Evaluating Anemia’s: Let’s take a deeper dive

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Disclosures

- I have no disclosures or conflicts of interest
Overview of Anemia

- Anemia is a grouping of signs and symptoms, rather than a disease.
- Anemia is a highly significant clinical finding.
- Severity of the anemia does not correlate with clinical significance or causality.
Review of terms.

- Anemia is a deficiency in the red blood cell mass (RBC or erythrocyte) and hemoglobin content.
- Anemia is revealed through a CBC (complete blood count) which is a measure of hemoglobin concentration, hematocrit, RBC mass and mean corpuscular volume (MCV).
- Hematocrit is the percentage of packed RBC’s in blood or the volume occupied by RBC’s after blood is spun down in a hematocrit tube.
- Various definitions of Anemia (hemoglobin and hematocrit levels):
  - Hemoglobin (Hgb) <12 in women and Hemoglobin (Hgb) <14 in men.
Signs and symptoms of anemia

- They are unreliable in predicting the severity of the anemia
- Time and onset of the anemia and health of the patient is most predictive of symptoms
- Patients with anemia which develops over time and occurs gradually can tolerate lower hemoglobin levels due to compensation.
- Patients with abrupt onset of anemia tend to be very symptomatic
- Patients complain of fatigue and shortness of breath
- On exam patients have pale mucous membranes, resting tachycardia and have a greyish hue about them
- Clues to the source of anemia on exam include splenomegaly, heme positive stools
How does the body compensate for anemia?

- Cardiac output increases resulting in tachycardia
- Plasma volume increases which allows remaining cells to move more efficiently due to decrease in red cell viscosity
- Decrease in oxygen affinity for hemoglobin which increases the delivery of oxygen to the tissues
  - This is accomplished through the increase in red cell 2,3-diphosphoglycerate which is a 3 carbon isomer found in red blood cells. Its increase enhances the ability of RBCs to release oxygen near tissues that need it most.
Classification of anemia

- By size of red blood cells
  - MCV – Mean corpuscular volume refers to the volume of the red blood cell
    - Microcytic – low MCV
    - Normocytic - normal MCV
    - Macrocytic - high MCV

- By mechanism causing the anemia
  - Increased loss - bleeding or hemolysis
  - Decreased production - impaired marrow production, nutritional deficiency
Macrocytic

Microcytic

Normocytic
Microcytosis (MCV < 80 fl)

- Microcytic anemia’s reflect a **defect** in hemoglobin synthesis
- Hemoglobin synthesis requires iron
  - **Lack of iron** can be due to a deficiency or the lack of availability of iron (sequestration of iron as part of an inflammatory process) which impairs delivery of iron to the developing red cell
- Thalassemia
  - **Genetic disorder** that leads to impaired production of hemoglobin
- Sideroblastic anemia’s
  - **Actual defect in the synthesis of the heme molecule** which leads to underhemoglobinization of erythroid precursors and microcytosis
Macrocytosis (MCV > 100 fl)

- Caused by red cell membrane defects OR DNA synthesis defects
- Red cell membrane defects occur in the setting of liver disease, hypothyroidism, aplastic anemia, renal disease and reticulocytosis
  - Review of smear demonstrates round red blood cells
- Defects in DNA synthesis is seen in B12 and Folate deficiency, chemotherapy and myelodysplastic syndrome
  - Review of smear demonstrates oval red blood cells.
Normocytic Anemia (MCV 80-100 fl)

- Red cells demonstrate normal size
- Very common, and does not give a clue to potential etiologies
- Can occur in early stage of whatever process is occurring
- Can occur when several processes are occurring at the same time
  - Iron deficiency and liver disease
- Can see normal MCV in
  - Anemia of inflammation
  - Acute hemolysis or blood loss
  - Renal disease
Using underlying mechanism as a tool for your differential

- Is there an increased RBC loss?
- Is there a decreased RBC production?

- The Reticulocyte count can help you differentiate this.
What is a reticulocyte?

