APPROACH TO ANEMIA IN FAMILY MEDICINE 2026

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Learning Objectives

1. By the end of this lecture, the learner should be able to:
2. **Define anemia** and recognize normal hemoglobin ranges.
3. **Classify anemia** by morphology and underlying mechanism.
4. **Interpret key laboratory findings** (MCV, RDW, iron studies, B12/folate).
5. **Differentiate common types of anemia** (iron deficiency, chronic disease, megaloblastic, hemolytic).
6. **Apply a structured clinical approach** to evaluation and initial management of anemia.

Definition of Anemia

Hemoglobin below the normal reference level for the age and sex of the individual

Reference range:

- **1-3 days:14.5 - 22.5g/dl**
- **6 months to 2 years:10.5 - 13.5g/dl**
- **Adult Men:13-18 g/dl**
- **Adult Women:11.5-15.5g/dl**

Anemia in older age

- **Older people >70 years:**

According to the National Health and Nutrition Examination Survey (NHANES III), :

30% caused by nutritional deficiencies

30% kidney disease and anemia of chronic disease

30% unexplained

Causes of Anemia based on Mechanism

Reduced red cell production

I. Fe, B12, folate (nutrition, malabsorption, chronic blood loss)

II. Bone marrow disorders: aplastic anemia, MDS, infiltration by tumor cells

III. Bone marrow suppression (chemotherapy, radiotherapy)

IV. Hormonal deficiencies (EPO, androgens, hypothyroidism)

V. Anemia of chronic disease/anemia of inflammation (reduced iron use in bone marrow)

GI tract does not absorb iron, remains in macrophages, reduced red cell survival

Causes of Anemia based on Mechanism

Increased red cell destruction

Anemia will become evident when bone marrow cannot replace >5% of red cell mass daily

i. Hereditary hemolytic anemias (spherocytosis, thalassemia, sickle cell anemia)

ii. Acquired hemolytic anemias (AAA, TTP, PNH)

Blood loss

Causes of Anemia based on Morphology

Macrocytic Anemia (MCV>100fL)

i. ↑ reticulocytes (hemolytic anemias, recovery from bleeding, repletion of iron, bone marrow recovery)

i. Impaired nucleic acid metabolism of the red cell precursors which inhibits nuclear division (B12 deficiency, folate deficiency, copper deficiency, drugs)

i. Myelodysplastic syndrome, multiple myeloma

i. Alcohol, liver disease, hypothyroidism

Macrocytic Anemia

Evaluation of RDW and MCV

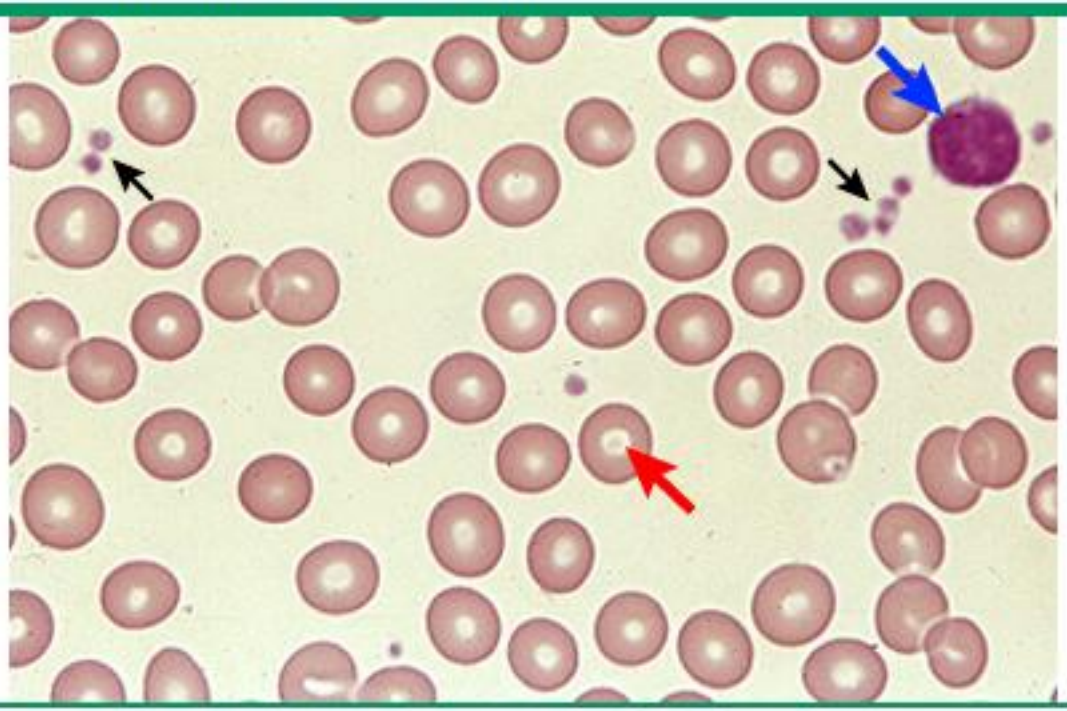
- **Normal RDW and high MCV:**
- **Aplastic anemia**
- **Chronic liver disease**
- **Chemotherapy/antivirals/alcohol**

