Anemia, General Approach

(See also *Harrison's Principles of Internal Medicine*, 17th Edition, Chapter 58)

Definition

- Serum hemoglobin level or hematocrit less than the expected value for age- and sex-matched normal persons
- Definition of anemia, according to World Health Organization criteria
    - Adult men
        - Blood hemoglobin concentration <130 g/L (<13 g/dL) **or**
        - Hematocrit <39%
    - Adult women
        - Blood hemoglobin concentration <120 g/L (<12 g/dL) **or**
        - Hematocrit <37%

Epidemiology

- Epidemiologic data are specific to the etiology of the anemia.
    - See specific Disease topics.
        - Iron-Deficiency Anemia
        - Vitamin B_{12} Deficiency Anemia
        - Pernicious Anemia
        - Anemia of Chronic Disease
        - Folate-Deficiency Anemia
        - Aplastic Anemia
        - Myelodysplastic Syndromes

Mechanism

- 3 major physiologic mechanisms cause anemia.
    - Marrow production defects: hypoproliferation
        - Reflects absolute or relative marrow failure in which the erythroid marrow has not proliferated appropriately for the degree of anemia
        - Can result from marrow damage, iron deficiency, or inadequate erythropoietin stimulation
    - Erythrocyte maturation defects: ineffective erythropoiesis
        - Nuclear maturation defects associated with macrocytosis and abnormal marrow development
        - Cytoplasmic maturation defects associated with microcytosis and hypochromia, usually from defects in hemoglobin synthesis
    - Decreased erythrocyte survival: blood loss or hemolysis

Symptoms & Signs

- Most often recognized by abnormal results on screening laboratory tests
- Signs and symptoms are varied, depending on the level of anemia and the time course over which it developed.
- Acute anemia (nearly always due to blood loss or hemolysis)
    - Losses of 10–15% of total blood volume

        - Hypotension
        - Decreased organ perfusion
    - Loss of >30% of blood volume
        - Postural hypotension
        - Tachycardia
    - Loss of >40% of blood volume
        - Hypovolemic shock
            - Confusion
            - Dyspnea
            - Diaphoresis
            - Hypotension
            - Tachycardia
    - Hemolytic disease
        - Presentation depends on mechanism that leads to erythrocyte destruction.
- Chronic or progressive anemia
    - Presentation depends on age of the patient and adequacy of blood supply to critical organs.
    - Possible findings
        - Fatigue
        - Loss of stamina
        - Breathlessness
        - Pale skin and mucous membranes
        - Palmar creases are lighter in color than the surrounding skin with the fingers extended (reflects hemoglobin concentration <8 g/dL).
        - Tachycardia (particularly with physical exertion)
        - Forceful heartbeat
        - Strong peripheral pulses
        - Systolic flow murmur
    - In patients with coronary artery disease
        - Anginal episodes may appear or increase in frequency and severity.
    - In patients with carotid artery disease
        - Lightheadedness or dizziness may develop.

Differential Diagnosis

- Hypoproliferative anemias (75% of cases)
    - Marrow damage
        - Infiltration/fibrosis
        - Aplasia
    - Iron deficiency (mild to moderate)
    - Decreased stimulation
        - Inflammation
        - Metabolic defect
            - Hypothyroidism
        - Renal disease
- Maturation disorder
    - Cytoplasmic defects
        - Iron deficiency (severe)
        - Thalassemia
        - Sideroblastic
    - Nuclear defects
        - Folate deficiency
        - Vitamin B_{12} deficiency
        - Drug toxicity
            - Methotrexate
            - Alkylating agents
            - Alcohol

        - Refractory anemia
            - Myelodysplasia
- Hemolysis/hemorrhage
    - Blood loss
    - Intravascular hemolysis
    - Metabolic defect
    - Membrane abnormality
    - Hemoglobinopathy
    - Autoimmune defect
    - Fragmentation hemolysis

