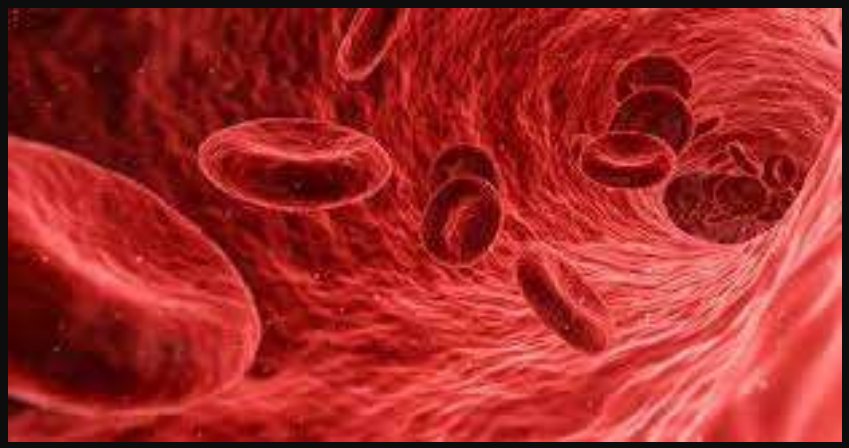
A diagnostic approach to anemia made simple



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Outline

- Case Presentation
- Defining anemia
- Eliciting a helpful patient history
- Conceptualizing anemia subtypes with peripheral smear review
- Special populations (pediatrics, pregnancy, bariatric surgery)
- Management of nutritional anemias
- Back to case presentation

Case Presentation

Chief complaint: fatigue, SOB, cold intolerance, dry skin, constipation

Past Medical History: Menorrhagia, Crohn's disease, GERD

Past Surgical History: None

Medications: Pantoprazole 20 mg PO daily, Fish oil, Tylenol PRN

Family History:
Mother (61 yo): Crohn's disease; **Father (63 yo)**: CAD, HLD; **Sister (33 yo)**: uterine fibroids, fibromyalgia; **Brother (34 yo):** HLD

GYN History:
No prior pregnancies, abortions or pregnancy losses
Prolonged menstrual cycles (9 days) which are heavy (8 overnight pads for the first 4 days) and painful

Social History:
No cigarette smoking, EthOH use or illicit drug use
Enrolled in nursing school full-time
Married without children

A.J.: 29 year-old woman

Detailed history & physical exam

History:
- Denies chest pain, DOE, presyncope or lightheadedness
- No lead exposures, drenching night sweats, chills, fevers or lymphadenopathy
-No recent infections or travel
- She was told she was anemic as a teenager, but doesn't know why; no prior blood transfusions

Physical Examination:
Temp: 37.9°C, **HR**: 94 **RR**: 18 **O2 sat**: 96% on room air
General appearance: tired, in in no acute distress
HEENT: conjunctival pallor noted
Cardiovascular: RRR, no murmurs, rubs or gallops
Respiratory: No wheezes, rales or rhonchi
Extremities: no swelling noted
Skin: Pallor of nailbeds noted, minor eczema on upper extremities
Neurologic: Gait is normal without ataxia

A.J.: 29 year-old woman

Next steps

What additional questions do you have for this patient?

What is your differential diagnosis?

What would you like to do next for her diagnostic work-up?

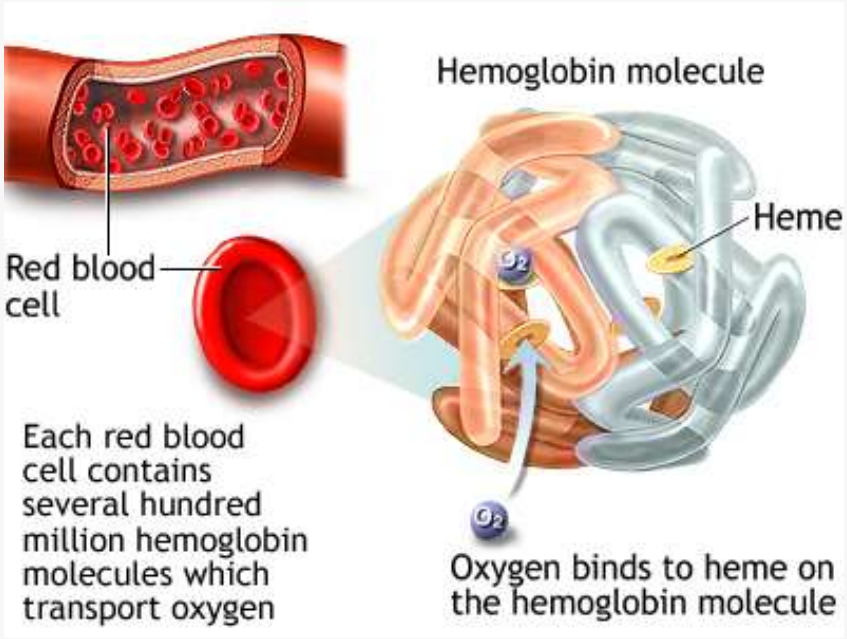
A.J.: 29 year-old woman

Definition of anemia

- Anemia: a reduction in ≥1 of the major RBC measurements obtained as a part of the CBC:
  - Hb, Hct, or RBC count

- Reference range depends on age and sex of the patient, as well as other factors such as altitude, prevalence of smoking in the normative population, & others

- General cut offs for Hb and Hct (should not superceed clinical judgement)
  - **Females**: Hb <11.5 g/dL or Hct <35%
  - **Males**: Hb <13.5 g/dL or Hct <40%



What is hemoglobin?

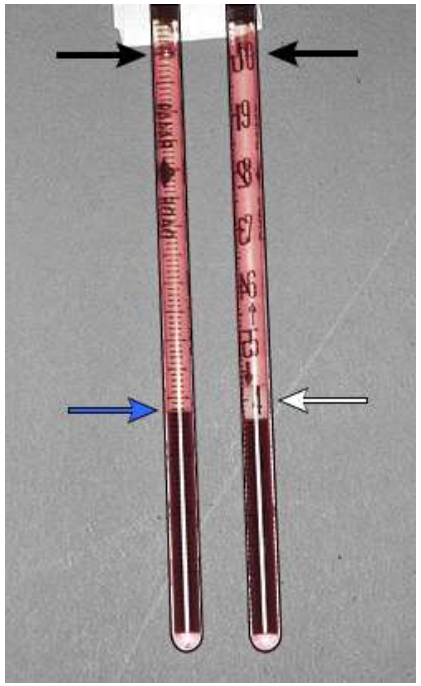
- 64.4 kd heterotetramer consisting of two pairs of globin polypeptide chains
- Consists of 1 pair of α chains and 1 pair of β chains, each surrounding a heme moiety
- Oxygenation and deoxygenation of hemoglobin occurs at the heme iron

Hemoglobin versus hematocrit

- **Hemoglobin:**
  - Reported as the [hemoglobin] in whole blood
  - Directly measured by an electronic counter (unlike Hct)
  - Often preferred by hematologists to measure anemia

- **Hematocrit (Hct; packed cell volume (PCV)):**
  - Percentage of blood volume occupied by RBCs
  - Calculated from the RBC count: HCT = ([RBC x MCV]/10)

- **Red cell count:**
  - # of RBCs contained in a specified volume of whole blood
  - Increased by microcytosis (and less reliable than Hb)



