Anemia is a laboratory diagnosis

<table>
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<tr>
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<th>Men</th>
<th>Women</th>
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<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>14-17.4</td>
<td>12.3-15.3</td>
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<tr>
<td>Hematocrit (%)</td>
<td>42-50%</td>
<td>36-44%</td>
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<tr>
<td>RBC Count (10^6/mm^3)</td>
<td>4.5-5.9</td>
<td>4.1-5.1</td>
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<tr>
<td>Reticulocytes (%)</td>
<td>1.6 ± 0.5%</td>
<td>1.4 ± 0.5%</td>
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<tr>
<td>WBC (cells/mm^3)</td>
<td>~4,000-11,000</td>
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<tr>
<td>MCV (fL)</td>
<td>80-96</td>
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<tr>
<td>MCH (pg/RBC)</td>
<td>30.4 ± 2.8</td>
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<tr>
<td>MCHC (g/dL of RBC)</td>
<td>34.4 ± 1.1</td>
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<tr>
<td>RDW (%)</td>
<td>11.7-14.5%</td>
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**Presentation/history**

- **Mild anemia:**
  - few or no symptoms; may be discovered accidentally on lab test
- **May complain of:**
  - Fatigue, decr. exercise tolerance, SOB, palpitations, CP, lightheadedness on arising
  - Sore tongue (glossitis), cracking mouth corners (angular cheilosis), peripheral paresthesias (numb toes, etc.)
- **Hx:**
  - EtOH use, FH anemia, pica, vegetarian diet, melena/hematochezia, malabsorption syndromes, Crohn’s disease

**Sites of absorption of iron and vitamin B12**
Presentation/history

- Symptomology is poorly related to absolute lab values
  - Patients with gradual onset may be asymptomatic with quite low Hb/HCT
  - Acute onset can cause symptoms with relatively less anemia
- Mild anemia may be “normal” or “OK” for a menstruating woman, but you should always seek a cause in a man or a postmenopausal woman (or child)

Anemia: Special Populations

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

Differential diagnosis

Consider:
- Anemia
- Hypothyroidism
- Depression
- Cardiac (congestive heart failure, aortic stenosis)
- Pulmonary causes of SOB/DOE
- Chronic fatigue syndrome, others

Physical examination

- Pallor (may be jaundiced—think hemolytic)
- Tachycardia, bounding pulses
- Systolic flow murmur
- Glossitis
- Angular cheilosis
- Decreased vibratory sense/ joint position sense (B12 deficiency, w/ or w/o hematologic changes)
- Ataxia, positive Romberg sign (severe B12/folate deficiency)
Labs

- For all: CBC, reticulocyte count, ± peripheral smear
- For some:
  - B12, folate, hemoglobin electrophoresis
  - Bone marrow aspirate to assess possible defective hematopoiesis
  - Other labs to assess other differential diagnoses (e.g. thyroid function tests, etc.)

Approach to anemia

- First, is the problem ineffective erythropoiesis, or is it destruction of RBCs?
- Ineffective erythropoiesis can come from a variety of causes
- What test will tell you which is the problem?
  Answer: _______________________

Ineffective erythropoiesis

- All with normal/low reticulocyte count
  - Microcytic: think Fe^{++} deficiency
  - Macrocytic: think B12/folate deficiency
  - Normocytic: think anemia of chronic disease, marrow problems, or other problems

Fe^{++} deficiency anemia

- Most commonly due to chronic bleeding and erythropoiesis limited by iron stores that have been depleted
- May be dietary (pica, lack of meat/vegetables, other)
- Iron balance is very close in menstruating women, so Fe^{++} deficiency is not uncommon with no other source of bleeding
Labs

- Iron and ferritin will be low
- TIBC (total iron binding capacity) will be high, since iron stores are not saturating their binding sites on transferrin
- Reduced RBC counts (definition of anemia)
- Microcytosis & hypochromia are hallmarks, but early Fe^{2+} may be normocytic (± hypochromic)
- Usually, MCH and MCHC will both be low (whereas in macrocytic anemia, the MCH may be normal while the MCHC is low, because of the larger cell size)

