HEMATOLOGICAL SYSTEM

1. Main functions:
    a. transporting oxygen and nutrients to the lungs and tissues
    b. forming blood clots to prevent excess blood loss
    c. carrying cells and antibodies that fight infection
    d. bringing waste products to the kidneys and liver, which filter and clean the blood
    e. regulating body temperature

RED BLOOD CELLS (ERYTHROCYTES)

ERYTHROPOIESIS

1. Regulated process of RBC production through series of steps:
    a. Occurs In bone marrow
        i. long bones, mandible, cranium, sternum, vertebrae, and pelvis
2. Greek 'erythro' meaning "red" and 'poiesis' meaning "to make" is the process which produces red blood cells (erythrocytes)
3. Normal amount 2.5 mill/sec RBC
4. It is stimulated by decreased tissue oxygenation (anemia, pulm. dz, high alt living)
5. detected by the kidneys (main) secrete the hormone erythropoietin
    a. Liver produces small amount of erythropoietin
6. Nutritional requirements
    a. B12 (cobalamin) folate (folic acid) B6, riboflavin, pantothenic acid, niacin, ascorbic acid, and Vitamin E
    b. Iron

RETICULOCYTES

1. Young RBCs from bone marrow
2. Normal retic count 0.5-1.5%
3. RBC span ~120 days, each day roughly 1-2% are removed from circulation and replaced by reticulocytes
4. Properly functioning bone marrow responds to anemia by increasing retic count >3%

HEMOGLOBIN SYNTHESIS

1. O2 carrying protein of the erythrocyte
2. Embryonic; fetal; adult
3. Types/Variants
    a. Hemoglobin A (most common type) 95-98% of adult Hb
    b. Hemoglobin A2 (2-3%)
    c. Hemoglobin F (fetal) <2%; Sickle Cell, Alpha & Beta-thalassemia; Hb C and Hb-E
4. 1 erythrocyte contains about 300 hemoglobin molecules
5. Hb increases O2 carrying capacity 100-fold

6. Each Hb molecule contains 2 pairs polypeptide chains (the globulins) and 4 iron complexes + protoporphyrin (hemes)
7. Take up O2 in lungs = exchange for CO2

HEMOGLOBIN SYNTHESIS

1. RBC destruction (normal)
    a. 100-120 days in circulation
    b. Removed by tissue macrophages (primary in spleen)
        i. If spleen dysfxn or absent, then Kupffer cells (in liver) take over process
    c. Digest by phagocytosis and proteolytic and lipolytic enzymes (lysosomes)
2. Heme and globulin dissociate easily
    a. Globin broken into AA
    b. Iron is oxidized, forming methemoglobin (Fe+++), and recycled

IRON METABOLISM/CYCLE

1. ~67% of total body iron is bound to heme in erythrocytes (hemoglobin) and muscle cells (myoglobulin)
    a. ~30% stores in macrophages, hepatic parenchymal cells (ferritin or hemosiderin)
    b. 3% lost in urine, sweat, bile, sloughing epithelial cells (skin & intestinal mucosa)
2. About 25mg iron required for daily erythropoiesis
3. Dietary 1-2 mg ONLY
4. Rest from Recycling RBCs

KEY TERMS

1. Ferritin=major intracellular storage protein
2. Apoferritin=does not have attached iron
3. Hepcidin=hormone that regulates iron cycle
4. Hemosiderin= iron storage complex of numerous micelles
5. Transferrin=transporter molecule in blood

B12 AND FOLATE

1. Both play critical role in DNA & RNA synthesis
    a. Deficiency care impair DNA synthesis
    b. Can arrest cell cycle, DNA replication errors, undergo apoptotic death
2. B12 principal role is co-factor in the reaction that recycles 5-methyl-tetrahydrofolate back to tetrahydrofolate (coupled to the conversion of homocysteine to methionine)
3. Folate principal role is in DNA synthesis to supply methyl groups to other molecules (a 1-carbon donor)
4. major effects of deficiencies
    a. Hematopoietic
    b. Megaloblastic changes

INEFFECTIVE ERYTHROPOIESIS

- Neuronal
- B12 involved in neuronal function exact mechanism unknown

DIAGNOSTIC WORKUP-RBCS LABORATORY

1. CBC with diff
2. Reticulocyte count
3. Serum iron studies
4. IgA-tTG
5. B12
6. folate
7. anti-intrinsic factor ab, anti-parietal cell ab
8. serum methylmalonic acid levels

