A 54 year old man with many medical comorbidities including HTN, HPL, CAD, DM, RA is found to have a hemoglobin of 10.4 on routine laboratory studies. His symptoms include general fatigue and he has no symptoms or family history of blood disease. PE is significant for conjunctival pallor, a prominent S4 on cardiac exam and venous stasis markings in his lower extremities.

What is the next step?
Anemia

- Reduction of RBC concentration below normal limits
  - Decreased Hb concentration (< 11.5 g/dL)
  - Decreased RBC count
  - Usually decreased hematocrit (cellular blood)
- Can be symptomatic or asymptomatic
- Symptoms
  - Fatigue
  - Dyspnea
  - Macroglossia
  - Pallor

- Decreased hematopoiesis
- Blood loss
- Hemolytic anemias
Initial Work-up for anemia: considerations

- Bleeding (past or present)?
- Iron Deficiency?
- B12/folate deficiency?
- RBC Destruction?
- Bone marrow suppressed?

Anemia of blood loss

- Acute blood loss – no time for compensation
  - Hemorrhage - may lead to hypovolemic shock
  - Loss of total blood volume more important than acute loss of hemoglobin
  - CBC initially normal (usually)
  - CBC drops over time and when IVF are given

- Chronic Blood Loss – body can compensate if able
  - Usually GI tract or uterine bleeding
  - Causes anemia only if blood loss >> capacity of bone marrow to replace lost RBCs
    - Intrinsic bone marrow diseases or nutritional deficiencies
    - Vitamin B12, Folate, Iron, Pyridoxine, Protein imbalance
Anemia of decreased RBC production

• Differential Diagnosis:
  • Iron Deficiency
  • Vitamin B12 Deficiency
  • Folic Acid/Folate Deficiency
  • Anemia of Chronic Disease
  • Anemia of Bone Marrow Stem Cell Failure
    • Primary failure
    • Secondary failure from malignancy

History IS important!

• History of comorbidities that are contributory
  • GI Bleeding, Renal Failure, Autoimmune disease, Chronic inflammation
• B symptoms: fever, chills, night sweats, unintentional weight loss
• Is anemia recent or long-standing?
• Symptoms: fatigue, dyspnea, somnolence, pica, ice craving
Physical Exam – still useful

- Pallor of conjunctiva: 50-70% reliable
- Jaundice
- Lymphadenopathy
- Hepatomegaly/Splenomegaly
- Bone tenderness: especially over sternum

Laboratory evaluation: go straight for the gusto

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<th>Component</th>
<th>Latest</th>
<th>Ref Range</th>
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<tr>
<td>WBC</td>
<td>3.70 - 11.00 k/μL</td>
<td>3.69</td>
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<tr>
<td>RBC</td>
<td>3.00 - 5.20 m/μL</td>
<td>4.53</td>
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<tr>
<td>Hemoglobin</td>
<td>11.5 - 15.5 g/μL</td>
<td>14.5</td>
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<tr>
<td>Hematocrit</td>
<td>36.0 - 46.0 %</td>
<td>42.1</td>
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<tr>
<td>MCV</td>
<td>80.0 - 100.0 μL</td>
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<td>MCH</td>
<td>26.0 - 34.0 pg</td>
<td>32.0</td>
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<tr>
<td>MCHC</td>
<td>30.5 - 36.0 g/μL</td>
<td>34.4</td>
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<tr>
<td>RDW-CV</td>
<td>11.5 - 15.0 μL</td>
<td>12.1</td>
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<tr>
<td>Platelet Count</td>
<td>150 - 400 k/μL</td>
<td>286</td>
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<tr>
<td>MPV</td>
<td>9.0 - 12.7 μL</td>
<td>10.7</td>
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<tr>
<td>Neut%</td>
<td>38.6 - 74.0 %</td>
<td>66.4</td>
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<tr>
<td>Abs Neut (ANC)</td>
<td>1.45 - 7.30 k/μL</td>
<td>5.31</td>
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<tr>
<td>Lymph%</td>
<td>15.9 - 47.3 %</td>
<td>32.6</td>
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</tr>
<tr>
<td>Abs Lymph</td>
<td>1.00 - 4.00 k/μL</td>
<td>2.96</td>
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<tr>
<td>Mono%</td>
<td>0.0 - 12.0 %</td>
<td>5.4</td>
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<tr>
<td>Abs Mono</td>
<td>0.00 - 0.86 k/μL</td>
<td>0.69</td>
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<tr>
<td>Eosin%</td>
<td>0.0 - 8.6 %</td>
<td>2.4</td>
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<tr>
<td>Abs Eosin</td>
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<td>Baso%</td>
<td>0.0 - 1.2 %</td>
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<tr>
<td>Abs Baso</td>
<td>0.00 - 0.10 k/μL</td>
<td>0.02</td>
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</table>
Typical peripheral blood smear

