Anemia
Definition of Anemia

- Deficiency in the oxygen-carrying capacity of the blood due to a diminished erythrocyte mass.

- May be due to:
  - **Erythrocyte loss** (bleeding)
  - **Decreased Erythrocyte production**
    - low erythropoietin
    - Decreased marrow response to erythropoietin
  - **Increased Erythrocyte destruction** (hemolysis)
Measurements of Anemia

- **Hemoglobin** = grams of hemoglobin per 100 mL of whole blood (g/dL)
- **Hematocrit** = percent of a sample of whole blood occupied by intact red blood cells
- **RBC** = millions of red blood cells per microL of whole blood
- **MCV** = Mean corpuscular volume
  - If > 100 → **Macrocytic anemia**
  - If 80 – 100 → **Normocytic anemia**
  - If < 80 → **Microcytic anemia**
- **RDW** = Red blood cell distribution width
  - = (Standard deviation of red cell volume ÷ mean cell volume) × 100
  - Normal value is 11-15%
  - If elevated, suggests large variability in sizes of RBCs
Laboratory Definition of Anemia

- **Hgb:**
  - Women: <12.0
  - Men: <13.5

- **Hct:**
  - Women: <36
  - Men: <41
Symptoms of Anemia

- Decreased oxygenation
  - Exertional dyspnea
  - Dyspnea at rest
  - Fatigue
  - Bounding pulses
  - Lethargy, confusion

- Decreased volume
  - Fatigue
  - Muscle cramps
  - Postural dizziness
  - Syncope
Special Considerations in Determining Anemia

- **Acute Bleed**
  - Drop in Hgb or Hct may not be shown until 36 to 48 hours after acute bleed (even though patient may be hypotensive)

- **Pregnancy**
  - In third trimester, RBC and plasma volume are expanded by 25 and 50%, respectively.
  - Labs will show reductions in Hgb, Hct, and RBC count, often to anemic levels, but according to RBC mass, they are actually polycythemic

- **Volume Depletion**
  - Patient’s who are severely volume depleted may not show anemia until after rehydrated
RBC Life Cycle

- In the bone marrow, erythropoietin enhances the growth of differentiation of burst forming units-erythroid (BFU-E) and colony forming units-erythroid (CFU-E) into reticulocytes.
- Reticulocyte spends three days maturing in the marrow, and then one day maturing in the peripheral blood.
- A mature Red Blood Cell circulates in the peripheral blood for 100 to 120 days.
- Under steady state conditions, the rate of RBC production equals the rate of RBC loss.
Normal Peripheral Smear
Causes of Anemia --

**Erythrocyte Loss**

- **Bleeding**
  - Chronic (gastrointestinal, menstrual)
  - Acute/Hemodynamically significant:
    - Gastrointestinal
    - Retroperitoneal
Anemia due to

Low Erythropoietin

- Kidney Disease
  - Normochromic, normocytic
  - Low reticulocyte count
  - Frequently, peripheral smear in uremic patients show “burr cells” or echinocytes
  - Target hemoglobin for patients on dialysis is 11 to 12 g/dL
    - Administer erythropoietin or darbropoietin weekly
    - Good Iron stores must be maintained
Echinocytes (“burr cells”)
Anemia due to Decreased Response to Erythropoietin

- Iron-Deficiency
- Vitamin B12 Deficiency
- Folate Deficiency
- Anemia of Chronic Disease
Anemia due to **Decreased Response to Erythropoietin**

- **Iron Deficiency**
  - Can result from:
    - Pregnancy/lactation
    - Normal growth
    - Blood loss
    - Intravascular hemolysis
    - Gastric bypass
    - Malabsorption
      - Iron is absorbed in proximal small bowel; decreased absorption in celiac disease, inflammatory bowel disease
  - May manifest as PICA
    - Tendency to eat ice, clay, starch, crunchy materials
    - May have pallor, koilonychia of the nails, beeturia
    - Peripheral smear shows **microcytic, hypochromic red cells with marked anisopoikilocytosis**.
Iron Deficiency Anemia
Iron Deficiency Anemia - koilonychia
Iron Deficiency Anemia – Lab Findings

- Serum Iron
  - Low (< 60 micrograms/dL)

- Total Iron Binding Capacity (TIBC)
  - High ( > 360 micrograms/dL)

- Serum Ferritin
  - Low (< 20 nanograms/mL)
  - Can be “falsely” normal in inflammatory states
Treatment of Iron Deficiency Anemia