Hct can be directly measured following centrifugation

Important aspects of the patient history

History	Suspected diagnosis
Melena, hematochezia, menorrhagia, blood loss	Iron deficiency anemia
Poor PO intake, impaired GI absorption (ex- Crohn's disease), h/o gastric bypass surgery	Nutritional anemias: iron, vitamin B12, folic acid, copper, vitamin C
Prescribed and over the counter medications	Medication-induced anemia (ex- due to myelosuppression, thrombotic microangiopathy, hemolysis)
Jaundice, pruritis, dark-colored urine, gallstones	Hemolytic anemia (immune or non-immune, acute or chronic)
Medical co-morbidities (ex- cancer, chronic kidney disease, type II DM, etc..)	Anemia of chronic inflammation; erythropoietin deficiency from CKD
Anemia with certain food or drug exposures (fava beans, oxidant drugs)	G6PD deficiency

Important aspects of the patient history

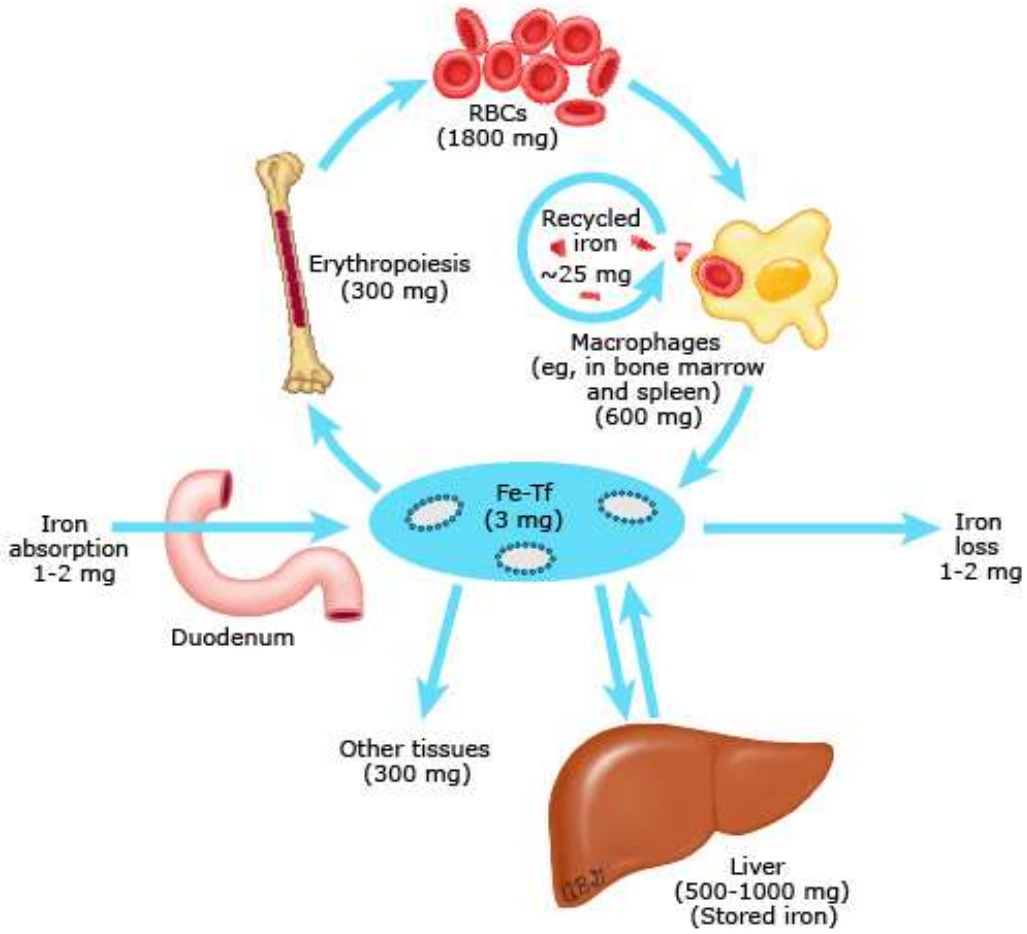
History	Suspected diagnosis
Family history of anemia and transfusion dependence	Inherited red cell disorders (ex- sickle cell disease, thalassemia)
Fevers, chills, recent travels	Extrinsic myelosuppression from infection (HIV), intraerythrocytic parasite (malaria)
Unexplained weight loss, drenching night sweats, palpable lymphadenopathy	Malignancy
Prior chemotherapy or radiation therapy	Secondary MDS or AML, bone marrow failure syndrome
Abdominal distention, jaundice, EthOH use	Cirrhosis-related anemia 2/2 to GI bleeding, spur cell hemolytic anemia
Early satiety, abdominal discomfort	Splenomegaly causing RBC sequestration

Helpful initial lab work-up by PCP

Lab	Utility
CBC with differential	Determine severity and trends of anemia
Comprehensive metabolic profile (CMP)	Screen for kidney or liver disease
Peripheral smear	Find microcytes, macrocytes, red cell structural issues (ex- bite cells, spur cells)
Reticulocyte count	Determine bone marrow response to anemia (hypo- vs hyperproliferative)
Iron studies (iron, TIBC, transferrin saturation, ferritin)	Screen for iron deficiency & anemia of chronic inflammation
Lactate dehydrogenase (LDH), total and indirect bilirubin, haptoglobin	Hemolysis (immune or non-immune); DAT and type and screen can help to distinguish

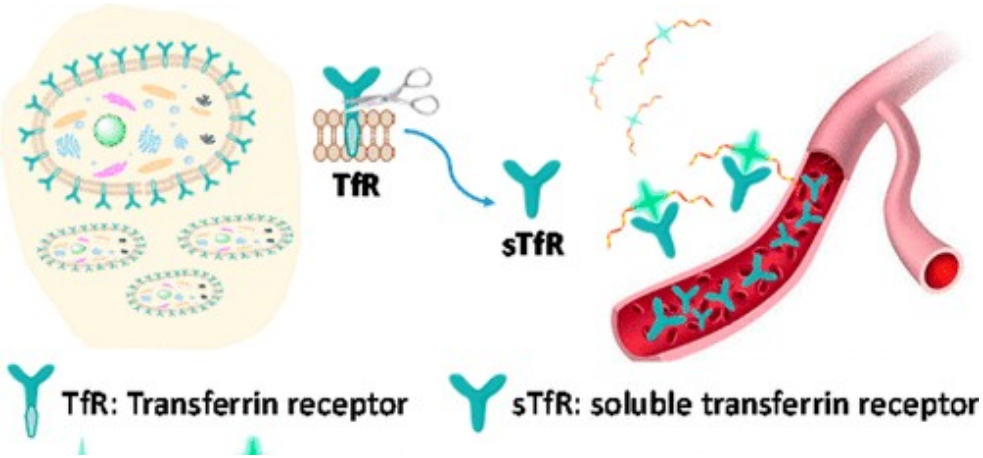
Overview of iron metabolism

- Fe circulates bound to transferrin, which receives most Fe from macrophages that phagocytize old RBCs & by enterocytes that absorb a minimal amount of dietary iron
- Most Fe is supplied to the bone marrow for RBC production
- Excess Fe is stored in the liver and macrophages as a reserve



