Anemia:
Mechanisms, Evaluation, and Management

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Hematology
March 9, 2022

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Disclosures

- None

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Outline

- Hematopoesis, Erythropoesis
- RBC indices
- Approach to anemia
  - Categorizations
  - Clinical history & labs
- Mechanisms, evaluation, management of select anemias
  - Iron deficiency
  - B12 deficiency
  - Folate Defeciency

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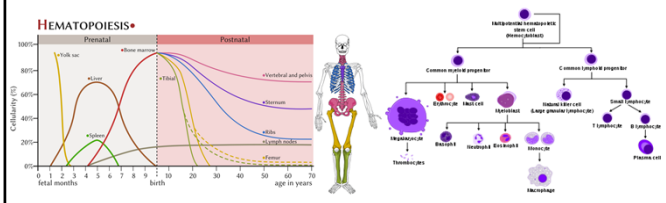
Hematopoeisis: The process by which the body produces blood cells



- Each day an adult human produces 200,000,000,000 (= 2 x 10^{11}) erythrocytes

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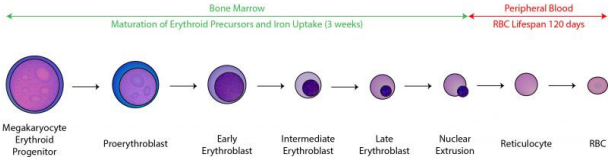
Erythropoiesis



- Each day an adult human produces 200,000,000,000 (= 2 x 10^{11}) erythrocytes
- More in response to hypoxemia
  - Which in turn is due to anemia, impaired gas exchange, increased oxygen demand
  - Increase in HIF2a leades to increase in EPO

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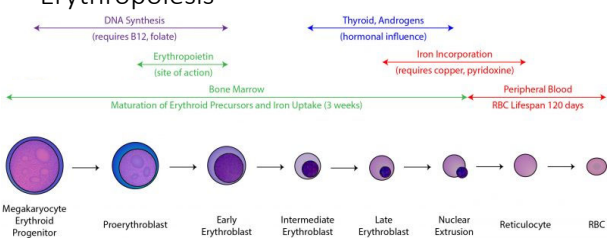
Erythropoiesis



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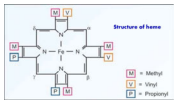
Heme(oglobin)

- The main component of a RBC is the pigmented (red) protein hemoglobin (HGB).
- HGB is a large molecule made of 4 proteins (globins)
  - 2 alpha chains
  - 2 beta chains
- Each globin is bound to one heme molecule
- Each Heme molecule contains one iron atom
- One iron atom can transport one oxygen molecule

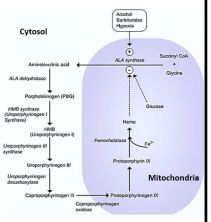
→ 1 RBC has 300 million hgb molecultes

→ 1 RBC can transport 1.2 billion molecules of oxygen

HGB Structure



Heme Structure



Heme Synthesis

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Terminology

- World Health Organization (WHO) Criteria for anemia
  - Men: hgb <13 g/dL
  - Women: hgb <12 g/dL
  - Pregnant women: hgb <11 g/dL
  - Intended for use within the context of international nutrition studies
- Hemoglobin (HGB)
  - the concentration of hemoglobin in whole blood (g/dL)
- Hematocrit (HCT)
  - percentage of blood volume occupied by RBC (%)
  - HCT is a calculated value: HCT= MCV x RBC/10
- RBC count
  - number of RBCs contained in a specified volume of whole blood (millions of cells/mcL)

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Red Cell Indices

- Mean Corpuscular Volume (MCV)
  - average volume (size) of the RBC
- Mean Corpuscular Hemoglobin (MCH)
  - average HGB content in an RBC
  - Low MCH leads to increased central pallor / hypochromia
- Mean Corpuscular Hemoglobin Concentration (MCHG)
  - Average hemoglobin concentration per RBC
- Red cell distribution Width (RDW)
  - Measure of variation in RBC size

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Reticulocyte Count

- The laboratory "reticulocyte count" is actually a percentage.
- The absolute count corrects for the level of anemia.
- The reticulocyte index determines if the reticulocyte count is appropriate for the level of anemia.

