ANEMIA

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Definitions

- Anemia is a reduction in the circulating red cell mass
- Hemoglobin is the concentration of oxygen carrying pigment
- Hematocrit is the percent of a whole blood sample occupied by RBCs, calculated (Hct=RBC X MCV)

Definitions

- MCV (mean corpuscular volume) is directly calculated as the average red cell volume
- MCH (mean corpuscular hemoglobin) =Hgb/RBC
- MCHC (mean corpuscular hemoglobin concentration) the average concentration of hemoglobin per volume of cells = Hgb/Hct
Definitions

- RDW (red cell distribution width) variance in red cell volume distribution (useful in anisocytosis)

MCV

- Normal is 80-100 femtoliters
- The MCV is the most clinically useful red cell index
- False increase seen in cold agglutinin disease and autoantibodies, (can be corrected by warming or prediluting)
- False decrease rarely seen in extreme hyperglycemia
MCHC
- Normal is 31 to 36
- Elevated classically in hereditary spherocytosis or autoimmune hemolysis
- Elevated in any condition where red cells are dessicated (sickle cell anemia)

RDW
- Is a quantitative estimation of anisocytosis
- RDW elevated maybe seen in iron deficiency anemia and hemolysis

Anemia
- Defined as more than 2 SD below the mean
  - Males: Hgb <13.5 g/dl, Hct < 41
  - Females: Hgb < 12.0 g/dl, Hct < 36
  - 2.5% of population will be below this number and normal
  - Normal ranges are very wide (Our lab: Male Hgb14-18 and females 12-16)
  - Special populations with higher hemoglobin: high altitude dwellers, athletes, smokers or increased exposure to carbon monoxide,
Anemia and Volume Status

- RBCs, HCT and HGB are all concentrations and depend on RBC mass and plasma volume
  - Acute blood loss (initial levels will be normal)
  - 3rd trimester pregnancy (RBC mass expands by 25%, Plasma volume by 50%, dilutional anemia)
  - Volume depletion

Lower hemoglobin

- African Americans have hgb 0.5 to 1.0 g/dl lower than Caucasians
- Athletes (dilutional anemia with increased plasma volume)
- Healthy elderly
  - NHANES study: 10-11% over 65 were anemic, 28% of non Hispanic blacks: 1/3 nutritional deficiency (iron/folate most common), 1/3 with chronic disease, 1/3 unexplained (but 15% satisfied criteria for MDS)

RBC Life Cycle

- Reticulocyte matures in about four days into mature erythrocyte,
- Mature RBC circulated for 120 days
Assessment of Anemia

- Mechanistic approach
- Morphologic approach

Mechanistic View of Anemia

Mechanistic Approach

- Decreased RBC production
  - Bone marrow disorders
  - Bone marrow suppression
  - Low levels of trophic hormones (erythropoietin)
  - Anemia of chronic disease/inflammation
  - Lack of nutrients (blood loss, malabsorption)
Mechanisms

- Increased RBC destruction
  - Inherited hemolytic anemia
  - Acquired hemolytic anemia

Mechanisms

- Blood loss
  - Obvious bleeding
  - Occult bleeding
  - Induced bleeding

Morphological Assessment of Anemia

- Normocytic anemia
- Microcytic anemia
- Macrocytic anemia
Normocytic Anemia

MCV within normal range between 80-100 femtoliters
- Acute blood loss
- Early iron deficiency
- Chronic renal insufficiency
- Endocrine dysfunction
- Chronic disease
- Bone marrow suppression
- Mixed anemia

Microcytic Anemia (MCV < 80)
- Iron deficiency anemia
- Thalassemia
- Anemia of chronic disease (less often)
- Sideroblastic (congenital, lead, drugs and ETOH)
- Copper deficiency
- Zinc poisoning (rare)
Evaluation of the Patient with Anemia

- Initial approach (history, physical, and basic labs)
  - Is the patient bleeding now or in the past?
  - Is there increased RBC destruction (hemolysis)?
  - Is the bone marrow suppressed?
  - Is there iron deficiency?
  - Is there folate or B12 deficiency?