IMAGING:

1. Abd U/S
2. X-rays
3. Upper GI endoscopy
4. Colonoscopy
5. Exp laparotomy
6. CT scan
7. Specialized tests:
    a. Bone marrow

RED BLOOD CELL INDICES

1. Mean Cell Volume (MCV)
    a. Size of erythrocytes
    b. Small or large cell size (micro, macro or normocytic)
2. Mean Cell Hemoglobin (MHC)
    a. Amount of hemoglobin per red blood cell (by wt.)
    b. Response should mirror MCV
3. Mean cell hemoglobin concentration
    a. % concentration of Hb in each erythrocyte
4. Red Cell distribution width (RDW)
    a. Variance of sizes of the RBCs
    b. Biomarker for mortality or morbidity
5. Reticulocyte Count
    a. newly released anucleate red cell that enters the blooduseful in evaluating the pathogenesis of anemia by distinguishing inadequate production from accelerated destruction

IRON FUNCTION (HB METABOLISM TESTING)

CHANGES RELATED TO AGE

1. Pediatric
    a. Higher RBC counts at birth 2/2 accelerated hematopoiesis during fetal life; respond to placental change to lung O2 supply results in decrease in formation
    b. Large number of reticulocytes in circ. Dec 50% every 12 hours
2. Erythrocyte life
    a. Premature 20-30 d
    b. Full term 60-80d
    c. Childhood 100-120d
1. Aged
    a. Little changes of composition as we age
    b. Replenished slower after bleeding
    c. 2/2 iron depletion
    d. Iron values are depleted
        i. Total, TIBC, intestinal iron abspt dec.
    e. Chronic disease
        i. Suppress erythropoietin

RBC DISORDERS

1. Anemia
    a. IDA, ACI, B12/folate Def
    b. Hemolytic Drug induced
2. Myelodysplastic syndromes
3. Hemoglobinopathies
4. Volume contraction
5. Polycythemias
    a. Primary polycythemia
    b. Secondary polycythemia
6. Other
    a. Athletic performance enhancing agents
    b. Cobalt toxicity
    c. POEMS syndrome
    d. Erythrocyte disorders

ANEMIA STARTING POINTS

1. Reduction of circulating red blood cells

    a. number or reduced ability of quality/quantity to deliver O2
2. Rate at which anemia develops is an important as the severity
    a. Rapid decline can overwhelm the compensatory mechanisms of the body
3. Mechanisms by which anemia can occur:
    a. excessive RBC loss
    b. abnormal RBC destruction
    c. inadequate or ineffective RBC production
    d. morphological characteristics

ANEMIA CLASSIFICATIONS

1. Kinetic Approach
    a. Address the underlying mechanism in RBC loss
        i. #1 decreased RBC production
        ii. #2 increased RBC destruction
        iii. #3 blood loss
2. Morphological Approach
    a. Categorize the anemia based on alterations to the RBC and reticulocyte response
        i. #1 Microcytic
        ii. #2 Macrocytic
        iii. #3 Normocytic

ANEMIA SIGNS/SYMPTOMS-GENERALIZED

1. Fatigue
2. Weakness
3. Headache
4. SOB /DOE /air hunger
5. Pallor (conjunctiva and vermillion)
6. Palpitations/tachycardia
7. Can occur with any etiology of anemia

MICROCYTIC ANEMIAS

- Iron deficiency
- Anemia of Chronic Disease
- Thalassemia-major/minor
- Sideroblastic

IRON DEF. ANEMIA STARTING POINTS

- Due to the decreased production of hemoglobin
    - 1- RBC progenitor cells in BM are large and they divide multiple times to produce smaller mature cells

- 2- microcytosis due to “extra” division to maintain hemoglobin concentration

1. Hemoglobin made of heme and globin
    a. Heme made up of iron and protoporphyrin
    b. A decrease in any of these components leads to anemia
2. Due to decreased levels of iron
    a. DEC iron >> DEC heme >> DEC hemoglobin = microcytic anemia
3. Most common type of anemia
4. Causes of IDA include
    a. Dietary deficiency
    b. Impaired absorption
    c. Increased requirement
    d. Chronic blood loss
5. PATHO: IRON >> absorbed in duodenum, enterocytes transport >> cross cell membrane to blood via ferroportin >> transferrin transports to liver & bone marrow macrophages for storage
6. Intracellular iron bound by ferritin which prevents iron forming FREE RADICAL damage via the Fenton reaction
7. Key features:
    a. PICA, RLS glossitis, angular stomatitis, DOE (in addition to common features of anemia)