Pearls about iron studies

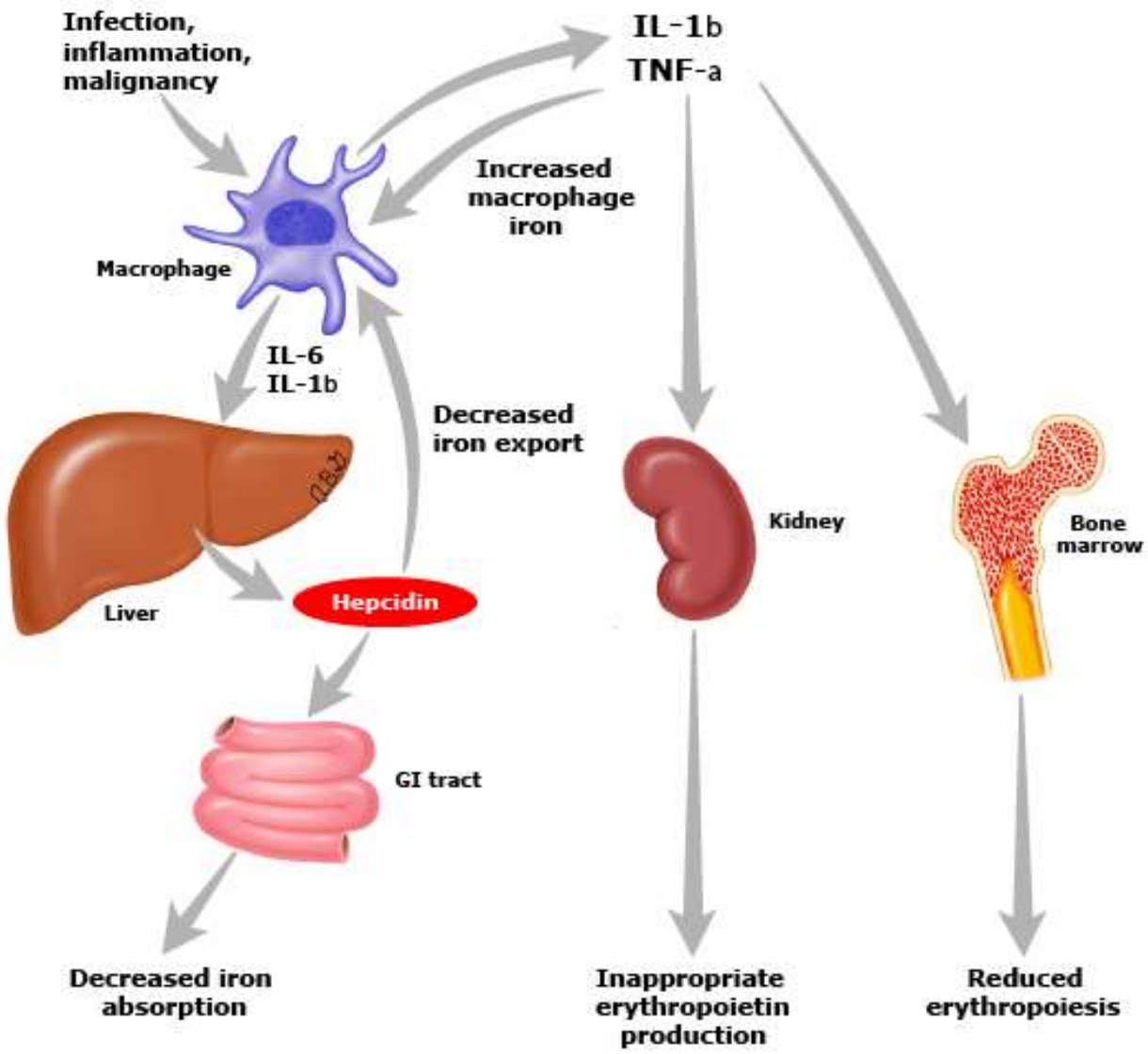
- Ferritin is an acute phase reactant and increased during times of acute inflammation or illness
- Soluble transferrin receptor is increased in iron deficiency, regardless of the presence of inflammation
- Transferrin saturation < 20% can also help to diagnose iron deficiency



Soluble transferrin receptor: circulating protein derived from cleavage of the membrane transferrin receptor on erythroid precursor cells in the bone marrow

Anemia of chronic inflammation

- Macrophage is stimulated to produce IL-6 and IL-1b, which induce the production of hepcidin by the liver
- **Hepcidin blocks ferroportin**, inhibiting iron absorption from the GI tract & decreasing release of iron from macrophages.
- IL-1b and TNF-a reduce erythropoietin production



Conditions which can cause anemia of chronic inflammation

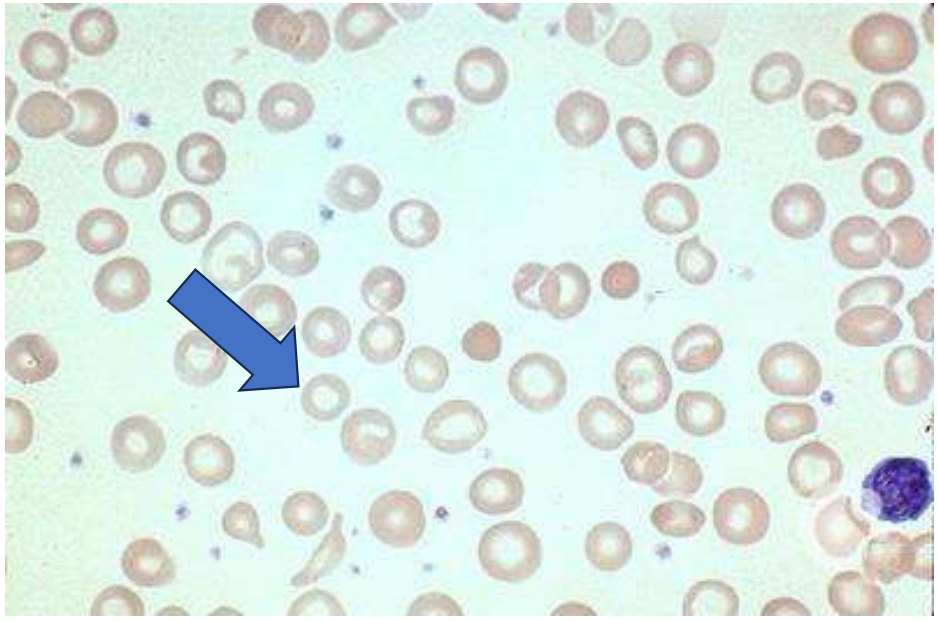
- Aging (partial effect)
- Autoimmune and autoinflammatory diseases
  - Inflammatory bowel disease
  - Rheumatoid arthritis
  - Sarcoidosis
  - SLE
  - Vasculitis
- Congestive heart failure
- COPD and pulmonary arterial hypertension
- Chronic kidney disease (advanced)
- Critical illness or trauma; infections; **obesity**
- Hematologic malignancies and other cancers

