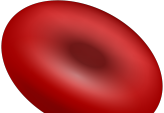
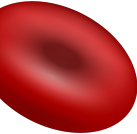


Iron Deficiency Anemia



Ahmad Khajeh-Mehrizi, MD-MPH
Tehran University of Medical Sciences

Feb 2025

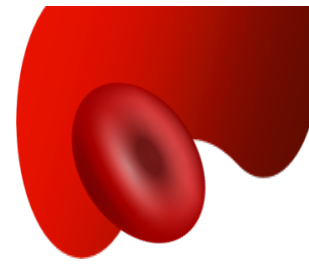
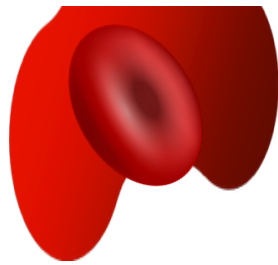
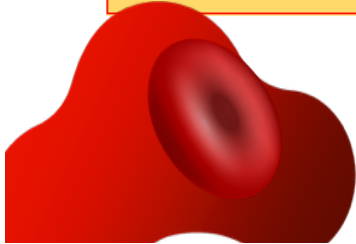
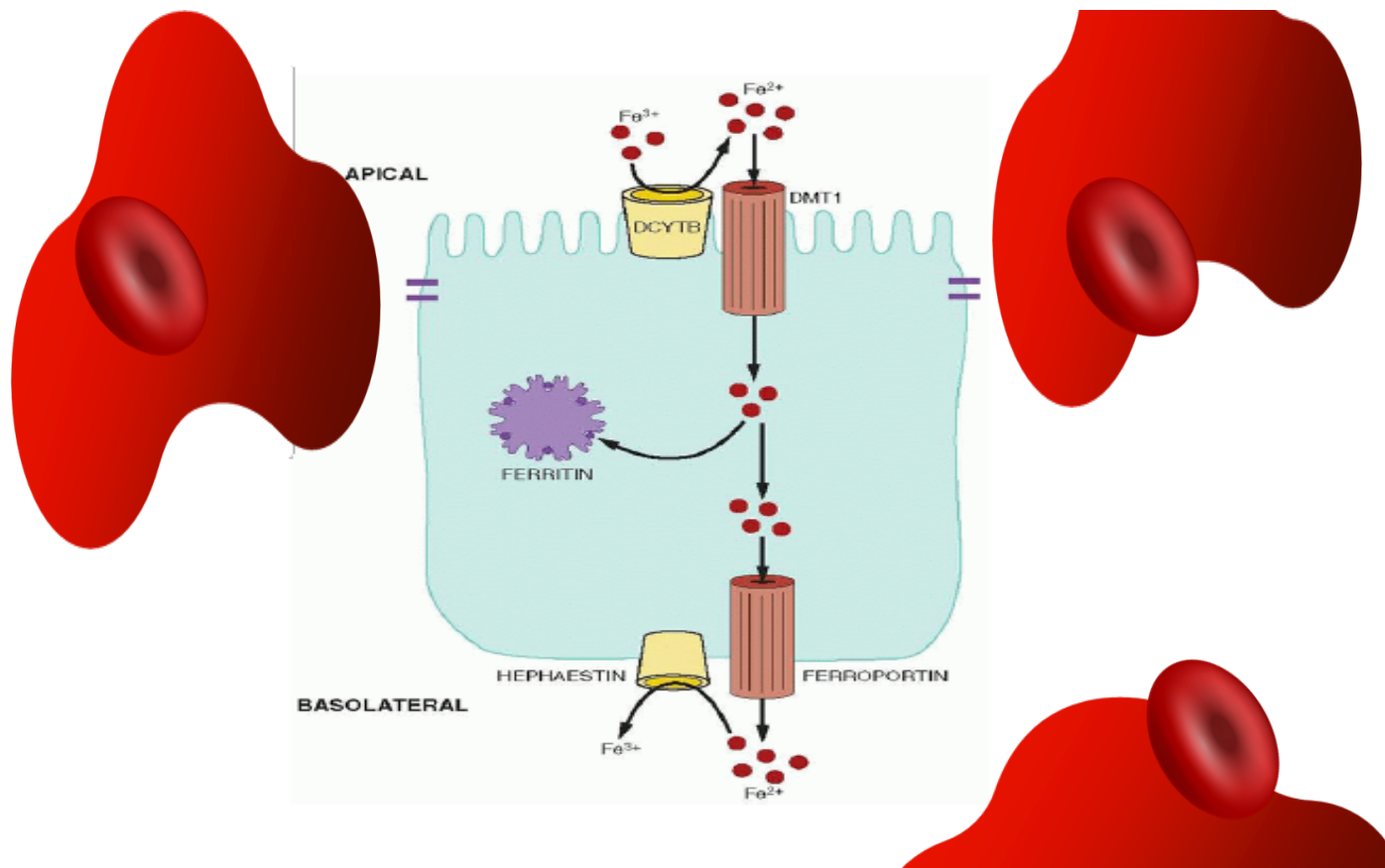


