Review of Anemia

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BUILT TO BEAT CANCER | NORTHSIDE HOSPITAL CANCER INSTITUTE

- There are no conflicts of interest with any planners or presenters. “

Objectives

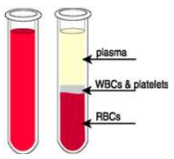
- Review the functions and major components of the blood
- Describe the characteristics, functions, and life cycle of red blood cells (RBCs)
- Discuss the pathophysiology of basic anemias
- Discuss the identification and treatment of basic anemias: iron deficiency, vitamin b-12 deficiency, folate deficiency, and anemias of inflammation & chronic disease

Functions of blood

- Transporting dissolved gases, nutrients, hormones, and metabolic wastes
- Regulating pH and ion composition of interstitial fluid
- Restricting fluid loss at injury sites
- Defending the body against toxins and pathogens
- Regulating body temperature by absorbing and redistributing heat

What is blood?

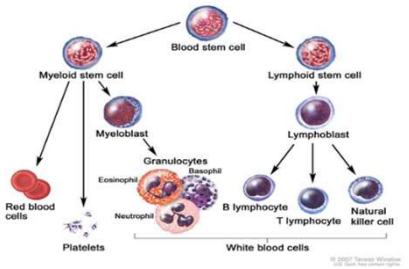
- Connective tissue in fluid form
- 54% Water-based plasma; 45% RBCs (oxygen, iron), WBCs (<1%, immunogenic defense), platelets (<1%, clotting)
- Fluid of life, growth and health
- Thicker than water (viscosity)
- pH: 7.35-7.45 normal
- Temperature - 100.40F



Hematopoiesis: Formation and Development

- In adults the cellular elements are produced in the bone marrow
- Some WBCs are produced in the lymphatic tissue and bone marrow
- Blood cells need certain nutrients to form properly
- Examples include…..
  - Iron
  - Folic acid
  - Vitamin B12
- All blood cells formed come from a hematopoietic stem cell
- These cells can become any blood cell

It All Starts With…..



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Blood cell types: RBCs

- Characteristics
  - Biconcave discs, anucleate, essentially no organelles
- Diameters larger than some capillaries
  - Require cell to change shape (contains spectrin)
- Filled with hemoglobin (Hgb) for gas transport
- Major factor contributing to blood viscosity

- Structural characteristics contribute to gas transport
  - Biconcave shape—huge surface area relative to volume
  - >97% hemoglobin (not counting water)
  - No mitochondria; ATP production anaerobic; do not consume O2 they transport
  - Takes ~ 7 days to mature

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Functions of RBCs

- Transport oxygen from lungs to the tissues (oxyhemoglobin)
- Transport carbon dioxide from tissues to lungs (carboxyhemoglobin)
- Hemoglobin acts as a buffer and regulates the hydrogen ion concentration (acid base balance)
- Carry the blood group antigens and Rh factor

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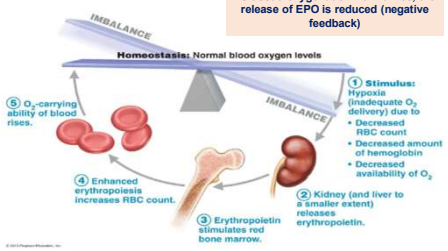
RBC formation

As tissue oxygenation normalizes, the release of EPO is reduced (negative feedback)



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Formation of RBCs

- Just how effective is Erythropoietin (EPO)?
- Without EPO: few RBCs produced
- With EPO (and all needed elements): RBC production can be 10x normal

What about other needed factors for RBC development?

- Iron
  - Available from diet
  - 65% in HgB; rest in liver, spleen, and bone marrow
  - Free iron ions toxic
    - Stored in cells as ferritin and hemosiderin
    - Transported in blood bound to protein transferrin
- Vitamin B12 and folic acid necessary for DNA synthesis for rapidly dividing cells (developing RBCs)

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Life Cycle of Red blood cell

- Circulate for about 120 days
- Macrophages in spleen and liver destroy worn out RBCs
- Hemoglobin is broken down into heme and globin
- Iron from heme returns to red bone marrow
- Bilirubin and biliverdin excreted in bile

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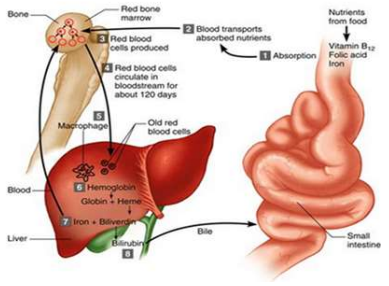
Life of RBC