Diagnostic Approach

- Careful history
    - Nutritional history related to drugs or alcohol intake
    - Family history of anemia
    - Persons of certain geographic backgrounds and ethnic origins are at higher risk.
        - Glucose-6-phosphate dehydrogenase deficiency and certain hemoglobinopathies are seen more commonly in persons of Middle Eastern, Mediterranean, or African origin.
    - Exposure to certain toxic agents or drugs
- Physical examination
    - May provide clues to the mechanisms of anemia
        - Infection
        - Blood in the stool
        - Splenomegaly and lymphadenopathy suggest an underlying lymphoproliferative disease.
        - Petechiae suggest platelet dysfunction.
- Laboratory assessment
    - Including review of past laboratory measurements to determine time of onset
- Physiologic classification of anemia (see Figures 1, 2, 3, 4, 5, 6, 7, 8, 9, 10)
    - Based on reticulocyte count and level of anemia, reticulocyte index is calculated.
    - Complete blood count (CBC), reticulocyte index <2.5, and normocytic, normochromic anemia
        - Hypoproliferative
            - Marrow damage: infiltration/fibrosis or aplasia
            - Iron deficiency
            - Decreased stimulation: inflammation, metabolic defect, renal disease
    - CBC, reticulocyte index <2.5, and microcytic or macrocytic anemia
        - Maturation disorder
            - Cytoplasmic defects: iron deficiency, thalassemia, sideroblastic
            - Nuclear defects: folate deficiency, vitamin B_{12} deficiency, drug toxicity, refractory anemia
    - CBC, reticulocyte index ≥2.5
        - Hemolysis/hemorrhage
            - Blood loss
            - Intravascular hemolysis
            - Metabolic defect
            - Membrane abnormality
            - Hemoglobinopathy
            - Autoimmune defect
            - Fragmentation hemolysis

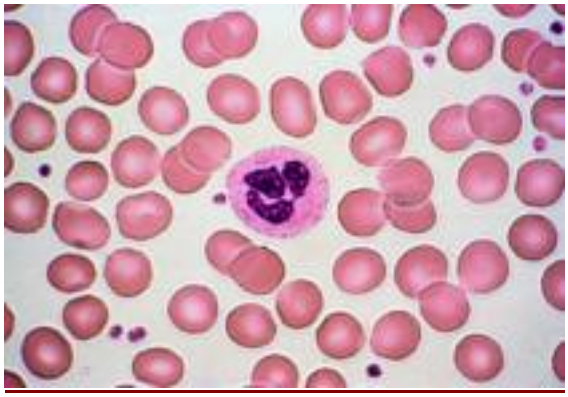

Figure 1: Normal blood smear (Wright's stain). High-power field showing normal red cells, a neutrophil, and a few platelets. (*From Hillman and Ault.*)

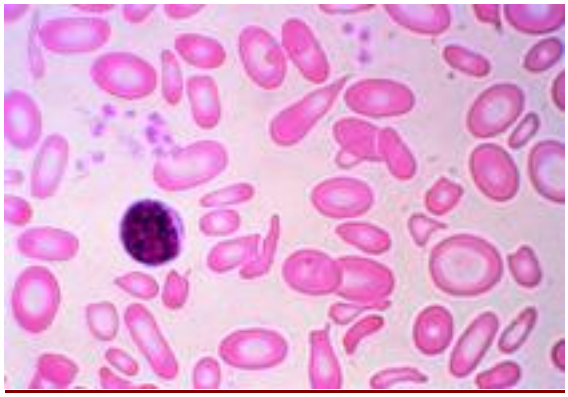

Figure 2: Severe iron-deficiency anemia. Microcytic and hypochromic red cells smaller than the nucleus of a lymphocyte associated withmarked variation in size (anisocytosis) and shape (poikilocytosis). (*From Hillman and Ault.*)

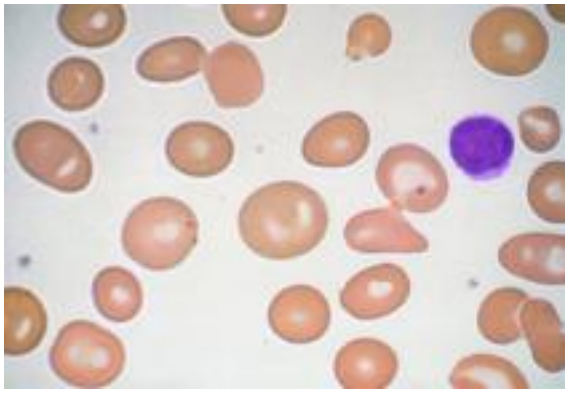

Figure 3: Macrocytosis. Red cells are larger than a small lymphocyte and well hemoglobinized. Often macrocytes are oval-shaped, so-called macroovalocytes.