FORMULA

Absolute reticulocyte count = # or % retics * (pt's Hct / normal Hct)

Reticulocyte index = absolute reticulocyte count / maturation factor

Maturation factors:

Hematocrit	Maturation factor
≥35%	1.0
25 to <35%	1.5
20 to <25%	2.0
<20%	2.5

FACTS & FIGURES

Interpretation:

Reticulocyte index	Interpretation
≥2	Adequate response
<2	Hypoproliferation

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Anemia: Signs and Symptoms are related to impaired oxygen delivery

- Oxygen content / carrying capacity
  - Affected by quantity of RBC hemoglobin present
- Oxygen delivery to tissues
  - Hemoglobin affinity for oxygen
  - Blood volume
  - Tissue perfusion
    - Blood pressure, pulse, cardiac output
    - Hypovolemia
- Rate of decline
  - Acute vs chronic anemias

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Anemia: categorizations

- Time
  - Acute vs Subacute vs Chronic
  - If chronic: how chronic? Acquired vs inherited?
- Size
  - Microcytic vs Normocytic vs Macrocytic
- Bone Marrow Response
  - Hypoproliferative vs hyperproliferative

Anemia *descriptors*

- Severity
  - Mild vs Moderate vs severe

⟸ Anemia *diagnoses*

- Mechanisms
  - Production problem vs Blood loss vs Hemolysis
  - Anemia may be multifactorial

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Anemia: Approach to evaluation

- Clinical Information
  - Medical conditions
  - Medication list
  - Family history
  - Causes of acquired anemia (diet, travel, infection, heavy menstrual bleeding, melena)
  - Chronicity of anemia
  - Symptoms that would suggest hemolysis (Dark urine, jaundice, history of gallstones, anemia with certain food or drug exposures like fava beans, oxidant drugs)
  - Hypersplenism on exam
  - Symptoms, if any, and rapidity of onset/progression
  - Transfusion History
- Laboratory evaluation:
  - CBC, reticulocyte count, renal panel, liver panel
  - Iron studies, B12, Folate, TSH
  - Peripheral smear
  - hemolysis labs (LDH, bili, haptoglobin, DAT)
  - Special testing: EBV/CMV PCR, hemoglobin electrophoresis, bone marrow biopsy, RBC solubility testing, hgb instability, genetic tests

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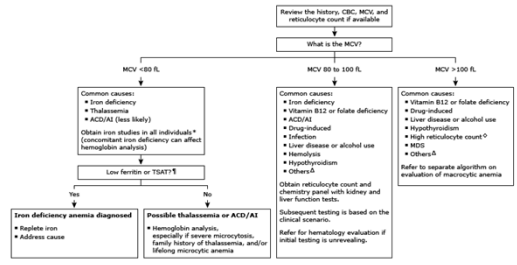
Anemia evaluation in outpatients (nonpregnant adults)



This algorithm addresses anemia in healthy outpatients, which is often an incidental finding or may be identified when a CBC is performed to evaluate mild symptoms such as fatigue. It is not appropriate for individuals who are acutely ill with fever, bleeding, neurologic symptoms, or any severe cytopenia (hemoglobin <7 to 8 g/dL; platelet count <50,000/microL, absolute neutrophil count [ANC] <1000/microL). Consider the history, CBC, MCV, and reticulocyte count (if available) simultaneously. Refer to UpToDate for details of testing for specific causes of anemia.

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Considerations for anemia evaluation in inpatients

- Iatrogenic anemia
  - Clinical lab draws
  - Research lab draws
- Medication related anemia
  - Antibiotics
  - Chemotherapy
- Surgical blood loss
- Single or multiple cytopenias
- Anemia of inflammation / chronic disease

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Selected anemias

- Iron Deficiency
- B12 Deficiency
- Folate Deficiency

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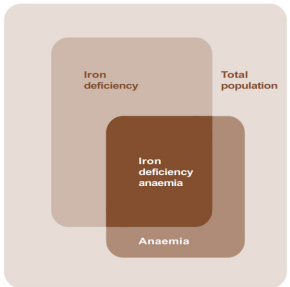
Iron Deficiency Anemia

- The most common anemia in the world
  - 15% of toddlers
  - 11% of nonpregnant adolescent girls
  - 9% of adult women age 20-39
- Even more are iron deficient without anemia

Criteria of Anemia: WHO guidelines	
6 mo-59 mo	<10 g/L
5-11 yrs	<11.5 g/L
12-14	<12.0 g/L
>15 years	
Females	
Pregnant	<11.0 g/L
Non-pregnant	<12.0 g/L
Males	< 13.0 g/L

Camaschella, Blood, 2019
https://www.who.int/nutrition/publications/en/ida_assessment_prevention_control.pdf.



Source: Adapted from Yip R. Iron nutritional status defined. In: Filer LJ, ed. *Dietary Iron: birth to two years.* New York, Raven Press, 1989:19-36.