Macrocytic Anemia (MCV >100)

- Alcohol abuse
- Folic acid deficiency
- B12 deficiency
- Myelodysplasia
- Liver disease
- Reticulocytosis
  - Hemolytic anemia
  - Bone marrow recovery
Evaluation of the Patient (cont.)

- Any medical conditions that may be contributing?
  - Chronic kidney disease
  - HIV
  - Rheumatoid Arthritis
  - Inflammatory bowel disease
  - Cancer

Evaluation of the Patient (cont.)

- What is the duration of the anemia?
- Patient’s ethnicity?
- Any medications that might contribute?

Signs and Symptoms

- Patients may be asymptomatic in mild anemia
- Common physical symptoms
  - varying degrees of fatigue
  - headaches
  - dizziness or vertigo
  - pallor
  - feeling cold
  - tachpnea or dyspnea
  - tachycardia
  - edema
Less Common Signs and Symptoms

- Brittle broken nails
- Pulmonary edema
- Cognitive impairment
- Angina or palpitations
- Menstrual irregularities
- Reduced libido or potency
- Indigestion
- Pica

Severe Anemia Signs Symptoms

- Lethargy
- Confusion

Life-threatening complications
- Congestive failure
- Angina
- Arrhythmias
- Myocardial infarction

Physical Examination

- Hepatosplenomegaly
- Bone tenderness
- Lymphadenopathy
- Signs of bruising or bleeding
- Glossitis (seen in folate and B12 def.)
- Nail spooning
Basic Laboratory Evaluation

- CBC
- Reticulocyte count
- Peripheral smear
- Iron, TIBC
- Ferritin
- B12
- Folate
- TSH
- ?ANA
- SPEP, UPEP
- Stool FOB
- UA
- Chest X-ray

Further Work up

- Lactate dehydrogenase
- Coombs test
- Haptoglobin level
- LFT’s
- Hemoglobin electrophoresis

Laboratory Evaluation
**WBC & Anemia**

- A low WBC with anemia suggests bone marrow suppression, replacement, hypersplenism, or B12/folate deficiency
- A high WBC with anemia suggests infection, inflammation, or malignancy

**Platelets & Anemia**

- Thrombocytopenia
  - Hypersplenism
  - Marrow involvement with malignancy
  - Sepsis
  - Autoimmune platelet destruction
  - B12/folate deficiency

- Thrombocytosis
  - Myeloproliferative disorders (often see giant platelets)
  - Iron Deficiency
  - Acute blood loss
  - Infection, inflammation, malignancy
### Pancytopenia

- Aplastic anemia
- B12 or folate deficiency
- Hematologic malignancy
- Hypersplenism
- Bone marrow suppression from sepsis or drugs

### Bone marrow evaluation

- In most cases of anemia, is not indicated
- Indicated in pancytopenia, presence of abnormal cells on peripheral smear, evaluation for myelodysplasia

### Iron Deficient Anemia
Iron Deficiency

- Blood Loss
  - Overt: menorrhagia, hematuria, GI loss, hematemesis, hemorrhage, hemoptysis
  - Occult: most often due to GI bleeding

- Decreased Absorption
  - Generalized malabsorption (sprue)
  - Achlorhydria (atrophic gastritis, H. Pylori gastritis)

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### Laboratory Tests for Iron Deficiency

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal</th>
<th>Range</th>
<th>Decreased Absorption</th>
<th>Hemolytic Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron, μg/dL</td>
<td>Normal</td>
<td>60-150</td>
<td>20-50</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Serum iron binding capacity</td>
<td>Normal</td>
<td>20-300</td>
<td>10-50</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Total iron binding capacity</td>
<td>Normal</td>
<td>80</td>
<td>400-500</td>
<td>&gt;500</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>Normal</td>
<td>12-15</td>
<td>9-12</td>
<td>&lt;9</td>
</tr>
<tr>
<td>Mean cell volume (MCV), fl</td>
<td>Normal</td>
<td>80-100</td>
<td>70-100</td>
<td>&lt;70</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>Normal</td>
<td>200</td>
<td>400-1000</td>
<td>50-150</td>
</tr>
<tr>
<td>Platelet count, x 10^9/L</td>
<td>Normal</td>
<td>150</td>
<td>100-400</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Serum ferritin, μg/L</td>
<td>Normal</td>
<td>100</td>
<td>1000-5000</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

