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Core Topic: Anemia

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SIDNEY KIMMEL MEDICAL COLLEGE

Core Topic: Anemia

Marisyl de la Cruz

August 27, 2020



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Thomas Jefferson University

Agenda

- 1st hour
 - Diagnosis and evaluation
 - Approach to anemia
 - Hypoproliferative
 - Hyperproliferative
 - Management of common anemias
- 2nd hour
 - Cases
- Q & A

Objectives

- Become familiar with signs and symptoms of anemia
- Use laboratory findings to differentiate anemias
- Review pathophysiology of anemia and recognize anemia as a symptom of other conditions
- Understand management of common anemias seen in primary care

Anemia - Definition

- Decrease in the number of circulating red blood cells
- Most common hematologic disorder by far
- Almost always a secondary disorder
- Critical to know how to evaluate and determine cause

Anemia - Causes

Blood loss

Decreased
production of
red blood cells

- Marrow failure

Increased
destruction of
red blood cells

- Hemolysis

Diagnosis and Evaluation

Evaluation of the Patient

- History and Exam
- CBC with indices (MCV)
- Reticulocyte count
- WBC, diff, platelets
- Blood smear

WBC and diff

- Low total WBC
 - Aplastic anemia
 - Bone marrow suppression or replacement
 - Hypersplenism
 - Cobalamin deficiency
- High total WBC
 - Presence of infection
 - Inflammation
 - Hematologic malignancy

Peripheral Blood Smear

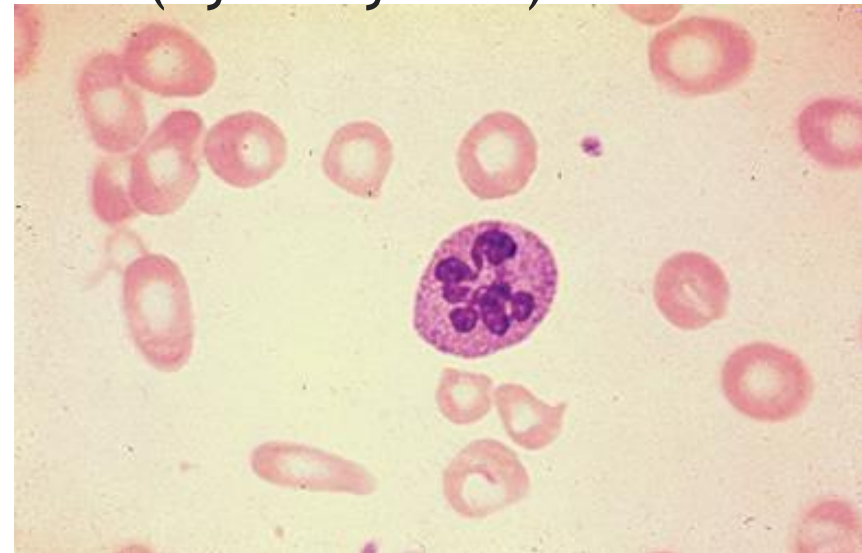
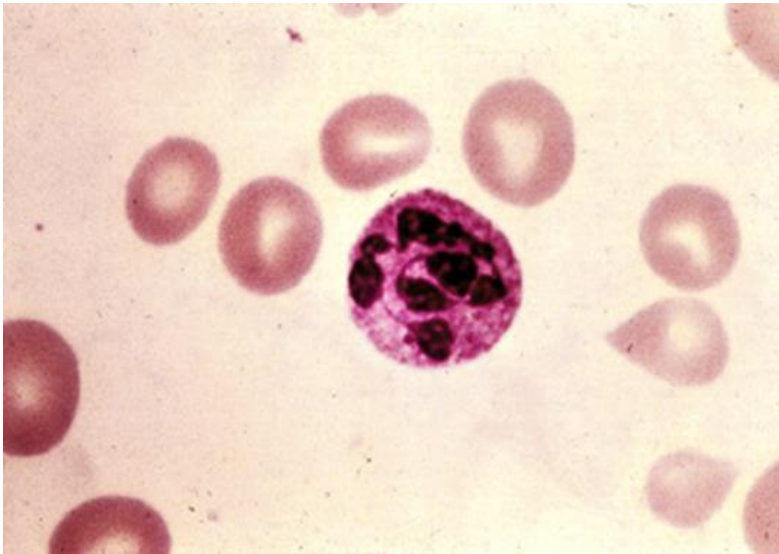
- Look for size and shape of RBC's - esp for variability in sizes & shapes
- Is there polychromasia present? (Often implies reticulocytosis)
- Are there platelet and WBC abnormalities?

Neutrophil Segmentation

>5 percent of PMNs with five+ lobes and/or the presence of one or more PMNs with six+ lobes

If found with macro-ovalocytic red cells:

- Disorders of vitamin B12 and folate
- Drugs interfering with nucleic acid synthesis (hydroxyurea)