- Reticulocytes are immature, nonnucleated RBC’s.
- They circulate the peripheral blood for about 1 day before losing RNA and becoming a mature red blood cell.
- The number of reticulocytes can be measured directly:
  - This is performed by automated analyzers by staining remnant RNA with fluorescent dye.
  - This is known as the **absolute reticulocyte count** (ignore %).
  - Old methods required the percent hematocrit to perform a correction that adjusts for hematocrit.
Usefulness of reticulocyte count

Elevated reticulocyte count
- Bone marrow is making more red blood cells.
  - Seen in blood loss
  - Seen in hemolysis

Normal reticulocyte count
- Bone marrow is not “kicking in” to increase production of red blood cells.
  - Seen in production causes of anemia
It all comes down to the following same concepts

- Problems of production
  - Factory problem - bone marrow malfunction
  - Part problem - problem with the supply chain
- Problems of destruction
  - Hemolysis
- Problems of loss
  - Bleeding
Anemia’s due to production problems

- Renal disease
- Inflammation/chronic disease
- Endocrine disease
- Iron deficiency
- Vitamin B12 deficiency
- Folate deficiency
- Copper deficiency
- Thalassemia
- Sickle cell disease and other hemoglobinopathies
- Bone marrow disorders
Production of red cells

- Must have a functioning marrow or “factory”
- Must have appropriate supplies: iron, B12, Folate
- Must have working production signals: erythropoietin
- Must have working processes to utilize the supplies
  - Acute phase reactants can interfere with the utilization process
Anemia of renal disease

- Due to lack of erythropoietin
- Decrease in renal function affects kidney’s ability to make erythropoietin
- Generally anemia does not occur until creatinine clearance is < 30 mL/min
- Patients with underlying inflammatory processes or those of advanced age can develop anemia with a creatinine clearance as high as 60 mL/min
- ACE inhibitors and Angiotension II Receptor blockers can decrease Erythropoetin (EPO) production
Testing in Anemia of renal disease

- CBC reveals Mild to moderate anemia
- MCV is usually normal
- Elevated BUN and Creatinine
- Erythropoetin level maybe decreased and not compensated for level of anemia or level maybe normal based on lab range but inappropriately low for the degree of anemia.
- Absolute reticulocyte count is usually normal
Anemia of inflammation or Anemia of chronic disease

- This is a diagnosis of exclusion
- Patient will have adequate iron stores but there is impaired delivery to the developing red cells.
- EPO production is depressed
- If a patient has anemia, EPO level is not increased and patient has adequate iron stores, then diagnosis is anemia of chronic disease.
- Ferritin will be high in this setting.
Mechanism of normal iron delivery to cells

- Iron is absorbed in the GI tract by enterocytes
- Once absorbed by enterocytes, it is released in circulation and binds to transferrin (this is where saturation of the transferrin occurs)
- Transferrin transports iron to the developing red blood cells
- Excess iron is stored in hepatocytes in the liver
Mechanism of abnormal iron delivery in anemia of inflammation

- Inflammatory cytokines suppress production of erythropoietin by the kidney resulting in decreased red cell production.
- Iron availability is suppressed by hepcidin which is an acute phase reactant.
  - *Hepcidin* is a key regulator of the entry of iron into the circulation in mammals. In states in which the *hepcidin* level is abnormally high such as inflammation, serum iron falls due to iron trapping within macrophages and liver cells and decreased gut iron absorption.
- Hepcidin blocks iron absorption by preventing release of iron from enterocytes in the gut.
- Decreased circulating iron results in desaturation of transferrin which cannot supply enough iron to the developing red cells.
- Iron stored in the hepatocytes is also impacted by Hepcidin as it prevents release of iron from the hepatocyte.
CBC shows mild anemia
- MCV could be low, normal or high
- Absolute reticulocyte count normal
- Lack of elevation of EPO and adequate iron stores is highly suggestive of anemia of chronic disease
Anemia related to endocrine diseases