Note: Tests may not be done in all cases and the exact test battery will depend on the urgency of the clinical situation.
Ferritin

- IS the standard for diagnosing iron deficiency in place of evaluating bone marrow iron in most patients
- Normal range is 40 to 200 ng/ml
- Any ferritin below 10 to 15 ng/ml is diagnostic for iron deficiency
- BUT any ferritin below 50 should raise concern for iron deficiency (sensitivity 92% and specificity of 98%)

Ferritin & Inflammatory States

- Ferritin is an acute phase reactant
- The effect of inflammation is to elevate serum ferritin approximately threefold
- divide the patient's serum ferritin concentration by three; a resulting value of 20 or less suggests concurrent iron deficiency

Serum Iron and TIBC

- Serum iron is decreased, TIBC (a measure of transferrin) is increased
- Transferrin saturation < 15% is 80% sensitive for iron deficiency
Bone Marrow Iron

- Was the gold standard, but has been replaced by ferritin
- In iron deficiency, iron is absent from macrophages and RBC precursors
- In anemia of chronic disease, no iron is seen in RBC precursors

Thalassemia

- Hypochromic and microcytic (microcytosis is much more profound)
- Red cell count will be elevated, unlike iron deficiency
- RDW in thalassemia trait tends to be normal since virtually all cells are hypochromic and microcytic
Differential Dx for Hypochromic Microcytic Anemia
- Sideroblastic Anemia
  - Ringed sideroblasts seen in the marrow
- Anemia of Chronic Disease
  - Serum iron and TIBC will be low, with normal or increased ferritin

Megaloblastic Anemia
- Folate Deficiency
- B12 deficiency

Folate Deficiency
- Serum folate is primarily a reflection of short-term folate balance
  - One good meal can replace serum folate levels
  - Pregnancy, alcohol intake, some anticonvulsants (phenytoin), and a few days of decreased intake can lower serum levels
  - RBC folate is a better indicator of body stores but more expensive
Folate Deficiency

- Serum folate concentration should be obtained as an initial screening test
- If the serum folate concentration is >4 ng/mL (9.1 nanomol/L), folate deficiency is ruled out. RBC folate levels in borderline levels
- Folate deficiency is treated with folic acid supplement

Folate Deficiency

- Folic acid can partially reverse some of the hematologic abnormalities of B12 deficiency, although the neurologic manifestations will progress
- Therefore important to rule out B12 deficiency before treating

B12 Deficiency

- Serum B12 concentrations fall during pregnancy, but these patients do not necessarily show evidence of deficiency
- Serum B12 concentration may be normal in up to five percent of patients with documented B12 deficiency
- In one study of 84 patients with low B12 values (<180 pg/mL), only 16 were confirmed to be B12 deficient (positive predictive value of 22 percent
B12 Deficiency

- >300 pg/mL (>221 pmol/L) — normal result; B12 deficiency is unlikely. (1 to 5 percent)
- 200 to 300 pg/mL (148 to 241 pmol/L) — borderline result; B12 deficiency possible
- 200 pg/mL (<148 pmol/L) — low; consistent with B12 deficiency (specificity of 95 to 100 percent)

WBCs

- Neutrophil hypersegmentation (>5% of neutrophils with 5 or more lobes and at least one neutrophil with 6 lobes) when seen with macroovalocytes is associated with impaired DNA synthesis in B12/folate deficiency

Image: Hypersegmented neutrophil. Blood smear from a patient with megaloblastic anemia, showing a neutrophil with an increased number of nuclear lobes. At least six discrete lobes are present. Normal neutrophils have five lobes or less. Courtesy of Stephen A. Laskow, MD, PhD.
Factors that may cause B12 Deficiency
- Gastrectomy/Bariatric surgery
- Pernicious anemia
- Vegetarian diet
- Crohn’s disease
- Chronic alcoholism
- Pancreatic insufficiency