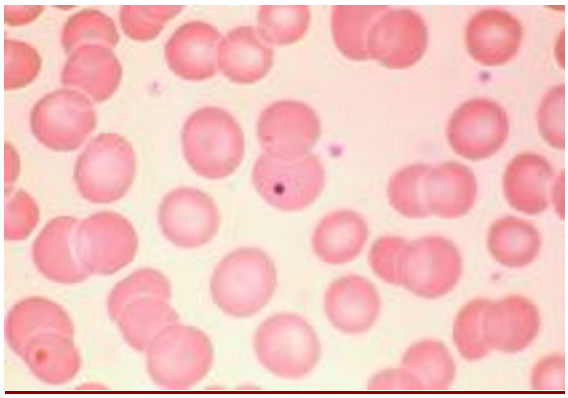

Figure 4: Howell-Jolly bodies. In the absence of a functional spleen, nuclear remnants are not culled from the red cells and remainas small homogeneously staining blue inclusions on Wright stain. (*From Hillman and Ault.*)

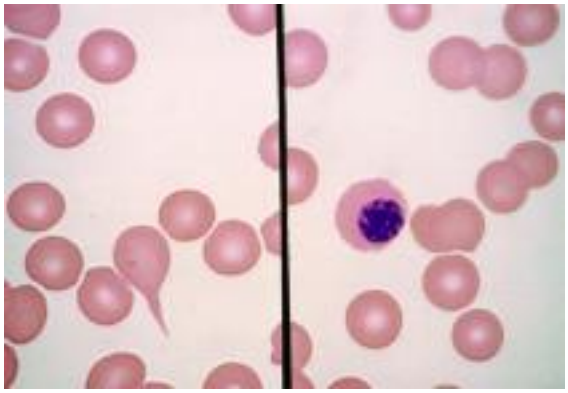

Figure 5: Red cell changes in myelofibrosis. The left panel shows a teardrop-shaped cell. The right panel shows a nucleated red cell. These forms are seen in myelofibrosis with extramedullary hematopoiesis.

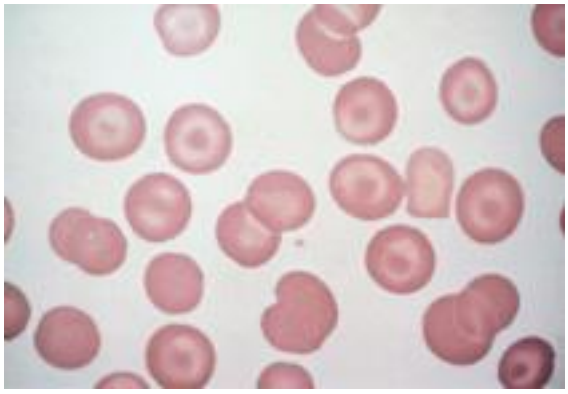

Figure 6: Target cells. Target cells have a bull's-eye appearance and are seen in thalassemia and in liver disease. (*From Hillman and Ault.*)

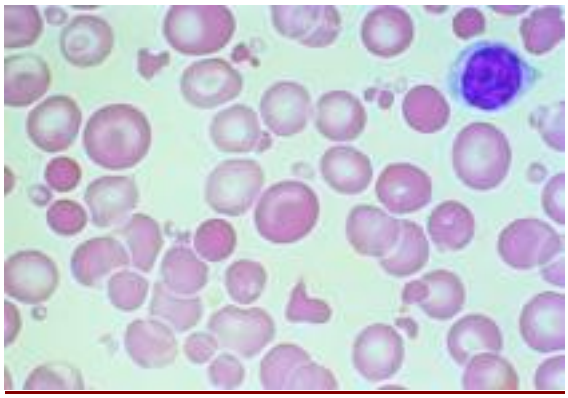

Figure 7: Red cell fragmentation. Red cells may become fragmented in the presence of foreign bodies in the circulation such as mechanical heart valves or in the setting of thermal injury. (*From Hillman and Ault.*)

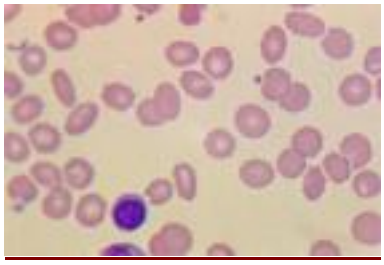

Figure 8: Uremia. The red cells in uremia may acquire numerous, regularly spaced, small spiny projections. Such cells, called burr cells or echinocytes, are readily distinguishable from irregularly spiculated acanthocytes shown in Figure 9.