Management of anemia of chronic inflammation = treatment of the underlying cause

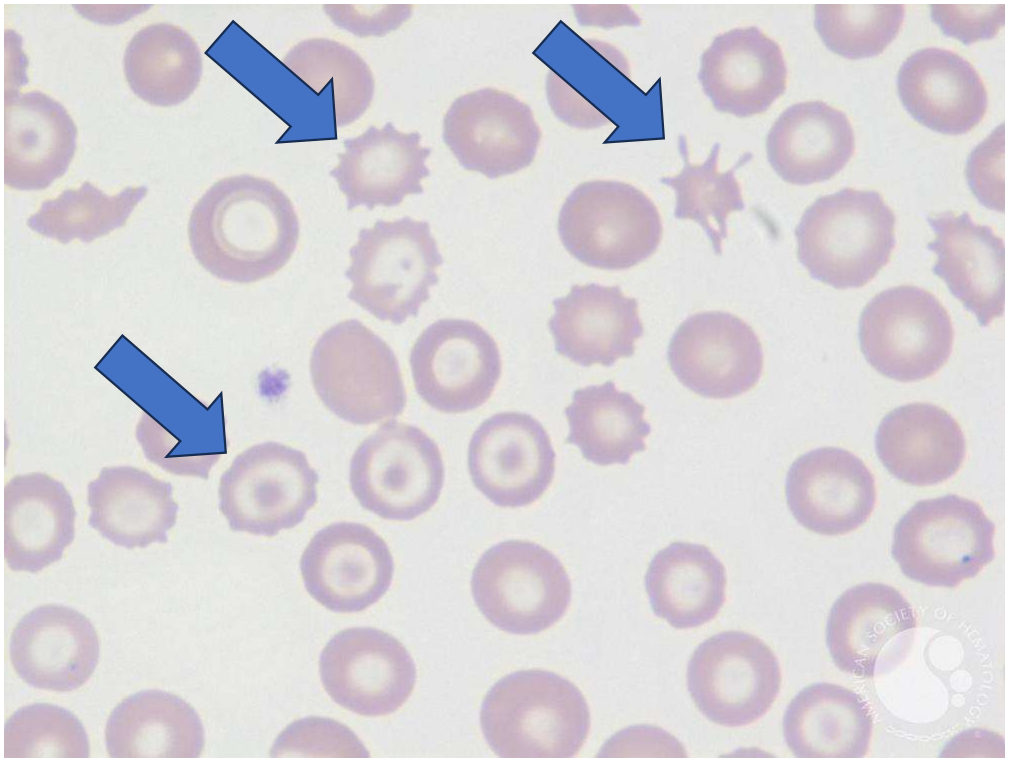
Iron supplementation is reserved for those with concurrent iron deficiency

Lab finding	Iron deficiency anemia	Anemia of chronic inflammation
Mean corpuscular volume (MCV)	Decreased	Normal to decreased
Mean corpuscular hemoglobin concentration (MCHC)	Normal to decreased	Normal to decreased
Red cell distribution width (RDW)	Increased	Normal to increased
Peripheral blood smear/RBC morphology	**Anisocytosis, hypochromia**	**Normal**
Serum iron	Decreased	Decreased
Total iron-binding capacity (TIBC); transferrin	**Increased**	**Decreased**
Transferrin saturation (TSAT)	Decreased	Normal to decreased
Serum ferritin	**Decreased**	**Normal to increased**
Soluble transferrin receptor	**Increased**	**Normal**
C-reactive protein	**Normal**	**Increased**

Iron deficiency with marked hypochromia and microcytosis



Target and spur cells in liver disease with concurrent iron deficiency anemia

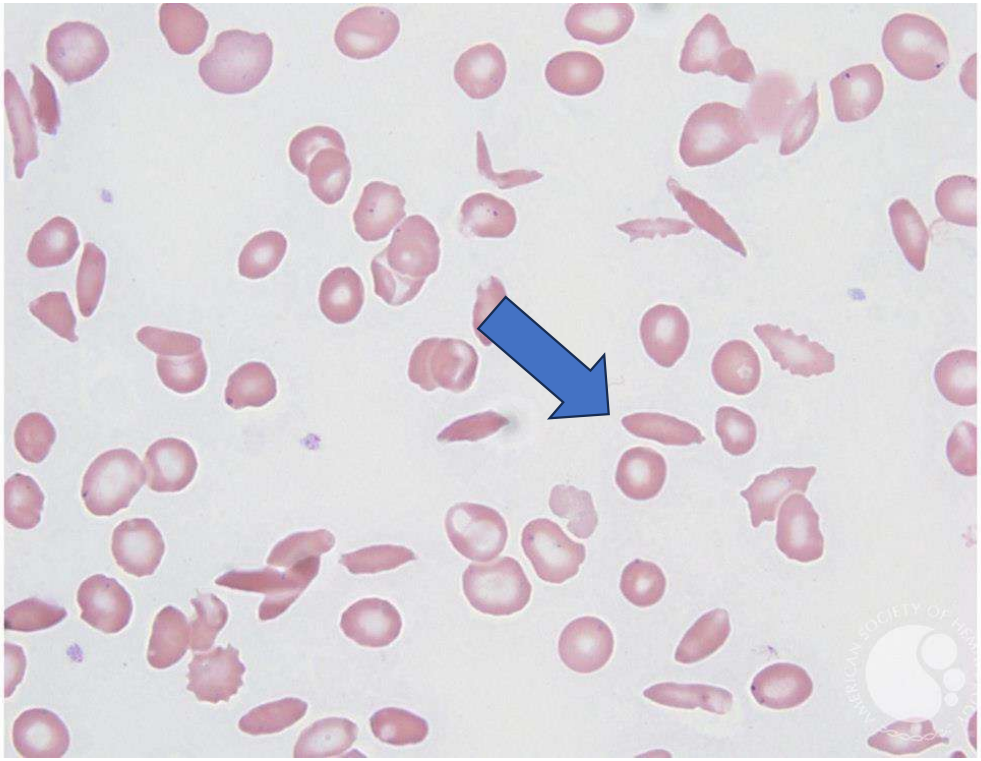


Spur red cells (liver disease) have elongated projections

Burr cells (uremia) have blunted borders

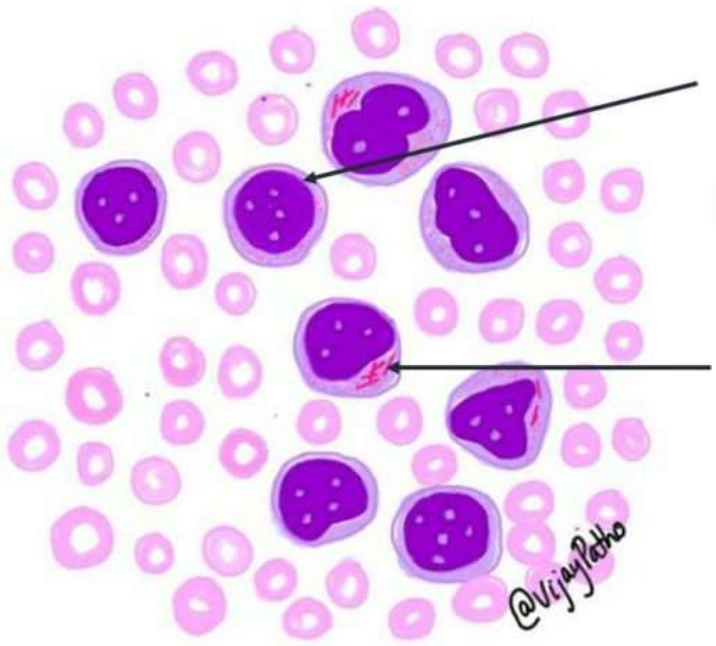
The "Burr" morphology in this case is artifactual related to slide preparation and not related to uremia

Sickle cells



Acute myelogenous leukemia with maturation

ACUTE MYELOBLASTIC LEUKEMIA

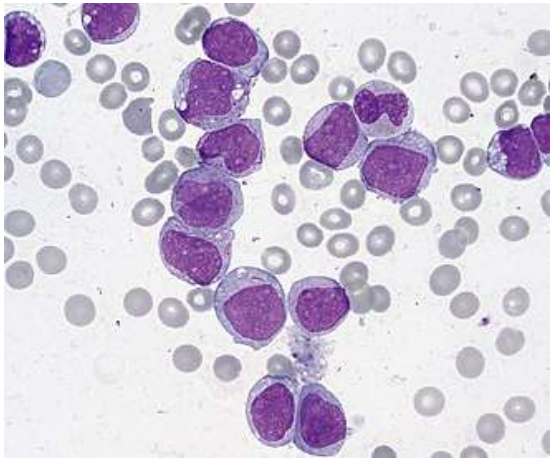


Large cell with round to oval nucleus, with fine chromatin, and 2 to 4 nucleoli and scanty cytoplasm with fine granules