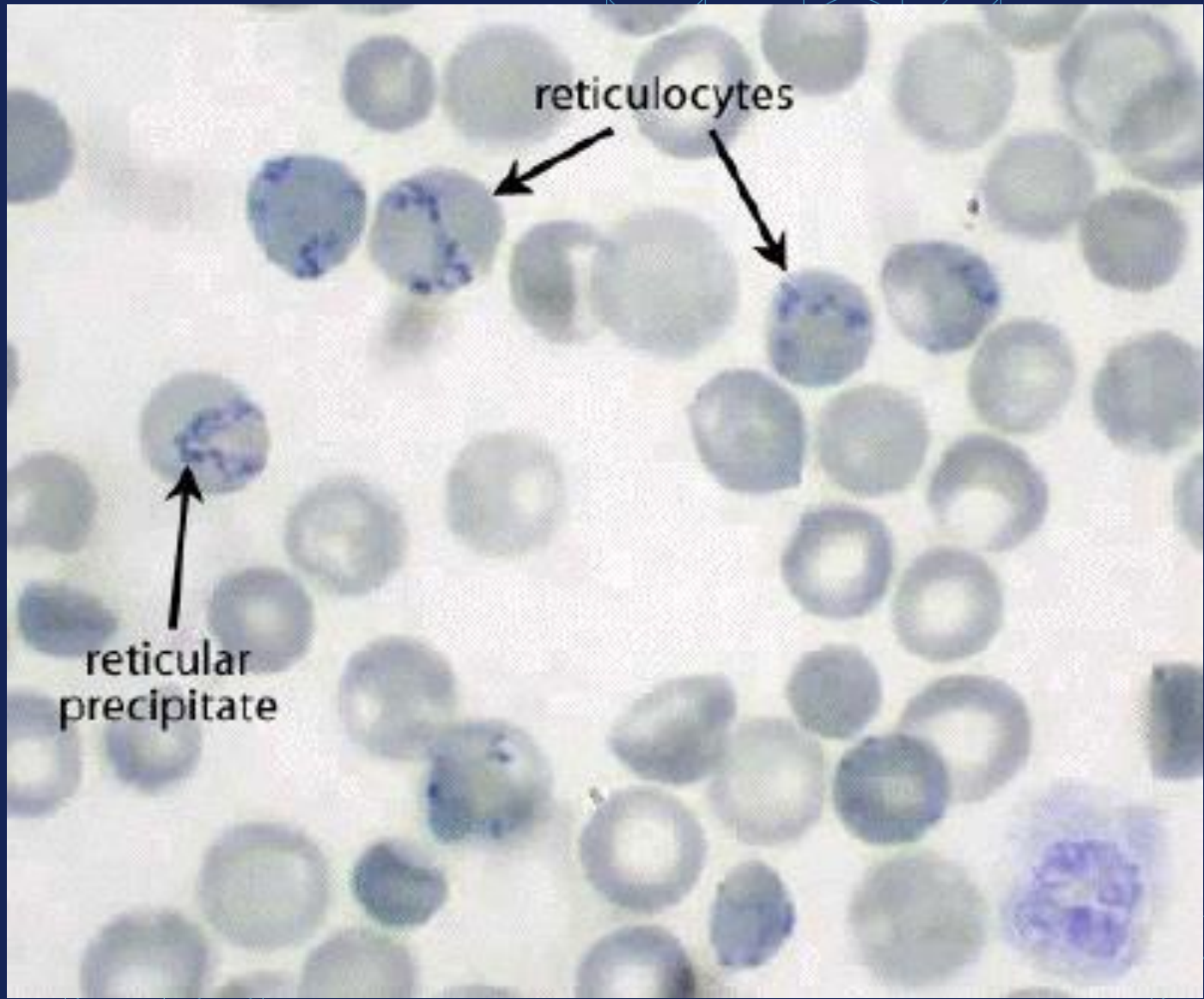
Anemia Workup

RETICULOCYTE COUNT

- If elevated, look for causes of increased destruction or bleeding
- If normal or decreased, look for causes of marrow failure

Reticulocyte Count - Absolute Value

- = Retic % x RBC Count
 - eg $0.01 \times 5,000,000 = 50,000$
- Normal up to $120,000/\mu\text{l}$
- More accurate way to assess body's response to anemia



reticulocytes

reticular
precipitate

Approach to Anemia

ANEMIA

Low Reticulocyte Index

(Hypoproliferative)

Microcytic

(MCV < 80)

Normocytic

(MCV 80–95)

Macrocytic

(MCV > 95)

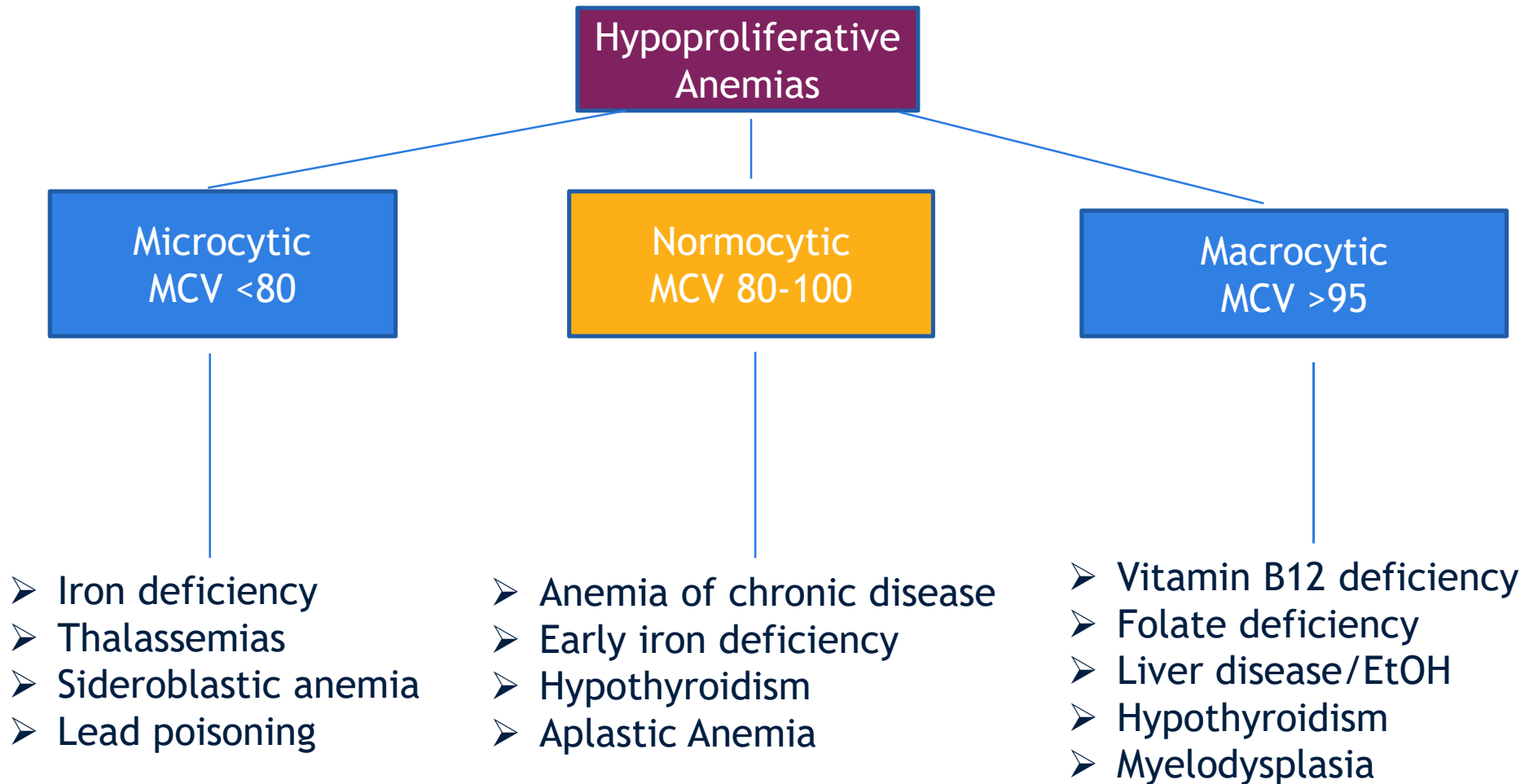
High Reticulocyte Index

(Hyperproliferative)