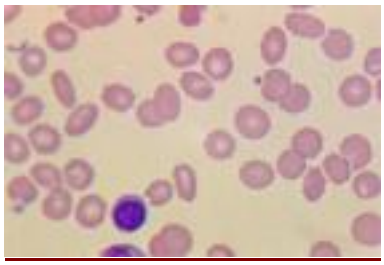

Figure 9: Uremia. The red cells in uremia may acquire numerous, regularly spaced,small spiny projections. Such cells, called burr cells or echinocytes,are readily distinguishable from irregularly spiculated acanthocytes.

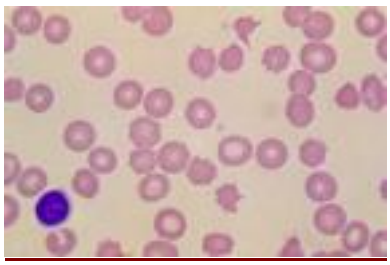

Figure 10: Spur cells. Spur cells are recognized as distorted red cells containing several irregularly distributed thornlike projections. Cells with this morphologic abnormality are also called acanthocytes. *(Courtesy of Elaine Jaffe, MD.)*

Laboratory Tests

CBC

- Erythrocyte count
  - Hemoglobin
  - Hematocrit
  - Reticulocyte count
- Erythrocyte indices
  - Mean cell volume (MCV)
  - Mean cell hemoglobin
  - Mean cell hemoglobin concentration
  - Red cell distribution width
- Leukocyte count
  - Cell differential
  - Nuclear segmentation of neutrophils
- Platelet count
- Cell morphology
  - Cell size
  - Hemoglobin content
  - Anisocytosis (variations in cell size)
  - Poikilocytosis (variations in cell shape)
  - Polychromasia
- Iron supply studies
  - Serum iron
  - Total iron-binding capacity (TIBC)
  - Serum ferritin, marrow iron stain

Hypoproliferative anemia

- Key tests in distinguishing among various forms of hypoproliferative anemia
  - Serum iron and iron-binding capacity
  - Serum ferritin, to assess iron stores
  - Evaluation of renal and thyroid function
  - Marrow biopsy or aspirate, to detect marrow damage or infiltrative disease
  - Iron stain of the marrow, to determine the pattern of iron distribution (occasionally)
- Anemia of acute or chronic inflammation shows a distinctive pattern of:
  - Low serum iron
  - Normal or low TIBC
  - Low percent transferrin saturation
  - Normal or high serum ferritin
- Mild to moderate iron deficiency anemia shows:
  - Low serum iron level
  - High TIBC
  - Low percent transferrin saturation
  - Low serum ferritin level
- Marrow damage by a drug; infiltrative disease, such as leukemia or lymphoma; or marrow aplasia can usually be diagnosed from:
  - Peripheral blood **and**
  - Bone marrow morphology
- Infiltrative disease or fibrosis
  - Marrow biopsy will likely be required.

Tests for distinguishing among various forms of anemia due to maturation disorders

- Vitamin B_{12}
- Folate
- Serum iron and iron-binding capacity
- Serum ferritin to assess iron stores
- Hemoglobin electrophoresis

Blood loss/hemolytic anemia

- Marrow examination is rarely indicated if reticulocyte production index is increased appropriately.
    - Blood loss
        - Acute blood loss is not associated with increased reticulocyte production index.
            - Time required to increase erythropoietin production and, subsequently, marrow proliferation
        - Subacute blood loss may be associated with modest reticulocytosis.
        - Anemia from chronic blood loss presents more often as iron deficiency than with the picture of increased erythrocyte production.
- Hemolysis
    - Hemoglobin electrophoresis
    - Screen for red cell enzymes
    - Direct or indirect antiglobulin test
    - Cold agglutinin titer

Imaging

- Not indicated

Diagnostic Procedures

- Marrow examination (not usually indicated)
    - Aspirate
        - Myeloid to erythroid precursors ratio
        - Cell morphology
        - Iron stain
    - Biopsy
        - Cellularity
        - Morphology
    - It is preferred to perform the biopsy before the aspirate.