- **Elevated RDW and high MCV :**
- **Folate or vitamin B12 deficiency**
- **Immune hemolytic anemia**
- **Chemotherapy**
- **Chronic liver disease**
- **Myelodysplastic syndrome**

Vitamin B12 (cobalamin)

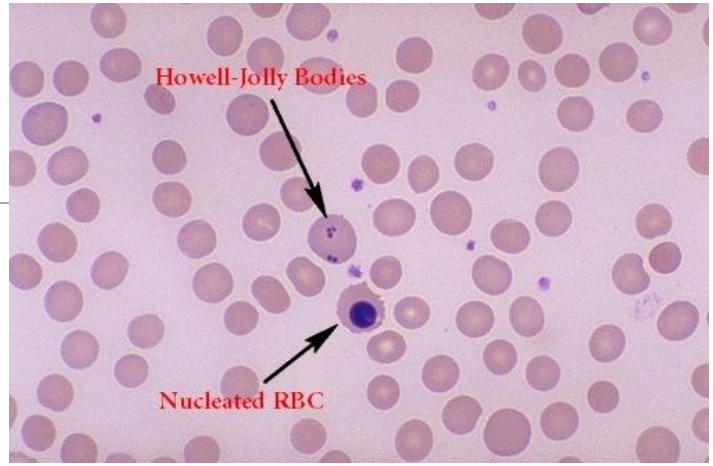
- ✓**In animal products including meats, dairy products, eggs. Clams and liver have the highest concentration.**
- ✓**A vegan diet does not contain B12 and should be supplemented**.

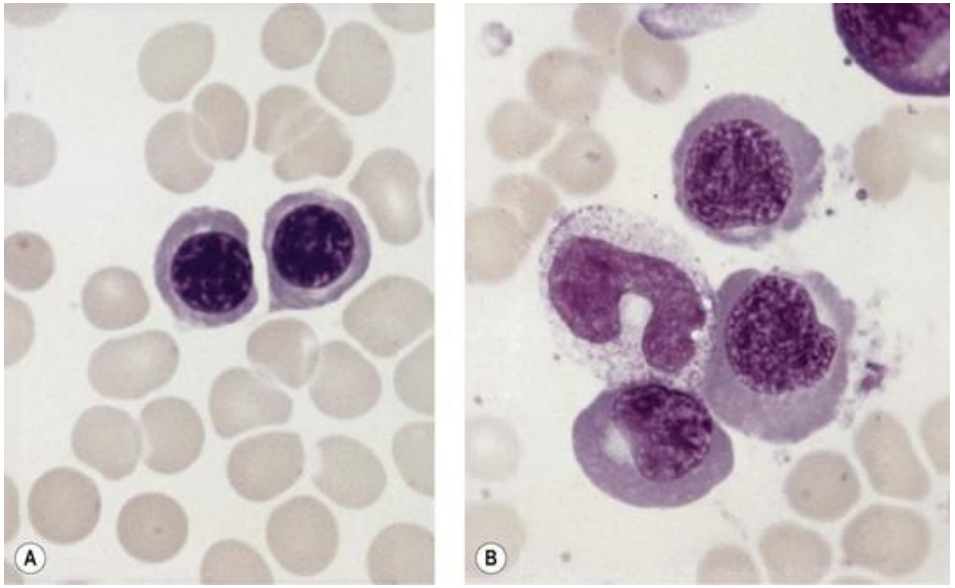
Normal peripheral blood smear



High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (red arrow) should equal one-third of its diameter.