Hemolytic Anemias

Blood loss

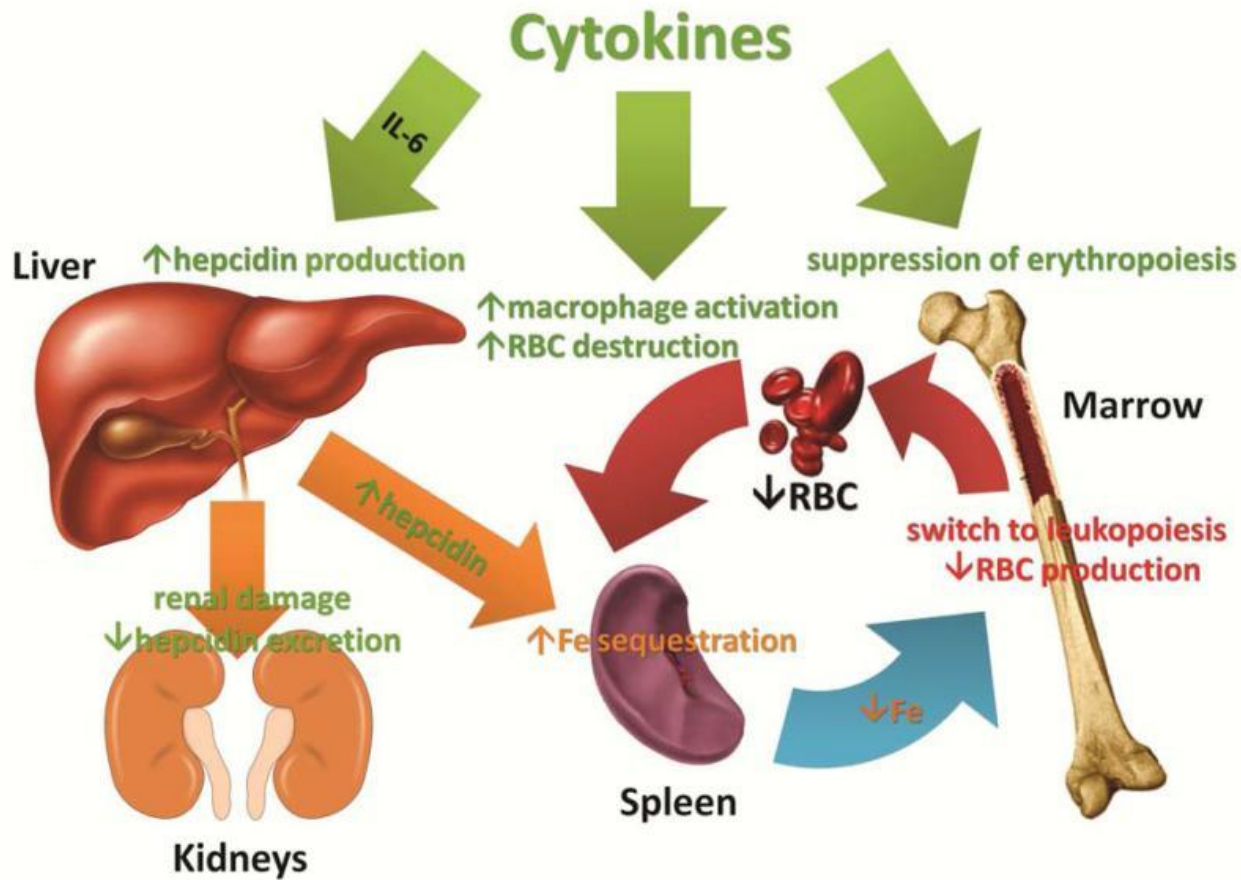
Approach to Anemia



Anemia - Normocytic (MCV 80-100)

- Most commonly caused by anemia of chronic disease (ACD)
 - Impaired absorption of iron from GI tract and iron trapping in macrophages
 - Prevents utilization of iron by the body
 - Because ACD results in iron-deficient erythropoiesis, various labs similar to those seen in iron deficiency

Anemia of Chronic Disease - Pathophysiology



Normocytic Anemia (MCV 80-100 fl)

<u>Type of anemia</u>	<u>Blood film</u>	<u>Ferritin</u>	<u>Fe</u>	<u>TIBC</u>	<u>Marrow Fe stores</u>
Chronic disease*	Normochromic, normocytic	NI or ↑	↓	↓	NI or ↑, clumped
Early Fe deficiency	Mild anisocytosis, hypochromia	NI or ↓	↓	↑	absent

*including anemia due to renal disease and AIDS

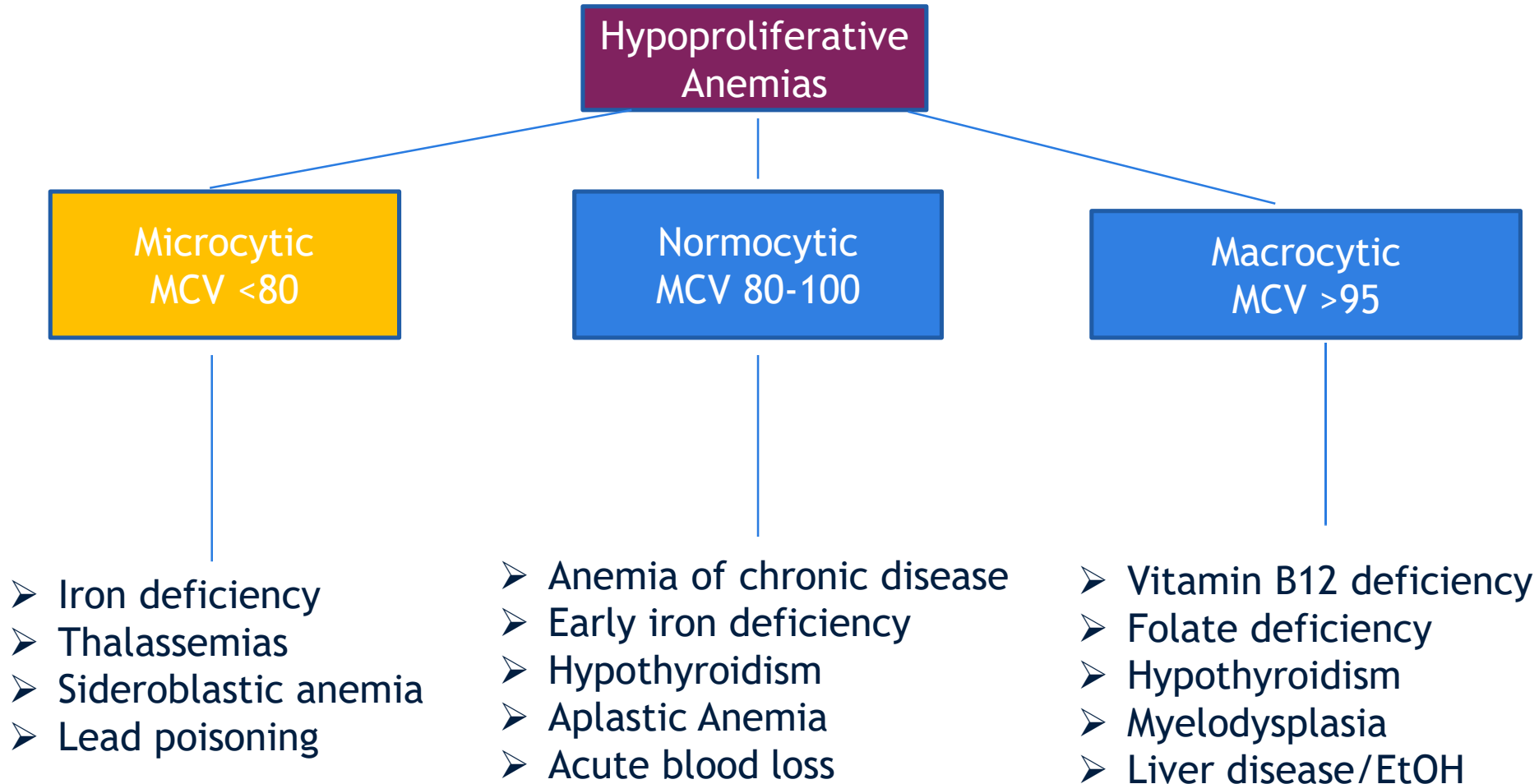
Causes of Anemia of Chronic Disease

- Anemia of chronic renal disease
- Cardiorenal anemia syndrome
- Cancer-associated anemia
- Acquired anemia in hospitalized patients
- Early iron deficiency often causes normocytic anemia as well

ANEMIA OF CHRONIC DISEASE - Causes

- Thyroid disease
- Collagen Vascular Disease
- Rheumatoid Arthritis
- Systemic Lupus Erythematosus
- Polymyositis
- Polyarteritis Nodosa
- Inflammatory Bowel Disease
 - Ulcerative Colitis
 - Crohn's Disease
- Chronic Infectious Diseases
 - Osteomyelitis
 - Tuberculosis
- Familial Mediterranean Fever

