by mixing patients erythrocytes with antihuman globulin containing antibody to IgG and C3
- Test positive if agglutination occurs
INDIRECT ANTIGLOBULIN TEST (INDIRECT COOMBS)

- Useful to detect antibodies present in patient’s serum
- Helpful in detecting alloantibodies induced by prior transfusion or by fetal transfer to mother
Direct Antiglobulin Test

- Antigen
- Erythrocyte
- In vivo antibody coating of erythrocytes
- Anti-IgG AHG reagent added after erythrocytes are washed
- AHG reagent causes IgG-coated erythrocytes to agglutinate

Indirect Antiglobulin Test

- Antibodies in serum
- Reagent erythrocyte
IMMUNE HEMOLYTIC ANEMIA

- 40-50% Idiopathic
- Induced by binding of antibody &/or complement to RBC membrane
- Caused by autoantibody directed against patients own RBCs or acquired alloantibody directed against transfused RBCs
- Coombs is only test that provides definitive evidence of immune hemolysis.
IMMUNE HEMOLYTIC ANEMIA

Warm-antibody Autoimmune Hemolytic Anemia

- Autoantibodies optimally reactive at 37C
- IgG present on RBC surface
- May also have C3
- Most cases idiopathic
- Can be a complication of underlying disease
IMMUNE HEMOLYTIC ANEMIA

Warm Antibody Related Diseases

- Chronic lymphocytic leukemia
- Collagen vascular diseases
- Ulcerative colitis
- Congenital immunodeficiency
TREATMENT OF WARM-REACTIVE AIHA

- Prednisone 1 mg/kg/d
- Folic acid
- Splenectomy if refractory to prednisone
- Immunosuppressive drugs
- IVIg, Rituximab
- TRANSFUSE LEAST INCOMPATIBLE BLOOD
**IMMUNE HEMOLYTIC ANEMIA**

- COLD ANTIBODY
  - Cold Agglutinin disease
    - idiopathic
    - chronic lymphocytic anemia
    - mycoplasma infection
    - infectious mononucleosis
  - Paroxysmal Cold Hemoglobinuria
TREATMENT OF COLD ANTIBODY AIHA

- Avoid cold exposure
- Folic acid therapy
- Treatment of underlying disorder
- Immunosuppressive agents
- Splenectomy of little value
- Rituximab
- Plasmapheresis
TREATMENT OF COLD ANTIBODY AIHA

- Transfusions of packed red blood cells:
- Compatibility testing should be done at 37°C
- Transfuse warm blood recommended but lacks proven efficacy
PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

- Acquired clonal stem cell disorder in which a mutation of PIG-A gene causes defective production of GPI Anchor Protein
- Only a portion of RBCs affected
- Defective platelets & WBCS
- Increased sensitivity of RBCS to complement mediated hemolysis
PNH: CLINICAL PRESENTATION

- May remain undiagnosed for a long period of time
- History of unexplained, chronic hemolysis, hemoglobinuria, pancytopenia & thrombotic events
- Intravascular hemolysis
- Absent haptoglobin, increased LDH, hemoglobinuria, & hemosidinuria
Can be found in the setting of another specified bone marrow disorder:

- Aplastic Anemia
- Refractory Anemia-MDS

Can be subclinical (no hemolysis)
PNH: DIAGNOSIS

Flow cytometry using antibodies directed against GPI-AP (glucosyl phosphatidylinositol-anchored proteins)
PNH: TREATMENT

- Folic acid
- Corticosteroids
- RBC Transfusions
- Iron (can precipitate hemolysis)
- Anticoagulation with warfarin
- Eculizumab (Solaris)
- Stem cell transplant
NONIMMUNE HEMOLYTIC ANEMIA

Inherited nonimmune hemolytic anemia

RBC membrane disorders:

- Hereditary spherocytosis
- Hereditary elliptocytosis
- Hereditary stomatocytosis
- G6PD deficiency
HEREDITARY SPHEROCYTOSIS

- Molecular defect in one or more of the proteins in the red blood cell cytoskeleton causing the cell to contract into a sphere shape. It has a high osmotic fragility and more prone to physical degradation.

- Osmotic fragility test
HEREDITARY SPHEROCYTOSIS

- Mild to severe hemolytic anemia
- Spherocytes on peripheral smear
- Increased osmotic fragility
- Negative direct antiglobulin test
- Aplastic crisis with viral infection
- Splenectomy is treatment of choice in severe cases
HEREDITARY SPHEROCYTOSIS
G6PD DEFICIENCY

- Most common enzyme deficiency worldwide.
- Different gene mutations cause different levels of enzyme deficiency and disease manifestations. G6PD helps protect hemoglobin from oxidation upon exposure to a drug or toxin that results in the generation of free radicals.
- Drugs associated with hemolysis: primaquine, sulfa, dapsone, nitrofurantoin.
- Fava beans will cause acute hemolysis shortly after ingestion.
G6PD DEFICIENCY

- Acute hemolysis lasts 2-4 days, self-limiting, rarely requiring transfusion
- Infections and diabetic ketoacidosis can trigger hemolysis
- “Bite” cells on peripheral smear and Heinz bodies (precipitated hemoglobin)
- Diagnosis made by level of G6PD, but may be normal in active hemolysis
HEINZ BODIES & BITE CELLS
HEMOGLOBINOPATHIES

- SICKLE CELL DISEASE - the bone marrow makes sickle shaped red blood cells due to qualitative defects of globulin chain synthesis
  - HbS >50%
  - Multiple genotypes and phenotypes
  - Sickle Cell Trait is not a disease
**A** Normal red blood cells

- Normal red blood cell (RBC)
- RBCs flow freely within blood vessel

**B** Abnormal, sickled, red blood cells (sickle cells)

- Sickle cells blocking blood flow
- Sticky sickle cells
- Cross-section of sickle cell
  - Abnormal hemoglobin form strands that cause sickle shape
- Cross-section of RBC
  - Normal hemoglobin
SICKLE CELL ANEMIA: COMPLICATIONS

- Painful episode - most common
- Acute chest syndrome
- Stroke (10% children)
- Osteonecrosis
- Proliferative retinopathy
- Venoocclusive complications
- Infectious complications
SICKLE CELL ANEMIA COMPLICATIONS

- HEMOLYSIS
  - Gallstones
  - Aplastic crisis
  - Osteopenia
  - Anemia
  - Nutritional deficiencies
SICKLE CELL ANEMIA: TREATMENT

- General medical care
- Pain management: AVOID MEPERIDINE!!
- Hydroxyurea
- Transfusion-limited, maintaining at baseline
- Stem cell transplant
APLASTIC ANEMIA

- Pure red cell aplasia
- Bicytopenia, pancytopenia
- Bone marrow failure
RED CELL APLASIA: CLASSIFICATION

- Congenital: Diamond Blackfan Syndrome
- Acquired: Idiopathic & Secondary
- Secondary:
  - Hematologic malignancies
  - Solid tumors
  - Immunologic disorders
  - Infectious diseases
  - Drugs
APLASTIC ANEMIA: DIAGNOSIS

- BONE MARROW BIOPSY: 4-5 cores showing cellularity of <30%
- Flow cytometry & cytogenetics to r/o the rarer variant - hypocellular MDS
APLASTIC ANEMIA: TREATMENT

- Antithymocyte globulin (ATG) & Cyclosporin (CSA)
- Stem Cell Transplant