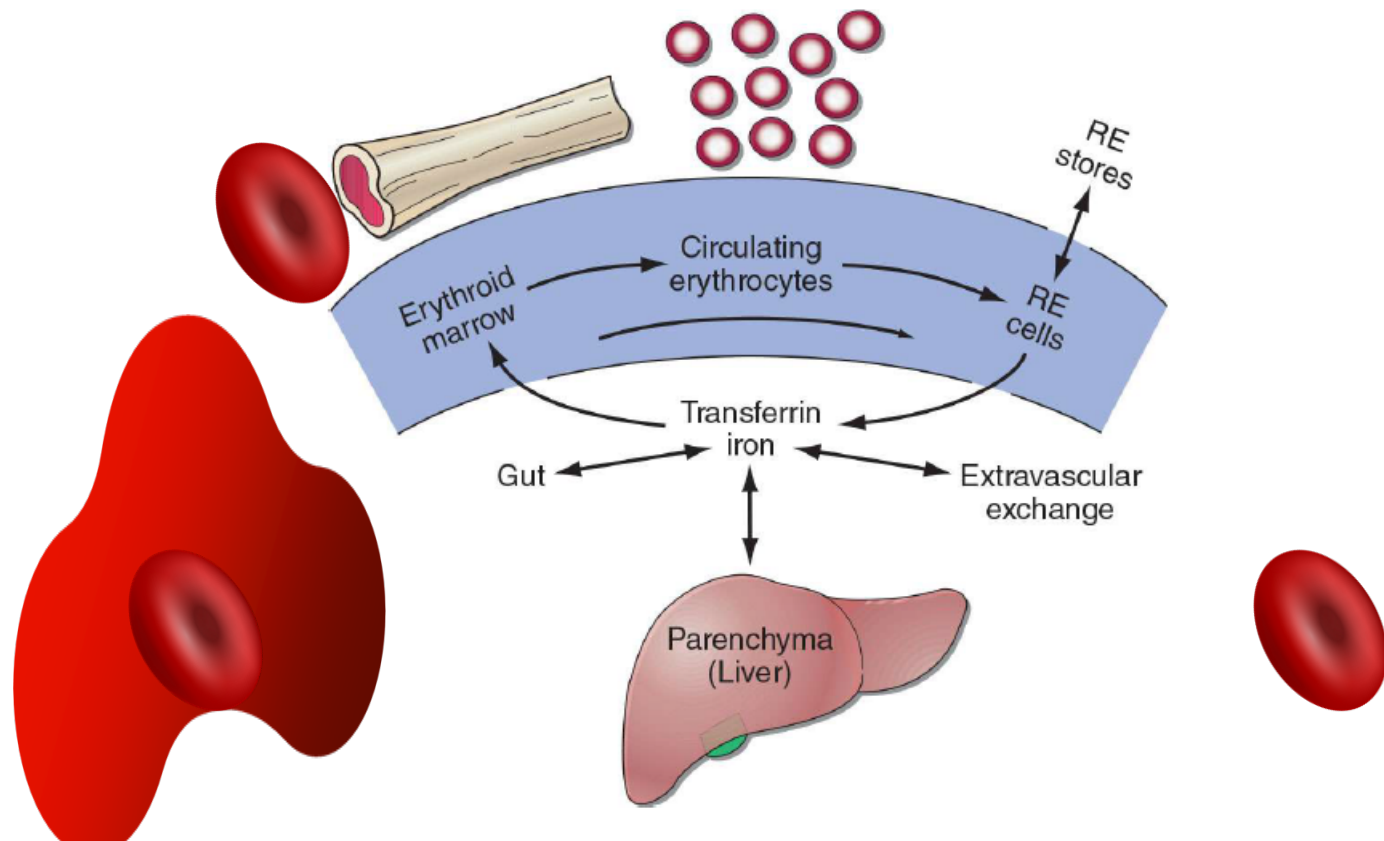
Table 25.1. Iron Distribution in Humans^a

Protein	Function	Fe amount
Hemoglobin	Erythrocyte oxygen transport	2.6 g
Ferritin	Intracellular iron storage	1 g
Transferrin	Plasma iron transport	3 mg
Myoglobin	Muscle oxygen storage	130 mg
Enzymes and other proteins	Electron transport, oxygen sensing, DNA synthesis and other processes	150 mg

^aAmounts estimated for a 70 kg adult male; adult females generally have lower iron stores (100–400 mg).







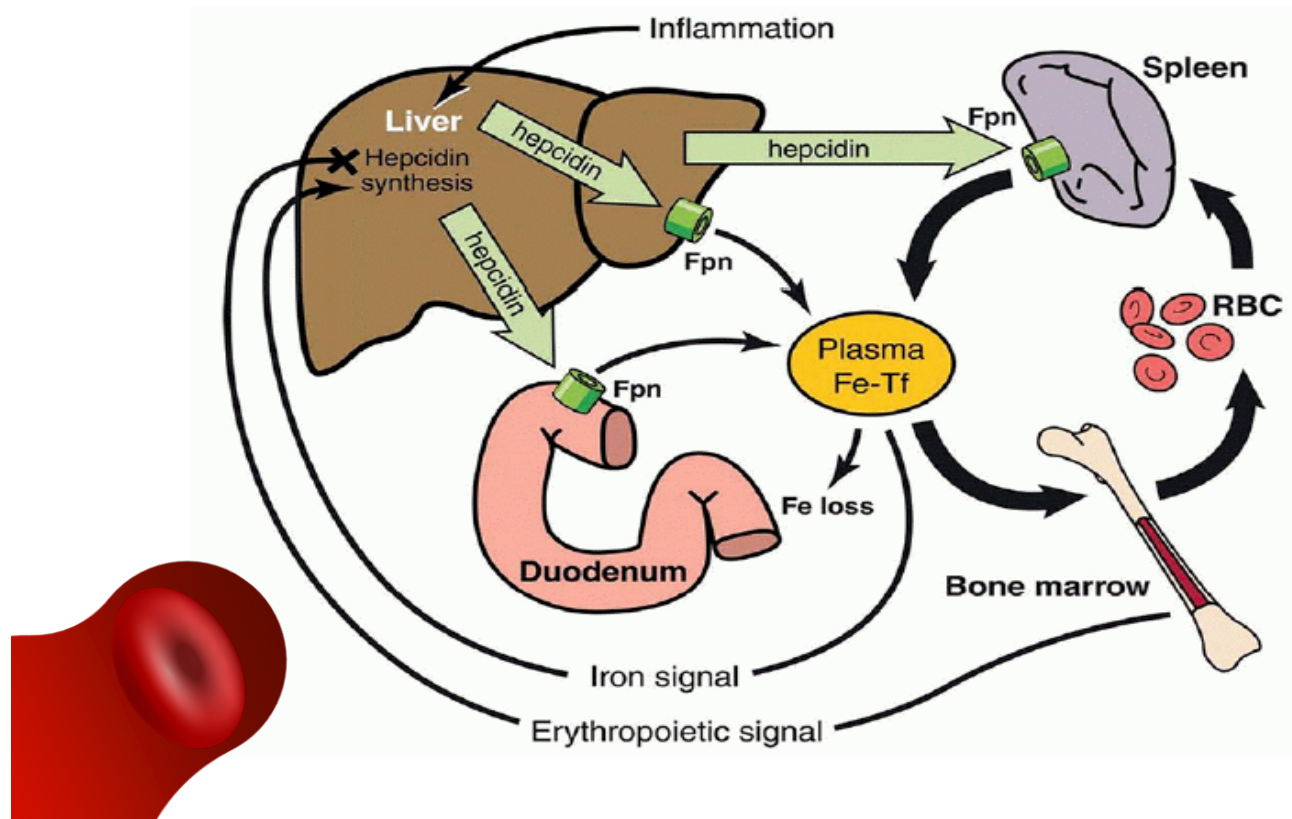


Table 25.8. Potential Role of Hepcidin in Diagnosis and Management of Patients With Iron-Restricted Erythropoiesis