Approach to Anemia



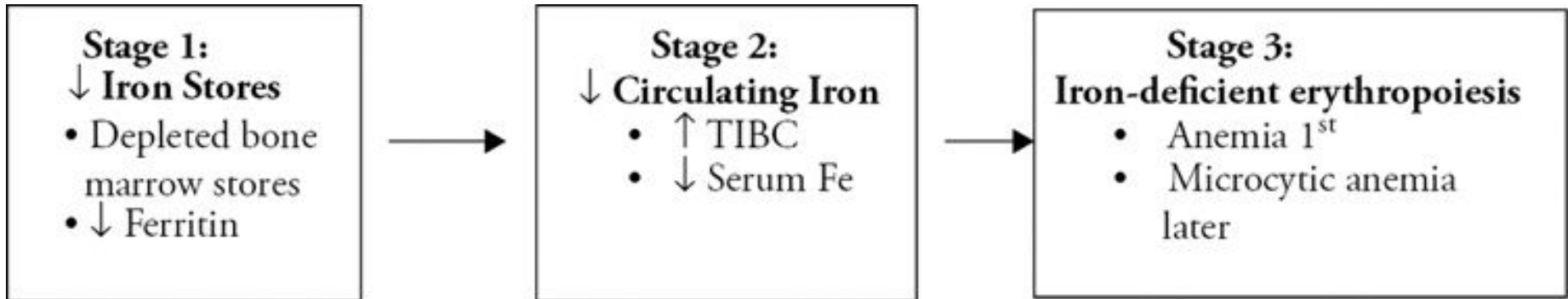
ANEMIA - Microcytic (MCV < 80)

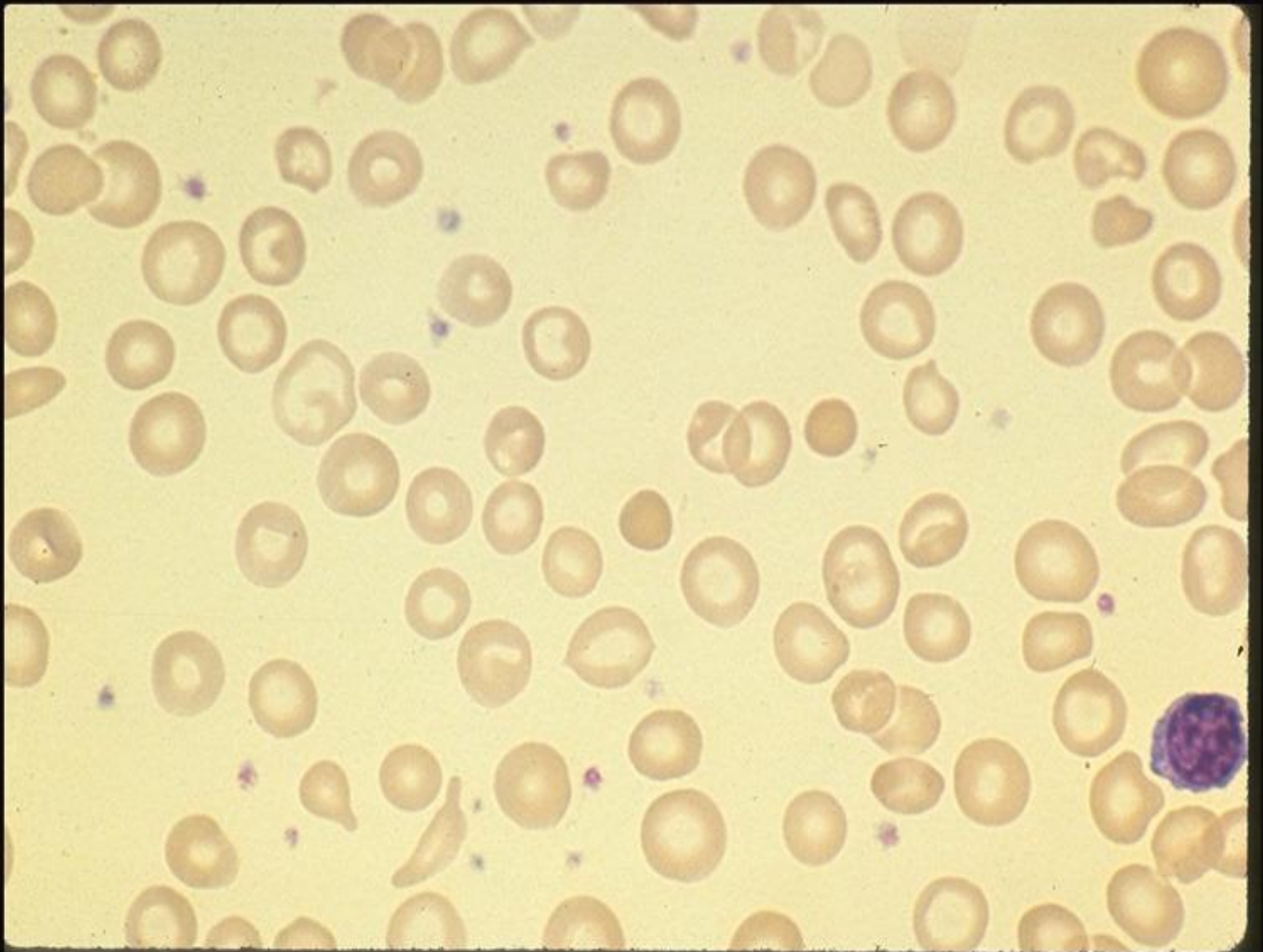
- Iron Deficiency - High RDW
- Thalassemia minor - Normal RDW
- Rare
 - Sideroblastic anemia
 - Metal poisoning (esp lead, aluminum)
 - Occasional hemoglobinopathies
 - Thalassemia major