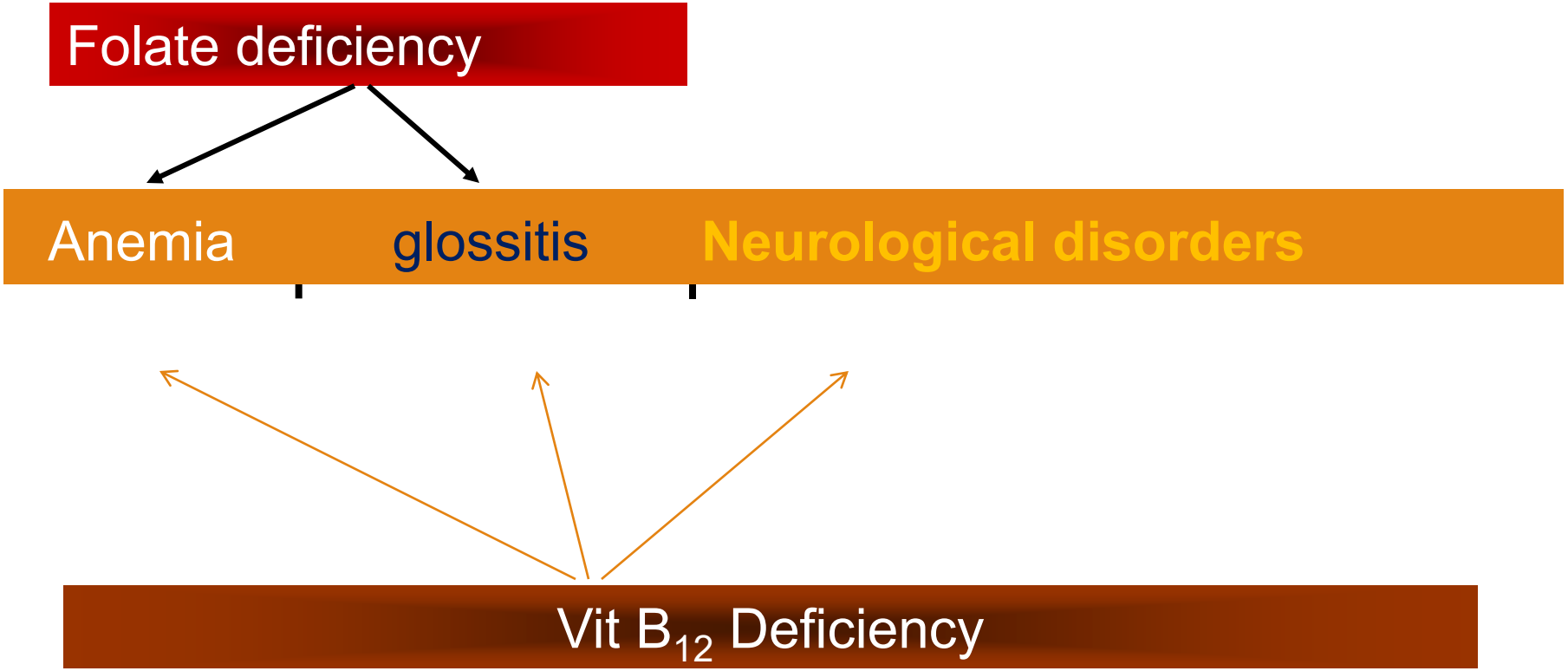
Courtesy of Carola von Kapff, SH (ASCP).



