Anemia

Background

1. Definition
    - Decrease in circulating RBC mass below age-/gender-specific limits
2. General information
    - Usually clinically defined by low hemoglobin or hematocrit on CBC
    - Most often discovered by laboratory evaluation since most patients are asymptomatic

Pathophysiology

1. Pathology
    - Decreased RBC production
        - Primary bone marrow diseases
            - Aplastic anemia, pure RBC aplasia, myelodysplasia or tumor
        - Bone-marrow suppression
            - Medication, chemotherapy, radiation
        - Nutrition
            - Deficiencies of vitamin B12, folate, iron, lead intake
        - Decreased stimulating hormones
            - Erythropoietin, thyroid, hormone, androgens
        - Chronic disease
    - Increased RBC destruction
        - Congenital hemolytic anemias
            - Hereditary spherocytosis, G6PD, sickle cell disease, thalassemia
        - Acquired hemolytic anemias
            - Coomb's positive autoimmune hemolytic anemia, malaria, hypersplenism
            - TTP, HUS
            - DIC, toxins, prosthetic valves
    - Increased RBC loss
        - Obvious bleeding
            - GI, trauma, menorrhagia
        - Occult bleeding
            - Slow GI bleed, retroperitoneal, upper thigh, pelvis
        - Iatrogenic bleeding
            - Postoperative, hemodialysis, recurrent blood donation
    - Increase in plasma volume
        - Pregnancy
        - Fluid overload
2. Incidence/prevalence
    - Males: 6.6/100
    - Females: 12.4/100
    - Increases with age to 44.4% among men $\geq$85 yo
    - 4.7 million Americans are anemic

3. Risk factors
    - Advancing age
    - Gender: women > men
    - Family history
4. Morbidity/mortality
    - Symptoms, morbidity and mortality depend greatly on how rapidly the anemia develops
        - Slow development leads to fewer symptoms
        - Rapid development leads to increased symptoms
            - eg, A young, healthy person can be expected to tolerate rapid loss of 500-1000 mL (10-20% of blood volume) with few or no symptoms, although about 5% of the population will have a vasovagal reaction
        - Mortality depends on the cause of the anemia (eg, dietary iron deficiency versus sickle cell disease)
    - Recent studies have shown anemia to be a powerful predictor of worsened outcomes in heart failure, with a hazard ratio of 1.39 for mortality and 1.55 for hospitalization (SOR:A)[3]

Diagnostics

1. History
    - Fatigue
    - Dyspnea on exertion
    - Melena/hematochezia
    - Hemoptysis
    - Menorrhagia
    - Falls/fractures
    - Invasive procedures
    - Chronic illness
2. Physical exam
    - General
        - Pallor, general ill appearance
        - Signs of chronic illness
    - HEENT
        - Decreased visual and auditory abilities
        - Retinal hemorrhages and/or exudates (severe anemia)
    - Cardiovascular
        - Tachycardia and/or flow murmurs
        - Dyspnea, tachypnea, and/or other signs of CHF (severe anemia)
    - Hepatosplenomegaly
    - Paresthesias in finger or toes; loss of position and vibration sense
    - Abnormal mental status (dementia, psychosis, depression)
3. Diagnostic tests
    - See also Anemia: iron studies
    - See also Anemia testing algorithms
    - CBC

        - Anemias generally classified by MCV as being microcytic, normocytic, or macrocytic
        - Microcytic
            - Thalassemias, iron deficiency, lead poisoning
            - Stool guaiac (occult GI bleed)
            - Ferritin (low if iron stores low but can be elevated as acute phase reactant)
            - Iron (decreased in deficiency)
            - Total iron binding (increased in deficiency)
            - Lead
            - Peripheral smear (may point to specific cause)
            - Hemoglobin electrophoresis
        - Normocytic
            - Hemorrhage, chronic disease, hemolysis, iron deficiency (up to 30% are normocytic)
            - Stool guaiac
            - Ferritin
            - Total iron binding capacity
            - Percent transferrin saturation (decreased with decreased iron stores)
            - Peripheral Smear
            - Reticulocyte index (elevated if healthy bone marrow is able to respond to anemia, eg, hemolysis, early blood loss; if suspicious for hemolysis then direct Coomb's test)
            - Haptoglobin (decreased in hemolysis)
        - Macrocytic
            - Folate/ vit B12 deficiency, thyroid disease, alcoholism, reticulocytosis
            - RBC folate
            - B12 level
            - TSH
            - Reticulocyte count
    - Other procedures
        - Imaging
            - Tagged RBC scan for slow lower GI bleed
            - Abdominal CT for suspected retroperitoneal bleeding
        - EGD/colonoscopy for suspected upper/lower bleeding
        - Bone-marrow biopsy if abnormal cells on peripheral smear or deficient reticulocytosis
            - Gold standard for iron deficit, evaluation of stem cell population and if dx not clear
4. Diagnostic criteria
    - Mild
        - Detectable only when exercising → Hgb 10-14 g/dL [6.2-8.7 mmol/L]
    - Moderate
        - Minimal exertion causes symptoms → Hgb 7-10 g/dL [4.3-6.2 mmol/L]

