Anemia Approach for the Primary Care Physician

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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

Anemia

Problems in the production of blood cells
  • Decreased hematopoiesis

Increased destruction or loss of blood cells
  • 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 Read</th>
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<tr>
<td>WBC</td>
<td>3.70 - 11.00 k/uL</td>
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<tr>
<td>RBC</td>
<td>3.80 - 5.20 m/uL</td>
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<tr>
<td>Hemoglobin</td>
<td>11.5 - 15.5 g/dL</td>
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<tr>
<td>Hematocrit</td>
<td>36.0 - 46.0 %</td>
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<tr>
<td>MCV</td>
<td>28.0 - 100.0 fL</td>
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<td>MCH</td>
<td>30.0 - 34.0 fL</td>
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<td>MCHC</td>
<td>38.5 - 36.0 g/dL</td>
<td>34.4</td>
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<tr>
<td>RDW/CV</td>
<td>11.5 - 15.0 /L</td>
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<tr>
<td>Platelet Count</td>
<td>150 - 400 k/uL</td>
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<tr>
<td>MPV</td>
<td>0.6 - 12.7 fL</td>
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<td>Neut%</td>
<td>39.5 - 74.0 %</td>
<td>58.4</td>
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<tr>
<td>Abb: Neut (ANC)</td>
<td>1.45 - 7.63 k/uL</td>
<td>5.31</td>
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<td>Lymph%</td>
<td>15.9 - 30.2 %</td>
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<td>Abb: Lymph</td>
<td>1.00 - 4.00 k/uL</td>
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<td>Mono%</td>
<td>8.0 - 12.0 %</td>
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<td>Abb: Mono</td>
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<td>Abb: Eosin</td>
<td>0.00 - 0.45 k/uL</td>
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<td>Baso%</td>
<td>0.0 - 1.2 %</td>
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<td>Abb: Baso</td>
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<td>Diff Type</td>
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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

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
  
  • \(\alpha\)-Thalassemias: decreased rate of production of \(\alpha\)-globin chains
    • Usually seen in patients of Asian descent
  
  • \(\beta\)-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

- Low Hepcidin
- Inflammation: High Hepcidin

**Anemia of Chronic Disease**

- 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 $\rightarrow$ 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)
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!