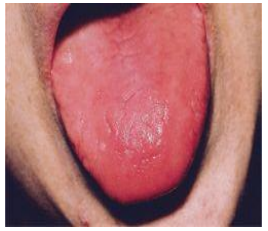


A. Normal bone marrow with polychromatophilic erythroblasts
B. Megaloblasts and giant metamyelocytes in MA

Clinical Signs of Megaloblastic Anemia



Physical



Gradual Anemia. Symptoms are present only in severely anemic patients. Lemon-like pallor due to intramedullary hemolysis

Hunter glossitis, splenomegaly

Neurological manifestations:

paresthesia and balance disorders

Peripheral neuropathy mainly of the lower extremities with lancinating pain

Loss of vibratory sense proprioception with Romberg +

Less frequently Babinski, hyporeflexia and clonus

Optic atrophy with visual disturbances

Dementia like psychological disturbances

Laboratory

Clinical suspicion of MA in cases with MCV>100 fl and hypersegmented neutrophils in the peripheral blood smear

MCV>115 fl rather specific for B12 or folate deficiency

Beware of cases of combined B12/folate and iron deficiency

30% of patients with B12 deficiency without anemia

Only 35% of pts with B12 deficiency have macrocytosis

Pancytopenia, reticulocytopenia

↑LDH, indirect bilirubin, ↓haptoglobin

↑ Fe, ferritin, transferrin saturation

Laboratory (II)

Methylmalonic acid and homocysteine levels in patients with borderline levels of B12 and folate and to confirm B12 deficiency.

↑MMA in B12 deficiency but not in folate deficiency

False ↑MMA in renal insufficiency

↑ homosysteine in both B12 and folate deficiency

B12> 300pg/ml: normal

B12= 200-300pg/ml: borderline, needs further testing

B12<200pg/ml: deficiency

FA<2 ng/ml: deficiency, >4 ng/ml: normal

MA-Treatment

B12 IM: initially 1mg/d for 1 week, then 1mg/week for 1 month and then monthly for lifetime

No toxicity, the surplus of the vitamin is excreted in the urine

Correction of the underlying disease

B12 peros: alternative method with the disadvantage of patient compliance and the unknown impact on neurologic disorder

MA-Treatment

Bone marrow normal in 1-2 days

- **↑RET in 7 days**
- **↑Hb in 10 days→normal in 8 weeks**

Hypersegmented neutrophils disappear in 3 weeks

The neuropsychiatric symptoms improve in 3-12 months, although severe/prolonged symptoms are irreversible in some cases.

Avoid transfusion in older patients if not necessary, evidence of congestive heart failure.

MA-Treatment

Folic acid 1-5mg/d peros (even in malabsorption)

1-4 months → hematologic improvement

Folate replacement will improve anemia but not the neurologic signs in case of B12 deficiency

Note: danger of hypokalemia due to the use of potassium from red cell precursors.

Causes of Anemia based on Morphology (II)

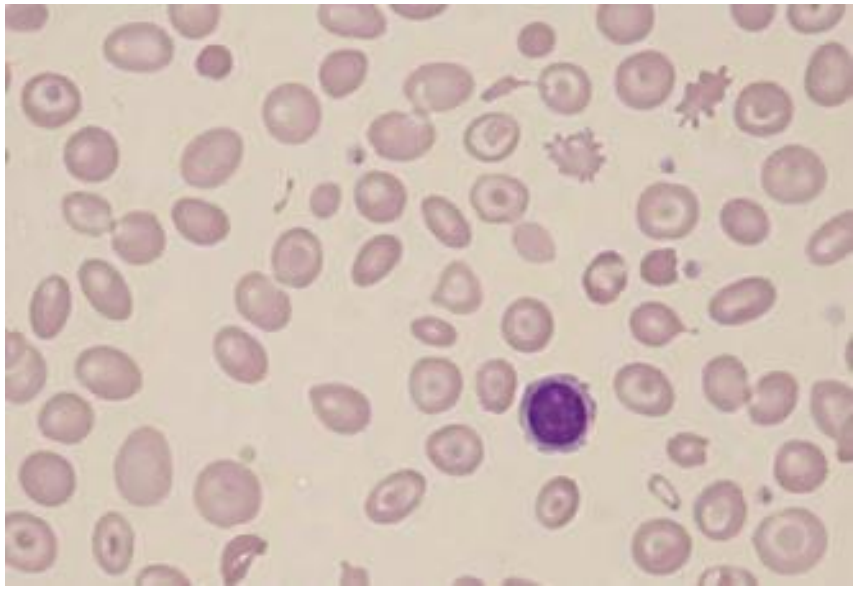
Microcytic Anemia (MCV<80fL)