- Severe
  - End-organ dysfunction (eg, myocardial/peripheral ischemia) → Hgb 3-7 g/dL [1.9-4.3 mmol/L]

Differential Diagnosis

1. Hypothyroidism
2. Depression
3. Adrenal insufficiency
4. Hyperthyroidism
5. CHF
6. CAD
7. Tuberculosis
8. Endocarditis/pericarditis
9. Malignancy

Therapeutics

1. RBC transfusions
   - End organ ischemia
   - Acute hemorrhage
     - >25% of blood volume
     - Blood loss > 1500 mL
   - Surgical /anticipated major blood loss
     - Hgb <7 g/dL [SI: <4.3 mmol/L]
     - Hgb <8 g/dL [SI: <5 mmol/L] prior to surgery
     - Hgb <10 g/dL [SI: <6.2 mmol/L] with cardiopulmonary disease
     - Hgb >10 g/dL [SI: >6.2 mmol/L] if symptomatic anemia
     - Loss >2 L
   - Chronic anemia
     - Hgb <7 g/dL [SI: < 4.3 mmol/L]
     - If symptomatic or underlying cardiopulmonary disease
   - Exchange or hypertransfusion for hemoglobinopathy
2. O2 if symptomatic
3. LR/NS up to 2L
4. Correct underlying etiology
5. Factor supplementation: iron, folate, vit B12
   - USPSTF recommends routine iron supplementation for asymptomatic children aged 6-12 months who are at increased risk for iron deficiency anemia (premature, low birth weight, fed cow's milk). Grade: B
   - USPSTF concludes that evidence is insufficient to recommend for or against routine iron supplementation for asymptomatic children aged 6-12 months who are at average risk for iron deficiency anemia. Grade: I
   - USPSTF concludes that evidence is insufficient to recommend for or against routine iron supplementation for non-anemic pregnant women. Grade: I
6. Erythropoietin (CRF, AIDS, inadequate endogenous erythropoietin production)
   - Combination of iron + erythropoietin has been shown to improve outcomes in anemic heart failure patients in small trials, larger trials underway (SOR:B)[7]

- Recent studies suggest that Erythropoiesis Stimulating Agents (ESA) treatment of cancer-related anemias does not improve outcomes and increases risk of thromboembolic disease
    - The FDA has issued an advisory strongly recommending that healthcare professionals discuss the risks of ESA-associated tumor progression and shortened survival in patients with cancer before starting or continuing ESA therapy
- For CRF, new information states that Hgb should be maintained with ESAs between 10-12. Higher Hgb levels have been associated with death and other serious morbidity (SOR:A)[8,9]

Follow-Up

1. Return to office
    - Quarterly monitoring of CBC
    - Sooner if increased fatigue, melena, external bleeding
2. Refer to specialist
    - Gastroenterology if suspected GI bleeding
    - Urology if suspected GU bleeding
    - Hematology if suspected hemolysis, primary bone marrow disease or malignancy
3. Admit to hospital
    - Acute blood loss, especially with underlying cardiovascular disease
    - Experiencing secondary organ effects of anemia
        - Angina, confusion, dyspnea
    - Hemodynamically unstable: admit to ICU

Prognosis

1. Varies depending upon underlying disease

Prevention

1. Prevention of underlying causes
2. Fall prevention
3. Good nutrition (sources of iron, vit B12, and folate)
4. Iron supplementation in pregnancy
5. Societal bans on lead paint in homes

Evidence-Based Inquiry

1. Are any oral iron formulations better tolerated than ferrous sulfate?

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