MYELOBLAST

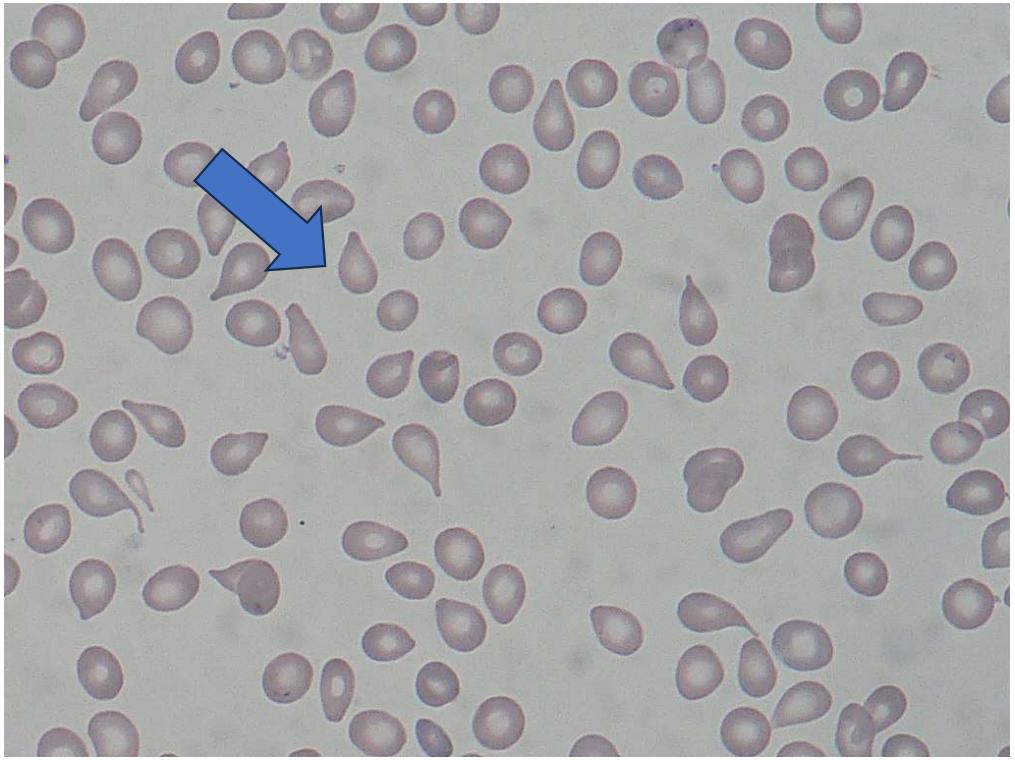
Crystalline cytoplasmic inclusions as a result of abnormal fusion of azurophilic granules

AUER RODS



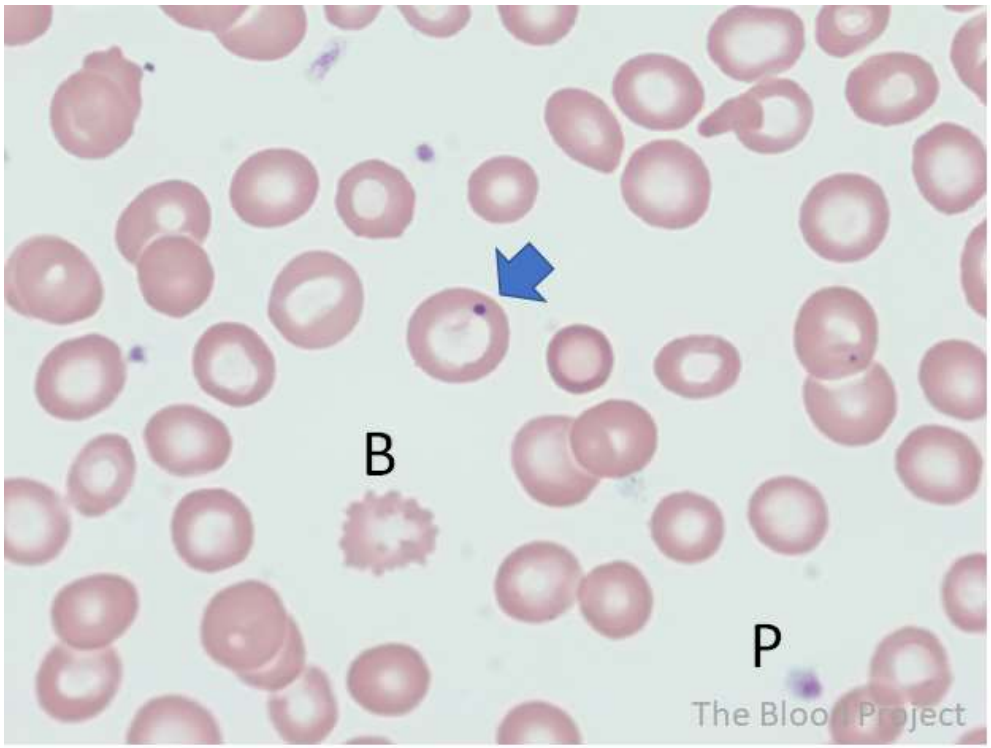
Pearl: if anemia is present with DIC, rule out infection and acute leukemia

Dacrocytes (tear drop cells)



Dacrocytes are associated with myelofibrosis, they are also theorized to be formed due to mechanically squeezing out from the bone marrow as a result of the infiltrative process

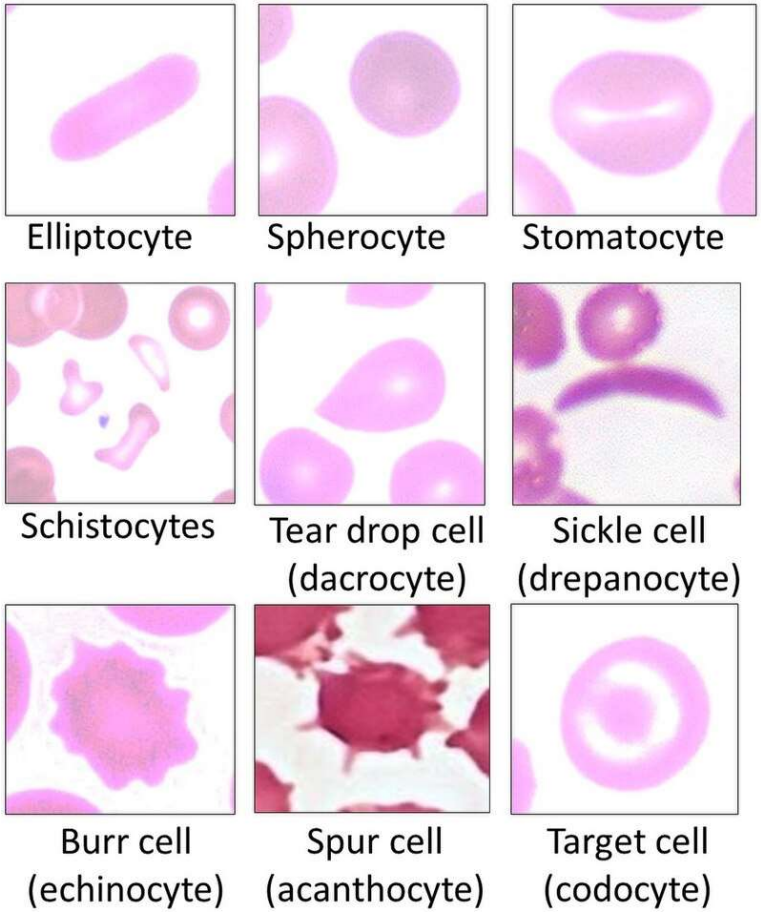
Howell Jolly body post-splenectomy



Formed when an aberrant chromosome becomes separated from the mitotic spindle and remains behind when the rest of the nucleus is extruded.

