Anemia: Recognition and Management Throughout the Lifespan

Wendy L. Wright, MS, RN, ARNP, FNP, FAANP
Adult/Family Nurse Practitioner
Owner - Wright & Associates Family Healthcare
Amherst, NH
Co-Owner – Anderson Family Healthcare
Concord, NH
Partner – Partners in Healthcare Education, LLC

Relevant Financial Relationship Disclosure Statement

Title of talk
• I will not discuss off label use and/or investigational use of any drugs/devices.
• I don’t have the following relevant financial relationships to report in relationship to this presentation.

Objectives
• Upon completion of this lecture, the participant will be able to:
  – Discuss the various causes of commonly encountered anemias across the lifespan.
  – Identify the laboratory tests needed to identify the various types of anemias
  – Review treatments for the various anemias

Red Blood Cell Formation
• Formed in bone marrow (erythropoiesis)
• When mature, the rbc is released into circulation
• Mature rbc has a life span of approximately 120 days
  – Many factors trigger an increase in the production of rbc’s by the bone marrow, but a decrease in O₂ is the most common.
  – Low tissue oxygen levels trigger the endothelial cells in the kidneys to secrete erythropoietin – which in turn, stimulates bone marrow red cell production

Anemia: Defined
• Anemia – comes from the Greek word “Anaimia” – meaning “without blood”
• A decrease in the number of red blood cells, hemoglobin, or hematocrit
  OR
A decrease in the oxygen carrying capacity of the blood

Statistics
• Approximately 3.5 million Americans have some form of anemia
• Approximately 17.5/1000 individuals in primary care practice have anemia
• Approximately 20% of all women have anemia
  – Iron deficiency anemia is by far the most common anemia, particularly in the women
  – Most common anemia in the older adult:
    • Anemia of Chronic Disease

The CBC - A Blessing or a Curse

- **RBC**
  - 4.1-5.1 m/mm³
- **Hemoglobin**
  - 12-16 g/dl
- **Hematocrit**
  - 36-46%

**The MCV allows you to classify the type of anemia to further determine the etiology**

- Mean Corpuscular Volume (MCV)
  - Normal: 80 - 100 m³/10⁹ cells
  - Microcytic: <80 m³/10⁹ cells
  - Macrocytic: >100 m³/10⁹ cells

The MCV is not always helpful, but the MCHC is.

- Mean Corpuscular Hemoglobin Concentration (MCHC)
  - Normal: 32-37%
  - Hypochromic: <32%

Classifications/Causes of Anemia

- **Macrocytic, Normochromic**
  - (↑MCV, Normal MCHC)
- Vitamin B12 Deficiency
- Folate Deficiency

- **Normocytic, Normochromic**
  - (Normal MCV and Normal MCHC)
- Anemia of Chronic Disease
- Acute Blood Loss
- Early Iron Deficiency
Classifications/Causes of Anemia

Microcytic, Hypochromic (↓ MCV and ↓ MCHC)
- Iron deficiency Anemia
- Thalassemia
- Lead Poisoning
- Sideroblastic Anemia
- Aluminum Toxicity
- G6PD

(Occasionally: Anemia of Chronic Disease)

RDW

- Red Cell Distribution Width
  - Normally all red cells are about equal in size
  - RDW is the degree of anisocytosis or the variability of the red cell size
  - Helps to differentiate between various causes of microcytic, hypochromic anemia
    - IDA, Thalassemia, and Anemia of Chronic Disease
      - Increased RDW - IDA
      - Normal RDW - Anemia of Chronic Disease
      - Normal or slightly increased RDW - Thalassemia

Reticulocyte Count

- The number of new, young, red blood cells found in 100 rbc's in circulation
  - It is expressed as a percentage with normal being approximately 1-2%
  - It is an index of the bone marrow’s health and response to the anemia

What Does an Elevated Reticulocyte Count Indicate?

ELEVATED RETICULOCYTE COUNT MEANS THAT THE BONE MARROW IS HEALTHY and/or YOUR TREATMENT IS WORKING BUT…Blood loss or destruction is likely occurring

Anemia is not a diagnosis; it is a sign of an underlying problem.