Classification

- Classification according functional defect in erythrocyte production
    - Marrow production defects: hypoproliferation
    - Erythrocyte maturation defects: ineffective erythropoiesis
    - Decreased erythrocyte survival: blood loss/hemolysis
- Classification by MCV
    - Microcytic: MCV <80 fL
    - Normocytic: MCV 80–100 fL
    - Macrocytic: MCV >100 fL

Treatment Approach

- Initiate treatment of mild to moderate anemia only when a specific diagnosis is made.
- Selection of the appropriate treatment is determined by the documented cause(s) of the anemia.
    - Often, the cause of the anemia may be multifactorial.
- In every circumstance, it is important to evaluate the patient's iron status fully before and during the treatment of any anemia.
- Rarely, in the acute setting, anemia may be so severe that red cell transfusions are required before a specific diagnosis is made.

Specific Treatments

Transfusion of packed red blood cells

- Indications
    - Acute: significant blood loss resulting in hypovolemic shock
    - Chronic: life-threatening symptoms, e.g., unstable angina, transient ischemic attacks
    - Adequate oxygen can be maintained with a hemoglobin content of 70 g/L in the normovolemic patient without cardiac disease.
        - Comorbid factors often necessitate transfusion at a higher threshold.
    - In most patients requiring transfusion, hemoglobin levels of 100 g/L are sufficient to keep oxygen supply from being critically low.

Specific therapy

- See specific disorders.
    - Iron-Deficiency Anemia
    - Vitamin B12 Deficiency Anemia
    - Pernicious Anemia
    - Anemia of Chronic Disease
    - Folate-Deficiency Anemia
    - Aplastic Anemia
    - Myelodysplastic Syndromes
    - Hemolytic Anemias, Acquired
    - Hemolytic Anemias, Inherited

Monitoring

- Monitoring recommendations depend on the etiology of the anemia.

Complications

- High-output cardiac failure
- End-organ ischemia or infarct, including
    - Myocardial infarction
    - Stroke
- Hypovolemic shock
- Death

Prognosis

- Prognosis depends on the etiology of the anemia.

Prevention

- Possible preventive strategies are specific to the etiology of the anemia.

ICD-9-CM

- 285.9 Anemia, unspecified

See Also

- Anemia in Hypometabolic States
- Anemia of Chronic Disease
- Anemia of Renal Disease
- Aplastic Anemia
- B_{12} Deficiency Anemia; Pernicious Anemia
- Folate Deficiency Anemia
- Iron-Deficiency Anemia
- Myelodysplastic Syndromes
- Pancytopenia
- Polycythemia
- Pure Red Blood Cell Aplasia

Internet Sites

- Professionals
  - Clinical Trials
    ClinicalTrials.gov, National Institutes of Health
- Patients
  - Anemia
    Medline Plus
  - Anemia/Iron Deficiency
    National Center for Health Statistics

References

- Hillman RS, Ault KA, Rinder HM: *Hematology in Clinical Practice*, 4th ed. New York, McGraw-Hill, 2005
- Bain BJ: Diagnosis from the blood smear. N Engl J Med 353:498, 2005 [PMID:16079373]
- Tefferi A et al: How to interpret and pursue an abnormal complete blood cell count. Mayo Clin Proc 80:923, 2005 [PMID:16007898]
- Ganz T: Hepcidin—a regulator of intestinal iron absorption and iron recycling by macrophages. Best Pract Res Clin Haematol 18:171, 2005 [PMID:15737883]

PEARLS

- Anemia may be multifactorial.
  - Finding 1 cause does not mean that no other forms of anemia are present.
  - Iron deficiency may occur together with folate or vitamin B_{12} deficiency, producing a dimorphic anemia in which some erythrocytes are large and some are small.
- Iron deficiency often means occult blood loss.
  - A single guaiac-negative stool is insufficient to rule out gastrointestinal blood loss because colorectal cancer may only bleed intermittently.
  - 3 to 6 stool samples should be examined over 2 to 3 weeks to assure the absence of stool occult blood.

- In a person with iron deficiency in whom a source for blood loss cannot be defined, don't forget to ask about blood donation.
    - Donation of 3 or 4 units per year can result in the loss of a gram of iron.