Iron deficiency and some cases of anemia of chronic disease

Decreased globin chains (thalassemia, HbC, E)

Decreased heme (congenital sideroblastic anemias and lead poisoning)

Iron deficiency and thalassemia are the most common causes in clinical practice



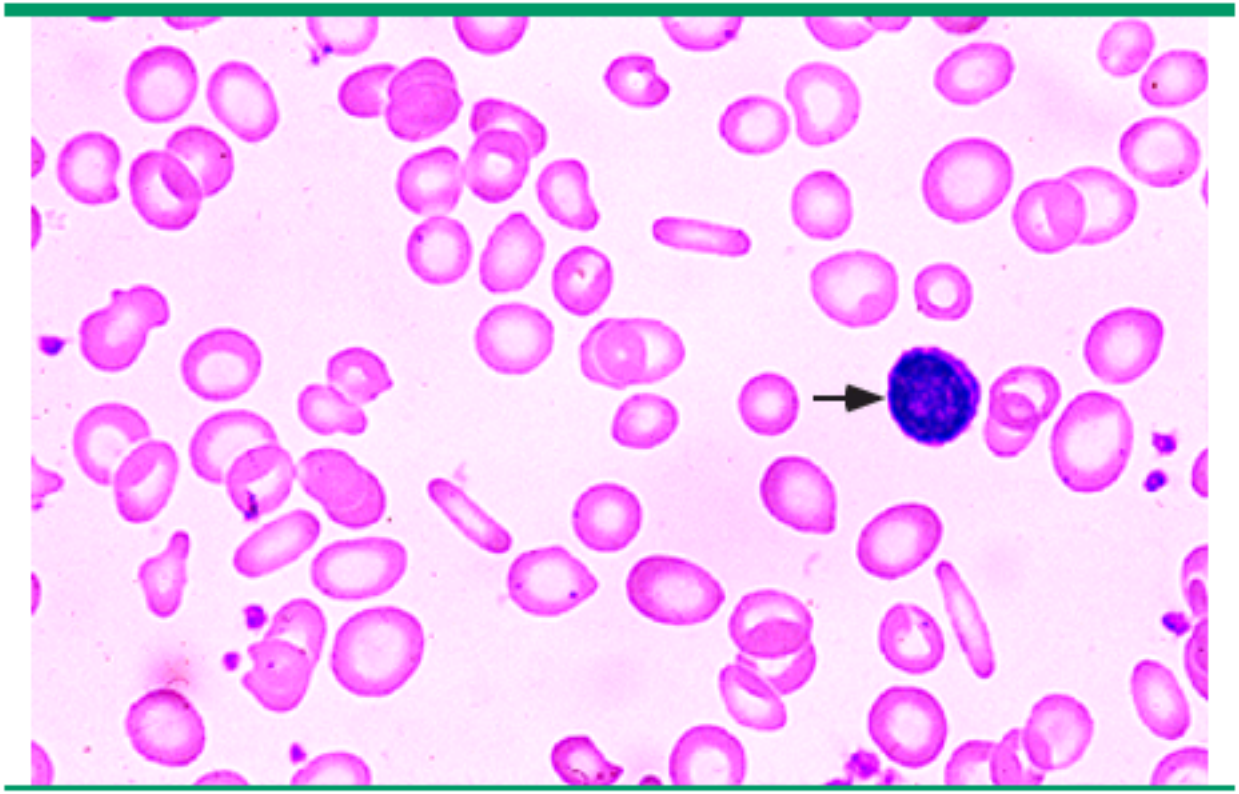
Microcytic Anemia

Evaluation of RDW and MCV

- Normal RDW and low MCV is associated with the following conditions:
- Anemia of chronic disease
- Heterozygous thalassemia

- Elevated RDW and low MCV is associated with the following conditions:
- Iron deficiency
- Sickle cell/β-thalassemia

Microcytic hypochromic red cells in iron deficiency anemia



Peripheral smear from a patient with iron deficiency shows pale small red cells with just a scant rim of pink hemoglobin; occasional "pencil" shaped cells are also present. Normal red cells are similar in size to the nucleus of a small lymphocyte (arrow); thus, many microcytic cells are present in this smear.
Courtesy of Carola von Kapff, SH (ASCP).