LABORATORY TESTING OF IRON STATUS

1. Serum iron- total iron in blood

2. Total iron-binding capacity (TIBC) –measure of transferrin molecules in blood

3. % saturation –transferrin bound to iron (nml 33%)

4. Serum ferritin – iron storage molecule in liver / macrophages

ANEMIA OF CHRONIC DISEASE

1. Associated with chronic inflammation
    a. endocarditis, autoimmune conditions
2. Due to acute phase reactants from the liver, including hepcidin
3. Hepcidin
    a. limits iron transfer from macrophages to erythroid precursors
    b. Suppresses erythropoietin
    c. Aim is to prevent bacteria from accessing iron which they need for their survival
4. Key Differentiation
    a. Signs and symptoms of underlying chronic disease

b. Infection
c. Cancer
d. Autoimmune disease
e. Kidney disease

THALASSEMIA ANEMIA

1. Due to decreased synthesis of globin chains of hemoglobin
    a. Inherited mutation
    b. protection from malaria
2. 2 types
    a. Alpha- thalassemia
    b. Beta- thalassemia
3. Key differentiation
    a. severe thalassemia
        i. usually, transfusion dependent from childhood
        ii. diagnosed early
    b. thalassemia minor
        i. may not be diagnosed until adulthood
4. Hemoglobin electrophoresis may help distinguish these disorders but can be normal
5. Epidemiology
    a. Most often seen in _____

SIDEROBLASTIC ANEMIA

a. Inherited or acquired
    a. X- linked –rare genetic condition
    b. Drug related such as TB drugs
b. Disruption in the hemoglobin chain
c. Can cause liver damage /hemochromatosis
d. Key differentiation
    a. Alcoholism can be a cause of a reversible sideroblastic anemia
    b. Hepatosplenomegaly is found in 1/3-1/2 of patients

MACROCYTIC ANEMIAS

1. Folate deficiency
2. Vitamin B12 deficiency
3. Macrocytosis Starting points
    a. MCV >100
    1. Main Etiologies
        i. Folate or B12 deficiency
        ii. Necessary for DNA precursors
        iii. impairment of division and enlargement of RBC precursors = megaloblastic anemia

iv. Impaired division of neutrophils leads to hyper segmented neutrophils
    1. Megaloblastic changes also seen in rapidly dividing epithelial cells
    2. ETOHism, liver dz, and drugs usually do not offer megaloblastic changes
2. Certain drugs can interfere with 1) DNA synthesis or 2) can cause hemolytic anemia (which increases MCV)
3. _____
4. Patho: def. leads to DNA synthesis issues. Results in "large" red blood cells

FOLATE DEFICIENCY

1. Absorbed in jejunum
2. Foods are green veggies & some fruits
3. Causes:
    a. poor diet (ETOH and elderly)
    b. increased demand (cancer, pregnancy, hemolytic anemia)
    c. Folate antagonists (methotrexate)
4. Patho: def. leads to DNA synthesis issues.
5. Labs: folate, B12, methylmalonic and homocysteine levels

VIT B12 DEFICIENCY

1. b12 binds w. intrinsic factor and transported through small bowel absorbed in ileum
2. food source: animal derived proteins
3. less common than folate, takes years to develop
4. vit b12 is cofactor and important in fatty acid metabolism
    a. can lead to demyelination of spinal cord
5. labs: b12, methylmalonic and homocysteine levels

MACROCYTIC ANEMIAS

1. Megaloblastic
2. Other causes
    a. drugs that interfere with DNA synthesis
    b. _____
    c. Autoimmune thyroid disease
    d. may coexist with pernicious anemia and atrophic gastritis
3. Test TSH if suspect autoimmune process.
4. Celiac, Crohns Dz.
5. Key differentiation:
    a. Swollen red tongue (folate)
    b. Hx of strict vegan, malabsorption