Normally, the spleen is very efficient in removing Howell-Jolly bodies from red cells

Summary of some key peripheral smear findings



High yield clues to help with anemia diagnosis

- Patient history (ex- jaundice, menorrhagia)
- Family history (ex- multiple family members needing RBC transfusions)
- **MCV, MCHC, reticulocyte count**
- Hemoglobin trends over time (months, years)
- Age (age > 60): more likely to have primary bone marrow disorder)
- Bi- or tricytopenias: more likely to have extrinsic myelosuppression from infections or meds, vs primary bone marrow disorder
- Presence of thrombocytosis may be reactive to iron deficiency or GI blood loss

Please always obtain a history of blood loss with every anemia encounter!

RBC Size/ MCV	Low or normal reticulocyte count	Increased reticulocyte count
Microcytic (MCV <80 fL)	Iron deficiency (late) Anemia of chronic disease/inflammation Sideroblastic anemias	Thalassemia
Normocytic (MCV 80 to 100 fL)	Bleeding (acute) Iron deficiency (early) Anemia of chronic disease/inflammation Bone marrow suppression (cancer, infection) Chronic renal insufficiency Hypothyroidism; hypopituitarism Excess alcohol Copper deficiency/zinc poisoning	Bleeding (with bone marrow recovery) Hemolysis Bone marrow recovery (eg, after infection, vitamin B12 or folate replacement, and/or iron replacement)
Macrocytic (MCV >100 fL)	Vitamin B12 or folate deficiency Excess alcohol; liver disease Myelodysplastic syndrome HIV infection Medications that interfere with nuclear maturation (hydroxyurea, methotrexate, some chemotherapy) Hypothyroidism	Hemolysis Bone marrow recovery (eg, after infection, vitamin B12 or folate replacement, and/or iron replacement)

Hemolytic anemias

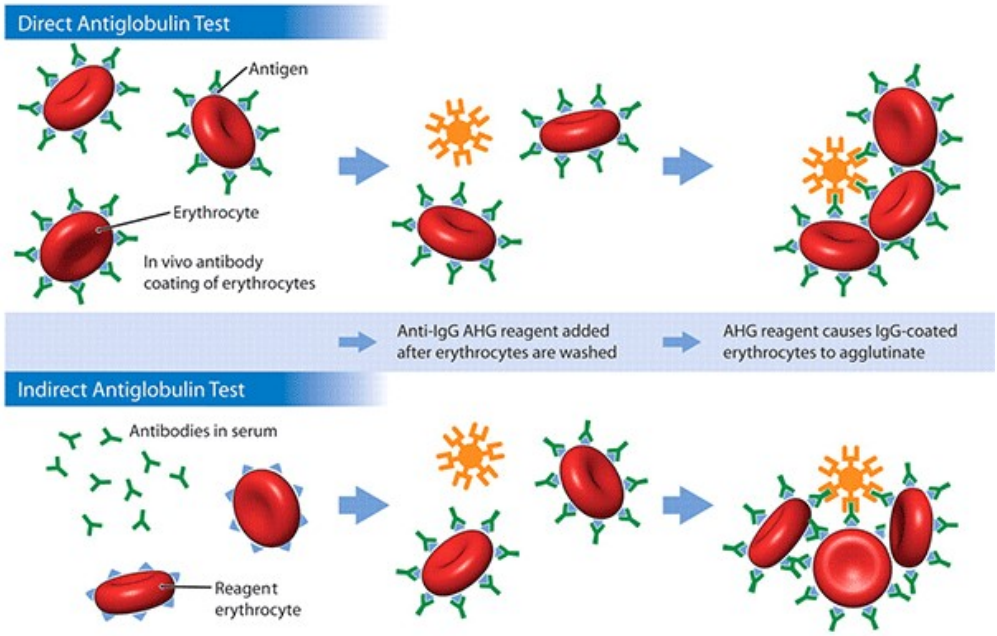
- Clinical history and physical examination may be notable for jaundice, dark-colored urine, scleral icterus, pruritis, fatigue, SOB, DOE
- May be immune or non-immune mediated; acquired or inherited
  - Chronicity of the anemia & patient symptoms may help distinguish this
- Carefully review the medication list for drug-induced etiologies
- At minimum, work-up should include CBC with differential, reticulocyte count, peripheral smear review, total and indirect bilirubin, LDH, haptoglobin, DAT (direct antiglobulin test)
- Treatment is aimed at the underlying etiology

Direct versus indirect antiglobulin tests (DAT vs. IAT)

Direct Coomb's Test

vs

Indirect Coomb's Test

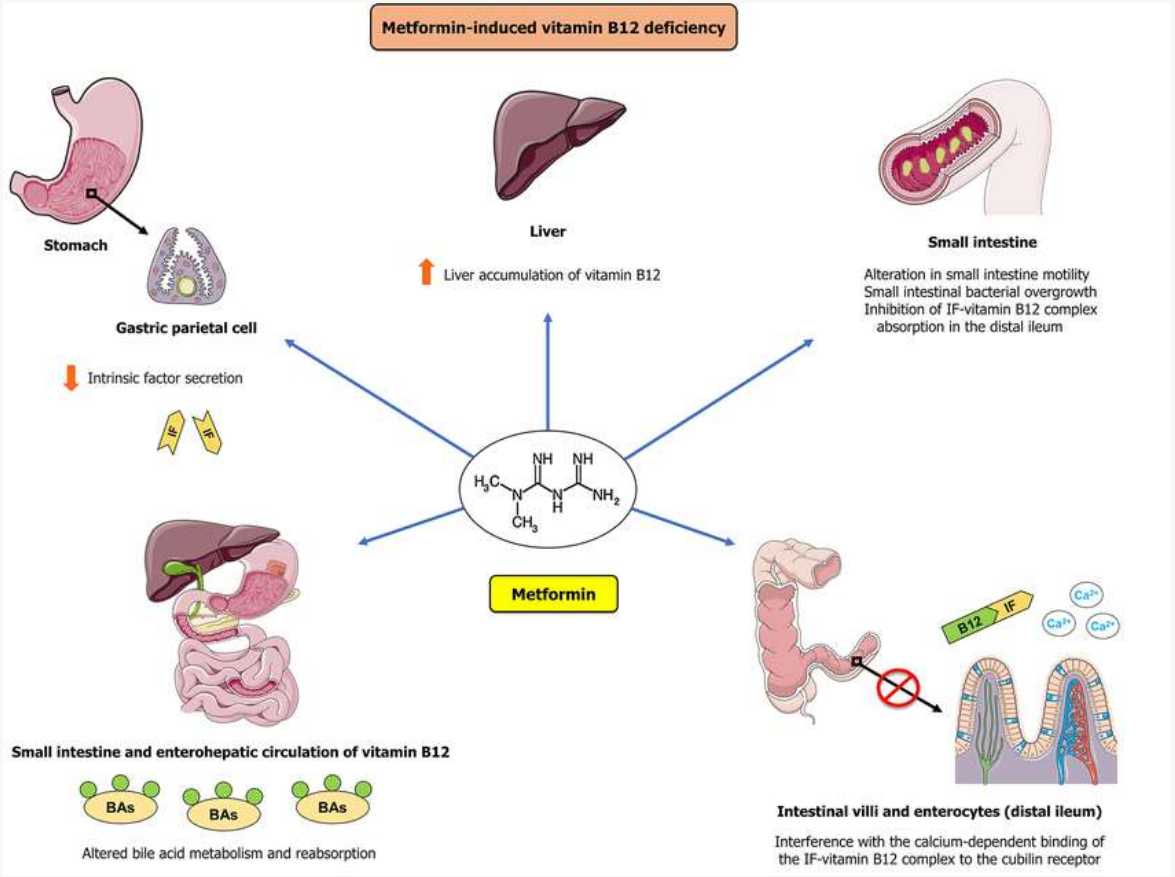


Helpful hint: DAT must be correlated with hemolysis labs, as 10% to 15% of hospitalized patients have a positive DAT without hemolysis