- Oral iron salts
  - Ferrous sulfate – 325 mg po Q Day
    - Side effects: constipation, black stools, positive hemmoccult test
  - Vitamin C can facilitate iron absorption.
Anemia due to Decreased Response to Erythropoietin

- **Cobalamin (Vitamin B12) Deficiency**
  - Macrocytic anemia
  - Lab Values
    - Cobalamin level < 200 pg/mL
    - Elevated serum methylmalonic acid
    - Elevated serum homocysteine
  - Vit. B12 is needed for DNA synthesis
  - Binds to intrinsic factor in the small bowel in order to be absorbed
    - Pernicious anemia: antibodies to intrinsic factor
    - Diagnosed by checking antibody levels (rather than Schilling test)
  - Deficiency can result in neuropsychiatric symptoms
    - Spastic ataxia, psychosis, loss of vibratory sense, dementia
    - Frequently not reversible with cobalamin replacement
  - Smear shows macrocytosis with hypersegmentation of polymorphonuclear cells, with possible basophilic stippling.
Vitamin B12 Deficiency
Treatment of Vitamin B12 Deficiency

- Vitamin B12 – 1000 micrograms intramuscularly monthly

-OR-

- Vitamin B12 – 1000-2000 micrograms po QDaily
Anemia due to Decreased Response to Erythropoietin

- **Folate Deficiency**
  - Macrocytic anemia
  - Lab Values
    - Low folate
    - Increased serum homocystine
    - NORMAL methylmalonic acid
  - Often occurs with decreased oral intake, increased utilization, or impaired absorption of folate
    - Folate is normally absorbed in duodenum and proximal jejunum – deficiency found in celiac disease, regional enteritis, amyloidosis
    - Deficiency frequently in alcoholics, because enzyme required for de glutamation of folate is inhibited by alcohol.
    - Deficiency often found in pregnant women, persons with desquamating skin disorders, patients with sickle cell anemia (and other conditions associated with rapid cell division and turnover)
  - Smear shows macrocytosis with hypersegmented neutrophils
Folate Deficiency
Treatment of Folate Deficiency

- Folate – 1 to 5 mg po Qday

- Vit. B12 deficiency must be excluded in folate-deficient patients, because supplemental folate can improve the anemia of Vit. B12 deficiency but not the neurologic sequelae.
# Vitamin B12 Deficiency Versus Folate Deficiency

<table>
<thead>
<tr>
<th></th>
<th>Vitamin B 12 Deficiency</th>
<th>Folate Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MCV</strong></td>
<td>&gt; 100</td>
<td>&gt; 100</td>
</tr>
<tr>
<td><strong>Smear</strong></td>
<td>Macrocytosis with hypersegmented neutrophils</td>
<td>Macrocytosis with hypersegmented neutrophils</td>
</tr>
<tr>
<td><strong>Pernicious anemia</strong></td>
<td>Yes</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Homocystine</strong></td>
<td>Elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td><strong>Methylmalonic Acid</strong></td>
<td>Elevated</td>
<td>NORMAL</td>
</tr>
</tbody>
</table>
Anemia due to **Decreased Response to Erythropoietin**

- **Anemia of Chronic Disease**
  - Usually **normocytic, normochromic** (but can become hypochromic, microcytic over time)
  - Occurs in people with inflammatory conditions such as collagen vascular disease, malignancy or chronic infection.
  - Iron replacement is not necessary
  - May benefit from erythropoietin supplementation.
Anemia due to **Decreased marrow response**

- **Thalassemia**
  - Microcytic anemia
  - Defects in either the alpha or beta chains of hemoglobin, leading to ineffective erythropoiesis and hemolysis
    - \( \alpha \)-thalassemia:
      - Prevalent in Africa, Mediterranean, Middle East, Asia
    - \( \beta \)-thalassemia:
      - Prevalent in Mediterranean, South East Asia, India, Pakistan
  - Smear shows microcytosis with target cells
Thalassemia
Anemia due to **Destruction of Red Blood Cells**

- Hemoglobinopathies
  - Sickle Cell Anemia

- Aplastic Anemia
  - Decrease in all lines of cells – hemoglobin, hematocrit, WBC, platelets
  - Parvovirus B19, EBV, CMV
  - Acquired aplastic anemia

- Hemolytic Anemia
Hemolytic Anemias

- **Hereditary spherocytosis**
  - Most common enzyme defect in erythrocytes
  - X-linked
  - Brisk hemolysis when patients exposed to oxidative stress from drugs, infections or toxins.

- **Glucose-6-phosphate dehydrogenase (G6PD) Deficiency**
  - Most common enzyme defect in erythrocytes
  - X-linked
  - Brisk hemolysis when patients exposed to oxidative stress from drugs, infections or toxins.