Krepzek Study

- Pathology was found in 50% of individuals diagnosed with iron deficiency anemia.
- Diagnoses included:
  - Cancer
  - Gastritis
  - Esophagitis
  - Gastric Ulcer
  - Duodenal Ulcer
  - Crohn’s

(Adenomas, Vas Malformations, Hemorrhoids)

(Journal of Digestive Diseases, June 1995)
Macrocytic, Normochromic Anemia

Vitamin B12 Deficiency

General Causes of Vitamin B12 Deficiency
- Inadequate intake
- Decreased absorption
- Inadequate utilization
- Most common cause: Inadequate absorption

Megaloblastic Anemia
- Vitamin B12 (cobalamin) is essential for the production of DNA
- Deficiency in Vitamin B12 results in the alteration in the production of DNA
  - Decreased rate of production
  - Enlarged red cell

Other Potential Causes
- Inadequate absorption or utilization
  - Crohn’s disease
  - Celiac disease
  - S/p Gastrectomy or Bariatric surgery
- Medications
  - Methotrexate or Fluorouracil
  - Altered gastric acid production
  - PPI’s

Macrocytic Anemia

General Causes of Vitamin B12 Deficiency
- Inadequate intake
- Decreased absorption
- Inadequate utilization
- Most common cause: Inadequate absorption

Other Potential Causes
- Inadequate absorption or utilization
  - Crohn’s disease
  - Celiac disease
  - S/p Gastrectomy or Bariatric surgery
- Medications
  - Methotrexate or Fluorouracil
  - Altered gastric acid production
  - PPI’s
Vitamin B12

- Food sources: animal products
- Amount provided in average diet: 5 – 15 ug/day (RDA – 2ug/day)
- Storage amount: 2 – 5 mg is stored mainly in the liver
- Takes 2 – 5 years to develop a deficiency even in the setting of severe malabsorption

Pernicious Anemia

- Most common cause of a vitamin B12 deficiency
- Autoimmune disease characterized by the presence of autoantibodies to the parietal cells in the stomach and their secretory product called intrinsic factor
  - Remember – intrinsic factor is essential for the absorption of vitamin B12 in the terminal ileum of the bowel

Pernicious Anemia

- Very commonly seen in the setting of other autoimmune conditions such as:
  - Hashimoto’s thyroiditis
  - Vitiligo
- Onset is usually insidious
- Begins in the 5th – 6th decade of life
- Women > men

Important History Questions

- Dietary intake
- Alcohol consumption
- Medication history
  - Chemotherapeutics
  - PPI’s
- PMH
  - Surgeries
  - Conditions affecting ileum/stomach

Signs and Symptoms of Pernicious Anemia

- Anemia with elevated MCV
- Smooth and beefy red tongue
  - Tongue is frequently very sore
- Diarrhea
- Anorexia
Neurologic Manifestations

- Neurologic manifestations are related to the inability to maintain myelin integrity
- Paresthesias
  - Pins and needles – stocking/glove distribution
  - Weakness in extremities
- Delirium/psychosis may occur
- Decreased position and vibratory sense
- Incoordination
- Depression

Diagnosis of Pernicious Anemia

- CBC
- Peripheral smear
- Vitamin B12 level
- Schilling test
  - This test will confirm that the Vitamin B12 deficiency is caused by an intestinal malabsorption due to a deficiency in the intrinsic factor rather than other malabsorptive conditions

Treatment of Vitamin B12 Deficiency

- Vitamin B12 Deficiency
  - Cyanocobalamin: 1000 iu/day x 5 days
    - Weekly until hemoglobin normal
    - 1000 ug/month for life
    - Reticulocytosis within 1 week
    - Increase in hemoglobin and hematocrit with 1 week
    - Normalization of h/h within 2 months
    - Rapid improvement in symptoms; however may take 12 – 18 months for all neurologic symptoms to improve

Words of Warning

- Patients who are severely vitamin B12 deficient can develop severe hypokalemia
- Monitor potassium levels as vitamin B12 is administered

Folate Deficiency

- Nascobal (cyanocobalamin)
  - 500 micrograms/0.1ml nasal gel
  - Maintenance of Vitamin B12 deficiency
  - Used after IM B12 has resolved the anemia
  - 1 spray into 1 nostril each week
Folate Deficiency

• Most often results from an inadequate intake of folic acid
  – Poor dietary intake such as the elderly, chronically ill, alcoholics, fad diets
• Occasionally
  – Increased need
  – Impaired absorption
  – Inadequate utilization

Reasons for Folate Deficiency

• Body has very little folate in storage
  – Very different from vitamin B12 where 3 – 5 years of B12 is held in storage
• Impaired absorption
  – Celiac disease
  – Giardia infection
  – Phenytoin