Non-immune hemolytic anemias	Immune-mediated hemolytic anemias
Hereditary Enzyme deficiencies (deficiencies of G6PD) Hemoglobinopathies (sickle cell disease, thalassemia) Membrane disorders (hereditary spherocytosis)	Warm autoimmune hemolytic anemia Drug-induced hemolytic anemia Hemolytic transfusion reactions (ABO incompatibility, alloantibodies) Paroxysmal cold hemoglobinuria Paroxysmal nocturnal hemoglobinuria
Acquired Liver disease Hypersplenism Infections (malaria, babesiosis) Oxidant agents (dapsone, nitrites) Toxins (lead, copper, snake+spider bites) Microangiopathic hemolytic anemia (TTP, HUS, drug-induced TMA, aortic stenosis, prosthetic valve leak)	Cold agglutinin disease Intravenous immune globulin (IVIG) or anti-RhD immune globulin

Medications that have been associated with warm autoimmune hemolytic anemia

- Antibiotics
  - Amoxicillin with and without clavulanic acid, ceftriaxone, cefixime, cefpodoxime, sulfamethoxazole plus trimethoprim, ciprofloxacin, norfloxacin, cloxacillin
- Furosemide
- Amphotericin B, acyclovir, fluconazole
- Azathioprine
- Ibuprofen, acetaminophen, diclofenac
- Insulin



Metformin can cause vitamin B12 deficiency anemia

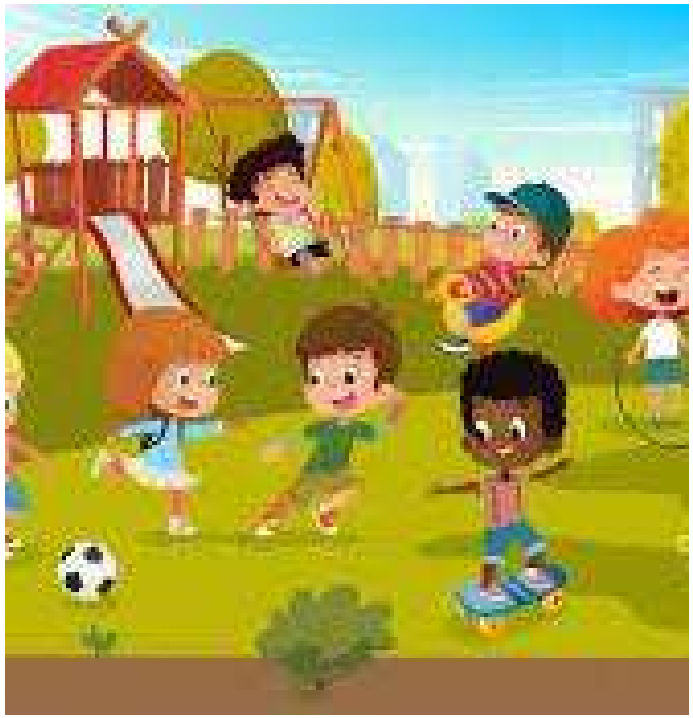
- Interference with Ca-dependent binding of intrinsic factor-vitamin B12 cmplex to receptor on enterocytes
- Altered bile acid metabolism and reabsorption
- Reduced intrinsic factor secretion by gastric parietal cells
- Increased accumulation of vitamin B12 in the liver

When to refer to a hematologist

Hematologic emergencies	Diagnostic uncertainties
Severe pancytopenia	Anemia with normal or inconclusive lab testing
Blasts or immature myeloid or lymphoid forms	Pancytopenia or bicytopenia (anemia with leukopenia or anemia with thrombocytopenia) in an older individual with normal vitamin B12, folate, and copper levels
Pancytopenia with hemolysis, thrombosis or bleeding	
Microangiopathic hemolytic anemia with schistocytes on peripheral smear	

Special populations to consider

- **Pediatrics**
- **Bariatric surgery**
- **Pregnancy**
- Coronary artery disease
- Elderly
- Perioperative, trauma

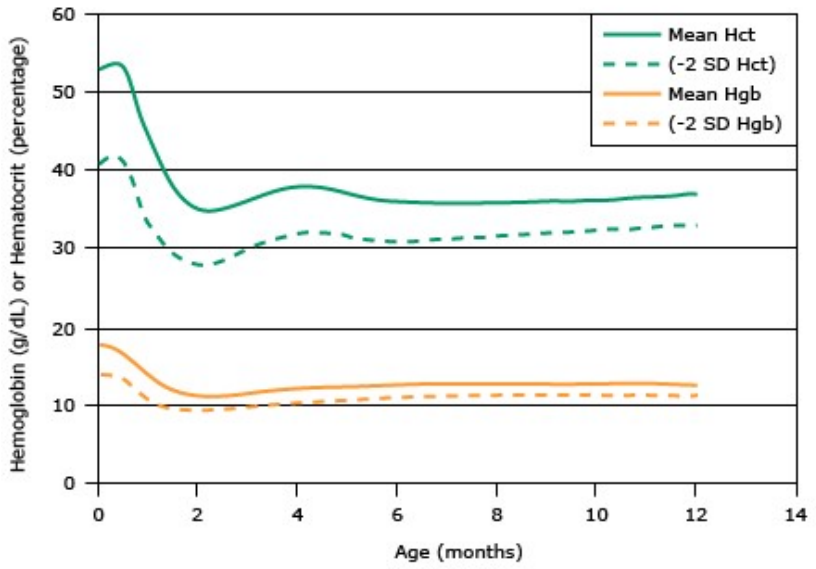


Anemia considerations in children

The threshold for defining anemia is a Hb or Hct that is ≤2.5th percentile for age and sex

- **6 mo - < 2 yrs**: Hb 11.0 – 13.5 g/dL
- **2 – 6 yrs**: Hb 11.0 – 13.7 g/dL
- **6-12 yrs**: Hb 11.2 – 14.5 g/dL
- **12-18 yrs**: Hb 11.4 – 14.7 g/dL (female); Hb 12.4 – 16.4 g/dL (male)

Hb levels are high (>14 g/dL) at birth and then rapidly decline, reaching a nadir of ~10 to 11 g/dL at 6-9 weeks of age, which is called "physiologic anemia of infancy"



Normal values of Hb and Hct in the first year of life

Common causes of anemia vary by age

Neonates and young infants

- alloimmune hemolytic disease due to maternal antibodies
- infection (ex- CMV, HSV, rubella, toxoplasmosis, adenovirus, etc.)
- hereditary disorders (ex- hereditary spherocytosis, pyruvate kinase deficiency, sickle cell disease, thalassemia, etc.)