Agents that Block B12 Absorption
- Proton pump inhibitors
- Biguanides (e.g., Metformin)
- Neomycin

Methylmalonic Acid and Homocysteine
- Testing should be reserved for those patients in whom a high degree of suspicion of B12 deficiency is present:
  - those with borderline serum B12 levels
  - otherwise unexplained neurologic complaints
  - uncover a treatable cause of dementia
Methylmalonic acid and Homocysteine

- Homocysteine and methylmalonic acid are elevated in B12 deficiency, due to a decreased rate of metabolism
- Only homocysteine is elevated in folate deficiency, since folate does not participate in MMA metabolism

Pernicious Anemia

- Presence of anti-intrinsic factor antibodies is highly confirmatory for the diagnosis of PA
- Anti-parietal cell antibodies are much less specific and may even be less sensitive (Schilling test is recommended only when more simple tests (eg, anti-IF antibodies) are normal)

Treatment of B12 deficiency

- B12 replacement; po, sublingual or IM
- Oral or sublingual B12 is also adequate, except in PA or concern over absorption
- Animal proteins provide the only dietary source of B12 (meats, fish, and dairy products)
Alcoholism

- Alcohol is a common cause of macrocytosis
- Approximately 90% of alcoholics have a macrocytosis with a MCV between 100-110
- Alcohol-induced macrocytosis occurs even though patients are folate and B12 replete and do not have liver disease
- Abstinence from alcohol results in resolution of the macrocytosis within two to four months

Liver Disease

- Liver disease particularly if caused by alcohol is another common cause of macrocytosis, which is often accompanied by target cell formation

Hypothyroidism

- Occasional patients with hypothyroidism and/or myxedema display macrocytosis without marrow megaloblastosis
Hemolytic Anemia

**Common Causes of Hemolytic Anemia in the Adult**

**Extravascular destruction of red blood cells**
- Inherited red blood cell defects
- Acquired disease (e.g., malaria, schistosomiasis)
- Autoimmune hemolytic anemia (AIHA)
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Spherocytosis (e.g., hereditary spherocytosis, elliptocytosis)

**Intravascular destruction of red blood cells**
- Liver disease
- Hyperparathyroidism
- Sickle cell disease
- Hemolytic uremic syndrome
- Other causes (e.g., malaria, schistosomiasis)

**Laboratory Tests**
- Hemoglobin
- Hematocrit
- Mean corpuscular volume (MCV)
- Red cell distribution width (RDW)
- Platelets
- Erythropoietin
- Reticulocyte count
- Serum bilirubin
- Total bilirubin
- Direct bilirubin

**Other Tests**
- Serum haptoglobin
- Antinuclear antibody
- Direct Coombs test
- Complement levels
- Serum immunoglobulins

**Diagnosis**
- Increased LDH and reduced haptoglobin is 90 percent specific
- Defined as shortening of RBC survival to less than 100 days
- Increase in erythropoietin production induced by anemia should raise the reticulocyte percentage above 4 to 5 percent

**Reticulocyte count**
- High retic count is increased erythropoiesis due to blood loss or continued hemolysis
- **BUT** low retic count can be seen in these situations if there is concurrent bone marrow suppression
Multiple Myeloma
Multiple Myeloma

- Etiology:
  - Multiple myeloma is a malignant proliferation of the plasma cells
  - These cancerous cells destroy normal bone tissue causing pain and compromising normal bone marrow function

Etiology

- Cause unknown
- Exposure to radiation, benzene, organic solvents, insecticides may have a role
- Increased risk in atomic bomb survivors, radiologists with high long-term exposure
- Chronic inflammatory diseases
- Kaposi's sarcoma-associated herpes virus (HHV8) has been found in some studies, but no clear pathogenesis
- Genetic factors unclear