Condition	Expected Hepcidin Levels	Iron Parameters	Iron Therapy Strategies	Potential Hepcidin Therapy
Absolute iron deficiency anemia	Low	Low Tsat and ferritin	PO or IV if poorly tolerated or malabsorbed	No
Functional iron deficiency (ESA therapy, CKD)	Variable, depending on $\pm$ CKD	Low Tsat, variable ferritin	IV	Antagonist (if hepcidin levels not low)
Iron sequestration (anemia of inflammation)	High	Low Tsat, normal to elevated ferritin	IV	Antagonist
Mixed anemia (AI/IDA) or (AI/functional iron deficiency)	Variable	Low Tsat, low to normal ferritin	IV ^a	Antagonist (if hepcidin levels not low)

^a Mixed anemia is a diagnosis of exclusion without a therapeutic trial of iron.

Abbreviations: CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; IV, intravenous; PO, oral; Tsat, transferrin saturation.

Source: L. T. Iron deficiency syndromes and iron-restricted erythropoiesis. *Transfusion*. 2012;52(7):1584-1592. Copyright © 2011 American Association of Blood Banks. Reprinted by permission of John Wiley & Sons, Inc.

Demands for (or losses of) iron exceeding the body's ability to absorb iron from the diet.

This stage results from a number of physiologic mechanisms, including blood loss, pregnancy (in which the demands for red cell production by the fetus outstrip the mother's ability to provide iron), rapid growth spurts in the adolescent, or inadequate dietary iron intake.

Blood loss in excess of 10–20 mL of red cells per day is greater than the amount of iron that the gut can absorb from a normal diet.

Under these circumstances, the iron deficit must be made up by mobilization of iron from RE storage sites. During this period, iron stores—reflected by the serum ferritin level or the appearance of stainable iron on bone marrow aspirations— decrease..

	Normal	Negative iron balance	Iron- deficient erythropoiesis	Iron- deficiency anemia
Iron stores				
Erythron iron				
Marrow iron stores	1-3+	0-1+	0	0
Serum ferritin (µg/L)	50-200	<20	<15	<15
TIBC (µg/dL)	300-360	>360	>380	>400
SI (µg/dL)	50-150	NL	<50	<30
Saturation (%)	30-50	NL	<20	<10
Marrow sideroblasts (%)	40-60	NL	<10	<10
RBC protoporphyrin (µg/dL)	30-50	NL	>100	>200
RBC morphology	NL	NL	NL	Microcytic/ hypochromic



Table 25.4. Stages in the Development of Iron Deficiency

	Stage 1 (Prelatent)	Stage 2 (Latent)	Stage 3 (Anemia)
Bone marrow iron	Reduced	Absent	Absent
Serum ferritin	Reduced	<30 µg/L	<30 µg/L
Transferrin saturation	Normal	<16%	<16%
Free erythrocyte protoporphyrin, zinc protoporphyrin	Normal	↑	↑
Serum transferrin receptor	Normal	↑	↑
Reticulocyte hemoglobin content	Normal	↓	↓
Hemoglobin	Normal	Normal	Reduced
Mean corpuscular volume	Normal	Normal	Reduced
Symptoms	Rare	Fatigue, malaise in some patients	Pallor, pica, epithelial changes

↑, increased; ↓, decreased.

Etiologies

Decreased Iron Intake

Inadequate diet

Impaired absorption

Achlorhydria

Gastric surgery

Celiac disease

Helicobacter pylori infection

Duodenal bypass

Drugs that increase gastric pH

Tannins, phytates

Competing metals

Inflammation, ↑ hepcidin



Increased Iron Loss

Blood donation

Iatrogenic:

diagnostic phlebotomy for testing

Gastrointestinal bleeding

Intestinal parasites

Anatomic lesions:

hemorrhoids, gastritis, diverticulosis, varices, hiatal hernia,

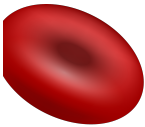
Meckel diverticulum, arteriovenous malformation, peptic ulcer

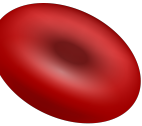
Neoplasm

Inflammatory bowel disease

Cow's milk protein allergy (infants and children)

Use of salicylate or nonsteroidal anti-inflammatory agents





Increased Iron Loss

Excessive menstrual flow

Gynecologic neoplasm

Bladder neoplasm

Epistaxis

Hemoglobinuria

Self-induced bleeding (autophlebotomy)

Pulmonary hemosiderosis

Tuberculosis

Bronchiectasis

Hereditary hemorrhagic telangiectasia

Anticoagulant, antiplatelet therapies

Chronic hemodialysis

Runner anemia



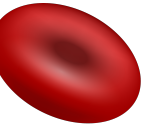


Increased Requirements

Infancy

Pregnancy

Lactation





Reproductive-aged women

Most common causes of ID and IDA:

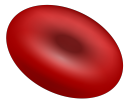
1-HMB

2-Unreplenished losses from Previous Pregnancy

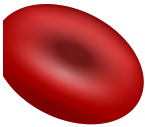
Menstrual blood losses account for approximately **1 mg of iron loss per day**

Heavy menstrual bleeding (HMB)

In women is defined as loss of more than **80 ml of blood** during a menstrual period



Questions to ask to help quantify blood loss during menses



How often do you change your sanitary pad/tampon during peak flow days?

How many pads/tampons do you use over a single menstrual period?

Do you need to change the pad/tampon during the night?

How large are any clots that are passed?

Has a medical provider told you that you are anemic?

Women with a normal volume of menstrual blood loss tend to:

Change pads/tampons at ≥ 3 hour intervals

Use fewer than 21 pads/tampons per cycle

Seldom need to change the pad/tampon during the night

Have clots less than 1 inch in diameter

Not be anemic

Up to **53%** of women of reproductive age in at risk of IDA.

