





ANEMIA OF DIMINISHED ERYTHROPOIESIS

Definition:

Anemias caused by reduced red cell production due to:




-  Nutritional deficiencies (iron, vitamin B12, folate)
-  Bone marrow failure (aplastic anemia)
-  Systemic inflammation (anemia of chronic inflammation)
-  Bone marrow infiltration (myelophthisic anemia)

Hallmark:

- Low reticulocyte count (reticulocytopenia)
 - Normocytic, microcytic, or macrocytic depending on cause
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IRON DEFICIENCY ANEMIA (IDA)

Epidemiology:



-  Most common nutritional deficiency worldwide
 - Prevalence:
 -  High-resource countries: ~10%
 -  Low-resource countries: 25-50%
 - Most frequent cause of anemia in both settings
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IRON METABOLISM



Normal total body iron:

-  Men: 3.5 g
-  Women: 2.5 g

Distribution:

- 80%:  hemoglobin,  myoglobin, and iron-dependent enzymes (catalase, cytochromes)
- 15-20%: storage pool (ferritin, hemosiderin) in macrophages (liver, spleen, marrow) & skeletal muscle

Key lab correlate:




-  Serum ferritin = best non-invasive marker of iron stores
 -  Bone marrow iron = gold standard (invasive)
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IRON TRANSPORT & STORAGE

Plasma transport:

- Bound to transferrin
- Normally 33% saturated
- Serum iron: 100–120 $\mu\text{g/dL}$
- Total Iron-Binding Capacity (TIBC): 300–350 $\mu\text{g/dL}$

Iron absorption:

- Duodenum = main site 
- Heme iron (from meat) = 20% absorbed 
- Non-heme iron (from plants) = 1–2% absorbed 

Transporters:



- DMT1 (apical) → ferrous iron (Fe^{2+}) into enterocytes
- Ferroportin (basolateral) → iron into plasma
- Iron oxidized to ferric form (Fe^{3+}) → binds transferrin

Iron fate in enterocytes:




- Transferred to plasma → binds transferrin
- Stored in ferritin → lost when epithelial cells exfoliate

HEPCIDIN REGULATION – CENTRAL TO IRON HOMEOSTASIS




Hepcidin = liver peptide hormone regulating ferroportin

-  High hepcidin: ↓ ferroportin → ↓ iron absorption
-  Low hepcidin: ↑ ferroportin → ↑ iron absorption

Regulation:



-  Iron levels: \uparrow iron sensed by HFE protein \rightarrow \uparrow hepcidin \rightarrow negative feedback
-  Inflammation: IL-6 \rightarrow \uparrow hepcidin \rightarrow anemia of chronic disease
-  Erythropoiesis: Erythroferrone (from erythroblasts) \rightarrow \downarrow hepcidin \rightarrow \uparrow iron availability


Clinical correlations:

-  β -thalassemia major \rightarrow \uparrow erythroferrone \rightarrow \downarrow hepcidin \rightarrow iron overload
-  Hereditary hemochromatosis \rightarrow HFE defect \rightarrow \downarrow hepcidin \rightarrow iron overload
-  Chronic inflammation \rightarrow \uparrow hepcidin \rightarrow \downarrow iron absorption \rightarrow anemia


FLOWCHART - IRON ABSORPTION & HOMEOSTASIS




Dietary iron (heme  + non-heme ) \rightarrow Duodenal absorption via DMT1 \rightarrow Enterocyte cytoplasm



i) Part stored in ferritin → lost via epithelial shedding
ii) Part exported via ferroportin → Fe^{3+} binds transferrin
→ plasma transport → Bone marrow → hemoglobin synthesis 

Regulators:



- ↑ Heparin → blocks ferroportin → ↓ iron absorption
- ↓ Heparin → ↑ iron absorption
- Inflammation  → ↑ heparin → functional iron deficiency









KEY EXAM POINTS FOR IRON DEFICIENCY

- Most common nutritional anemia worldwide 
- Early stage: normocytic, normochromic
- Chronic stage: microcytic, hypochromic
- Labs: ↓ serum iron, ↑ TIBC, ↓ ferritin, ↓ transferrin saturation

- Peripheral smear: microcytosis, hypochromia, anisocytosis, poikilocytosis
- Complications (severe/long-standing):
 - Pica
 - Koilonychia (spoon nails) 
 - Angular cheilitis 
 - Plummer-Vinson syndrome (rare)

Summary Table - Iron Metabolism & Clinical Relevance

Component	Location / Role	Clinical Relevance
 Hemoglobin	RBCs	80% body iron
 Myoglobin / Enzymes	Muscle & tissues	Oxygen storage / enzymatic function



 Ferritin	Macrophages / liver / marrow	Storage, serum marker of iron
 Hemosiderin	Macrophages	Storage (secondary)
 Transferrin	Plasma	Iron transport, 33% saturated normally
 DMT1	Enterocyte apical membrane	Absorption of Fe^{2+}
 Ferroportin	Basolateral membrane	Export to plasma
 Hepsidin	Liver	Master regulator (↓ absorption when high)
 Erythroferrone	Bone marrow	Suppresses hepcidin → ↑ iron for erythropoiesis
 HFE protein	Liver	Senses plasma iron → regulates hepcidin

PATHOGENESIS



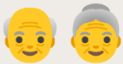
Iron deficiency develops insidiously and can arise from multiple settings:

MAJOR CAUSES BY SETTING

1] Chronic Blood Loss

- Higher-resource countries:
 - GI tract bleeding: peptic ulcers, colon cancer, hemorrhoids 
 - Female genital tract: menorrhagia, metrorrhagia, endometrial cancer 
 - Mechanism: Repeated RBC loss → iron stores depleted → anemia
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2] Low Dietary Intake