- **Thrombotic Thrombocytopenic Purpura (TTP)**
  - Thrombocytopenia and microangiopathic hemolytic anemia, fever, renal insufficiency, neurologic symptoms
  - Schistocytes on smear

- **Hemolytic Uremic Syndrome**
  - Thrombocytopenia, Microangiopathic hemolytic anemia, renal insufficiency

- **Autoimmune Hemolytic Anemia**
  - **Warm-antibody mediated**
    - IgG antibody binds to erythrocyte surface
    - Most common
    - Diagnosed by POSITIVE Coomb’s Test (detects IgG or complement on the cell surface)
    - Can be caused by drugs
    - Treated with corticosteroids or splenectomy if refractory

  - **Cold agglutinin Disease**
    - IgM antibodies bind to erythrocyte surface
    - Does not respond to corticosteroids, but usually mild.

- **Infections**
  - Malaria
  - Babesiosis
  - Sepsis

- **Trauma**
  - Includes some snake, insect bites
Sickle Cell Anemia
Spherocytosis
TTP / HUS – microangiopathic hemolysis with schistocytes
Malaria
Babesiosis
Lab Analysis in Hemolytic Anemia

- Increased indirect bilirubin
- Increased LDH
- Increased reticulocyte count
  - Normal reticulocyte count is 0.5 to 1.5%
  - > 3% is sign of increased reticulocyte production, suggestive of hemolysis
- Reduced or absent haptoglobin
  - < 25 mg /dL suggests hemolysis
  - Haptoglobin binds to free hemoglobin released after hemolysis
Evaluating the Patient with Anemia

- Check Hemoglobin/Hematocrit
  - If female, is Hgb < 12 or Hct < 36?
  - If male, is Hgb < 13.5 or Hct < 41?
  - If Yes, Patient has ANEMIA!
  - If No, they are fine and this lecture was not necessary.
Evaluating the patient with Anemia

- Any history of medical problems that could cause anemia?
  - Sickle cell Disease?
  - Thalassemia?
  - Renal Disease?
  - Hereditary Spherocytosis?
Evaluating the Patient with Anemia

- Are the other cell lines also low?
  - If WBC and platelets are both low, consider APLASTIC ANEMIA!
    - Check medication list
      - NSAIDS (phenylbutazone), Sulfonamides, Acyclovir, Gancyclovir, chloramphenicol, anti-epileptics (phenytoin, carbamazepine, valproic acid), nifedipine
      - Check parvovirus B19 IgG, IgM
      - Consider hepatitis viruses, HIV
  - If Platelets are low consider TTP or HUS!
    - Must check smear for schistocytes (for sign of microangiopathic hemolytic anemia)
    - If renal failure, E. Coli O157:H7 exposure → HUS
    - If renal failure, neurologic changes, fever → TTP
Evaluating the Patient with Anemia

☐ Is the patient bleeding?!
  ■ Any bright red blood per rectum (hematochezia) or black tarry stools (melena)?
    ☐ Check stool guaiac, may consider sigmoidoscopy or colonoscopy
  ■ Any abdominal pain, or recent femoral vein/artery manipulation?
    ☐ Consider retroperitoneal hematoma
Evaluating the Patient with Anemia

- If other cell lines are okay, what is the MCV and RDW?
  - If MCV < 80, then it’s a microcytic anemia
    - Check serum iron, ferritin, TIBC
      - If iron-deficiency anemia, look for sources of chronic bleeding – heavy menstrual bleeding, consider colonoscopy
    - Consider lead poisoning, copper deficiency, thalassemias
  - If MCV 80-100, then it’s a normocytic anemia
    - Any inflammatory conditions that could result in anemia of chronic disease?
    - Consider checking indirect bili, LDH, haptoglobin, reticulocyte count
  - If MCV > 100, then it’s a macrocytic anemia
    - Check Vit. B 12, folate
    - Consider liver disease, alcoholism, myelodysplastic syndrome
    - Check medications: hydroxyurea, AZT, methotrexate
Evaluating the Patient with Anemia

- Any jaundice, elevated bilirubin, suspicious for hemolysis?
  - Check for increased indirect bilirubin, increased LDH, decreased haptoglobin, increased reticulocyte count
- Any sign of infection? Malaria? Babesiosis?
- Is Coombs test positive?
  - If yes, may be warm antibody hemolytic anemia; Consider drug as cause
Case #1