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Anemia: Background

- Anemia as defined by World Health Organization (WHO)
- Men: HgB < 13 g/dL, Women HgB < 12 g/dL
- Reduction of O2 carrying capacity = SYMPTOMS
- Affects 1.6 billion people
- 25% world population
- Morbidity and mortality in other disease states
- 3.5 million Americans, many go undiagnosed
- Most common blood condition in the U.S.
- Elderly- ↑ hospitalization & mortality, ↓ QOL
- Peds- leading cause of infant morbidity and mortality

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Anemia- Etiology

- > 400 types divided into three groups:
  1. **Hemorrhage/hemolysis**
     - Blood loss
  2. **↓ or faulty RBC production**
     - Iron deficiency anemia (IDA)
     - B12 deficiency
     - Folate deficiency
     - Anemia of inflammation (AI)
     - Anemia of chronic disease (ACD) or critical illness
  3. **↑ RBC destruction**
     - Sickle cell disease
     - Thalassemias

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RBC Homeostasis

- Iron is an important component of Hgb production
- There is no mechanism to excrete iron in the body
- Iron is lost overtime through shedding of the GI mucosa, blood loss, and sweat
- Rate of loss is 1 mg/day (men), 1.5-2 mg/day (women)
- The typical diet contains 10-20 mg of iron
- Only about 10-20% of this is absorbed

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Anemia: Signs and Symptoms

SYMPTOMS

- ↓ exercise tolerance
- Fatigue- chronic
- Dizziness- acute
- Irritability
- Weakness- chronic
- Palpitations
- Vertigo- chronic
- SOB- acute
- Chest pain

SIGNS

- Tachycardia- acute
- Pallor (paleness)- chronic
- ↓ mental functioning
- ↑ intensity of murmurs

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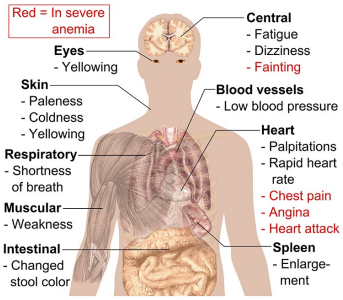

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Severe Anemia

- Patients with life threatening anemia should always be treated with RBC transfusion
- Correction of iron deficiency anemia requires time for administration and incorporation into new RBCs
- Includes patients who are actively bleeding, and/or if any evidence of end organ ischemia
- Each unit of RBCs:
  - Total volume of 300ml, of which 200ml is RBC
  - 200mg of iron
  - Should increase HgB by 1 g/dL
  - Increase Hct by 3%

ANEMIA: SIGNS AND SYMPTOMS

Iron deficiency	B12 deficiency	Folate deficiency
Sore mouth	Numbness/paresthesias	Depression
Smooth tongue	Imbalance/gait disturbance	Personality changes
PICA	Personality changes	Irritability
Pagophagia	Depression	Memory impairment
Reduced saliva	Burning sensation in mouth	Sore tongue

Anemia: Definitions

- Hemoglobin (HgB)
  - Amount of HgB per unit volume of blood (g/dL)
- Hematocrit (Hct)
  - Actual volume of RBCs/unit of whole blood (%)
- Mean Corpuscular Volume (MCV) - size of RBC
  - Average volume of RBC
  - Determines whether microcytic, macrocytic, or normocytic

Anemia: Definitions

- Mean Corpuscular Hemoglobin (MCH)
  - % volume of Hb in an RBC
  - Iron supply
- Mean Corpuscular Hemoglobin Concentration (MCHC)
  - Hb/Hct
  - Weight of HgB per volume of cells
  - Low MCHC= hypochromic

Anemia: Special Populations

- Higher HgB/Hct:
  - Patients living at high altitudes
  - Smokers and patients living in air pollution areas
  - Endurance athletes have increased Hct
- Lower Hgb/Hct:
  - African-Americans have 0.5 to 1 g/dl lower HgB than do Caucasians
  - Elderly (slowed erythropoiesis)
  - Pregnant women (hemodilution)

Anemia: Definitions

- Reticulocyte count (Retic)
  - Circulate 2 days before maturing
  - Usually around 1%
  - Production of immature RBCs
  - Decreased retic = decreased RBC production
  - Elevated retic = hemolysis or blood loss
- Microcytic - smaller RBCs
- Macrocytic - larger RBCs
- Normocytic - normal sized RBCs