- Hypogonadism can cause anemia in men.
- Testosterone sensitizes erythroid precursors to the effects of EPO
  - Explains why men have a higher hemoglobin concentration, hematocrit and RBC count than women
  - Ask older men with anemia if they have to shave anymore.......if they don’t they may have anemia related to low testosterone! (usually it is mild, Hgb 12-13)
- Hypothyroidism can lead to macrocytic or normocytic anemia
- Endocrine related anemia’s are considered anemia’s of chronic disease
  - Correct the endocrine disorder and the anemia should correct.
Anemia related to iron deficiency

- Iron deficiency anemia occurs when there is a negative iron balance
- Negative iron balance occurs through blood loss or increase iron demand
- Negative iron balance leads to a reduction in total body stores
- Stage I: Iron depletion
  - There is a decrease in iron stores, but serum iron or hemoglobin levels are WNL
  - Serum ferritin is low but serum iron is WNL
- Stage II:
  - Abnormal iron test: decreased transferrin saturation, increase total iron binding capacity
- Stage III: Decreased hemoglobin concentration below the limits of normal
Causes of anemia related to iron deficiency

- Blood loss
  - GI bleed, most common reason for blood loss in men and postmenopausal women
  - Menstrual bleeding
- Impaired absorption
  - Gastrectomy, gastric bypass
  - Celiac disease
  - PPI use
  - H. pylori infection
  - Strict vegan diet
Diagnostic testing for iron deficiency:

- RBC indices, serum iron and TIBC and iron saturation have been traditionally performed.
- They can be confusing and are either poorly sensitive or poorly specific.
- Serum ferritin DIRECTLY correlates with iron stores.
- A serum ferritin greater than 100g/ml rules out iron deficiency in most patients.
- Very low ferritins are diagnostic of iron deficiency.
- Older patients maybe iron deficient with ferritins in the 50-80 range.
- Rule of thumb the ferritin should be greater than the patient’s age to rule out iron deficiency!
All unexplained cases of iron deficiency anemia need GI referral for colonoscopy/upper endoscopy. Do not assume menstruation or hemorrhoids to explain iron deficiency anemia in young patients. We are seeing a rise of colorectal cancer in young patient’s 20-40 years of age.
B 12 Deficiency and Folate deficiency

- Produces a macrocytic anemia
- Serum vitamin B 12 levels can be inaccurate
- Test of choice is:
  - MMA (methylmalonic acid)
  - MMA is more sensitive and specific as it is an indicator of tissue stores
  - MMA levels rise in the absence of vitamin B 12

- Produced a macrocytic anemia
- Serum folate levels can be inaccurate
- Test of choice is:
  - Serum Homocystine
  - Homocystine is a more sensitive and specific measure of tissue stores of folate
  - Homocystine levels rise in the absence of folate as well as in the absence of vitamin B 12
  - MMA is normal in Folate deficiency
Etiologies of B12 and Folate Deficiencies

**B12 Deficiency**
- Inadequate intake
- Abnormal absorption due to gastric bypass, Use of H2 blockage or PPI’s, H. pylori infection
- Deficient intrinsic factor-pernicious anemia
- Small bowel or mucosal abnormalities

**Folate Deficiency**
- Increased requirements: pregnancy, hemolytic anemia, psoriasis
- Absorption problems
- Drugs: OCP and anticonvulsants
- Alcoholism: Alcohol interferes with folate metabolism, inability to mobilize folate stores and can have depleted tissue stores
B 12 deficiency can cause neurological symptoms

- Paresthesia
- Decrease vibratory sense
- Ataxia or gait disturbances
- Increase deep tendon reflexes
- Memory loss
- Personality changes
- Orthostatic hypotension
Copper deficiency
Copper is key to normal hematopoiesis

- Straight forward testing
- Ceruloplasmin assay
  - Ceruloplasmin is the copper carrying protein (low result in copper deficiency)
- Serum copper
- Seen in anorexia, bariatric surgery patients and excessive zinc intake
- Classic signs
  - Anemia
  - Neutropenia
  - Thrombocytopenia (rare)
  - Neurological findings such as peripheral neuropathy
Thalassemia