Iron Deficiency Anemia Treatment

- Red cell transfusion in severe cases (myocardial ischemia, hemodynamic compromise)
- Oral iron is effective for most patients (excluding gastrectomy)
- May be inadequate for ongoing blood loss, patients with IBD, common gastrointestinal side effects, administration for several months
- IV iron: effective, more rapid correction of anemia, ability to administer large doses in a single infusion, adherence is assured
- IV iron requires equipment and personnel to treat rare allergic or infusion reactions

Causes of Anemia based on Morphology (III)

Normocytic Anemia (MCV 80-100fL)

i. Acute blood loss
ii. Anemia of chronic disease/chronic inflammation
iii. Bone marrow infiltration
iv. Aplastic anemia
v. Anemia of renal disease
vi. Less frequently hypothyroidism, adrenal insufficiency

Normocytic Anemia

Evaluation of RDW and MCV

- **Normal RDW and normal MCV:**
- Anemia of chronic disease
- Acute blood loss or hemolysis
- Anemia of renal disease

- **Elevated RDW and normal MCV:**
- Early iron, vitamin B12, or folate deficiency
- Dimorphic anemia (for example, iron and folate deficiency)
- Sickle cell disease
- Chronic liver disease
- Myelodysplastic syndrome

Evaluation of Patients with Anemia

History

Onset of symptoms (recent onset indicates acquired disease ≠long standing symptoms and family history usually indicate heritable conditions)

Underlying systemic diseases (renal disease, RA)

Medications

History of transfusions

Environmental toxic condition

Evaluation of Patients with Anemia (II)

Physical

Vital signs and evaluation of postural hypotension

Presence of hemorrhagic manifestations (petechiae, non palpable purpura, ecchymosis)

Rectal exam for blood and fecal occult blood test

Liver, spleen, lymph node enlargement, bone pain (skeletal metastases), sternum pain (bone marrow expansion due to infiltration)

Anemia with reticulocytosis

RESPONSE OF THE BONE MARROW TO BLOOD LOSS OR HEMOLYSIS

Anemia with low reticulocytes

LOW RED CELL PRODUCTION, INEFFECTIVE HEMOPOIESIS

Pancytopenia with reticulocytopenia

EXCLUDE APLASTIC ANEMIA

Evaluation of Patients with Anemia (III)

Evaluation of WBC

Neutrophilia→infection, steroid treatment

High monocyte value→MDS, tuberculosis, malignant diseases

Lymphocytosis→viral diseases, lymphoproliferative disorders

Eosinophilia→parasitic infestations (hookworm of the duodenum-IDA)

Neutropenia→chemotherapy toxicity, T-LGL, acute leukemia

Lymphopenia→HIV, SLE, lymphomas, chronic steroid use

Evaluation of Patients with Anemia (IV)

Evaluation of Platelets

Thrombocytopenia→hypersplenism, autoimmune thrombocytopenia, medications, bone marrow infiltration, B12-folate deficiency

Thrombocytosis→myeloproliferative diseases, iron repletion, infections, vasculitis, malignancy

Specific platelet morphology (giant or hypogranular)→MDS

Hemolytic Anemia

Hereditary Hemolytic Anemias (red cell properties)

i. RBC membrane disorders (hereditary spherocytosis, elliptocytosis, stomatocytosis)

ii. RBC metabolic abnormalities (G-6PD and pyruvate kinase deficiency)

iii. Hemoglobinopathies (thalassemia, HbS, unstable hemoglobin variants)

Acquired Hemolytic Anemias (extracorpuscular)

i. Antibody mediated (AAA)

ii. Non-immune mediated (e.g hypersplenism, drugs and toxins, mechanical trauma)

Hemolytic Anemia
Site of destruction

Intravascular Hemolysis (primarily within the vasculature)

i. Thermal burns

ii. Defective mechanical valves

iii. Complement induced lysis (PNH)

iv. Bacterial toxins(clostridial sepsis)

v. Thrombotic microangiopathies (TTP, HUS)

vi. Acute hemolytic transfusion reaction

Free serum hemoglobin, low haptoglobin, urine hemoglobin, urine hemosiderin (several days after hemolysis)