Labs

- Most practitioners would agree that if a patient has microcytic hypochromic anemia with a low reticulocyte count, it would be reasonable to use a trial of FeSO4 to diagnose
- 5-10 days after initiating therapy, a robust rise in reticulocytes confirms the diagnosis

Treatment

- Iron, oral in most cases, parenteral in cases of malabsorption
- All forms of iron are constipating; the amount of constipation directly relates to the amount of elemental iron delivered
  - If intolerant of FeSO4 (cheapest), reduce the dose, rather than switching form
  - Start 325 mg QD, increase slowly to TID
- Follow up the cause of the iron deficiency!

Macrocytic anemia with ineffective erythropoiesis

- Low/normal reticulocyte count, macrocytosis
- Most common is folate/B12 deficiency
  - Dietary: folate far more common, B12 may occur in strict vegans
  - Pernicious anemia: lack of B12 protection in stomach and gut
  - Poor uptake in terminal ileum (e.g. in Crohn’s disease)
  - B12 and folate are essential for cell maturation and DNA synthesis, erythrocytes end up large, usually normochromic, since iron is not lacking
- Other: drugs, toxins, myelodysplasia
<table>
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<tr>
<th>Folate deficiency</th>
<th>B12 deficiency</th>
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<tr>
<td>• Folate intake is usually dietary, and may be deficient with low fresh fruit &amp; vegetable intake</td>
<td>• Less common, usually caused by absorption problems, rather than dietary deficiency</td>
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<tr>
<td>• Folate supplementation of bread prevents neural tube defects in pregnancy</td>
<td>• B12 needs Intrinsic Factor for protection from degradation in gut</td>
</tr>
<tr>
<td>• PE may include neurological effects if severe deficiency</td>
<td>– Produced by parietal cells of stomach, protects through gut for uptake at terminal ileum</td>
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<td></td>
<td>– Pernicious anemia from immune attack of IF production</td>
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<td></td>
<td>– EtOH-related gastritis can affect IF production, and liver disease may also contribute to macrocytosis</td>
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<tr>
<th>Neurological effects</th>
<th>Labs</th>
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<tr>
<td>• Deficiency results in damage to dorsal columns (sensory) and lateral columns (motor) of spinal cord</td>
<td>• Folate and B12 levels</td>
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<td>• Decreased vibration sense and position sense of joints detectable, and may affect gait, etc.</td>
<td>• Schilling test may be useful to establish etiology of B12 deficiency</td>
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<tr>
<td>• May have positive Romberg’s test</td>
<td>– Assesses radioactive B12 absorption with and without exogenous IF</td>
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<tr>
<td>• Severe effects may include ataxia and dementia</td>
<td>• Other tests if pernicious anemia is suspected</td>
</tr>
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<td></td>
<td>– Anti- parietal cell antibodies, anti-IF antibodies</td>
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<tr>
<td></td>
<td>– Secondary causes of poor absorption should be sought (gastritis, ileal problems, ETOH, etc.)</td>
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**Treatment—supplementation**

- Do NOT correct folate levels unless B12 is OK
  - Correction of folate deficiency will correct hematologic abnormalities without correcting neurological abnormalities
  - Check B12 and correct first
- B12 usually 1000 mg I.M. q month
  - B12 stores take a long time to deplete; missed doses are not usually a problem
  - Oral supplementation is gaining support; usually effective in pernicious anemia (1-2 mg PO QD)
- Reticulocyte count should respond in 1 wk

**Anemia of chronic disease**

- Normocytic anemia with ineffective erythropoiesis (reduced reticulocyte count)
- May be normochromic or hypochromic
- Results from
  - Chronic inflammation (e.g. rheumatologic disease): Cytokines released by inflammatory cells cause macrophages to accumulate iron and not transfer it to plasma or developing red cells (iron block anemia)
  - Renal failure (erythropoietin from kidneys)
  - Endocrine (e.g. hypothyroid)
  - Hepatic disease
- Bone marrow suppression (EPO is elevated)