CASE 1

- HPI: WC is a 35 yo woman seen for easy fatigue for many months. She is now 24 weeks pregnant with her 3rd child in 3 years. She does not see any obstetrician and does not take any vitamins. Lately, she has developed a taste for eating ice. She has no other complaint. She does not smoke or drink. Physical examination is positive for pale conjunctiva, mild spooning of nails, and a II/IV systolic murmur at left lower sternal border. Stools are negative for occult blood.
- VS: BP 118/51 mm Hg, P 85 bpm, RR 18, T 36.2°C, pulse oximetry 98% in room air; Wt 88 kg, Ht 5'7"
- OTHER: Peripheral blood smear: hypochromic, microcytic red blood cells, HgB/Hct 8.0/26.3 and ferritin is 13 ng/ml, iron sat is 10% and TIBC is 450
- Candidate for oral or IV iron?

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Iron Deficiency Anemia (IDA)

- Affects a large proportion of world's population, especially women of childbearing age, children, and individuals living in low-and middle-income countries.
- With women of childbearing age IDA is attributed to menstruation and childbirth
- Women more likely to have iron deficiency without anemia
- IDA also more common in older adults ≥65 yo
- Blood donors
- Major cause is blood loss, overt or occult

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Blood Loss Anemia: Causes

- Traumatic hemorrhage
- Hematemesis or melena
- Hemoptysis
- Heavy menstrual bleeding
- Pregnancy and delivery
- Hematuria
- Frequent blood donation
- Excessive diagnostic testing
- Underestimation of degree of menstrual bleeding
- Pregnancy and lactation, increased likelihood as number of pregnancies increase
- GI bleeding such as gastritis, malignancy, angiodysplasia
- Exercise induced losses
- GI parasites (hookworm, whipworm)

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Iron Loss

- Iron loss during pregnancy estimated at 1000mg for pregnancy, delivery, and nursing. Menstrual blood loss accounts for 1mg iron lost per day.
- Iron loss during hemodialysis may be as much as 2000mg per year. HD highly likely to produce iron deficiency.
- Gastrointestinal tumors associated with iron loss.

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Iron Deficiency

- Reduced iron absorption: iron absorbed in upper GI tract, duodenum is site of maximal absorption
- Diets such as vegetarian or vegan
- Celiac disease/atrophic gastritis/H pylori
- Medications, such as proton pump inhibitors, histamine receptor blocker or antacid. Acid gastric environment facilitates absorption of iron. Medications that increase the risk of GI bleeding, such as NSAIDs ,aspirin, anticoagulants
- Use of ESAs, especially in the setting of maintenance hemodialysis
- Bariatric surgery, which promote weight loss by limiting gastric reservoir capacity/and or shortening the length of small intestine, resulting in malabsorption

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Normal Body Iron Content

- Normal body iron content in an adult is ~3-4 g
- RBCs ~ 2 g corresponding to ~ 2000ml of RBCs
- Iron containing proteins (myoglobin, cytochromes, catalase) ~400mg
- Plasma iron bound to transferrin- 3-7mg
- Storage iron in the form of ferritin or hemosiderin (0.8-1 g in men, 0.4-0.5 g in women)

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Evaluating Labs

- Common presentation of IDA includes:
  - Low levels of ferritin
  - Serum iron (Fe)
  - Increased levels of transferrin (TIBC)
  - Low percent saturation of transferrin, stated as a percentage (FE/TIBC or FE/Tf)
  - On CBC, low red blood cells (RBC), hemoglobin (HgB) hematocrit (Hct)
  - Low absolute reticulocyte count
  - Low mean corpuscular volume (MCV) and low mean corpuscular HgB (MCH)

Normal Values for Lab Tests

- Serum iron measures circulating iron
  - Normal value 60-150 mcg/dL
  - Low in IDA
    - As well as anemia of chronic disease (ACD) or anemia of inflammation
  - Can fluctuate with dietary intake and normal diurnal variation
  - By itself it is not diagnostic
- Serum transferrin
  - Circulating transport protein for iron
  - Increased in IDA
    - But can be decreased in ACD
  - Transferrin can also be reported as TIBC
    - Transferrin conc (in mg/dL) can be converted to the TIBC (in mcg/dL) by multiplying by 1.389
    - Normal value 240-450 mcg/L