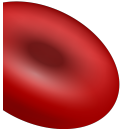
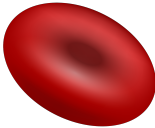


Screen females with **HMB + Recurrent or Refractory IDA** without **uterine organic lesions** for **congenital bleeding disorders (CBDs)** such as:



Platelet function disorders
Von Willebrand disease (VWD)

CBDs are present in approximately **20%–30%** of females with HMB and can result in unnecessary hysterectomy.



2 Billion

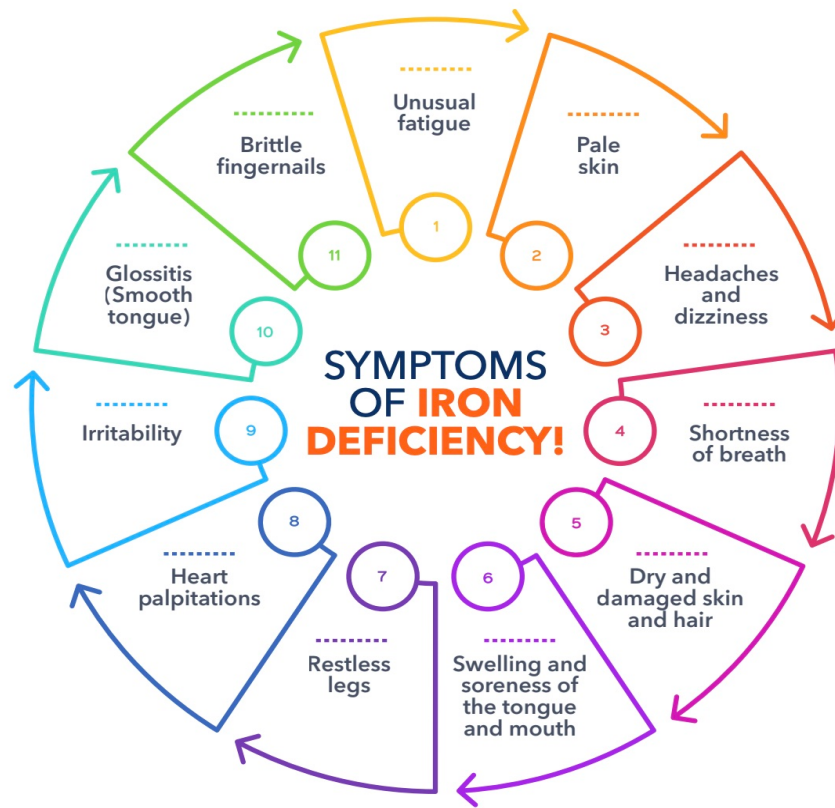
CLINICAL MANIFESTATIONS

Signs and symptoms of ID/IDA

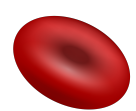
Fatigue, Lethargy, Chills, Dizziness, Dyspnea, Tinnitus, Pallor, Heart palpitations, Restless legs syndrome, headache & Cognitive decline

RLS

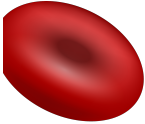
- In a 2023 series of 987 of **ID**, 398 (**40 %**) of the records mentioned **RLS**
- Some clinicians will give a trial of iron therapy **even when iron parameters are normal**
- Complete Improvement **after 72 hr** of treatment



Epithelial Lesions Associated With Iron Deficiency



Site	Finding
Nails	Flattening
	Koilonychia
Tongue	Soreness
	Mild papillary atrophy
	Absence of filiform papillae
Mouth	Angular stomatitis
Hypopharynx	Dysphagia
	Esophageal webs
Stomach	Achlorhydria
	Gastritis



Diagnosis & Screening



WHO IDA Criteria:

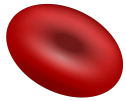


- Men : **Hb** < 13^U (13.6)
- Nonpregnant Women : **Hb** < 12^U (11.9)
- Pregnant Women : **Hb** < 11

In **Older individuals**, there's a common occurrence of **vitamin B12 and folate deficiency**.

Consequently, relying solely on **MCV** assessment isn't reliable for ruling out iron deficiency anemia in the elderly.

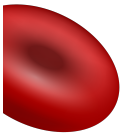
Hepcidin is **limited** primarily to research settings and rarely used in the clinical setting in some European hospital laboratories.





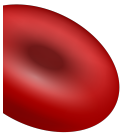
EHA 2024 guideline from the screening IDA

- **All people who menstruate**
- **Anyone who is pregnant**
- **Athletes**
- **Vegetarians**
- **Individuals with bleeding disorders or receiving an anticoagulant**
- **Individuals with a history of gastric surgery**
- **Patients with chronic infections**
- **Any patients undergoing major surgery**
- **Patients at risk for reduced access to medical care**
- **Older adults (especially with chronic conditions)**
- **Adolescents, due to increased iron requirements during growth spurts**





Screening of adolescent and adult females of childbearing age:



Every 5 Years

If there is extensive menstrual blood loss, low iron intake, or a history of
ID:

Annually

Ferritin levels WHO (2022)

- Children older than 5 years, adolescents, and adults **<15 ug/L**  **<20**
- Children younger than 5 years **< 12 ug/L** **ID <30**
- Adults aged **> 65 years** **< 45 µg/L** (if not 100 µ g/L)
mainly when specific comorbidities occur, such as **CKD or CHF**
 GI Guideline 2020: **45 µg/L**
- In **Pregnancy**, there is **No Standardized** serum ferritin thresholds.

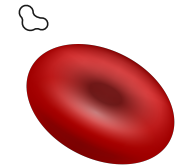
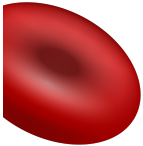
Many authors suggested 30 µg/L

Higher sensitivity (from 85% to 92%) and unchanged specificity (98%)

Ferritin Reflect iron stores **but** are rarely informative about actual iron availability for erythropoiesis. For this reason, other parameters such as:

- **Transferrin saturation (TSAT)**
Adults < 15 %  < 20 %
Pediatrics < 7 %
- Soluble transferrin receptor / Ferritin (**sTfR** > 2)
- Percentage of hypochromic erythrocytes (% **HYPO** > 2.5%)
- Reticulocyte hemoglobin content (**CHr** < 29 pg)

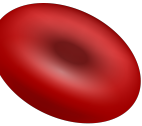
are useful to identify an inadequate iron supply to erythropoiesis





Median ferritin levels for increasing CRP

- **CRP <10 (least inflammation) – Ferritin 85**
- **CRP 10 to 80 – Ferritin 193**
- **CRP > 80 (greatest inflammation) – Ferritin 342**



Lower serum albumin also associate with higher serum ferritin levels.