NON-MEGALOBLASTIC

1. Likely causes include
    a. alcohol misuse, myelodysplastic syndrome, chronic liver disease, and congenital bone marrow failure syndromes.
2. Key differentiation:
    a. Hx of above-mentioned illnesses
    b. Stigmata of chronic ETOHism or liver dz.
    c. ??benzene/petroleum exposure
    d. F/C/malaise/weakness think myelodysplastic synd
3. Clues to diagnosis
    a. Megaloblastic
        i. MCV >110-115 (severe)
        ii. Macro-ovalocytes (macrocytosis)
        iii. B12 or Folate; drug induced megalo.
        iv. Hyper segmented neutrophil+
        v. Myelodysplasia
        vi. Neutrophils <3 lobed
        vii. Myelodysplasia
    b. Non-megaloblastic
        i. Target cell >> liver dz

NORMOCYTIC ANEMIA

- Hemolytic
- Hemorrhagic
- Sickle cell
- G6PD
- Aplastic

1. Anemia with normal size RBCs 80-100 MCV
2. Due to 2 mechanisms
    a. increased peripheral loss/destruction
    b. underproduction in BM
3. Reticulocyte count to determine
    a. Normal <2%
    b. >3% indicating a peripheral loss/destruction anemia is present

ANEMIA DUE TO BLOOD LOSS

1. Acute or chronic blood loss
    a. Acute >> loss of intravascular volume
        i. If massive will lead to cardiovascular collapse

        ii. >20% hypovolemic shock
    b. Chronic >> iron stores are depleted leads to an anemia of underproduction
2. Etiologies include
    a. Acute: Trauma
    b. Chronic: GIB, gynecologic disturbances
3. Anemia due to peripheral destruction (hemolysis)

HEMOLYTIC ANEMIAS

1. Hemolysis (peripheral destruction)
2. Intravascular or extravascular
    a. Both result in anemia w/ good BM response
    b. Shortened RBC life span
    c. Elevated erythropoietin levels
    d. Accumulation of hemoglobin degradation products
3. Macrophages in liver, spleen, and BM
4. Etiologies include:
    a. Immune mediated
    b. inherited/genetic

2 TYPES

1. Extravascular >> reticuloendothelial system (splenic macrophages, liver, and lymph nodes) induced destruction of RBCs
    a. Hyperbilirubinemia, jaundice, splenomegaly
    b. bilirubin rich gall stones w/ risk of cholelithiasis

2. Intravascular >> destruction of RBCs within blood vessels
    a. Mechanical forces (turbulence)
    b. Biochemical or physical agents
    c. Loss of iron and presence of hemoglobinemia, hemoglobinuria and hemosiderinuria

INTRINSIC VS EXTRINSIC DEFECTS

1. Intrinsic
    a) Hemoglobinopathies
    b) SCD
    c) Thalassemia
    d) Unstable hemoglobin variants

2. RBC membrane defects
    a) Hereditary Spherocytosis
    b) Hereditary Elliptocytosis

3. RBC metabolic deformities
    a) G6PD
    b) Pyruvate kinase

EXTRINSIC

1. Antibodies against RBC components
2. Autoimmune hemolytic
3. Drug induced
4. Hypersplenism
5. Mechanical trauma
6. Oxidizing compounds
7. Pathogens

HEREDITARY SPHEROCYTOSIS

1. Autosomal dominant
2. PATHO: Inherited defect of the RBC cytoskeleton-membrane tethering proteins
    a. Leads to sphere shaped instead of disc shaped RBCs
    b. Spleen involved and sequesters spherocytes for destruction
    c. Extravascular hemolysis
        i. Jaundice w/ unconjugated bili, increased risk of gallstones
3. Key features
    a. Anemia**
    b. pallor
    c. Splenomegaly**
    d. >75%
    e. Jaundice**
    f. Fatigue
4. Laboratory findings
    1. CBC w/ diff
        a. MCHC
    2. Retic count
        a. ___%
    3. Peripheral blood smear
        a. _____
    4. LDH
    5. Haptoglobin
    6. Direct Antiglobulin test