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Impact of iron deficiency

- Impairs cognitive performance, behavior, and physical growth
  - Infants, preschool, school-aged children
- Immune status and morbidity from infections
- Adverse outcomes of pregnancy for mothers & newborns
- Decreased physical capacities
  - Skeletal muscle & cardiac muscle myoglobin rely on iron
- Cognitive decline in the elderly
- Increased risk of heavy-metal poisoning
  - Increased absorption capacity of divalent heavy metals (ie lead, cadmium)

https://www.who.int/nutrition/publications/en/ida_assessment_prevention_control.pdf *Auerbach, Blood Transfus, 2017.*

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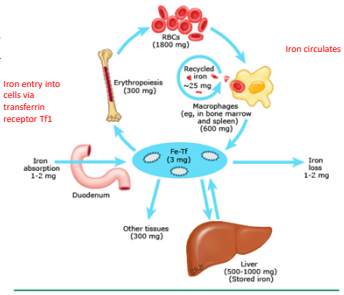
Inhibit iron absorption:
- Calcium (Milk, mild products)
- Tea/Coffee (tannins)
- Phytates in cereals, legumes, nuts
- Dietary fiber
- Zinc, Calcium, manganese, copper supplements
- Medications
  - Antacids
  - Tetracyclines
  - Quinolones
  - Pancreatic enzyme supplements
  - Bisphosphonates
  - Cholestyramin

Facilitate iron absorption:
- Vitamin C
- Acidic food – tomatoes, citrus
- Nonenteric iron tablets
- Fasting ingestion of iron tabs
- Heme based iron (meat, fish, seafood)

Regulation of iron absorption, transport, and homeostasis



Iron entry into cells via transferrin receptor Tf1

Iron circulates in plasma bound to transferrin

Mechanisms of iron loss:
- Sloughing of skin and intestinal c
- Menstrual blood loss

Schematic showing iron homeostasis. Refer to UpToDate for details of the regulation of iron absorption, transport, and storage in the body.

RBCs: red blood cells; Fe-Tf: transferrin-bound iron, the major transport form in the body.

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Table 1. Main causes of absolute iron deficiency/iron deficiency anemia

Type of cause	Condition	Pathophysiologic mechanism
Increased iron requirements	Infants, preschool children, adolescents	Rapid growth
	Pregnant women: second and third trimesters	Expansion of maternal and fetal erythroid mass
	ESA treatment	Acute expansion of erythroid mass
Low iron intake	Malnutrition*	Insufficient dietary iron: low heme iron or scarcely bioavailable iron (eg, chelated by phytates)
	Vegetarians, vegans	
Decreased intestinal iron absorption	Gastrectomy, duodenal bypass, bariatric surgery	Decreased absorptive surface
	Gluten-induced enteropathy	
	Autoimmune atrophic gastritis	Increased pH
	Helicobacter pylori infection	Increased pH and blood loss
	Drugs: proton pump inhibitors, H_2 blockers	Blocking of gastric acid secretion
	Genetic IRIDA†	High serum hepcidin levels

Camaschella, Blood, 2019.

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Chronic blood loss	Hookworm infestation*	Bleeding from gastrointestinal tract
	Gastrointestinal benign and malignant lesions	
	Salicylates, corticosteroids, nonsteroidal anti-inflammatory drugs	
	Heavy menses, hematuria	Bleeding from genitourinary system
	Intravascular hemolysis (PNH, march hemoglobinuria)	Urinary loss of hemoglobin (iron)
	Drugs: anticoagulants, antiplatelet compounds	Systemic bleeding
	Defects of hemostasis (hereditary hemorrhagic telangectasia, von Willebrand disease)	
	Frequent blood donors	Repeated blood letting
Multiple causes (absolute iron deficiency associated with inflammation)	Chronic infections in malnutrition*	Reduced intake, increased proinflammatory cytokines
	Chronic kidney disease	Decreased iron absorption, increased blood loss, reduced hepcidin excretion and increased production, drugs, ESAs
	Chronic systolic heart failure	Decreased iron absorption, increased inflammation, blood loss
	Inflammatory bowel diseases	Decreased iron absorption, increased blood loss, high hepcidin
	Postoperative anemia of major surgery	Blood loss, increased proinflammatory cytokines

Camaschella, Blood, 2019.

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Iron Deficiency

- Symptoms
  - Fatigue
  - Pica (desire or compulsion to eat substances not fit as food)
    - Ice (pagophagia), clay or dirt (geophagia), paper products, corn starch fabric softener sheets, raw rice or pasta (amylophagia)
  - Restless leg syndrome
  - Headache
  - Exercise intolerance
  - Exertional dyspnea
  - Weakness
- Signs
  - Pallor
  - Dry or rough skin
  - Atrophic glossitis
  - Cheilosis / angular cheilitis
  - Koilonychia (spoon nails)
  - Esophageal web

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Labs: CBC

- CBC findings occur in proportion to, and lag behind, changes in iron studies
- Slight hgb decline precedes microcytosis
- In early iron deficiency, CBC may be relatively normal
- Later findings:
  - Low RBC count ← unlike thalassemia
  - Low hgb/hct
  - Low absolute reticulocyte count
  - Low MCV and MCH ← microcytic, hypochromic RBCs
  - Platelet count may be high ← Stimulation of platelet precursors by epo
  - Low reticulocyte hemoglobin (<26 pg/cell)