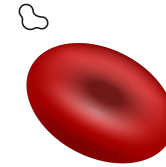
Ferritin concentrations can increase in:

- **Liver disease (including NASH)**
- **Obesity**
- **Inflammation**

Modern Automated Hematology Analyzers

The Percentage of hypochromic red blood cells (%HYPO RBC)

Reflects iron-restricted erythropoiesis during **2-3 months ago**



The Reticulocyte hemoglobin content (CHr)

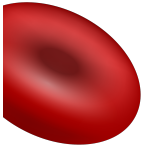
Reflects iron-restricted erythropoiesis during **3-4 days ago**

 **Used in CKD , Unaffected by inflammation, Unreliable in Thalassemia**



Soluble transferrin receptor (sTfR) and sTfR-ferritin index

 **Unaffected by inflammation, Influenced hemolysis and EPO**





Celiac disease should be considered in patients:

Non-Anemic ID and all adult patients with IDA

 **1 in 70 to 1 in 300 (0.3 to 1 %) in Europe**



Men and post-menopausal women with IDA are at high risk of bleeding GI lesions and should be considered for **upper and lower gastrointestinal endoscopy**.

Autoimmune gastritis and **H.pylori** should be considered in all patients; especially in those who do **not adequately respond** to oral iron.

Pre-menopausal women with IDA should be considered for Bi-endoscopy

if

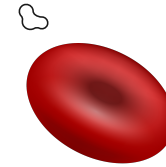
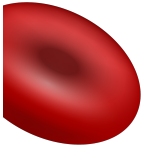
- Symptoms of gastrointestinal disease
- No clear explanation for IDA, such as HMB

If upper and lower endoscopic studies is normal:

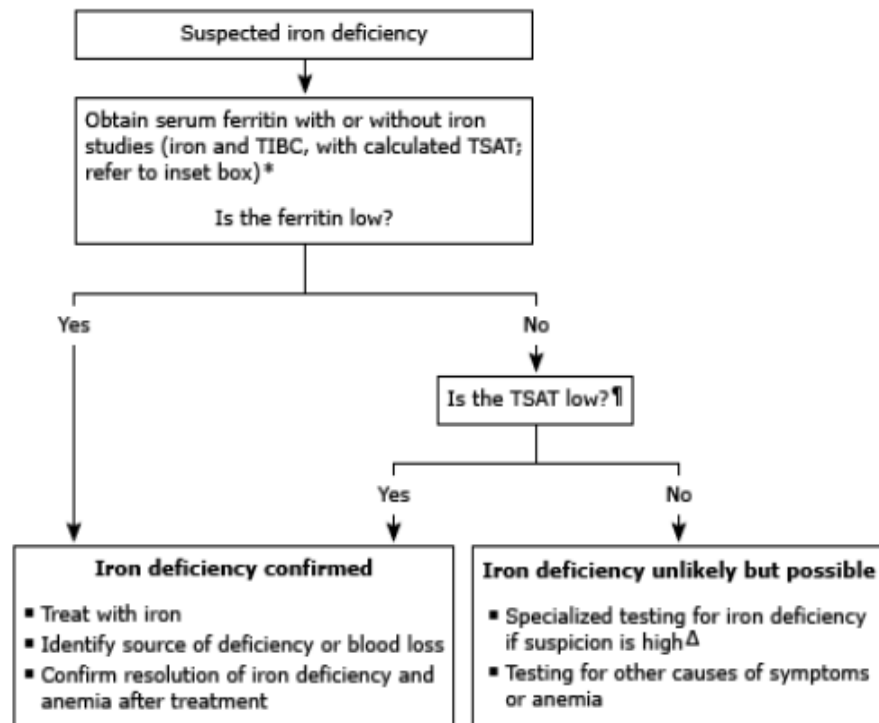
STOP More Assessment

except

Recurrent, Refractory, or Severe IDA



Diagnosis of iron deficiency in adults



Findings in iron deficiency (selected examples)

History:

- Symptoms of anemia such as undue fatigue
- Pica, pagophagia, or restless legs syndrome
- Autoimmune gastritis or celiac disease
- Heavy menses or prior pregnancies
- GI bleeding or frequent blood donation

Examination:

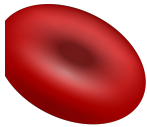
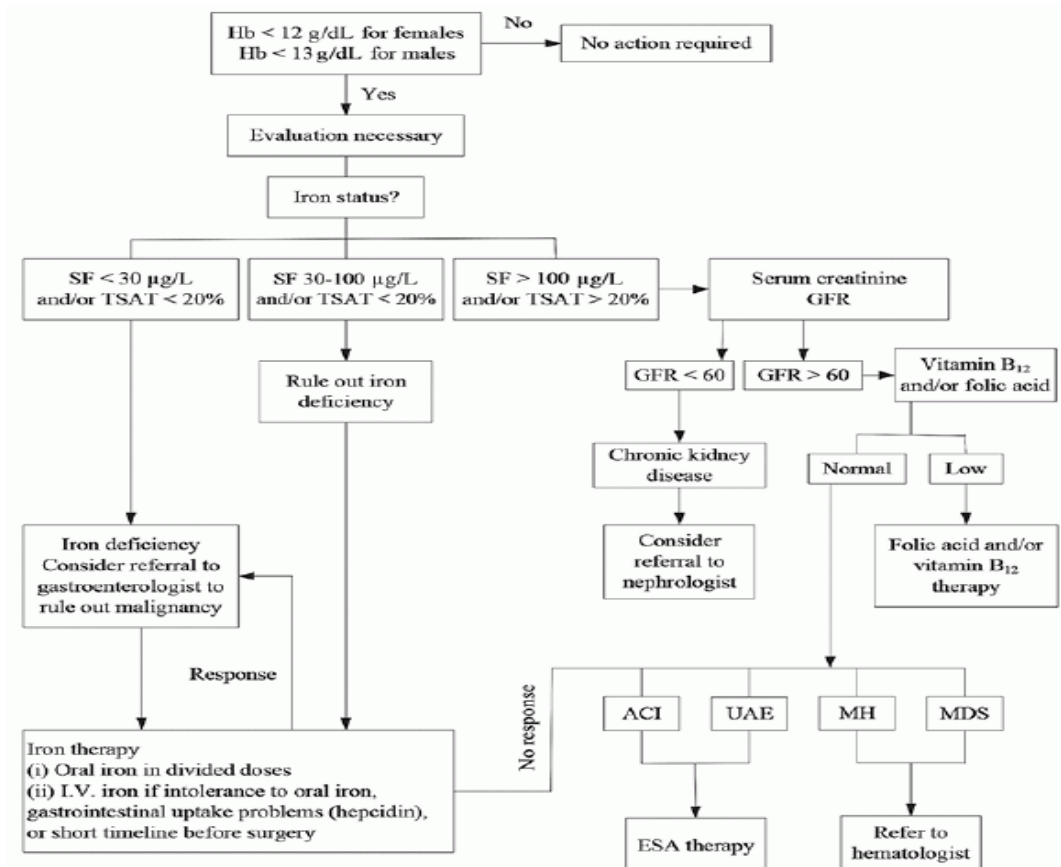
- Pallor, brittle skin
- Fingernail changes (spoon shape, horizontal lines)
- Cheilosis, loss of tongue papillae
- Occult blood in stool