Hemolytic Anemia
Site of destruction

Extravascular Hemolysis (primarily via macrophages of the reticuloendothelial system in liver, spleen, bone marrow)

i. Autoimmune (AAA)

ii. Hemoglobinopathies

iii. Heinz bodies anemias

iv. RBC membrane/cytoskeletal disorders

v. Red cell enzyme deficiencies

vi. MAHA

vii. Hypersplenism

Hemolytic Anemia

Signs and Findings

i. Pallor, tachycardia and jaundice

ii. Splenomegaly (chronic hemolysis)

iii. Anemia, ↑ indirect bilirubin, ↑RET, ↑LDH, low haptoglobin

iv. DAT positive (if autoimmune)

v. Free serum hemoglobin, dark urine (urine hemoglobin and hemosiderin)

Hemolytic Anemias

Peripheral Blood smear is mandatory

i. Spherocytes, elliptocytes and stomatocytes suggest hereditary RBC membrane disorders

ii. Schistocytes (TTP, DITMA)

iii. Microspherocytes suggest warm AIHA or drug-induced hemolytic anemia

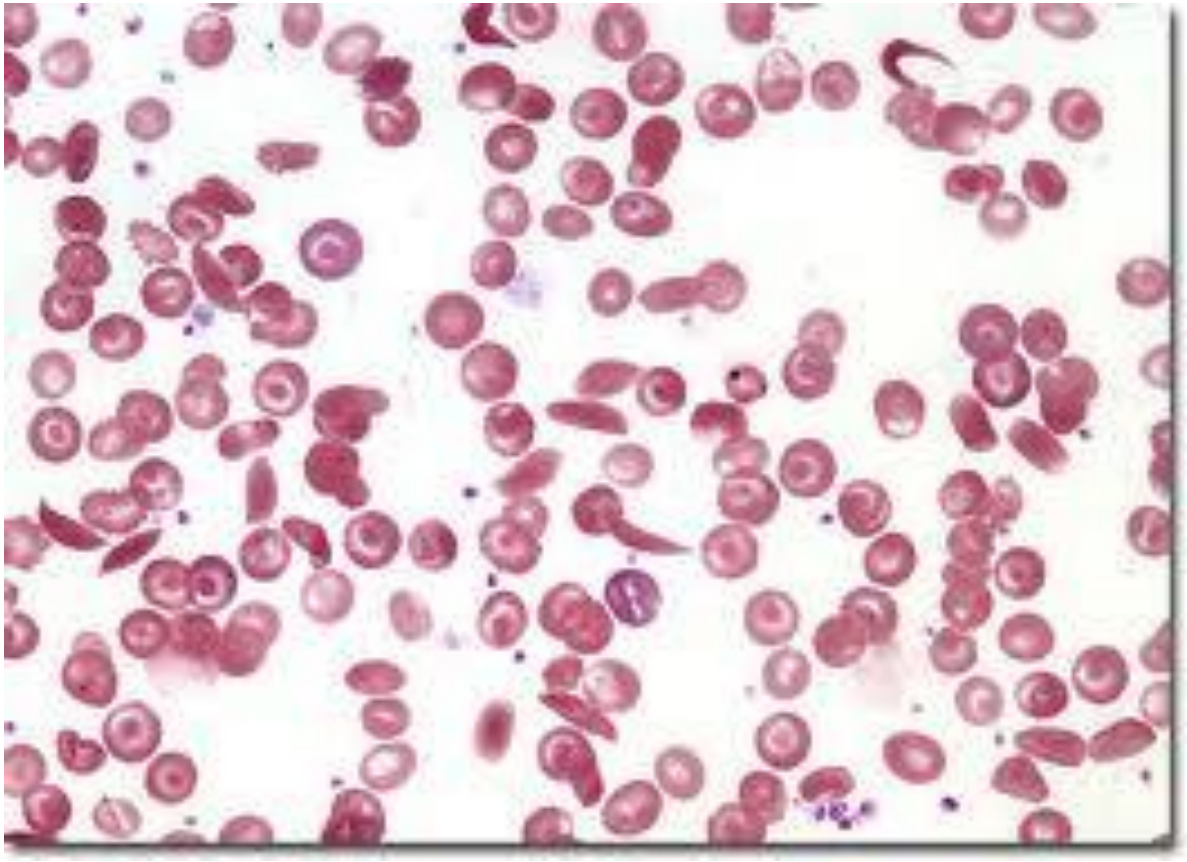
iv. In certain infections, microorganisms on a thick smear (malaria)