- A 41-year old male with a history of HIV with a CD4 count of 150 who presents with a Hgb of 11, Hct of 33, which is down from a Hgb of 14 with a Hct of 42.
Case #1

☐ Denies hematochezia, melena, any source of bleeding

☐ Denies any yellowing of the skin

☐ No recent fevers, nausea or vomiting.
Case #1

- **PMH:** HIV/AIDS
  - No history of sickle cell disease, cancer, anemia

- **Allergies:** Sulfa

- **Meds:**
  - Efavirenz
  - Emtricitabine
  - Tenofovir
  - Dapsone

- **Social History:**
  - No recent travel, no recent sick exposures, lives alone; occasional alcohol use, no tobacco use, no IV drug use; Works as attorney

- **Family History:**
  - No family history of cancer
Case #1

- P.E.: 37.8, 123/68, 73, 16, 99% on RA
- Gen: Alert and oriented x 3; in NAD;
- HEENT: no scleral icterus, no lymphadenopathy
- CV: RRR
- Resp: LCTA
- Abd.: soft, nontender
- Ext.: no LE edema
Case # 1

LABS:
- WBC: 4.3
- Hgb: 11
- Hct: 33
- Platelets: 224
- Sodium: 137
- Potassium: 3.8
- Chloride: 101
- CO2: 25
- Glucose: 102
- Tot. Protein: 5.3
- Albumin: 3.1
- Total Bili: 1.4
- Dir. Bili: 0.2
- AST: 23
- ALT: 42
- Alk. Phos: 122
- Haptoglobin: 20
- Reticulocyte count: 3.2%
Case #1

- What lab test do you want to make sure patient has had already or might you want to check?
- What might you see on peripheral smear if his total bilirubin was elevated, and his platelets were low?
Case #2

A 34-year old woman presents to your office with a 1-week history of generalized weakness, easy fatiguability and shortness of breath. One hour ago, she developed a headache a left hemiparesis. Two days ago, she noted easy bruisability and bleeding gyums. Three days ago, she developed a fever. A history reveals that she had no previous serious illnesses and review of systems is normal.
Case #2

- Physical Exam:
  - Temp: 40°, 120/70, 70, 16, 96% on RA
  - Gen: Alerti oriented, in NAD, but appears weak
  - HEENT: petechiae on soft palate with some fresh blood on gingiva
  - CV: RRR; II/VI high-pitched holosystolic murmur
  - Resp: LCTA bilaterally
  - Neuro: mild left hemiparesis with hyperactive reflexes and positive babinkski on the left
  - Skin: scattered purpuric lesions on lower extremities
Case # 2

- Hgb: 6 g/dL
- MCV: 80
- RDW: 20%
- WBC: 15
- Reticulocyte count: 200
- Platelet: 9
- Creatinine: 1.0
- Total Bili: 3.0
- Direct Bili: 0.2
- LDH: 3500
- UA: 2+ protein, 30-40 RBCs, 5 WBCs
Case #2
Case # 2

☐ The most likely diagnosis of this patient’s disorder is:
(A) Acute leukemia
(B) Bacterial endocarditis
(C) Thrombocytopenic purpura
(D) Hemolytic uremic syndrome
(E) Systemic Lupus erythematosus
Case # 3

A 64-year old woman is hospitalized because of progressive SOB and palpitations over the past few weeks. She has also noticed a yellow tinge to her eyes during this time. She occasionally drinks wine excessively but says that she has abstained since the onset of her symptoms. For the last 6 months she has not eaten meat or fish, and her diet has consisted mostly of toast with margarine, tea, and an occasional banana. She says her social security checks do not stretch as far as they used to.
Case # 3

- Physical Exam:
  - Vitals: Pulse: 110, RR: 22
  - General: pale, blue-eyed, gray-haired disheveled female with mild scleral icterus.
  - CV: RRR
  - Resp: crackles that do not clear with coughing are heard at both lung bases
  - Ext: mild pitting edema at both ankles
  - Neuro Exam: Normal
Case #3

☐ Labs:

- Hgb: 5.1 g/dL
- MCV: 112
- RDW: 21%
- Platelets: 109
- WBC: 4.6
**Case #3**

- Which of the following blood levels are most likely in this patient?

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<thead>
<tr>
<th></th>
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<th>Folate</th>
<th>Methylmalonic Acid</th>
<th>Homocysteine</th>
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<tbody>
<tr>
<td>(A)</td>
<td>Low</td>
<td>Normal</td>
<td>High</td>
<td>High</td>
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<tr>
<td>(B)</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
<td>High</td>
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<tr>
<td>(C)</td>
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<tr>
<td>(D)</td>
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