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**Treatment**

- Correct or manage underlying disease when possible
  - May need EPO injection ($$$$)
- EPO is the treatment of choice for anemia of renal failure
- In bone marrow deficiency/malignancy, treat if possible, remove precipitating drugs, may require BMT

**Normochromic, normocytic anemia with effective erythropoiesis**

- **INCREASED** reticulocyte count
- Acute blood loss
  - Very acutely, with hypovolemia, may have normal blood counts, will become anemic with volume replenishment
- Hemolytic anemia
  - Increased reticulocyte production cannot keep pace with loss of RBCs peripherally
<table>
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<tr>
<th>Immune hemolytic anemia</th>
<th>Coomb’s test</th>
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| • IgG or IgM labeled as “warm” or “cold”  
  – Antibodies on RBC result in hemolysis  
• Usually acute, often with jaundice  
• May be drug-induced  
• Cold hemolytic anemia often post-infectious, generally not severe, worsens with exposure of periphery to cold temperatures |
| • Detects presence of either antibody on RBC or of antibody in serum  
• Helpful in determining if a hemolytic anemia is immune-mediated |

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<tr>
<th>Treatment</th>
<th>Special cases of hemolytic anemia</th>
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| • Withdraw offending drug (PCN, quinidine, quinine, rifampin, others)  
• Steroids/splenectomy – reduces immune function and RBC sequestration, respectively |
| • Glucose-6 Phosphate Dehydrogenate deficiency  
  – More common in African and Mediterranean populations  
  – Lack of RBC enzyme makes cells very sensitive to oxidative stress (infection, certain drugs)  
  – Treatment: avoid triggers if possible, especially inciting drugs |
Sickle cell disease

- More in PAS 658
- African background
- Abnormal hemoglobin causes change in RBC shape, resulting in constant RBC destruction by the spleen, functional asplenia, susceptible to infection
- Arterial occlusion leads to infarcts, pain crises, acute chest syndrome, stroke, MI
- Keep hydrated, treat pain, take infection seriously
- Also sickle-C and sickle-β-thalassemia

Thalassemias

- Decreased production of normal hemoglobin polypeptide chains.
- Classified according to hemoglobin chain that is affected (α, β, γ, δ)
- Common, variable severity of hemolysis
- Characterized by hypochromic microcytic red cells (MCV markedly decreased while MCHC only slightly decreased)
- Beta Thalassemia most common in this country and can be suspected if electrophoresis shows a compensatory increase in Hb A2 and/or F (fetal). (Note: Hb A2 generally does not increase above 10%)

Case Studies

Anemia Case Study #1

A 72 year old male has the CBC findings shown. Peripheral RBCs are hypochromic & microcytic.
**Anemia Case Study #1**

- What test would you order for this patient?
  - A-Hemoglobin Electrophoresis
  - B-Retic count
  - C-Stool for occult blood
  - D-B12 Assay
  - E-Bone marrow biopsy

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**Anemia Case Study #1**

- Two questions:
  - What is your diagnosis?
  - What is the next step for this patient?

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**Anemia Case Study #2**

A 48 year old male has become progressively more fatigued at the end of the day. This has been going on for months. In the past month he has noted paresthesias with numbness in his feet. A CBC demonstrates the findings shown.

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**Anemia Case Study #2**

A peripheral blood smear (the slide is representative of this condition) shows red blood cells displaying macro-ovalocytosis and neutrophils with hypersegmentation.
Anemia
Case Study #2

Which of the following tests would be most useful to determine the etiology?
A. Hemoglobin electrophoresis
B. Reticulocyte count
C. Stool for occult blood
D. Vitamin B12 assay
E. Bone marrow biopsy

Questions:
- What is the diagnosis from these findings?
- How do you explain the neurologic findings?