In older children, acquired causes of anemia are more likely, particularly iron deficiency anemia (dietary or due to blood loss)

Anemia in pregnancy

(WHO) defines anemia by trimester:

- Hb <11 g/dL in the 1st trimester
- Hb <10.5 g/dL in the 2nd trimester
- Hb <10.5 to 11 g/dL in the 3rd trimester
- Hb <10 g/dL postpartum

Physiologic anemia of pregnancy (due to expansion of maternal plasma volume) and iron deficiency are the two most common causes of anemia in pregnancy

Screening for anemia should occur at minimum at the first prenatal visit and again at 24-28 weeks

Anemia in pregnancy

Oral iron typically used in first trimester (60 mg elemental iron every other day), as safety data for IV iron are lacking

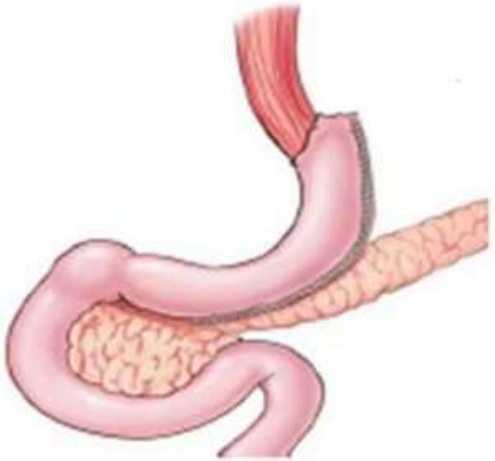
Iron deficiency has been reported in up to 50% of pregnant women

IV or oral iron can be used in the 2nd and 3rd trimester (IV iron sucrose (Venofer) has the most safety data in pregnancy

- Recommend giving IV Venofer in doses of 300 mg or 400 mg until 1,000 mg IV iron is given

Anemia after bariatric surgery

- Micronutrient deficiencies are a common 2/2 to alterations in the digestive anatomy from the operative procedures bypassing portions of the stomach, duodenum, and/or proximal jejunum
  - Risk is influenced by the patient's diet & eating habits
- Nutrient assessment should occur every 3-6 months for the first year after surgery, and then at least annually
- Iron and vitamin B12 deficiency are the most common causes of nutritional anemia
  - Oral iron poorly absorbed, need to give IV iron
- Copper, folic acid and vitamin C deficiency anemia are less common



Treatment of nutritional anemias

Nutritional deficiency causing anemia	Repletion
Iron	Slow release oral iron with vitamin C to maximize absorption (daily or every other day) IV iron (1,000 mg total): may need to be split into several doses depending on formulation.
Copper	2 mg elemental copper daily
Vitamin C	Ascorbic acid 300 mg PO daily
Vitamin B12 (cyanocobalamin)	**Intramuscular:** 1,000 mcg 1 to 3 times/week or once daily for 1 week, then 1,000 mcg once weekly for 4 to 8 weeks Oral, sublingual: 1,000 to 2,000 mcg once daily
Folic acid	Folic acid 1 mg PO daily

Consider IV iron for patients with prior gastric bypass surgery, poor tolerance of PO iron, or those with very symptomatic iron deficiency anemia

Consider slow release oral iron formulation (OTC) with vitamin C

Back to our patient….

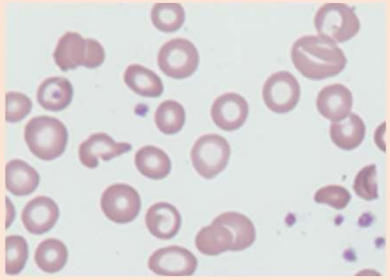
Labs are notable for:

8.4 (L)	
6.2	480 (H)
25.2 (L)	

MCV: 76 (L)
MCH: 24 (L)

Ferritin: 5 (L)
Transferrin saturation: 10% (L)
TIBC: 500 (H)
Iron: 29 (L)

TSH: 5.9



Hypochromic, microcytic RBCs

A.J.: 29 year-old woman

Back to our patient….

Patient opts to seek treatment with IV iron (1,000 mg IV Dextran) due to severe symptoms

Levothyroxine initiated for hypothyroidism, which can exacerbate anemia

Uterine fibroids identified on transvaginal ultrasound, patient referred to GYN for management

Labs 3 months later show resolution of iron deficiency, anemia and reactive thrombocytosis

A.J.: 29 year-old woman

Summary of key points

- For anemia work-ups, **always obtain a history of blood loss** (melena, hematochezia, menorrhagia)
- Make sure patient is up to date with age-appropriate cancer screening
- At minimum, would begin work-up with:
  - CBC with differential, reticulocyte count, iron, TIBC, transferrin saturation, ferritin
- Consider slow-release oral iron formulation with vitamin C for iron deficiency (ferritin < 20% of transferrin sat < 20%)
- Helpful clues include MCV, Hb trends, retic count & age
- Consider hematology referral for bi- or tricytopenias, particularly in elderly patients

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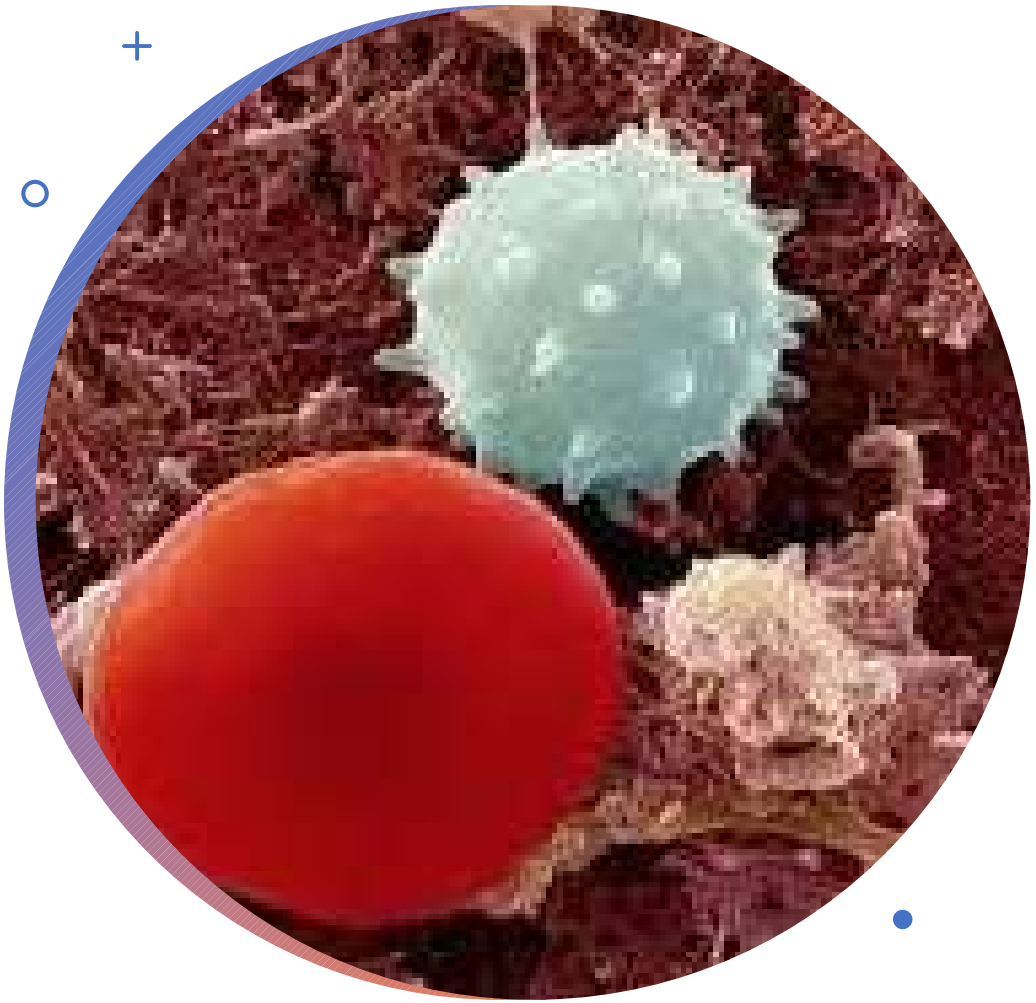

Thank you

Questions ?