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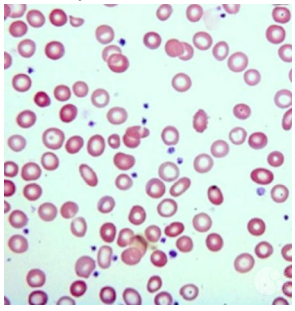
ASH Image Bank — Image ID: 60223

Iron Deficiency Anemia Moderate



A patient with a history of a gastrectomy presented for difficulty swallowing and fatigue.

Laboratory findings included: hemoglobin 7 g/dL, MCV 61 fL, platelet count 750 thou/µL, normal WBC, reticulocytes 2.5%, serum ferritin 6 ng/mL, serum iron 12 ug/dL, and transferrin 400 µg/dL.

Peripheral smear showed thrombocytosis (normal morphology), hypochromia, and anisopoikolocytosis.

The patient was found to have Plummer-Vinson syndrome, esophageal webs, causing the swallowing difficulties. This manifestation of iron deficiency is not frequently encountered.

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Table 2. Laboratory Tests for the Measurement of Iron Status in Adults.

Test	Iron Deficiency	Functional Iron Deficiency	Iron-Deficiency Anemia	IRIDA	Anemia of Chronic Diseases	Iron-Deficiency Anemia and Anemia of Chronic Diseases	Normal Value
Current							
Iron — μmol/liter	Low	Low–normal	Low	Low	Low	Low	10–30
Transferrin saturation — %	≥16	Low– normal	<16*	<10	Low–normal	Low–normal	>16 to <45
Ferritin — μg/liter	<30†	Normal	<10	Variable	>100‡	<100‡	
Men							40–300
Women							20–200
Hemoglobin — g/dl	Normal	Normal	Low	Low	Low	Low	
Men							>13
Women							>12
Mean corpuscular volume — fl	Normal	Normal	<80	Very low	Low–normal	Low	80–95
Mean corpuscular hemoglobin — pg	Normal	Normal	<27	Very low	Low–normal	Low	27–34
Proposed							
sTFR — mg/liter§	High	High	High	High	Low–normal	Variable	Varies¶
sTFR/log ferritin index‖	NA	NA	>2	NA	<1	>2	Varies¶
Hepcidin	Low	Low	Very low	Normal–high	High	Normal–high	Varies¶
Zinc protoporphyrin**	Normal	High	High	High	High	High	Varies¶
Reticulocyte hemoglobin content — pg††	<25	<29	Low	Low	Low	Low	31.2±1.6
Perl's staining of bone marrow for iron	Negative	Variable	Negative	Positive	Strongly positive	Positive	Positive

Camaschella, N Engl J Med, 2015.

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Table 2. Laboratory Tests for the Measurement of Iron Status in Adults.

Test	Iron Deficiency
Current	
Iron — μmol/liter	Low
Transferrin saturation — %	≥16
Ferritin — μg/liter	<30†
Men	
Women	
Hemoglobin — g/dl	Normal
Men	
Women	
Mean corpuscular volume — fl	Normal
Mean corpuscular hemoglobin — pg	Normal
Proposed	
sTFR — mg/liter§	High
sTFR/log ferritin index‖	NA
Hepcidin	Low
Zinc protoporphyrin**	Normal
Reticulocyte hemoglobin content — pg††	<25
Perl's staining of bone marrow for iron	Negative

WHO guidelines:
Ferritin <15

Ferritin <30
Sensitivity 93%
Specificity 83%

- Inadequate iron incorporation
- Lack of Iron stores

Camaschella, N Engl J Med, 2015.

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Current			
Iron — μmol/liter	Low	Low–normal	Low
Transferrin saturation — %	≥16	Low– normal	<16*
Ferritin — μg/liter	<30†	Normal	<10
Men			
Women			
Hemoglobin — g/dl	Normal	Normal	Low
Men			
Women			
Mean corpuscular volume — fl	Normal	Normal	<80
Mean corpuscular hemoglobin — pg	Normal	Normal	<27
Proposed			
sTFR — mg/liter§	High	High	High
sTFR/log ferritin index‖	NA	NA	>2
Hepcidin	Low	Low	Very low
Zinc protoporphyrin**	Normal	High	High
Reticulocyte hemoglobin content — pg††	<25	<29	Low
Perl's staining of bone marrow for iron	Negative	Variable	Negative

Camaschella, N Engl J Med, 2015.