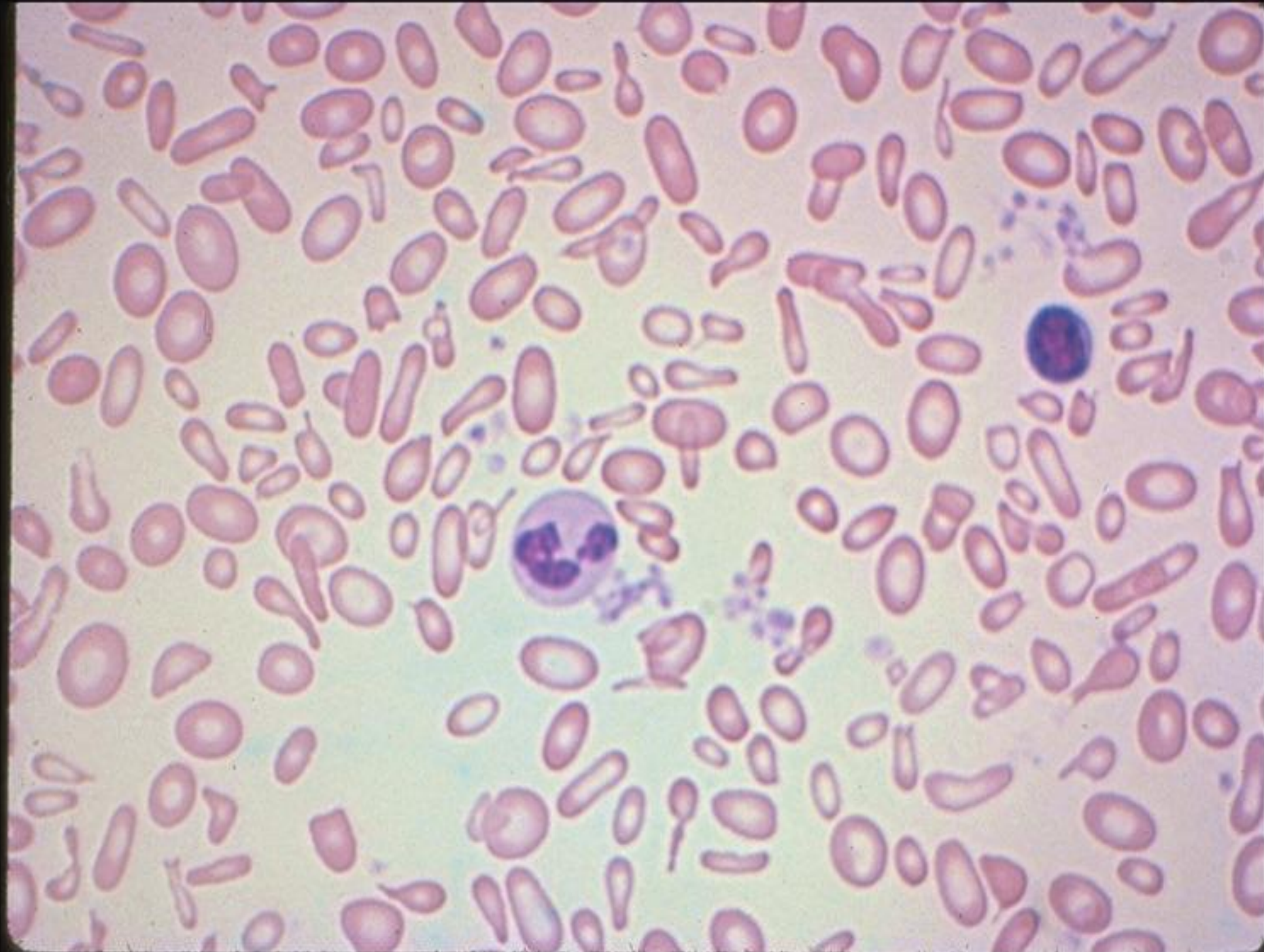
Iron Deficiency Anemia - Ferritin

- Obtain a serum ferritin level in patients with $MCV < 95$
- Reflects iron stores - most accurate test to diagnose iron deficiency anemia (usually <50)
- An acute phase reactant - can be elevated in chronic inflammation or infection