- Lower-resource countries: Vegetarian diets → low iron intake & poor bioavailability
 - High-resource countries: Rare, but may occur in:
 - Infants fed only milk 
 - Food insecurity situations 
 - Elderly 
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3 Increased Iron Requirements

- Pregnancy → ↑ maternal and fetal iron demands
 - Infancy → rapid growth → ↑ iron needs
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4 Malabsorption Disorders

- Celiac disease 
 - Gastritis or atrophic gastritis 
 - Post-gastrectomy patients 
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PATHOGENESIS FLOWCHART

Insult → chronic blood loss / low intake / ↑ demand / malabsorption → Iron stores depleted first → ↓ serum ferritin → No stainable iron in marrow macrophages → Serum iron ↓, transferrin ↑ → Impaired synthesis of hemoglobin, myoglobin, iron-containing enzymes → Microcytic, hypochromic anemia → Clinical manifestations: fatigue, pallor, cognitive impairment, immunodeficiency

CLINICAL FEATURES


- Often mild or asymptomatic
- Nonspecific signs:
 - Weakness 
 - Listlessness 
 - Pallor 
- Long-standing anemia → characteristic features:
 - Fingernail changes: thinning, flattening, "spooning"

- Pica: craving non-food items (dirt, clay)

Peripheral smear:

- Microcytosis
- Hypochromia
- Anisocytosis & poikilocytosis may appear

Lab Features:

- ↓ Hematocrit
- ↓ Serum iron & ferritin
- ↓ Transferrin saturation 
- ↑ Total iron-binding capacity (TIBC)
- ↑ Erythropoietin levels, but marrow response blunted
- Platelet count often ↑ (unclear mechanism)

EXAM PEARL 

- Microcytic hypochromic anemia in well-nourished persons is almost never a primary disease—it is

usually a symptom of an underlying disorder (e.g., colon cancer causing chronic blood loss) ⚠️

- People rarely die from iron deficiency anemia itself, but from its underlying cause 💡

FLOWCHART - IRON DEFICIENCY DEVELOPMENT

Cause (blood loss / low intake / ↑ demand / malabsorption) → ↓ Iron stores (↓ ferritin, no marrow stainable iron) → ↓ Serum iron, ↑ Transferrin → Impaired hemoglobin / myoglobin synthesis → RBCs become microcytic & hypochromic → Clinical manifestations → Fatigue / Pallor / Spoon nails / Pica → Labs: ↓ Hct, ↓ serum iron/ferritin, ↑ TIBC, ↑ EPO → Response to iron therapy if cause addressed

IRON ABSORPTION & REGULATION

□] NORMAL PLASMA IRON / SYSTEMIC INFLAMMATION (↑

Hepcidin)

(e.g., anemia of chronic disease)

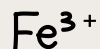
Dietary Iron Intake 🍴🍷

→ Heme iron (meat sources)

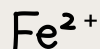
→ Non-heme iron (plant sources)

Intestinal Lumen (Duodenum)

- Non-heme iron:



↓ *(reduced by Duodenal Cytochrome B)*



↓ *(transported via DMT1)*

- Heme iron:

↓ *(via Heme transporter)*


Fe^{2+} inside enterocyte

Inside Enterocyte 🏠


→ Fe^{2+}


→ Attempted export via Ferroportin

BUT

- ↑ Heparin (from liver)
- Heparin binds ferroportin
- Ferroportin destroyed 

Result:

- Iron trapped in enterocyte
- Iron lost when epithelial cells shed 
- ↓ Iron delivery to plasma

Systemic Effects 

- ↓ Plasma iron
- ↓ Transferrin-bound iron
- ↓ Iron available to erythroid marrow
- Functional iron deficiency despite normal or ↑ iron stores

② LOW PLASMA IRON / INEFFECTIVE ERYTHROPOIESIS /
HEMOCHROMATOSIS (↓ Heparin)

(e.g., iron deficiency, thalassemia, hereditary hemochromatosis)

Low plasma iron sensed 

→ ↓ Hepcidin production by liver

Dietary Iron Intake 

→ Heme iron

→ Non-heme iron ($\text{Fe}^{3+} \rightarrow \text{Fe}^{2+}$ via Duodenal Cytochrome B)

Intestinal Absorption (Duodenum)

→ Fe^{2+} enters enterocyte via DMT1 / heme transporter

→ Ferroportin remains active 

Iron Export Pathway

Fe^{2+}

→ exported via Ferroportin

→ oxidized by Hephaestin ($\text{Fe}^{2+} \rightarrow \text{Fe}^{3+}$)

→ enters portal blood 

→ binds plasma transferrin

Distribution 🎯

- Liver (storage as ferritin / hemosiderin)
- Erythroid marrow (Hb synthesis)

Result:

- Increased iron absorption
 - ↓ Iron loss via epithelial shedding
 - Progressive iron accumulation (if unchecked)
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③ Role of Mucosal Ferritin & Epithelial Shedding 🧬

- Enterocyte iron can be stored as mucosal ferritin
 - If ferroportin blocked → iron remains trapped
 - Shedding of enterocytes → Iron lost in stool 🚽
 - This is a major regulatory mechanism of iron balance
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KEY EXAM PEARLS ★

- Hepcidin is the MASTER regulator of iron homeostasis 🧠

- \uparrow Heparin \rightarrow \downarrow serum iron (iron sequestration)
 - \downarrow Heparin \rightarrow \uparrow intestinal absorption & iron overload
 - Anemia of chronic disease = iron present but unavailable
 - Iron deficiency = true depletion of iron stores
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-> The End <-