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Iron — μmol/liter	Low	Low–normal
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Ferritin — μg/liter	<30†	Normal
Men		
Women		
Hemoglobin — g/dl	Normal	Normal
Men		
Women		
Mean corpuscular volume — fl	Normal	Normal
Mean corpuscular hemoglobin — pg	Normal	Normal
Proposed		
sTFR — mg/liter§	High	High
sTFR/log ferritin index‖	NA	NA
Hepcidin	Low	Low
Zinc protoporphyrin**	Normal	High
Reticulocyte hemoglobin content — pg††	<25	<29
Perl's staining of bone marrow for iron	Negative	Variable

FID
Insufficient iron incorporation into erythroid precursors in the face of apparently adequate body iron stores.

No anemia

Camaschella, N Engl J Med, 2015.

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Ferritin — μg/liter	<30†	Normal	<10	Variable	>100‡
Men					
Women					
Hemoglobin — g/dl	Normal	Normal	Low	Low	Low
Men					
Women					
Mean corpuscular volume — fl	Normal	Normal	<80	Very low	Low–normal
Mean corpuscular hemoglobin — pg	Normal	Normal	<27	Very low	Low–normal
Proposed					
sTFR — mg/liter§	High	High	High	High	Low–normal
sTFR/log ferritin index‖	NA	NA	>2	NA	<1
Hepcidin	Low	Low	Very low	Normal–high	High
Zinc protoporphyrin**	Normal	High	High	High	High
Reticulocyte hemoglobin content — pg††	<25	<29	Low	Low	Low
Perl's staining of bone marrow for iron	Negative	Variable	Negative	Positive	Strongly positive

Camaschella, N Engl J Med, 2015.

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Camaschella, N Engl J Med, 2015.

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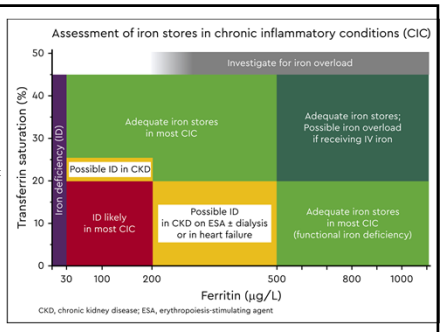
Accuracy of ferritin to rule out iron deficiency is lost in the presence of inflammation due to acute-phase reaction:
Infection/ tissue injury
→ Trigger IL-6, IL-1, TNF
→ Hepatocytes increase synthesis of acute-phase proteins
→ Including ferritin & hepcidin
→ Reduces iron absorption and export out of cells
→ Reduces iron available to be scavenged by pathogens

Iron deficiency on BM would be diagnostic, but invasive.

TSAT identifies patients who are more likely to benefit from iron supplementation.



Kleber Yotsumoto Fertrin, Diagnosis and management of iron deficiency in chronic inflammatory conditions (CIC): is too little iron making your patient sick?, Hematology Am Soc Hematol Educ Program, 2020,

American Society of Hematology

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Table 2. Characteristics and side effects of most commonly available oral iron supplements

Iron formulation (example US brand names) (dose per tablet/Fe dose)	Usual dose	Most common side effects (>1%)	Observations
Ferric citrate (Auryxia) (1000 mg/210 mg Fe)	2 tablets once daily (LR)	>20%: fecal discoloration, diarrhea; 10-20%: constipation, nausea; 1-10%: hyperkalemia, cough.	Phosphate binder, approved for use in ID in ndCKD.
Ferrous fumarate (Ferretts, Ferrimin, Hemocyte) (324 or 325 mg/106 mg Fe)	1 tablet every other day (>100 mg Fe per dose)	>10%: constipation, fecal discoloration, nausea, stomach cramps, vomiting; 1-10%: dental discoloration, diarrhea, urine discoloration	Cereals, dietary fiber, tea, coffee, eggs, and milk may decrease absorption.
Ferrous gluconate (Ferate) (240 mg/27 mg Fe; 324 mg/38 mg Fe)	3-4 tablets every other day (>100 mg Fe per dose)	>10%: constipation, fecal discoloration, nausea, stomach cramps, vomiting; 1-10%: dental discoloration, diarrhea, urine discoloration.	
Polysaccharide iron complex (EZFE, Ferrex, NovaFerrum) (50 mg Fe)	2 tablets every other day (>100 mg Fe per dose)	>10%: constipation, fecal discoloration, nausea, stomach cramps, vomiting; 1-10%: dental discoloration, diarrhea, urine discoloration.	
Ferrous sulfate (several) (324 or 325 mg/65 mg Fe)	2 tablets every other day (>100 mg Fe)	>50%: fecal discoloration, abdominal pain, nausea; 20-50%: constipation, vomiting, diarrhea.	
Ferric polymaltose (Maltofer; not available in the US) (357 or 370 mg/100 mg Fe)	1-3 tablets once daily (LR)	>10%: fecal discoloration; >1%: diarrhea, nausea, abdominal pain, constipation.	—
Heme iron polypeptide (Proferrin) (10.5-12 mg Fe)	1 tablet once daily (LR)	Incidence unknown: constipation, abdominal pain, diarrhea, muscle cramps.	—
Ferric maltol (Accrufer) (30 mg Fe)	1 tablet twice daily (LR)	1-10%: fecal discoloration, constipation, diarrhea, abdominal pain, nausea, vomiting.	Absorption may be decreased with food.