Other Cell Types
Microcytic/Hypochromic Anemia

Important initial laboratory studies

- Hemoglobin/Hct
- MCV
- RDW (variability in RBC size)
- Iron
- TIBC
- Transferrin saturation
- Ferritin
- Reticulocyte count
- LDH
Iron Deficiency

• Most common etiology of microcytic, hypochromia
  • 11 million cases per year in US

• Iron loss from chronic bleeding
  • Menstrual blood loss (reproductive age women)
  • GI bleeding (age >50 in men or woman)

Iron Deficiency

• Most common nutritional disorder throughout world
  • 80% of Fe$^{2+}$ found in Hb
  • 20% found in myoglobin, cytochromes, catalase, others

• Fe Storage Pool: Ferritin and Hemosiderin
  • Ferritin: Protein-Fe complex found mostly in liver, spleen, bone marrow and skeletal muscle
  • Hemosiderin: Brown pigment in macrophages
Iron deficiency

• Laboratory Tests for Fe:
  • Serum Fe: concentration of tranferrin-bound iron
  • Ferritin: proportional to total body Fe stores
  • Total Iron-Binding Capacity: amount of iron carried by blood
  • %Transferrin Saturation: iron/TIBC x 100

• Usual results in iron deficiency anemia:
  • Serum Fe: Decreased
  • Serum Ferritin: Decreased
  • Serum TIBC: Increased
  • Transferrin Saturation: Low
  • Platelets: Often high

Treatment

• Ferrous sulfate 325 mg (65mg of elemental iron)
  • Daily, BID, TID depending on degree of deficiency

• Niferex – polysaccharide-coated 150mg
  • Daily, BID, TID depending on degree of deficiency

• Liquid Iron - $$$

• Side-effects: aversion, nausea, constipation, dark stools
Parenteral Iron Infusion

- Iron dextran – INFED
- Ferric gluconate – Ferrlecit
- Iron sucrose – Venofer
  - Only formulation with robust data in pregnancy
- Ferric carboxymaltose – Injectafer
  - Most convenient (30 minute infusion x 2 weekly doses)
- Ferumoxytol – Feraheme

- Any formulation can cause adverse reactions
  - Local infusion reactions → anaphylaxis

B12/folate Deficiency

- Megaloblastic/macrocytic anemia:

- Vitamin B12/Cobalamin:
  - Requires intrinsic factor for absorption
  - IF is secreted by parietal cells in stomach
  - IF/B12 complex is absorbed in the terminal ileum (last 100cm)
    - GI surgery or IBD
    - Neuropathy can be present

- Folic Acid/Folate Deficiency:
  - Usually a nutritional problem (alcoholism)
  - Pregnancy
Vitamin B12/Folate deficiency: Hypersegmented neutrophils

More rare, but always a possibility...

• Thalassemia
• Sickle-cell anemia

• Hemoglobin electrophoresis is used to diagnose
Sickle-cell Anemia

Hemoglobin Structure
Thalassemias

- Decreased production of globin chains
  
  - α-Thalassemias: decreased rate of production of α-globin chains
    - Usually seen in patients of Asian descent
  
  - β-Thalassemias: decreased rate of production of beta-globin chains
    - Usually seen in patients of African/Mediterranean descent

Target Cells
Anemia of chronic disease

• Anemia of Chronic Disease: Chronic inflammatory diseases may impair the handling of iron in the body

• 3 Major Categories of Inflammatory Diseases:
  • Autoimmune Disorders: collagen vascular diseases, IBD, general inflammation
  • Malignant Neoplasms
  • Infectious Diseases: osteomyelitis, bacterial endocarditis, lung abscess

Anemia of chronic disease

• Defect of iron incorporation into Hb molecules during erythropoiesis:
  • Problem in mobilizing Fe from storage pool

• Usually normocytic, normochromic
  • Serum Fe: Decreased/Normal
  • Serum ferritin: Normal/Increased (inflammation)
  • Total Iron-binding capacity (TIBC): Decreased
  • Transferrin saturation: Normal or decreased
Anemia of Chronic Disease Mechanism: Hepcidin

- Erythropoietin level is important
  - Often inappropriately low/normal
  - May indicate renal disease

- Can use erythropoietin stimulating agents to boost Hb
  - Procrit (recombinant erythropoietin)
  - Aranesp (darbepoietin) – fragment of recombinant erythropoietin
No Solution?
Time to get the Hematologist involved....