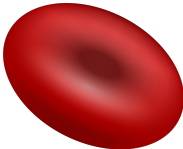
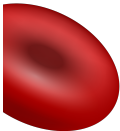
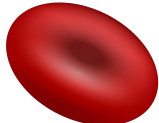
CBC:

- Anemia, low RBC count
- Normocytic or microcytic RBCs
- Low reticulocyte count
- High platelet count

Iron studies:

- Ferritin <30 ng/mL (or <41 ng/mL if anemia and comorbidities are present)*
- TSAT <20%†



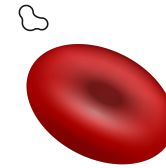
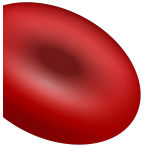


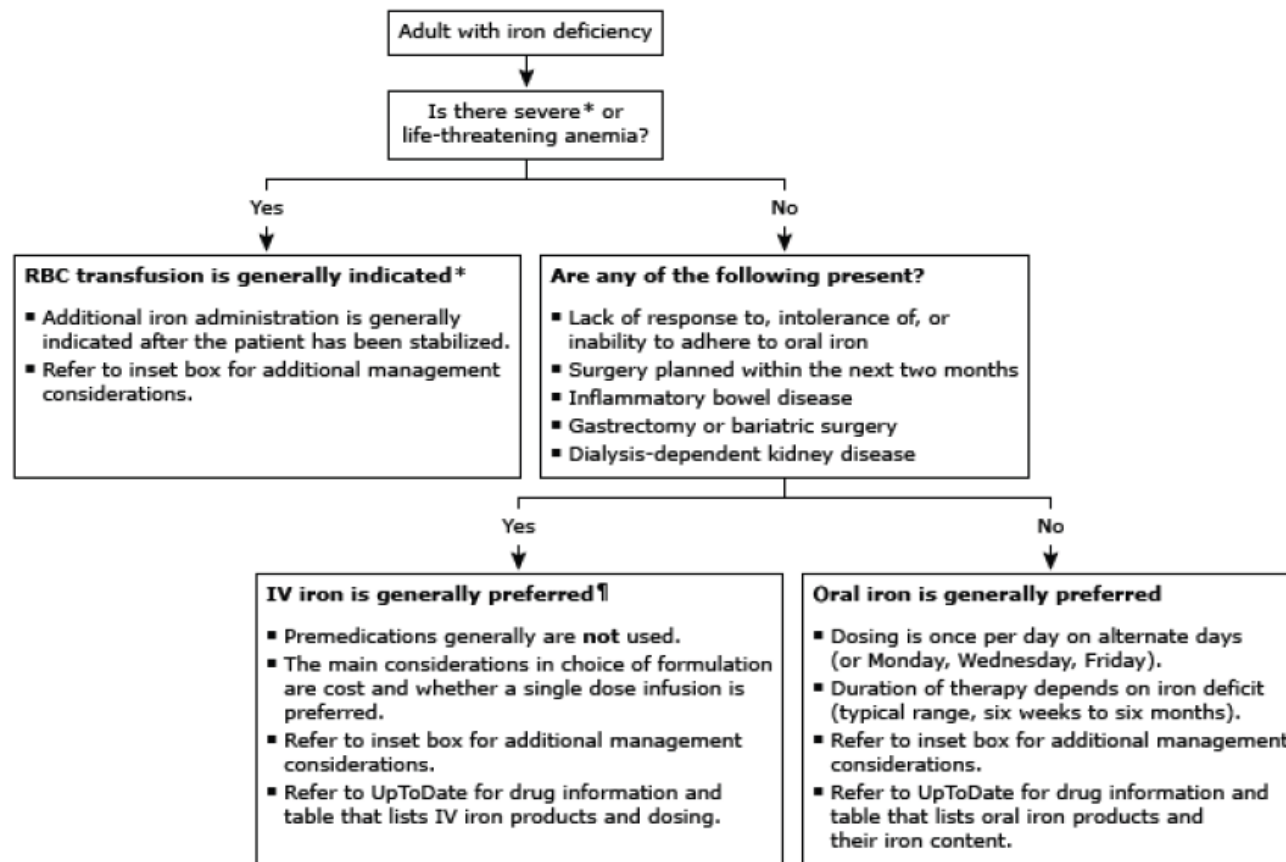
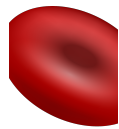
THERAPY/MANAGEMENT

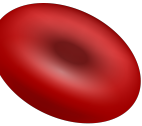
ID

The benefit of treating ID even in the absence of anemia is proven is increasingly recognized in patients with some comorbidities, such as CHF.