Fertrin, Hematology Am Soc Hematol Educ Program, 2020.

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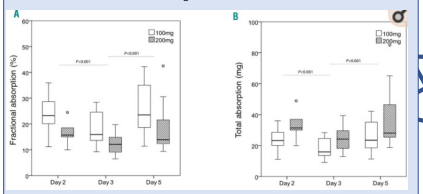
Stoffel NU, **Iron absorption from supplements is greater with alternate day than with consecutive day dosing in iron-deficient anemic women**. Haematologica. 2020.



Day 3= consecutive day: reduced fractional absorption, reduced total absorption

Day 5 = alternate day: improved fractional absorption, improved total absorption

A single dose of 60 mg of elemental iron administered on alternate days can be adequate and maximize tolerability.

Fertrin, Hematology Am Soc Hematol Educ Program, 2020.
Auerbach, Blood Transfus, 2017

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- Slow release or enteric-coated formulations
  - Fewer GI side effects
  - Less iron per dose
  - More expensive than iron salts
  - May release iron below the duodenum; too distal for significant absorption

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Table 3. Indications for Parenteral Iron Therapy.

Established indication
- Failure of oral therapy
- Iron intolerance or with low iron levels that are refractory to treatment (e.g., after gastrectomy or duodenal bypass, with *Helicobacter pylori* infection, or with celiac disease, atrophic gastritis, inflammatory bowel disease, or genetically induced IRIDA*)
- Need for quick recovery (e.g., with severe iron deficiency in the second or third trimester of pregnancy or with chronic bleeding that is not manageable with oral iron, as may occur in patients with congenital coagulation disorders)
- Substitution for blood transfusions when not accepted by patient for religious reasons
- Use of erythropoiesis-stimulating agents in chronic kidney disease

Potential indication
- Anemia of chronic kidney disease (without treatment of erythropoiesis-stimulating agents)
- Persistent anemia after use of erythropoiesis-stimulating agents in patients with cancer who are receiving chemotherapy
- Anemia of chronic disease unresponsive to treatment with erythropoiesis-stimulating agents alone

Potential indication with insufficient supporting data
- Iron deficiency in heart failure
- Transfusion-sparing strategy in surgical patients

Ganzoni formula

Total iron dose = [weight (kg) × (15- Hb)] × 2.4 + iron stores (mg)

^500 mg for adults

- Inconvenient to calculate
- Inconsistently used
  - Product labels state specific dosing regimens
  - FDA approved labeling for many products recommends total dose of 1000 mg
  - Data suggest that majority of patients with IDA likely need 1500 mg

Camaschella, N Engl J Med, 2015.
Auerbach, Blood Transfus, 2017.

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Table 4. Iron Preparations for Intravenous Use.*

Formulation	Dose per Infusion	
	Standard	Maximum per Single Infusion
Ferric gluconate (Ferlecit)	125 mg/10–60 min	250 mg/60 min
Iron sucrose (Venofer)	100–400 mg/2–90 min	300 mg/2 hr
Low-molecular-weight iron dextran (INFeD)†	100 mg/2 min	1000 mg/1–4 hr)
Ferumoxytol (Feraheme)†	510 mg/>1 min	510–1020 mg/15–60 min
Ferric carboxymaltose (Ferinject)†	750–1000 mg/15–30 min	750–1000 mg/15–30 min
Iron isomaltoside (Monofer)†‡	20 mg/kg of body weight/15 min	20 mg/kg of body weight/15 min

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Table 4. Iron Preparations for Intravenous I

Formulation	Pricing	MRI interval	Hypophos?	Test dose?
Ferric gluconate (Ferlecit)	$600 / 1000 mg	1 wk		maybe
Iron sucrose (Venofer)	$400 / 1000 mg	1 wk		maybe
Low-molecular-weight iron dextran (INFeD)†	$400 / 1000 mg			yes
Ferumoxytol (Feraheme)†	$2500 / 1020 mg	12-24 wk		no
Ferric carboxymaltose (Ferinject)†	$2700/ 1500 mg	1 wk	yes >10%	no
Iron isomaltoside (Monofer)†‡	$3000 / 1000mg	4 wk	yes 1-10%	no

- Variable/similar risks: hypotension, hypersensitivity reactions, hypertension, nausea, vomiting, abdominal pain, dizziness, etc
- Pricing affected by institutional agreements
- Pricing of drug does not include administration/facility costs
  - The higher dosing / less visits allowed by the newer formulations may be more cost effective overall

Camaschella, N Engl J Med, 2015.