Iron Deficiency Anemia

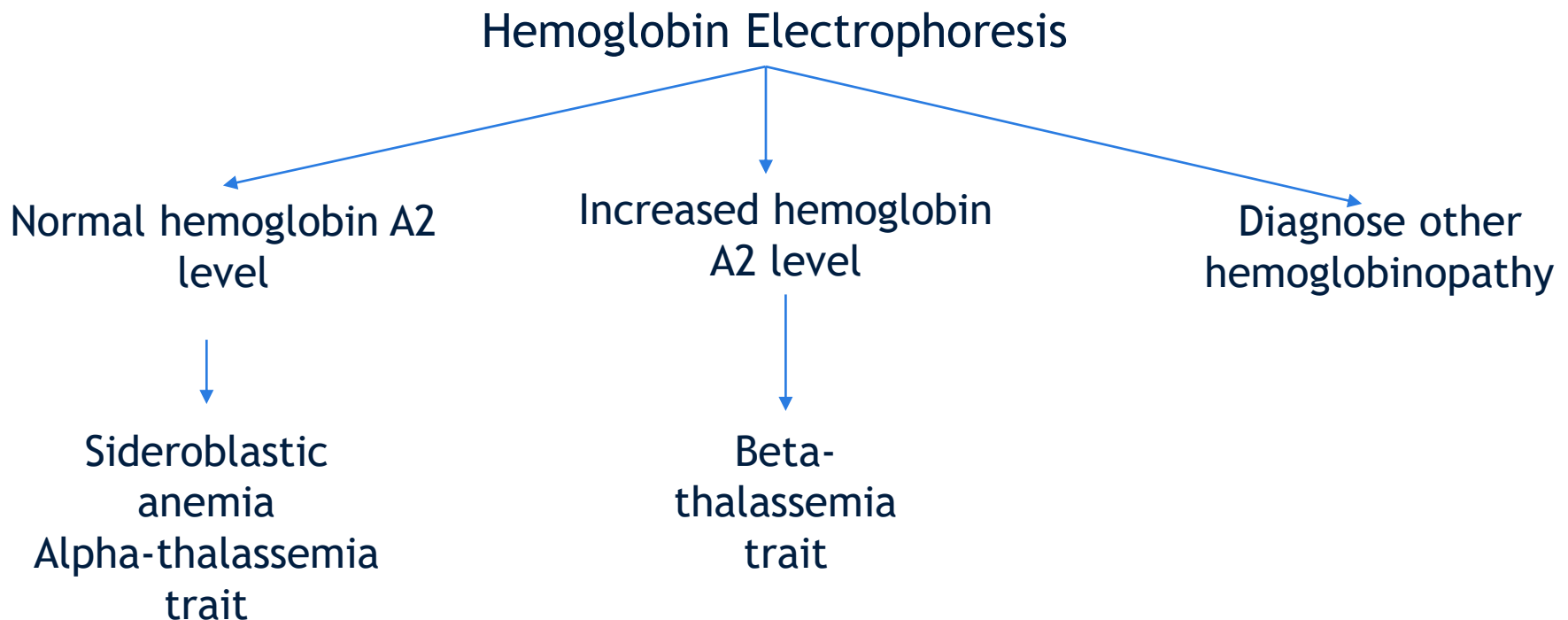




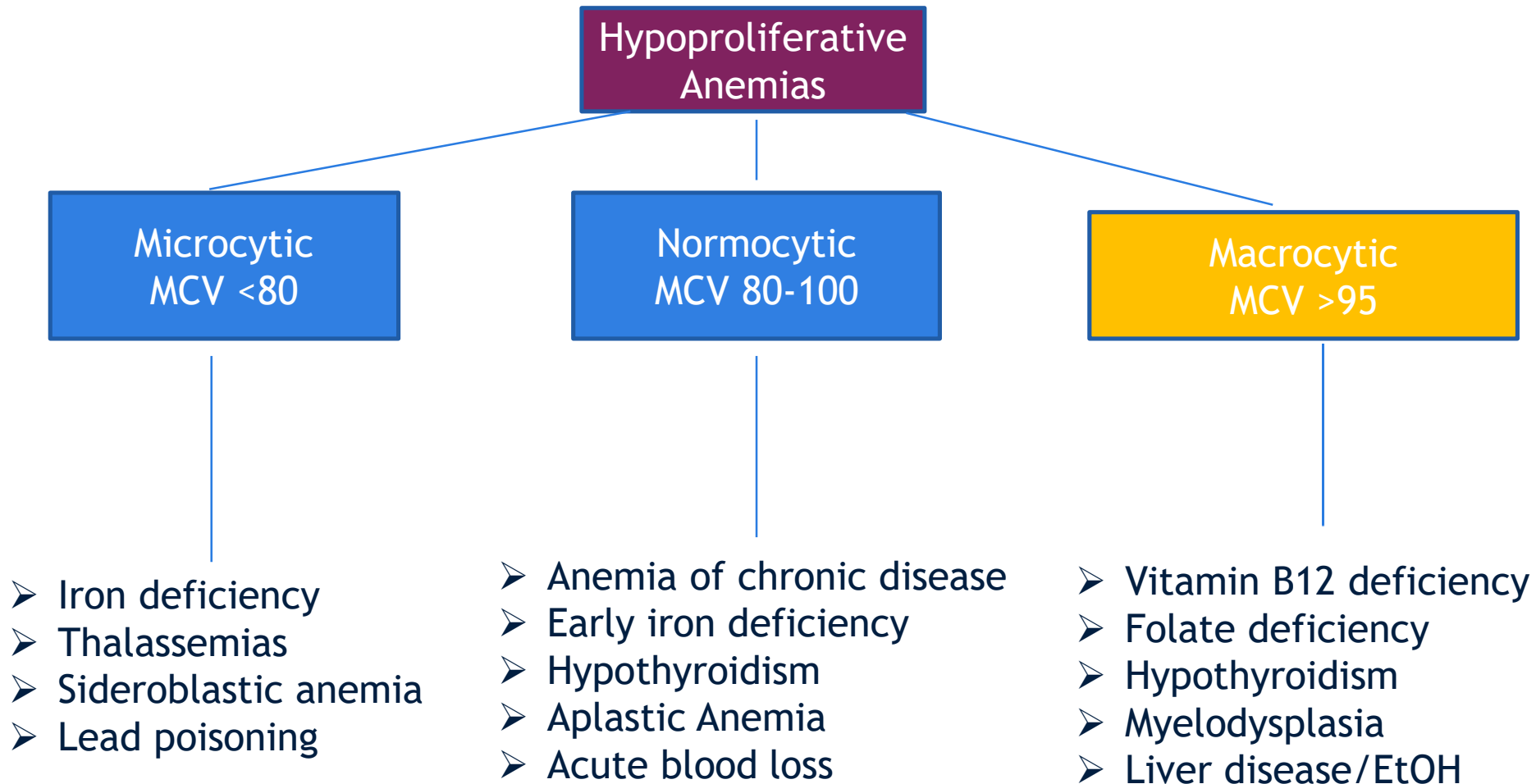


Thalassemias - low MCV

Ferritin normal to high, serum iron normal/increased, normal TIBC, transferrin saturation normal/increased



Approach to Anemia



Anemia - Macrocytic (MCV > 100)

- If MCV > 110 fl, almost always folate or cobalamin deficiency
- If MCV 100-110 fl, must look for other causes of macrocytosis

Macrocytosis (MCV > 100 fl)

- Abnormal nucleic acid metabolism of erythroid precursors
 - Drugs (cytotoxics, immunosuppressants, anticonvulsants)
 - B₁₂/folate deficiency
- Abnormal RBC maturation
 - Myelodysplastic syndrome
 - Leukemias
 - Marrow infiltration (malignancy, fibrosis)
- Alcohol
- Liver disease
- Hypothyroidism
- Less common
 - Aplasia
- ‘Artifactual’
 - Cold agglutinins
 - Hyperglycemia
 - Hyperleukocytosis

Macrocytosis of Alcoholism

- 25-96% of alcoholics
- MCV elevation usually slight (100-110 fl)
- Minimal or no anemia
- Macrocytes round (not oval)
- Neutrophil hypersegmentation absent
- Folate stores normal

Megaloblastic Hematopoiesis

- Marrow failure due to disrupted DNA synthesis & ineffective hematopoiesis
- Neutrophil hypersegmentation & macroovalocytes in blood
- Anemia (and often leukopenia & thrombocytopenia)
- Almost always due to cobalamin or folate deficiency

Evolving Cobalamin Deficiency

- Usual sequence:
 - Serum Cobalamin falls
 - Serum methylmalonic acid & homocysteine rise
 - MCV rises within the normal range, with hypersegmentation of neutrophils
 - MCV rises above normal
 - Anemia and/or neuropathy
 - Symptoms

Table 2. Clinical Manifestations of Vitamin B₁₂ Deficiency

Cutaneous

Hyperpigmentation

Jaundice

Vitiligo

Gastrointestinal

Glossitis

Hematologic

Anemia (macrocytic, megaloblastic)

Leukopenia

Pancytopenia

Thrombocytopenia

Thrombocytosis

Neuropsychiatric

Areflexia

Cognitive impairment (including dementia-like symptoms and acute psychosis)

Gait abnormalities

Irritability

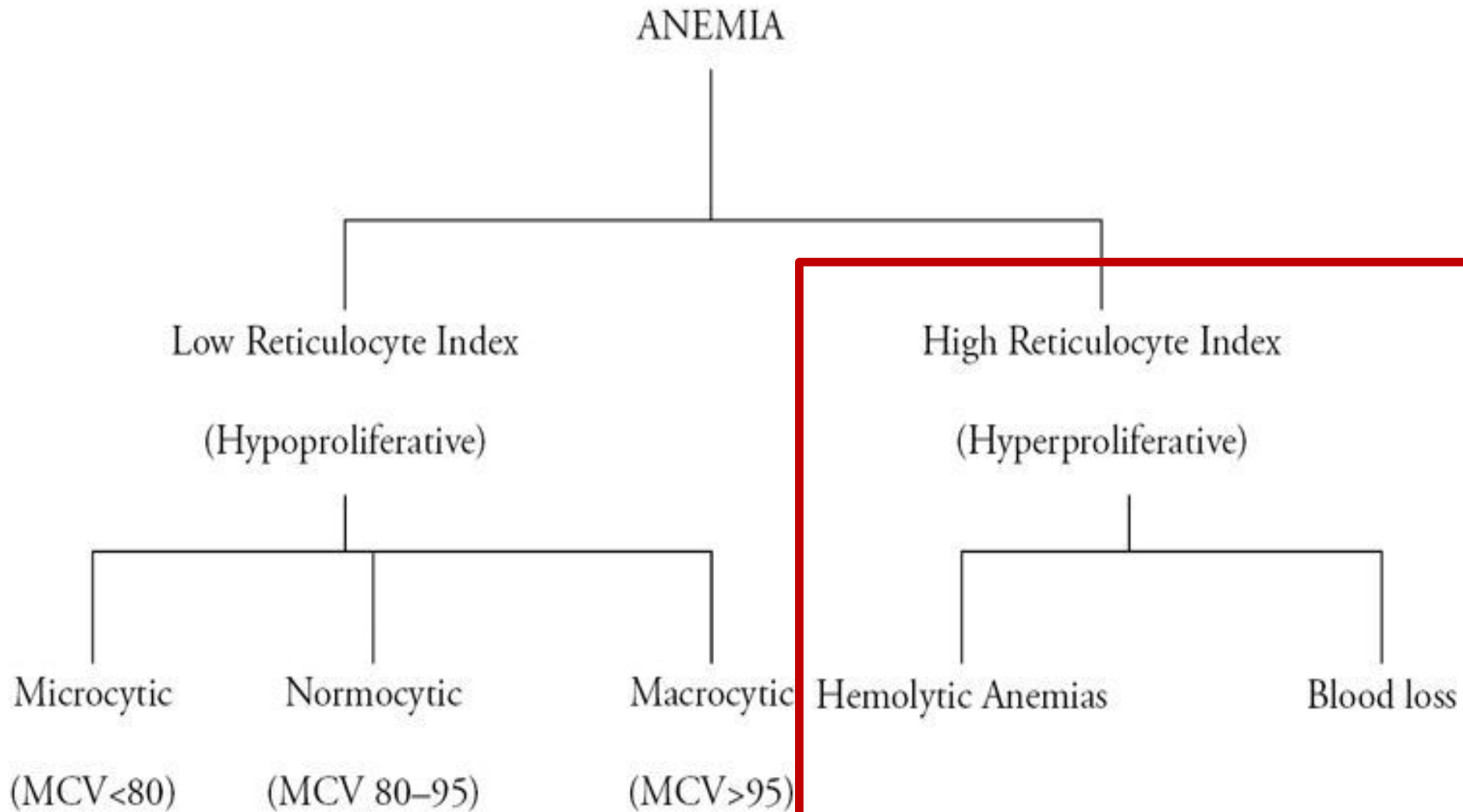
Loss of proprioception and vibratory sense

Olfactory impairment

Peripheral neuropathy







Hemolytic Anemia

- High reticulocyte count - hyperproliferative
- Anemia of increased destruction
 - Normocytic, normochromic anemia
 - Shortened RBC survival
 - Reticulocytosis - Response to increased RBC destruction