Myeloma

- Clinical findings
  - Anemia is common in myeloma
  - Two-thirds of Myeloma patients at diagnosis
  - Skeletal destruction- osteolytic lesions
  - Most frequent involvement: skull, vertebral bodies, ribs, pelvis, proximal long bones
  - Bone pain
  - Fractures
  - Hypercalcemia in 28%
  - Renal insufficiency
  - Recurrent bacterial infections,
Epidemiology

- MM accounts for 1% of all malignancies and 10% of hematologic malignancies
- More frequent in men, and twice as common in blacks versus whites
- Median age is 66 (10% <50, 2% <40)
- U.S. incidence is approximately 15,000 new cases per year
- Deaths estimated 11,000 per year

Clinical Manifestations

- Peripheral neuropathy is uncommon, usually due to amyloidosis
- Plasmacytomas can be seen as soft tissue or bony masses

Initial Laboratory Evaluation

- CBC and peripheral smear
- Serum calcium, creatinine, albumin, lactate dehydrogenase, beta-2 microglobulin
- Serum protein electrophoresis with immunofixation and quantitation of immunoglobulins
- Routine urinalysis and a 24-hour urine for electrophoresis and immunofixation
Initial Laboratory Evaluation

- Metastatic bone survey including the humeri and femoral bones
- Serum levels of beta-2 microglobulin, C reactive protein, and lactate dehydrogenase serve as important prognostic factors

Laboratory Findings

- Normocytic, normochromic anemia
- Rouleaux formation is found in more than one-half of patients
- Plasmacytosis in the peripheral smear is infrequent
- Erythrocyte sedimentation rate is >20 mm/h in 84 percent, and >100 mm/h in one-third.
- Leukopenia and thrombocytopenia
## Diagnostic Criteria—International Myeloma Working Group

- Presence of M protein
- Presence of bone marrow clonal plasma cells (usually >10%) or plasmacytoma
- Organ or tissue impairment (increased plasma calcium level, renal insufficiency, anemia, lytic bone lesions)

## Monoclonal Proteins

- Most important diagnostic finding in myeloma
- SPEP shows a localized band in 82 percent
- Immunofixation of the urine reveals an M protein in approximately 75 percent
- Among the 20 percent with no localized band on SPEP, hypogammaglobulinemia is seen in about one-half
Monoclonal Proteins

- IgG monoclonal protein: 51.5%
- IgA: 21 percent
- Light chain (Bence Jones): 16 percent
- IgD: 2%
- Biclonal: 2%
- IgM: 0.5%
- No monoclonal protein: 7%
Differential Diagnosis

- Monoclonal gammopathy of undetermined significance (MGUS)
  - Asymptomatic
  - M protein < 3 gm
  - <10% plasma cells in marrow
  - No bone lesions, anemia, hypercalcemia, renal insufficiency

MGUS Followup

- SPEP should be repeated in 6 months and if stable, annually for life
- Risk of progression to myeloma is 1% per year or 5-25% lifetime risk
<table>
<thead>
<tr>
<th>Ddx</th>
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<tbody>
<tr>
<td>Smoldering myeloma</td>
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<tr>
<td>• M protein &gt; 3 gm, &gt;10% BM plasma cells</td>
</tr>
<tr>
<td>• No anemia, lytic lesions, hypercalcemia, renal insufficiency</td>
</tr>
<tr>
<td>• Probably 3-5% rate of progression per year to myeloma</td>
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<tbody>
<tr>
<td>Primary Amyloidosis</td>
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<tr>
<td>• Tissue deposits of light chains</td>
</tr>
<tr>
<td>• Hepatomegaly, nephrotic syndrome, CHF</td>
</tr>
<tr>
<td>• No lytic lesions, BM plasma cells &lt;10%</td>
</tr>
<tr>
<td>• DX: amyloid staining of bone marrow, abdominal fat, rectal biopsy, or kidney</td>
</tr>
<tr>
<td>• 0.4% risk of progression to myeloma</td>
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</tbody>
</table>

| Anemia is a SYMPTOM not a Diagnosis |