- Thalassemia’s are inherited genetic disorders
- Thalassemia’s are diseases of hemoglobin synthesis which result in impaired production of hemoglobin
- Most common types are alpha and beta thalassemia
- Alpha thalassemia is found in Africa, Mediterranean area and Southeast Asia
- Beta thalassemia is found in the Mediterranean area and southeast Asia
- Hemoglobin electrophoresis can assist in the diagnosis of beta thalassemia.
  - Hemoglobin A2 is increased
- Alpha thalassemia is often a diagnosis of exclusion as there is no increase in hemoglobin A2
Sickle cell disease

- Sickle cell disease is a group of genetic disorders characterized by the predominance of Hgb S
- Hallmarks of the disease are chronic hemolytic anemia and vaso-occlusion
- Screening test is the sickle solubility test
- Definitive diagnosis is with hemoglobin electrophoresis
Bone marrow disorders

- Myelodysplastic syndrome MDS
  - Often seen in older patients
  - Labs often show a macrocytic anemia with a non-elevated absolute reticulocyte count
  - Bone marrow evaluation is necessary to diagnose
  - Other cytopenias are also seen
Plasma cell Myeloma/Multiple Myeloma

- Plasma cell malignancy
- Seen usually in older patient
- Be suspicious if patient presents with back pain or renal disease
- Testing should include:
  - Serum protein electrophoresis with immunofixation
  - Serum free light chain analysis (10% of myeloma only secretes light chains)
Interpretation of SPEP and Serum Free Light chains.

- SPEP with immunofixation will show a monoclonal protein
  - IgG or IGM or IgA

- Serum Free Light Chains
  - Ratio of lambda to kappa
    - The ratio is the key, indicating clonal change. In a chronic renal disease patient, they may have a significant elevation in both kappa and lambda due to proteinuria, but the ratio is normal.
Anemia due to loss of red blood cells

- Hemolysis
- GI bleeding
- Sequestration
Hemolysis is destruction of red blood cells
- Can be a result of an autoimmune process
- Can be a result of mechanical destruction (heart valve)
- Can be a result of drugs (antibiotics, Tylenol, methyldopa)
- Can be a result of paroxysmal nocturnal hemoglobinuria
Testing for hemolysis

- Haptoglobin - most sensitive test for RBC destruction
  - It sequesters free hemoglobin released from hemolyzed RBC’s
  - In hemolysis will be low
  - Unfortunately it can be misleading in acute or chronic liver disease

- LDH-
  - In hemolysis it will be high often >400

- Indirect bilirubin
  - In hemolysis it will often be elevated, but not always!

- Reticulocyte count
  - In hemolysis it will be elevated

- Direct coombs
  - Helps determine if an antibody is the cause
GI blood loss

- Will cause iron deficiency over time
- GI consult necessary
- Patient may need both blood transfusion support and eventually iron replacement
Organ sequestration

- Liver and spleen function as “filters”
- Cirrhosis, chronic liver disease (hepatitis) and myeloproliferative diseases can cause hypersplenism
- Blood circulates through the liver and spleen and if enlarged, can remove blood from circulation like an oil filter in your car
- If the filter is bigger than it is supposed to be, mild anemia and/or pancytopenia can occur.
Critical points to remember:

- It is important to determine if the presenting anemia is a production problem or a loss problem
  - The reticulocyte count can answer this question and then the result will guide further work up and additional tests.
- Ferritin level is the most specific test for iron deficiency and directly correlates with iron stores.
- If the patient is not iron deficient, don’t give iron. It will not help and only cause side effects.
- Remember Ferritin is an acute phase reactant and result can be increased in inflammatory processes such as chronic disease, but the iron cannot be utilized.
- A referral to a hematologist should be considered in hemolysis and most production problems.
- Referral to gastroenterology in unexplained iron deficiency.