Tests Used to Diagnose Hemolysis

- Reticulocyte count (combined with serial Hb)
- Haptoglobin
- Unconjugated bilirubin
- Serum LDH

- UA

TABLE 3**Initial Laboratory Tests for Hemolysis**

Test	Finding in hemolysis	Cause
Haptoglobin	Decreased	Binds free hemoglobin
Lactate dehydrogenase	Elevated	Released from lysis of red blood cells
Peripheral blood smear	Abnormal red blood cells	Based on cause of anemia
Reticulocyte count	Increased	Marrow response to anemia
Unconjugated bilirubin	Increased	Increased hemoglobin breakdown
Urinalysis	Urobilinogen, positive for blood	Free hemoglobin and its metabolites

Blood morphology in hemolytic anemias

Sickle cells

Sickle cell anemia

Hb crystals

Hb CC disease

Fragments, helmets

Microangiopathic hemolysis

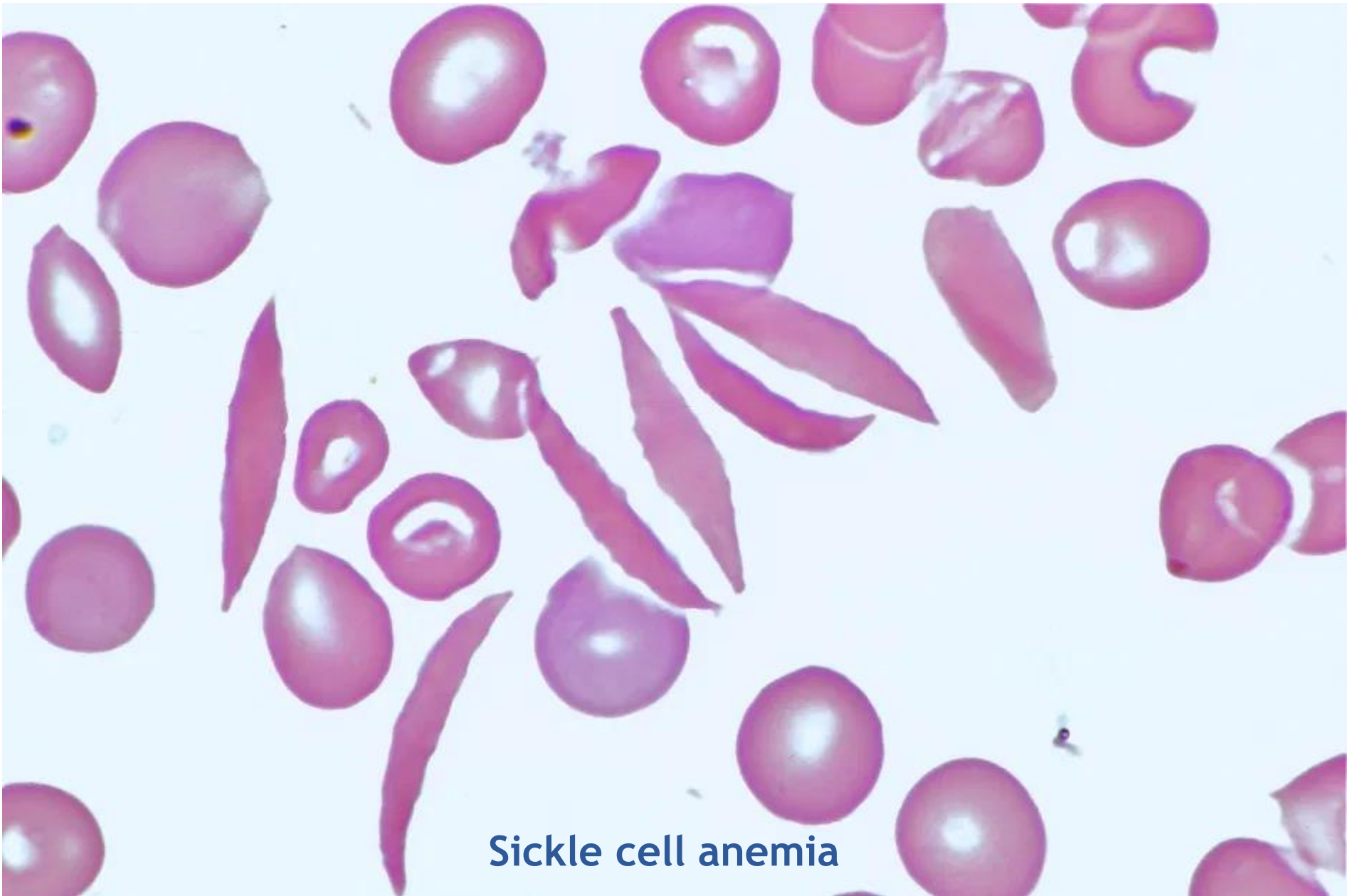
Microspherocytes

Hereditary spherocytosis
Immune hemolysis

Elliptocytes

Hereditary elliptocytosis

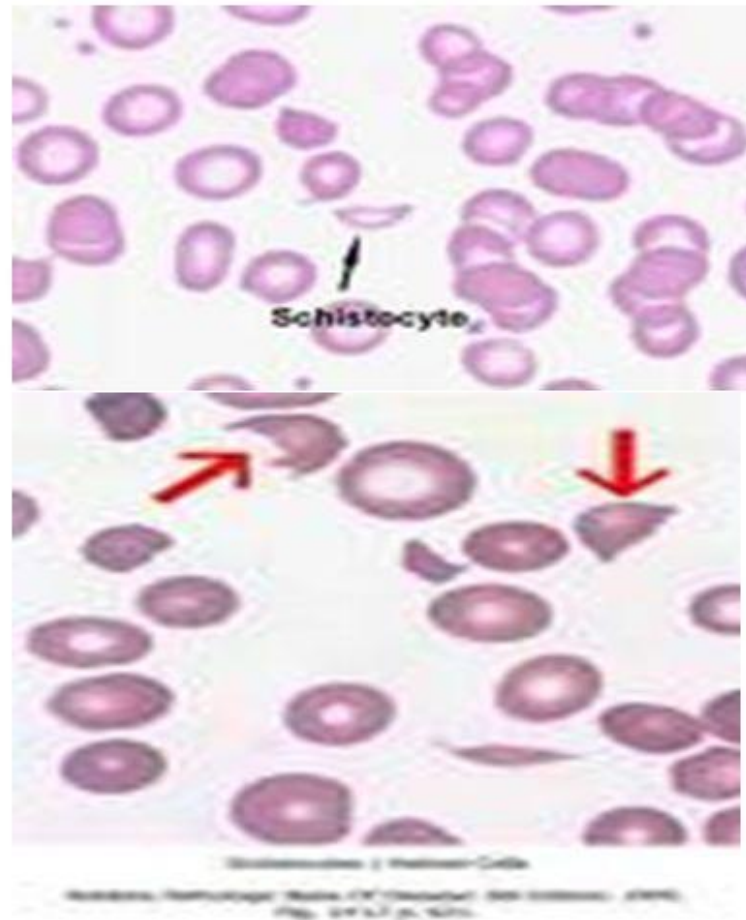
Note: hemolysis is not excluded by a normal blood smear



Sickle cell anemia

MICROANGIOPATHIC HEMOLYTIC ANEMIA

- Fragmented RBC's
- Schistocytes (black arrows)
- Helmet cells (red arrows)
- Causes:
 - TTP
 - HUS
 - DIC
 - Prosthetic Heart Valve
 - HELLP syndrome in pregnancy