Fertrin, Hematology Am Soc Hematol Educ Program, 2020.

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Response to iron supplementation

- Pica, fatigue, restless leg syndrome may improve within first 1-3 days
- If moderate-severe anemia → modest reticulocytosis, peak in 7-10 days
- Hb rise after 1-2 weeks
  - Deficit halved by 1 month
  - Normalize by 6-8 weeks
- Recheck iron studies after 4 weeks
- Approach to lack of response
  - Compliance limited by side effects?
  - Reduced absorption?
    - Screen for H. pylori, autoimmune gastritis, celiac disease
  - Blood loss > iron intake
  - Incorrect initial diagnosis
  - Multiple diagnosis
  - Recurrent bleeding
  - Inflammatory state

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Iron Deficiency

- Very common
- Under-recognized & under-treated
- Replace iron
  - Dietary iron is usually not sufficient
  - IV iron safe, well tolerated, fast, effective
- Evaluate and treat (if possible) cause of iron deficiency
  - Heavy menstrual bleeding
    - Tranexamic acid 1.3g po Q8hrs during menses
    - Evaluate for bleeding disorder (vwd, etc)
  - GI bleeding/ GI cancer screen
  - Malabsorption
  - Etc.
- Continue to monitor for recurrence of deficiency

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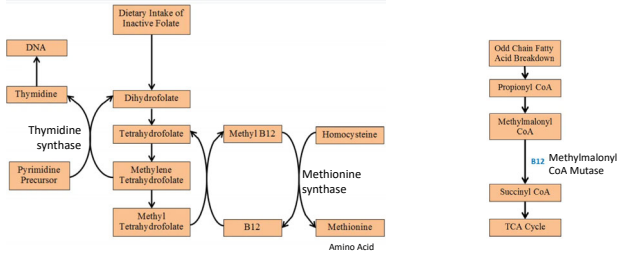
B12 & Folate



Folate is sequentially reduced then transfers methyl groups

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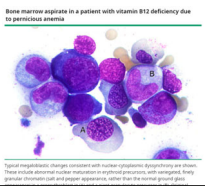
Heme Manifestations of B12 & Folate deficiency

- Defective DNA synthesis -> dysynchrony in nuclear-cytoplasmic asynchrony -> cells divide slowly until daughter cells die in the marrow or are arrested at various stages of the cell cycle
- Megaloblastic anemia & neutrophil hypersegmentation
- Pancytopenia
- Mild leukopenia and/or thrombocytoepnia



Typical megaloblastic changes consistent with nuclear-cytoplasmic dyssynchrony are shown. These include abnormal nuclear maturation in erythroid precursors, with variegated, finely granular chromatin (salt and pepper appearance, rather than the normal ground glass.

Neuro Manifestations

- Neuropsych symptoms may precent heme findings

B12 deficiency

- Defective myelin synthesis due to accumulation of MMA & incorporation of abnormal fatty acids into neuronal lipids
- Subacute combined degeneration
  - Sensory impairment; motor impairment; spastic paraparesis
- Peripheral neuropathy
- Optic neuropathy
- Myelopathy

B12 & folate deficiency

- Mood disorders, chronic fatigue syndrome, psychosis
- Cognitive impairment

Adami, Nutrients, 2013.

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Medications that cause B12 deficiency

- PPI, H2 antagonists
- Metformin
  - Mechanism unknown
- Nitrous oxide abuse
  - Impaired cobalamin metabolism
  - Rapid B12 depletion
- Oral contraceptives

Table 6-7 Select causes of vitamin B_{12} deficiency

Impaired absorption
- Deficiency of intrinsic factor or IF-bound vitamin B_{12} uptake
  - Pernicious anemia
  - Congenital intrinsic factor deficiency
  - Gastric bypass surgery
- Decreased ileal absorption of vitamin B_{12} (Imerslund-Gräsbeck syndrome)
- Hypochlorhydia (impairs release of B_{12} from dietary proteins)
  - Age
  - Gastric atrophy (*Helicobacter pylori* or autoimmune gastritis)
  - Medications (proton-pump inhibitors or H_2 antagonists)
- Inadequate pancreatic protease (vitamin B_{12} remains sequestered by haptocorrin)
- Intestinal competition for host vitamin B_{12} (tapeworm *Diphyllobothrium latum*)
- Ileal resection or bypass
- Ileal dysfunction (Crohn disease, celiac disease, intestinal lymphoma, bacterial overgrowth from blind loop syndrome)
- Medications (metformin [mechanism unknown], nitrous oxide abuse)