Reasons for Folate Deficiency

• Increased need
  – Pregnancy
  – Hyperthyroidism
  – Malignancy
  – Chronic inflammatory disorders – Crohn’s
• Impaired utilization
  – Methotrexate
  – Metformin
  – Trimethoprim

Important Information

• Source
  – Green, leafy vegetables, beans, grains, liver, wheat
• RDA: 100 ug/day
• Amount in diet: 200 – 300 ug/day
• Storage amount: 5 – 10 mg

Clinical Presentation

• May be asymptomatic
• Glossitis
• Similar presentation to vitamin B12, when severe

Diagnosis

• Serum folate level
• Additional tests
  – MMA (methylmalonic acid)
  – Homocysteine (Hcy)
  – Both will be elevated in vitamin B12 deficiency
  – Only homocysteine will be elevated in folate deficiency
Treatment of Folic Acid Deficiency

- Folic Acid Deficiency
  - 1mg po qd
  - May increase to 5 mg/day
  - Review cause with patient – i.e. dietary sources
  - Reticulocytosis within 1 week
  - Hematocrit and hemoglobin should improve within 1 week
  - Hematocrit should normalize in 2 months

Treatment of Vitamin B12 or Folic Acid Deficiency

- If anemia fails to resolve, remember IDA coexists in 1/3 of patients with these types of anemia

Microcytic Anemia

Iron Deficiency Anemia

- Most prevalent anemia worldwide
- Causes
  - Increased iron loss
  - Dietary inadequacy
  - Malabsorption
  - Increased iron needs

Important History

- Medications?
- Any Blood Loss?
  - Menorrhagia
  - Black or Blood Stools
  - Hematuria
  - Hemoptysis
  - Blood Donation
- Family History of Anemia?
  - Celiac disease (sprue)

Blood loss is the number ONE cause for IDA in individuals > 4

Dietary Intake?
Alcohol Intake?
Any Chronic Disease?
Any Surgeries?
• Gastric bypass
However…

• Signs and symptoms of iron deficiency anemia are determined by…
  – Degree of anemia
  – Acuteness of the anemia
  – Presence of underlying disease states

Diagnosis of Iron Deficiency Anemia

• Ferritin
  – Measurement of iron stores
  – Level < 16 is diagnostic of IDA
  – Normal: 10 - 210
  – Keep in mind that this can be falsely elevated in the individual with febrile illness, malignancy, liver disease, inflammatory diseases

• Iron
  – Normal: 50 - 160
  – Amount of circulating iron
  – Low level coupled with an elevated TIBC is suggestive if IDA

Diagnosis of Iron Deficiency Anemia

• TIBC
  – Normal: 250 - 350
  – Number of cells not bound with iron
  – Higher the iron, lower the TIBC
  – Lower the iron, higher the TIBC

• Peripheral Blood Smear
  – Anisocytosis
  – Poikilocytosis
  – Microcytosis, hypochromia

Red Cell Morphology

• Spherocyte – hereditary condition; hemolytic anemia
• Schistocyte – prosthetic heart valve
• Elliptocyte or ovalocyte – iron deficiency anemia
• Teardrop cells – Iron deficiency anemia
• Sickle cells – sickle cell disease
• Target cells – thalassemia
• Basophilic stippling – Thalassemia, lead toxicity
• Bite cells – G6PD deficiency

Most Important Take Away Message!

• Find out why
  – Colonoscopy
  – UGI/Endoscopy
  – Chest X-ray
  – Urinalysis
  – Endometrial biopsy

Treatment of IDA

• Increase Iron Rich Food Intake
  – liver, beef, lamb, pork, veal, chicken, eggs, fish, beans, prunes, green leafy vegetables

• Iron Supplements
  – Ferrous Sulfate 325mg: 1 po tid
  – Ferrous Sequel: 1 po tid
Treatment of IDA

• Chromagen Forte
  – Capsules
  – 1 capsule daily
  – Iron, plus folic acid

• If the bone marrow is healthy
  – Within 5 days, the reticulocyte count will increase
• With adequate treatment
  – The hematocrit should rise 1 point each week
    • For instance, if someone’s hematocrit is 28
      – Goal is 36-40
      – It will take 8-12 weeks to correct

• If the bone marrow is healthy
  – Within 5 days, the reticulocyte count will increase
• With adequate treatment
  – The hematocrit should rise 1 point each week
    • For instance, if someone’s hematocrit is 28
      – Goal is 36-40
      – It will take 8-12 weeks to correct