Tests to define the cause of hemolysis

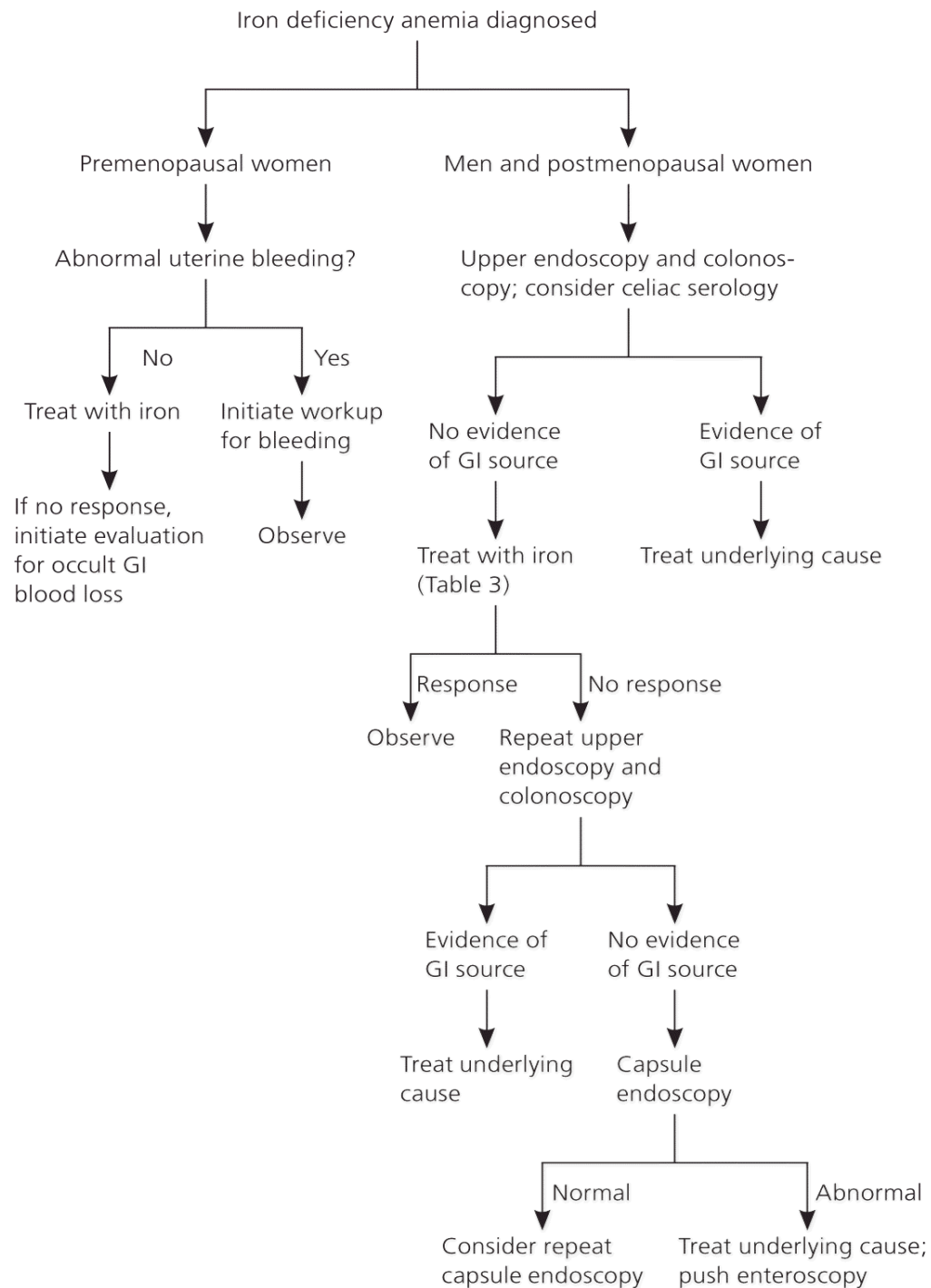
- Hemoglobin electrophoresis
- Hemoglobin A₂ (beta-thalassemia trait)
- RBC enzymes (G6PD)
- Direct & indirect antiglobulin tests (immune)
- Cold agglutinins
- Osmotic fragility (spherocytosis)
- Acid hemolysis test (PNH)
- Clotting profile (DIC)

Management of Anemias

Management

- Anemia of Chronic Disease
 - Treatment of underlying disorder
 - Iron supplementation reserved for those who have concomitant iron deficiency
 - RBC transfusions reserved for life-threatening symptomatic anemia

Management of Iron Deficiency Anemia



Management - Iron Deficiency Anemia

- PO Iron
 - Treatment dose typically 120 – 150 mg of elemental iron per day
 - 325 mg ferrous sulfate tablet (65 mg of elemental iron)
 - GI effects: epigastric discomfort, nausea, diarrhea, and constipation
 - Ferrous fumarate (43%) > ferrous gluconate (31%) > ferrous sulfate (30%)
 - Strategies to improve tolerability
 - Change interval to every other day
 - Take with food or milk although can reduce absorption
 - Switch to formulation with lower amount of elemental iron
 - Switch from tablet to a liquid

Management - Iron Deficiency Anemia

- IV iron
 - Most common indications:
 - GI effects
 - Worsening symptoms of inflammatory bowel disease
 - Unresolved bleeding
 - Renal failure–induced anemia treated with erythropoietin
 - Insufficient absorption in patients with celiac disease
 - Dose depends on whether the goal is to treat anemia or to fully replace iron stores

Table 3. Iron Therapy: Formulations and Dosing

<i>Form</i>	<i>Formulation</i>	<i>Elemental iron</i>	<i>Adult dosage</i>
Intravenous			
Sodium ferric gluconate (Ferrlecit)	Solution for injection	12.5 mg per mL	Based on weight and amount of desired change in hemoglobin*
Iron dextran	Solution for injection	50 mg per mL	
Iron sucrose	Solution for injection	20 mg per mL	
Ferumoxytol	Solution for injection	30 mg per mL	
Oral			
Ferrous fumarate	324-mg tablet	106 mg	One tablet twice per day
Ferrous gluconate	300-mg tablet	38 mg	One to three tablets two or three times per day
Ferrous sulfate	325-mg tablet	65 mg	One tablet three times per day

*—Elemental iron (mg) = $50 \times (0.442 [\text{desired hemoglobin level in g per L} - \text{observed hemoglobin level in g per L}] \times \text{lean body weight} + 0.26 \times \text{lean body weight})$.²

Information from references 2 and 16.

Short et al. AFP
2013 Jan 15;87(2):98-104

Management - Iron Deficiency Anemia

- Hgb rises slowly, usually ~ 1-2 weeks after treatment
 - Will increase approximately 2 g/dL over the next three weeks
- Hgb deficit should be halved by approximately one month
- Hgb level should return to normal by 6-8 weeks

Management - Vitamin B12 deficiency

- Parenteral therapy or oral therapy (1000 mcg)
- Replacement usually daily for first week, weekly for first month, then monthly for life
- If vitamin B12 deficiency coexists with folate deficiency, vitamin B12 should be replaced first to prevent subacute combined degeneration of the spinal cord

Management - Folate Deficiency

- Treat with folic acid PO 5 mg daily x 4 months
- Continued treatment depends on underlying disease
- Lifelong therapy may be needed in chronic inherited anemias, myelofibrosis, renal dialysis

Summary

- Anemia is a symptom of an underlying disease
- Looking at the CBC (MCV, MCH, and RDW) and reticulocyte count provides clues to diagnosis
 - If reticulocyte count elevated, look for causes of increased destruction or bleeding
 - If retic count normal or decreased, look for causes of marrow failure
- Correction of the underlying disorder often results in resolution of the anemia

Questions?



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