Oral Iron is the first line treatment in uncomplicated cases





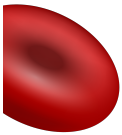


GENERIC NAME	TABLET (IRON CONTENT), mg	ELIXIR (IRON CONTENT), mg IN 5 mL
Ferrous sulfate	325 (65)	300 (60)
	195 (39)	90 (18)
Extended release	525 (105)	
Ferrous fumarate	325 (107)	
	195 (64)	100 (33)
Ferrous gluconate	325 (39)	300 (35)
Polysaccharide iron	150 (150)	100 (100)
	50 (50)	

Dose 100-200 mg preferably without food;

Should be continued until the Hb normalizes which may take **6-12 weeks**

Continued for **at least 3 months** after Hb restoration, to adequately replenish iron stores;
(with an ideal target of ferritin > **100**)

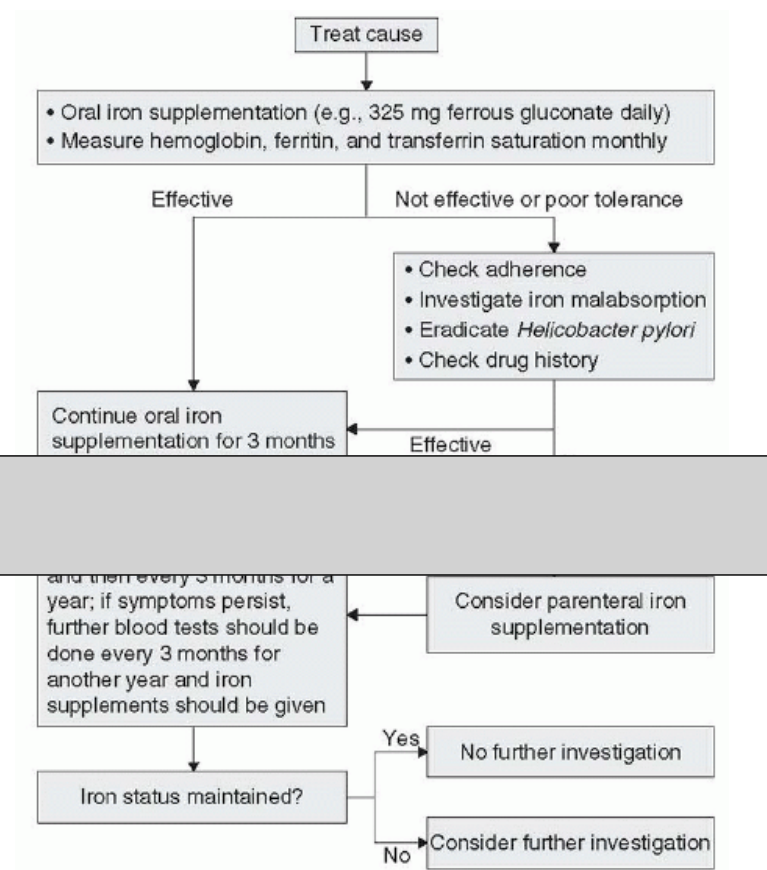
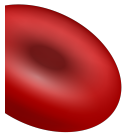


Hb response Check Hb and Retic count **after 2 weeks**;

The Hb should rise by **at least 1 g/dL**

Monitoring Hb Every **3 months** for 12 months then every **6 months** for 2–3 years

There are insufficient data to recommend its routine use **ferritin** for monitoring



Causes for lack of response to oral iron therapy

A coexisting condition is interfering with bone marrow response to iron repletion

Infection

Inflammatory disorder (eg, rheumatoid arthritis)

Concomitant malignancy

Coexisting folate and/or vitamin B12 deficiency

Bone marrow suppression from another cause

Patient is not iron deficient; possible correct diagnoses include

Thalassemia

Lead poisoning

Anemia of chronic disease/anemia of inflammation

Copper deficiency (zinc toxicity)

Myelodysplastic syndrome/refractory sideroblastic anemia

Patient is not taking the medication

Prescription has not been filled

Prescription has been filled but patient is no longer taking the medication

Medication is being taken but is not being absorbed

Rapid intestinal transport bypasses area of maximum absorption

Enteric coated product: coating is not dissolving

Patient has an acquired condition that causes malabsorption of iron (eg, sprue, atrophic or autoimmune gastritis, *Helicobacter pylori* infection)

Patient is taking an agent that interferes with absorption (eg, antacids, tetracycline, tea)

Patient has a congenital cause for iron malabsorption (eg, iron-resistant iron deficiency anemia [IRIDA])

Continued blood loss or need in excess of iron dose ingested

Treatable cause of blood loss (eg, bleeding peptic ulcer)

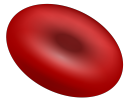
Cause of blood loss that is not treatable (eg, hereditary hemorrhagic telangiectasia [Osler-Weber-Rendu syndrome]) or need cannot be met by oral iron preparation (eg, kidney failure or a malignancy being treated with erythropoietin)



Heme iron polypeptide (HIP), polysaccharide iron complex (PIC), and ferric citrate should be taken with meals; HIP and PIC are expensive but have better tolerability;
However, there are limited clinical data on both

Vitamin C neither enhances the hematological response nor diminishes the side effects.

Under study commonly 80 mg Vitamin C	Control – 21 percent
	Vitamin C 80 mg – 27 percent
	Vitamin C 500 mg – 31 percent
	Coffee – 10 percent

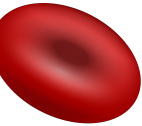




Options to improve absorption and tolerability of oral iron supplements

Improve absorption^{*}

- Avoid enteric coated or timed-release products
- Take separately from foods that may impair absorption
 - Meals
 - Coffee
 - Eggs
 - Oxalates (spinach, kale, beets, nuts, chocolate, tea, wheat bran, rhubarb, strawberries, some herbs)
 - Phytates (soy, fiber, cereals, some nuts, beans, lentils, peas)
 - Tannates (tea, cocoa, some spices, some berries)
 - Calcium (milk, yogurt, cheese, some greens, fish)

- 
- 
- Minimize exposure to medications that decrease gastric acidity
 - Antacids (take iron 2 hours before or 4 hours after the antacid)
 - Histamine receptor blockers (discontinue if no longer needed)
 - Proton pump inhibitors (discontinue if no longer needed)
 - Take with foods/supplements that may increase absorption
 - Vitamin C
 - Orange juice

Improve tolerability*

- Use a titratable (eg, liquid) form[¶]
- Change from every-day to every-other-day dosing
- Dietary modifications (eg, take with food)^Δ
- Take a product with less elemental iron^Δ
- Use a stool softener or laxative