Normal Values for Lab Tests

- Transferrin saturation (TSAT) is the ratio of serum iron to TIBC: (serum iron +TIBC x 100), normal values in the range of 25-45%
- Serum ferritin
  - Circulating iron storage protein that is increased in proportion to body iron stores, but also an acute phase reactant.
  - Can increase independently of iron stores in disorders associated with inflammation, infection, liver disease, heart failure, and malignancy.
  - Normal ferritin is 30-200 ng/mL

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Absolute Versus Functional Iron Deficiency

- Absolute iron deficiency refers to the absence of or severely reduced storage iron in the monocyte-macrophage system, including bone marrow, liver and spleen
- Functional iron deficiency (iron restricted erythropoiesis) occurs when an individual has adequate iron stores for normal hematopoiesis, but the iron is not available for RBC production

CASE 2

- ML is a 69 year old diabetic with history of chronic foot infection. He has been hospitalized for one month for IV antibiotics. His HgB has fluctuated but most recently is 9.0 g/dL and Hct 28.6%. Iron studies reveal ferritin of 486, iron saturation of 20%, iron of 26 g/dL and TIBC of 229.
- Is oral or IV iron indicated in ML?

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Functional Iron Deficiency

- Anemia of chronic disease/anemia of inflammation- a block in iron release from macrophages back into the circulation, (increased hepcidin production). Causes include infections, malignancy, bariatric surgery, or chronic medical conditions such as diabetes, IBD, SLE, RA, COPD, CHF, obesity, sepsis and major trauma.
- Use of Erythropoiesis-stimulating agents (CKD and cancer). Iron stores may be available but their release into the circulation may not be rapid enough to support the increased erythropoietic rate.

Findings in Anemia of Chronic Disease/Anemia of Inflammation

- Increased hepcidin and other cytokines (IL-1, IL-6, IL-22) cause iron to be retained within cells of macrophages/monocytes. Hepcidin also decreases the absorption of iron in the small intestine.
- Lab values include low circulating iron, low TSAT and normal or high concentration of iron storage protein ferritin. Low reticulocyte count.
- Give supplemental iron if ferritin is <100 ng/mL or TSAT is <20%, IV more effective than oral iron due to increased hepcidin production
- Second most common cause of anemia, after iron deficiency anemia.
- Treatment of underlying disorder improves anemia.

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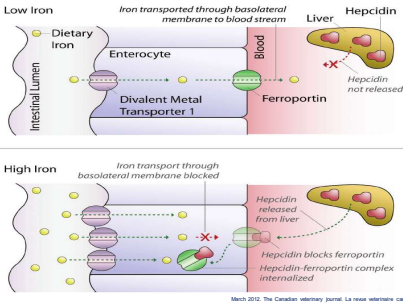
Anemia of Chronic Disease



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Management of Iron Deficiency: Oral Iron

- Ferrous sulfate, ferrous fumarate, and ferrous gluconate are common forms available
- Dose: 3-6 mg/kg/day of elemental iron should increase HgB by 0.25-0.4 g/dL
- Recent data suggests daily or every other day dosing is more beneficial. Use of liquids or tablet appropriate
- Be mindful of how much elemental iron a product contains
- Example: 325 mg ferrous sulfate = 65 mg elemental iron, 325 mg ferrous gluconate = 36 mg elemental iron
- Onset: >2 months to see correction of HgB

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Management of Oral Iron

- Adverse effects
  - Constipation, GI upset, nausea, vomiting, discoloration of stool and urine
  - Food tends to decrease absorption
  - 70% of patients experience side effects
- Drug interactions
  - Chelation: tetracyclines, methyldopa, levodopa, fluoroquinolones
    - Decreased absorption of these drugs
  - Increased absorption: ascorbic acid (Vit C)
  - Decreased absorption: iron chelators, phosphate, calcium, zinc, antacids

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Examples of oral iron supplements

Drug	Elemental Iron Content	US Brand names
Ferrous fumarate	106mg/324 mg tab	Ferrimin 150, Ferrocite, Hemocyte
Ferrous gluconate	36mg/325 mg tab	Fergon, Ferrotabs
Ferrous sulfate	65mg/325 mg tab	Ferro-Bob, FerrouSul
Polysaccharide-iron complex (PIC)	Number in the name is the amount elemental iron	Ferrex 150, Myferon 150