Treatment of IDA

• Once hematocrit has normalized, it takes 3-6 months to replenish iron stores
  – This is provided that the bleeding or dietary issue is corrected
• Many providers stop the iron too quickly

• Intravenous Iron Dextran may be necessary if the individual is unable to absorb the iron or when the rate of blood loss exceeds absorption
  – Increased risk of anaphylaxis
• Should be performed in setting capable of handling this potentially life-threatening emergency

Normocytic Anemia

• Frequently accompanies chronic disorders
  – Acute and chronic infections
  – Malignancy
  – Inflammatory disorders
  – HIV disease
• Hypoproliferative state
• Commonly confused with iron deficiency

Chronic Disease
### Pathophysiology
- Usually caused when there is a trapping of iron by macrophages
- Renders iron unavailable for erythropoiesis
- Inflammatory processes also suppress erythropoiesis leading to diminished production of rbc's

### Clinical Presentation
- Asymptomatic
- Fatigue
- Tachycardia
- Pallor
- Similar presentation to an IDA

### Laboratory Diagnosis
- Anemia – Normal MCV, normal MCHC
- Rarely will the hematocrit go below 25% with an ACD
- Serum iron is often low
- TIBC is also often low – differentiates it from IDA
- Ferritin will be normal or even increased – very helpful to differentiate ACD from early IDA

### Treatment of Normocytic Anemia
- Renal disease
  - Erythropoietin, Procrit, Aranesp
- Malignancies
  - Chemotherapy
- Inflammatory disease
  - Optimal control
- Hypothyroidism
  - Goal: TSH = 1.5

### Treatment
- Severity of anemia determines treatment
  - Blood
  - Epoetin alfa
  - Darbepoetin alfa
- FDA, American Red Cross recommend treating early and conservatively using blood as last resort.

### Treatment: Blood
- Benefits
  - Immediate elevation of Hgb and HCT
  - Immediate improvement in energy level
- Drawbacks
  - Temporary
  - Risk of reaction
  - Risk of transmission of blood-borne infections
  - Administered in hospital or outpatient facility
  - Limited supply
  - Religious beliefs may influence willingness to receive blood
Epoetin Alfa

- **Dosing**
  - CKD: 50-100 units/kg 1x/week – every two weeks
  - Cancer: 150 units/kg 1x/week
  - HIV: 50-100 units/kg 1x/week
- Administered IV or subcutaneously
- Less frequent dosing if often performed
- No known drug interactions

Aranesp (darbepoetin alfa)

- **Indications**
  - Anemia: related to CRF
  - Chemotherapy induced anemia
- **Advantages**
  - 3 fold longer half life than Epoetin alfa
  - Early and sustained effect
  - Less frequent dosing

Recent Warnings

- Caution regarding increasing hemoglobin > 12 in individuals using any of these products
- Goal: hemoglobin at 10 - 11
- Increased risk of MI

Case - 1

86 year old woman in for a complete physical.
Labs: wbc 7.1, rbc 4.64, hgb 8.8, hct 28.1, MCV 84, MCHC 32.8, RDW 13.0, normal diff.
What type of anemia?
What would you order?

Case Study - 3

18 year old female presents with fatigue and sob while cheerleading. Increase in ice consumption. PE-pallor, pale conjunctiva, systolic murmur, and tachycardia.
What type of anemia does she have?
What would you order?
Case Study-4

26 year old male presents for a complete physical. He is asymptomatic. Routine labs reveal the following: CBC: wbc 7.78, rbc 5.84, hgb 11.5, hct 38.5, MCV 68.2, MCHC 28.1, RDW 14.9; Normal diff. Peripheral Smear: 1+microcytes, ovalocytes, target cells, and basophilic stippling. Remainder of labs normal.
What type of anemia does she have?
What would you order next?

Monday, September 25

17 year old male presents with a 3 week history of fatigue, nasal discharge-clear; seen by MD 1 week prior and started on Augmentin. Not feeling any better. PE: pallor, tachycardia, diaphoretic; Lungs clear, HEENT-normal; CBC: wbc: 8.9; rbc: 1.54; hgb: 5.5, hct: 17.2, MCV: 112, MCHC: 32; platelet: 32; Bands: 0; Segs: 5 (L) Monocytes: 21, Abnormal lymphocytes: 33.

Thank You!!
I Would Be Happy to Answer Any Questions You May Have

Wendy L. Wright, MS, RN, ARNP, FNP
Amherst, New Hampshire
(W) 603 249-8883
(H) 603 472-6776
(F) 603 472-2597
e-mail: WendyARNP@aol.com