• Not usually necessary

• Not as bad as most people think
  • Usually an outpatient procedure that lasts 15-20 minutes

In all honesty......

• Bone Marrow biopsy usually only employed when ≥2 cell lineages are depleted with no good clinical explanation
  • RBC
  • WBC
  • Platelets
Hypocellular bone marrow

Hypercellular bone marrow
Malignancy of bone marrow

• Leukemias
• Lymphomas
• Myeloma
• Myelofibrosis
• Metastatic bone disease

MGUS --> myeloma....can be sneaky

• Elevated Protein/albumin ratio in CMP can be clue
• Elevated gamma globulins can be a clue

• Check SPEP (serum protein electrophoresis)
  • Looks for a monoclonal protein being made by malignant plasma cells
Rare causes of anemia

- **Aplastic Anemia**
  - May occur at any age and no gender preference
  - Hypocellular bone marrow
  - Almost no maturing myeloid cells

- **PNH (paroxysmal nocturnal hemoglobinuria)**
  - Loss of CD55/CD59 on RBCs (normally inhibit complement)
  - Leads to activation of terminal complement (C5-9)
  - Eculizumab is treatment

- **Pure Red Cell Aplasia:**
  - Rare form of bone marrow failure leading to erythroid aplasia only
  - granulopoiesis and thrombopoiesis are not affected

Hemolytic Anemia: Increased destruction

- RBCs usually live for 120 days

- **Causes**
  - Mechanical Injury (valves)
  - Autoimmune complement fixation on surface membrane
  - Exogenous toxic Factors (medications)
  - RBC membrane abnormalities
  - Enzyme abnormalities
Hemolytic anemia

• Clinical picture
  • Anemia symptoms (fatigue, dyspnea)
  • Jaundice (destruction of Hb → bilirubin)
  • Sometimes hepatomegaly/splenomegaly

• Laboratory picture
  • Decreased Hb
  • Decreased haptoglobin (binds Hb to prevent toxicity)
  • Increased LDH (lactate dehydrogenase)
  • Increased Reticulocytes (immature RBCs)

Hemolytic Anemia

• Autoimmune Hemolytic Anemia (AIHA)
• Warm vs Cold (usually warm)

• Presence of Ig on the surface of RBCs
  • Autoantibodies
  • Coomb’s positive (Direct anti-globulin test)
Autoimmune Hemolytic Anemia (AIHA)

Cold Agglutinin Immune Hemolytic Anemia

- IgM auto-antibodies bind to RBCs
  - IgM is pentameric and binds best at low temps
  - Exacerbated in winter months in northern climates

- Associations:
  - MGUS (monoclonal gammopathy of unknown significance)
  - Lymphoma, CLL
  - Infections (Adenovirus and Mycoplasma pneumoniae)
Hemolytic Anemia: Hereditary spherocytosis

- Inherited disorder of erythrocytes
- Abnormal membranes and shape of RBCs
  - Mutated Spectrin, ankyrin, band 3 protein, or protein 4.2
- Spherocytes less deformable, therefore more likely to be sequestered in splenic sinusoids
- Seen most commonly in Northern European descendants (1 in 5,000)
  - Usually autosomal dominant

Spherocytes
Hemolytic Anemia: Glucose-6-Phosphate Dehydrogenase Deficiency:

- Key enzyme in the hexose monophosphate shunt (HMP)
- Deficiency causes oxidation of globin chains which leads to denatured hemoglobin (Heinz bodies)
- Deficiency is present in ~ 10% of African-Americans or those of Mediterranean ancestry
  - Autosomal recessive inheritance
  - Variable phenotypic expression of the disease
- Usually caused by infection or drug exposure
  - Anti-malarial
  - Sulfa-drugs

Heinz Bodies (G6PD Deficiency)

© 1995
Bite Cells in G6PD Deficiency

Other Diseases associated with hemolysis

• HELLP – pregnant women
• HUS – bacterial infections
• TTP – thrombotic thrombocytopenic purpura
Microangiopathic Hemolytic Anemia

Anemia Summary

- Cause: Bleeding, poor production, destruction
- History and Exam are important clues
- Laboratory evaluation can confirm or lead to further etiologies
- Primary care role: assess common causes
  - Bleeding, iron and folate/B12 deficiency, consider chronic disease anemia
  - Erythropoietin can be helpful

- If unexplained or more than 1 cell line is decreased (WBC, RBC, platelets) refer to hematology for further consideration
Thank You!