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

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

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)

IRON TRANSPORT & STORAGE 🚚

Plasma transport:

- Bound to transferrin
- Normally 33% saturated
- Serum iron: 100–120 µg/dL
- Total Iron-Binding Capacity (TIBC): 300–350 µg/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

HEPICIDIN REGULATION – CENTRAL TO IRON HOMEOSTASIS 🛡️

Hepcidin = liver peptide hormone regulating ferroportin

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

Regulation:

- 🧪 Iron levels: ↑ iron sensed by HFE protein → ↑ hepcidin → negative feedback
- 🦠 Inflammation: IL-6 → ↑ hepcidin → anemia of chronic disease
- 🧫 Erythropoiesis: Erythroferrone (from erythroblasts) → ↓ hepcidin → ↑ iron availability

Clinical correlations:

- 🩸 β-thalassemia major → ↑ erythroferrone → ↓ hepcidin → iron overload
- 🧬 Hereditary hemochromatosis → HFE defect → ↓ hepcidin → iron overload
- 🦠 Chronic inflammation → ↑ hepcidin → ↓ iron absorption → anemia

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FLOWCHART – IRON ABSORPTION & HOMEOSTASIS 🔄

Dietary iron (heme 🥩 + non-heme 🥦) → Duodenal absorption via DMT1 → 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:

- ↑ Hepcidin → blocks ferroportin → ↓ iron absorption
- ↓ Hepcidin → ↑ iron absorption
- Inflammation 🦠 → ↑ hepcidin → 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
🧬 Hepcidin	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 🌍

1️⃣ 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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2️⃣ 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 👴👵

3️⃣ Increased Iron Requirements 🤰👶

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

4️⃣ Malabsorption Disorders 🩺

- Celiac disease 🌾
- Gastritis or atrophic gastritis 🔥
- Post-gastrectomy patients 🏥

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

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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

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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:

  Fe^{3+}

  ↓ *(reduced by Duodenal Cytochrome B)*

  Fe^{2+}

  ↓ *(transported via DMT1)*

- Heme iron:

  ↓ *(via Heme transporter)*

  Fe^{2+} inside enterocyte

Inside Enterocyte 🫓

→ Fe^{2+}

→ Attempted export via Ferroportin

BUT

→ ↑ Hepcidin (from liver)

→ Hepcidin 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

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

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

Low plasma iron sensed 📉

→ ↓ Hepcidin production by liver

Dietary Iron Intake 🍽️

→ Heme iron

→ Non-heme iron (Fe^{3+} → 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 (Fe^{2+} → 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)

3️⃣ 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

KEY EXAM PEARLS ⭐

- Hepcidin is the MASTER regulator of iron homeostasis 🧠

- ↑ Hepcidin → ↓ serum iron (iron sequestration)
- ↓ Hepcidin → ↑ intestinal absorption & iron overload
- Anemia of chronic disease = iron present but unavailable
- Iron deficiency = true depletion of iron stores

-> The End <-