v. Bite cells indicate hemolysis in G-6PD deficiency

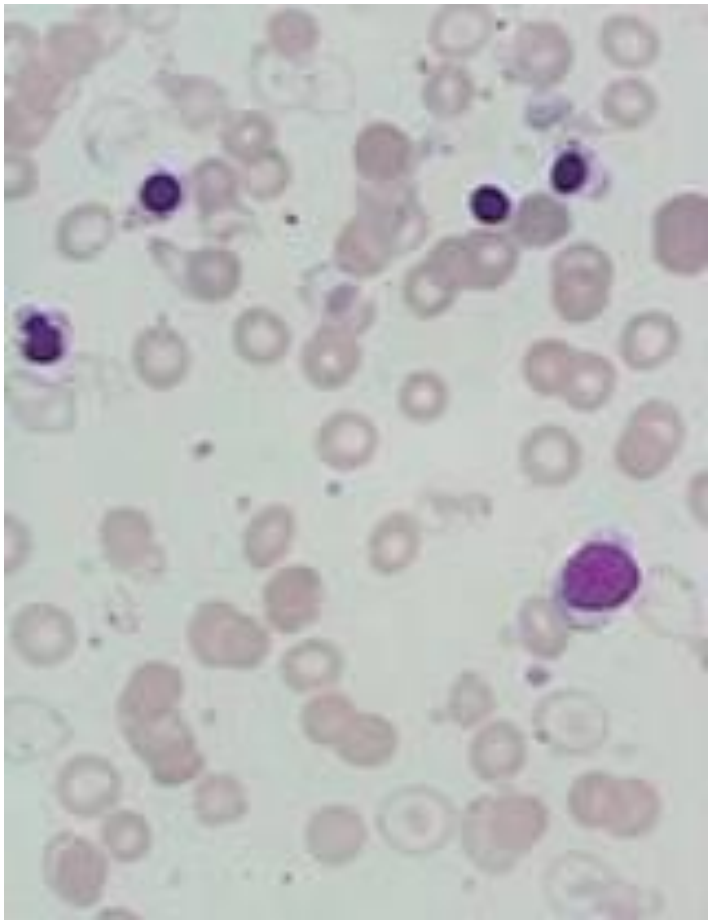
vi. RBC agglutination suggests cold-agglutinin disease

vii. Nucleated cells, sickled cells (thalassemia, sickle cell disease)

Sickle cell anemia



B-Thalassemia major



Anemia of Chronic Disease/Chronic Inflammation

Pathogenesis-Epidemiology

Second most common anemia in adults

Multifactorial etiology

- ✓Increase in pro-inflammatory cytokines and subsequent increase in hepcidin levels.
- ✓Low response of EPO for the degree of anemia
- ✓Ineffective hematopoiesis
- ✓Decreased rec cell survival in states of acute inflammation.

Anemia of Chronic Disease/Chronic Inflammation

Causes

i. **Malignancies-Lymphomas**

ii. **TBC**

iii. **HIV**

iv. **SLE, RA**

v. **Inflammatory Bowel Disease**

vi. **Renal Disease**

vii. **Heart Failure**

viii. **Old Age**

Anemia of Chronic Disease/Chronic Inflammation

Laboratory

i. **Normocytic anemia with low RET**

ii. **↓ Fe και TIBC**

iii. **Normal to increased ferritin, elevated CRP**

iv. **Normal sTfR**

v. **Low TSAT**

vi. **sTfR-ferritin index ≤1**

vii. **Bone marrow with iron staining: normal or increased storage iron in bone marrow macrophages.**

Evaluation of Anemia
Indication for Bone Marrow Examination

Unexplained pancytopenia

Abnormal lymphocytes, blasts or immature cells in blood smear

Unexplained elevations in blood counts (leukocytosis, thrombocytosis)

Unexplained splenomegaly

Suspected myeloma

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