SICKLE CELL ANEMIA

1. Normocytic w/ extravascular hemolysis
2. Autosomal recessive mutation of B-chain hemoglobin
    a. 10% carrier in African descent – protective against malaria
    b. 2 genes must be present for disease manifestation
3. Diagnosed by hemoglobin electrophoresis
    a. Dz= 90% Hbs, 8% Hbf , 2% Hba2, NO Hba1
    b. Trait= 55% Hba, 43% Hbs, 2% Hba2
    c. HBF IS PROTECTIVE IN 1ST FEW MONTHS OF LIFE
    d. >90% Hb s in RBCs
4. Hypoxia, dehydration and acidosis are increased risk factors for acute crisis Vaso-occlusive crisis ensues
5. Clinical Presentation
    a. Family history
        i. Presents in Early childhood
    b. Anemia
        i. Pallor
    c. Jaundice
        i. Aplastic crisis
    d. Vaso-occlusive crisis
    e. Pain
    f. Dactylitis
    g. Fevers
    h. PNA chest syndrome
6. Diagnostic Work up
    a. CBC w/ diff
        i. MCHC
    b. Retic count
        i. ___%
    c. Peripheral blood smear
        i. _____
7. Genetic testing
8. Xrays
9. Pulse ox

VASO-OCCLUSIVE CRISIS

1. Cells sickle and de-sickle, get clogged while passing microcirculation and result in complications of intravascular and extravascular hemolysis
2. Dactylitis
3. Autosplenomectomy
4. Acute chest syndrome (most common cause of death in adults)
5. Pain crisis
6. Renal papule necrosis

7. Increased risk of infection encapsulated organisms Strep pneumoniae, H. influenzae (most common cause of death in children)

G6PD (GLUCOSE-6-PHOSPHATE DEHYDROGENASE) deficiency

1. X-linked recessive disorder
    a. resulting in reduced ½ life of G6PD
    b. Renders cell susceptible to oxidative stress, particular H2O2 which is normally neutralized by glutathione
    c. NADPH a by-product, is needed to regenerate glutathione
    d. Leads to increased injury to cell and intravascular hemolysis
2. Mediterranean and African variants
    a. High carrier frequency likely related to malaria protection
3. Patho:

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

1. Acquired defect of myeloid stem cell which renders cell susceptible to complement destruction
2. Intravascular hemolysis occurs sporadically at night during sleep
3. PATHO: Mild resp acidosis develops with slower breathing activates complement RBC/WBC/Platelets are lysed intravascular hemolysis leads to hemoglobinuria & hemoglobinemia (especially in AM) hemosiderinuria a few days later
4. Main complication and cause of death is thrombosis of hepatic, portal, or cerebral veins
    a. Also iron def anemia
    a. Acute myeloid leukemia

APLASTIC ANEMIA

1. Damage to hematopoietic stem cells resulting in pancytopenia
2. Low reticulocyte count
3. Caused by:
    a. Drugs, chemicals, viral infections and autoimmune
    b. Treatment includes remove offending cause
4. Supportive with transfusions and bone marrow stimulating factors
5. EPO, GM-CSF and G-CSF
6. Clinical presentation
    a. >recurrent infections
    b. Fatigue, pallor
    c. Easy bruising or bleeding
    d. Tachycardia & dyspnea

1. Diagnostic Workup
    a. CBC w/ diff
    b. Retic count

c. BM biopsy
d. Serum B12/folate levels
e. HIV testing
f. LFTS

OTHER RBC DISORDERS

Polycythemia

Polycythemia Vera

Polycythemia Starting points

2. Abnormal elevation of H&H
    a. HgB
        i. >16.5 male
        ii. >16.0 female
    b. HCt
        i. >49% male
        ii. >48% female

Classifications

- Relative
- Absolute
- Primary
- Secondary

POLYCYTHEMIA VERA STARTING POINTS

1. Neoplastic proliferation of mature myeloid cells especially RBCs
    a. Granulocytes and platelets are also increased
    b. JAK2 kinase mutation
2. Treatment is phlebotomy, 2nd line hydroxyurea
    a. Without RX death within 1 yr.
3. Patho: mutations in BM (by JAK2) result in erythropoietin receptor signaling issues, causing expansion of the all 3 lineages causing plethoric sx related to hyper viscosity.
4. Clinical Presentation
    a. Symptom's r/t viscosity of blood and features of thrombosis
    b. Blurry vision, headache
    c. Increased risk of thrombosis, hepatic, portal and cerebral

    d. Plethora
    e. Itching
5. DD incudes reactive polycythemia
    a. Secondary polycythemia
    b. Essential thrombocytopenia
    c. CML
6. Diagnostic Work up
    a. H&H
    b. WBC
    c. Platelets
    d. LFTS
    e. JAK2 gene