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Management: IV Iron

- Anemia refractory to oral iron treatment
- Patient is unable to absorb oral iron (ex. post bariatric surgery)
- Patients unable to tolerate oral iron
- Patients who are poorly compliant of oral iron
- Moderate-severe anemia
- Onset: >3 weeks to see correction of Hgb
- Adverse reactions
- Hypersensitivity reactions and infusion reactions
- Transient fever, arthralgias, myalgias, or flushing are seen in ~0.5-1% of infusions

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Management: Iron Deficiency

Drug	Concentration of elemental iron	Dosing	Test Dose
Ferric carboxymaltose (FCM) Injectafer®	50 mg/mL	Weight ≥ 50 kg, 750mg qwk x 2 doses, if ≤50 kg dose 15 mg/kg x 2 doses, or flat 1g dose	Not required
Ferric gluconate (FC) Ferrlecit®	12.5 mg/mL	Multiple doses of 125-250 mg	Not required
Ferumoxytol Feraheme®	30 mg/mL	2 doses of 510 mg, given 3-8 days apart; or 1 dose of 1020 mg	Not required
Iron dextran, low molecular weight (LMW ID) – INFeD®	50 mg/mL	Multiple approaches to dosing, iron deficiency calculation or empiric Range of dosing 100-1000 mg	Yes, 25 mg
Iron sucrose Venofer®	20 mg/mL	Multiple doses of 200, 300, 400 or 500 mg	Not required

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IV Iron: Premeds and Infusion Reactions

- Premeds are not indicated for most products
- For patients with asthma or more than one drug allergy use methylprednisolone 125mg IV with 20mg of famotidine as premeds.
- Diphenhydramine is not appropriate as a premed or for management of infusion/hypersensitivity reactions. May cause hypotension, flushing, dizziness, wheezing, nasal congestion, somnolence and SVTs.
- Patients with inflammatory arthritis (RA) are also more likely to have infusion reactions

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IV Iron: Infusion reactions

- Serious allergic reactions are rare
- Most patients experience non-allergic infusion reactions including transient fever, self-limiting urticaria, palpitations, dizziness, neck and back spasm. Drug may be held and started at slower rate.
- Patients should be advised that these may occur up to 24 hours after infusion.
- Reactions which include hypotension, tachypnea, tachycardia, wheezing, stridor or periorbital edema, drug should be held.

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Folate Deficiency: Causes

- Impaired absorption (ex,. post bariatric surgery)
- Severe malnutrition or reduced intake
- Chronic alcohol use
- Chronic hemolytic anemia with increased red blood cell turnover
- Conditions associated with high cellular turnover (ex, severe eczema)
- Test for B12 deficiency in ALL patients with suspected folate deficiency
- Folate replaces tetrahydrofolate and corrects anemia, but will not correct other side effects of B12 deficiency (ex. neurologic changes)

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Management Folate Deficiency

- IV, IM, SQ, and PO formulations
- Consider parenteral route in patients with impaired absorption or symptomatic anemia
- Dose: 1-5 mg IV/IM/PO daily
- Onset: 1-2 weeks to see correction of Hgb
- Few adverse reactions
- Generally well tolerated with some cases of flushing or GI upset

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B12 Deficiency: Causes

- Impaired absorption
- Dietary deficiency
- Normal daily requirement is ~2 mcg
- Most patients with vitamin B12 present asymptomatically
- Severe B12 deficiency can result in GI and neuropsychiatric changes
- GI: glossitis (pain, swelling, tenderness, and loss of papillae of the tongue)
- Neuro: symmetric paresthesias or numbness, gait problems, depression or mood impairment, insomnia, cognitive slowing, psychosis, visual disturbances

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Management B12 deficiency

- IM, PO, sublingual, and intranasal formulations
- Consider parenteral route in patients with impaired absorption or symptomatic anemia
- Intranasal route not recommended due to variable absorption and side effects
- Dose: 500-1,000 mcg PO daily (consider doses >2,000 mcg in patients with impaired absorption); or 1,000 mcg IM once per week for four weeks, followed by 1,000 mcg once per month
- Onset: 1-2 weeks to see correction of Hgb
- Few adverse reactions
- Generally well tolerated with some cases of pruritus or GI upset

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Reference list

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- Cook K. Chapter 80. Anemias. In: DiPiro JT,Talbert RL,Yee GC, Matzke GR, Wells BG, Posey L. Pharmacotherapy: A Pathophysiological Approach

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