Absolute ID



❖ Take detailed history for etiology

- Overt bleeding (AUB, HMB, GI bleeding, hematuria, epistaxis); consider the possibility of occult bleeding
- Nutritional (anorexia/malnutrition, vegan or vegetarian diet, poor meat intake)
- Increased iron need (e.g., during pregnancy or lactation), even in the past (e.g., previous multiple pregnancies)
- Malabsorption (GI symptoms, weight loss, diarrhea or previous bariatric surgery)
- Regular blood donors or endurance athletes
- Ongoing pregnancy/lactation
- Multiple pregnancies



❖ Initiate IRT (unless colonoscopy is planned urgently*)

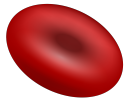
❖ Concomitantly, start evaluations for underlying etiology

- Urine analysis
- Celiac disease serology (tissue transglutaminase)
- FIT
- Helicobacter Pylori
- Gynecology consultation if history is suggestive of AUB/HMB
- Upper endoscopy and colonoscopy** in selected patients (FIT positive, FIT negative men or post-menopausal women with IDA)



❖ Inadequate response to IRT or recurrence of IDA

- Additional work-up for
 - small intestines (capsule endoscopy)
 - renal tracts (urology consultation)





IV IRON

Indications for intravenous iron treatment include:



- Intolerance to oral IRT
- Inadequate response to oral IRT (**Hb < 10** by the **4 week** of oral IRT)
- Rapid iron replacement (Symptomatic patient or Preoperative whenever less than **6 weeks** is available up to surgery)
- IBD
- CKD
- CHF
- Intestinal malabsorption
- Ongoing abnormal uterine bleeding if gynecological intervention is delayed
- IDA in the **2th** or **3th** trimester of pregnancy
- IRIDA (Iron-refractory iron deficiency anemia)



Total amount of iron

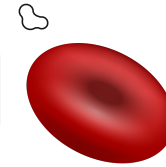
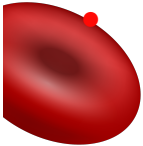
Weight(kg) x (Target Hb-Patient's Hb) x 2.4 + Storage iron

Target Hb:

- Weight < 35 kg is **13**
- Weight > 35 kg is **15**

Storage iron is calculated:

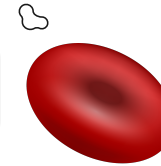
- Weight < 35 Kg is **15 mg/kg**
- Weight > 35 Kg is **500 mg**



Total amount of iron



iron

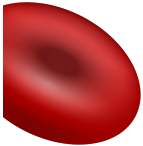


60 kg woman with a Hb = 8 g/dL :

Parenteral iron product is **iron sucrose** (C = 20 mg elemental iron/mL)

Hemoglobin iron deficit = $60 \times (14 - 8) \times (2.145) + 500 \text{ mg} = 1272 \text{ mg}$

Volume of iron sucrose needed = $1272 \div 20 = \mathbf{63.6 \text{ mL}}$ ◇



Ferric carboxymaltose (Ferinject)



- Weight ≥ 50 kg: 1 or 2 doses of 750 mg, given 7 or more days apart
- Weight < 50 kg: 1 or 2 doses of 15 mg/kg, given 7 or more days apart

 European product labeling specifies a maximum single dose of **20 mg/kg of body weight**

 US Product labeling specifies a maximum single dose of **15 mg/kg of body weight**

Other formulations

The total amount of iron calculated is given at divided doses every 1 to 2 weeks until iron stores are replenished.



Premedication is not recommended before infusions **except** for patients:



Asthma or multiple drug allergies, we often give **Methylprednisolone** and a H2 blocker
e of

Severe infusion reactions or higher prevalence of infections are **rare**.

Low-molecular-weight iron dextran

Test dose is recommended and infusion time of **2–6 hr**

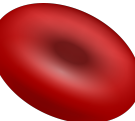
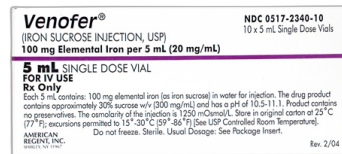
Should not be applied in patients with: **Sepsis as bacterial growth** may be stimulated

Reassessment 3 months after the final infusion dose





Iron sucrose (Venofer) is the most commonly preferred formulation
(100-300 mg/infusion in adolescents)



Iron dextran (INFeD)

LMW ID (100 mg multiple dose or 1000 mg single dose)
(Although the package insert specifies multiple doses; we use a single dose)

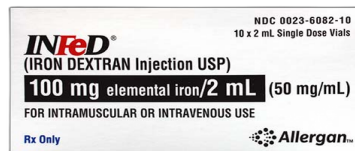
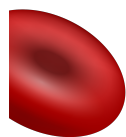
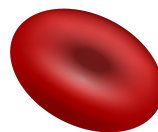


TABLE 3 Intravenous iron formulations.

Formulation	Amount per dose (mg)	Infusion time
LMW-iron dextran	25 mg initial test dose 100 mg/dose	2–6 hours
Iron sucrose	200–300 mg/dose	100 mg/30 min
Ferrous gluconate	125 mg	12.5 mg/min
Ferumoxytol	510 mg	15 min
Ferric carboxymaltose	750–1000 mg (differs according to brand)	15 min
Iron isomaltoside	Differs according to brand	Differs according to brand



PREGNANCY



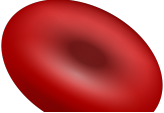
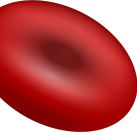
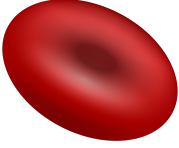
Table 25.6. Iron Balance in Pregnancy

Iron Fate	Mean Amount (mg)
Lost to fetus	– 270
Lost to placenta	– 90
Expansion of maternal RBC mass	– 450
Baseline maternal body iron loss	– 230
Total iron needs during pregnancy	– 1040
RBC mass contraction after delivery	+ 450
Iron lost with bleeding at delivery	– 150
Net pregnancy iron loss to the mother	– 740
Abbreviation: RBC, red blood cell.	



- **Every other day** dosing has been reported to increase iron absorption with higher tolerability to GI side effects in nonpregnant women.
- **Oral iron salts** are the only IRT formulations recommended during the **first trimester** of pregnancy.
- **IV Iron** In the **second trimester** of pregnancy, if the **Hb < 10.5** or **third trimester**
- There is **no evidence-based screening time** for ID/IDA during pregnancy 
- **4 to 6 weeks after IRT initiation**, testing for **serum ferritin** is recommended.





Thanks!

Do you have any questions?