Insufficient dietary intake (strict vegans, some vegetarians, and breastfed infants of vitamin B_{12}–deficient mothers)

Defects in bodily transport
- Congenital disorders of vitamin B_{12} transport (defects in cubam, transcobalamin, others)

Pernicious anemia is the most common cause of B12 deficiency

- Autoimmune gastritis
- Atrophy of mucosa of the body & fundus of the stomach
- Reduces number of parietal cells that produce IF -> less B12 absorption
- Associated with other AI disorders
  - T1DM, thyroiditis, hyperthyroidism, vitiligo

Adami, Nutrients, 2013.
ASH SAP

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Diagnosis of B12 deficiency

- What B12 level is considered low/deficient?
  - <200 pg/mL
  - (200-300 pg/mL borderline)
- What are the limitations of the test/result?
  - Assay lacks sensitivity and specificity, highly variable results
    - Significant intraindividual variation
    - Large range of "normal"
    - Folate deficiency, MM, HIV, pregnancy, may falsely lower B12 levels
    - MPN, leukemia, lymphoma, liver disease, may give falsely normal values and *mask* true deficiency
  - Antibodies to intrinsic factor may interfere
- What further testing can be done?
  - Methylmalonic acid and homocysteine
    - May be falsely elevated in renal impairment, age
  - I check these if B12 <400
    - 10% of true B12 deficient adults have values in the low-normal range

Adami, Nutrients, 2013.

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Treatment of B12 deficiency

- B12 IM
  - 1mg daily x 1 week
  - 1mg weekly x 4 weeks
  - 1mg monthly for life
- Oral daily dosing 1-2 mg may be sufficient for mild deficiency
  - With close follow up

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Folate (B9) deficiency

- Body stores of folate are small
  - Deficiency can occur over weeks to months (unlike B12)
- Routine folic acid fortification has largely irradicated folate deficiency
  - Region/country specific
- Medications
  - Methotrexate
    - inhibits dihydrofolate reductase
  - Antibiotics: trimethoprim, pyrimethamine
    - inhibit DHFR
  - Antiseizure agents- phenytoin, valproate, carbamazepine
    - affect folate absorption/cellular utilization)

Table 6-8 Select causes of folate deficiency

Impaired absorption
- Intestinal dysfunction (Crohn disease, celiac disease)
- Congenital abnormality in intestinal folate transporter (mutations in *PCFT*)

Insufficient dietary intake
- Poor intake of fruits and vegetables or prolonged cooking of these foods
- Alcoholism (alcohol also increases renal folate excretion and impairs its intracellular metabolism)

Increased requirements
- Increased cellular proliferation
- Pregnancy
- Lactation
- Hemolytic anemia (sickle cell anemia, warm autoimmune hemolytic anemia)
- Malignancies (associated with a high proliferative rate)
- Exfoliative dermatitis
- Hemodialysis
- Medication that affect folate metabolism or possibly absorption (methotrexate, phenytoin, carbamazepine)

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Diagnosis of folate deficiency

- What serum folate concentration is consistent with folate deficiency?
  - <2ng/mL
  - 2 – 4 ng/mL - borderline

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Treatment of folate deficiency

- Oral folate 1-5 mg daily
- Sufficient even if there is malabsorption
- (recommended dietary allowance is only 0.2mg)
- IV folate if
  - Unable to take PO
  - Severe or symptomatic anemia due to folate deficiency
- Screen/treat B12 deficiency first
  - Folate repletion may normalize hgb and mask B12 deficiency

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- Response to B12 / folate repletion
  - Megaloblastosis reverses in 24 hrs
  - Normal marrow hematopoiesis in 48 hrs
  - Retic increases in 3-4 days, peaks in 1 week
  - Incr hgb in 1 week
  - Normalization of CBC in 8 weeks
  - B12 deficiency related neurologic abnormalities response but residual may persist

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Approach to Transfusion

- Stable patients: target hgb >7
  - 1 RBC at a time, with a followup CBC
  - Transfuse over 1-4 hours
    - Shorter if young, no significant medical issues
    - Longer if older, CKD/AKI, cardiac dysfunction, cirrhosis/liver disease, medically complex
- Unstable patients:
  - More # and pace of RBC transfusion
  - Transfuse to vital signs, particularly if active brisk bleeding
  - Target hgb may be higher >9 or 10
  - CBC results should be interpreted with other clinical signs to guide transfusion
  - Think ahead, order product ahead
  - Volume considerations are still important

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The end

- Hematopoesis, Erythropoesis
- RBC indices
- Approach to anemia
  - Categorizations
  - Clinical history & labs
- Mechanisms, evaluation, management of select anemias
  - Iron deficiency
  - B12 deficiency
  - Folate Deficiency

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