

Iron Metabolism

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Case

ID and CC:

- 45 year old man
- Sepsis
- UTI vs. Sacral Wound
- Hemodynamic compromise
- Urgent surgical debridement

PMH:

- Paraplegic due to GSW
- Noncompliance with urinary self-catheterization
- Chronic sacral wounds
- Bipolar disorder
- Anemia

Laboratories:

- Hgb 8.0 g/dL (14-17g/dL)
- Hct 24% (41-51%)
- MCV 75 fL (80-100 fL)
- RDW 12.0 (11-14)
- Ferritin 250 ng/mL (15-200 ng/mL)
- Transferrin 100 mg/dL (188-341 mg/dL)
- Percent saturation 8% (15-50%)

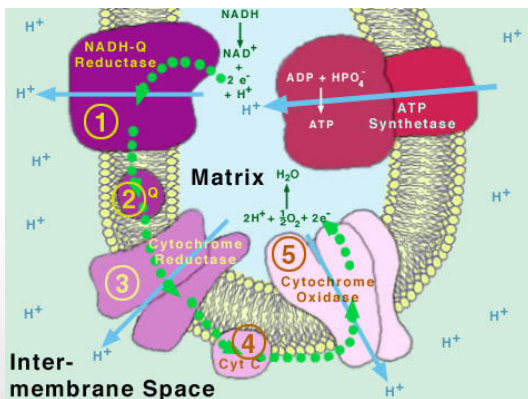
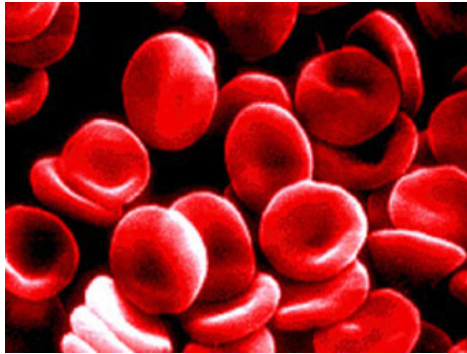
Which of the following statements accurately describes the cause of this patient's anemia?

- A. This patient is iron deficient and the elevated ferritin is due to his infection.
- B. This patient is not iron deficient and his anemia is due to chronic disease.
- C. The amount of information given is not enough to determine whether or not the patient is iron deficient.

Objectives

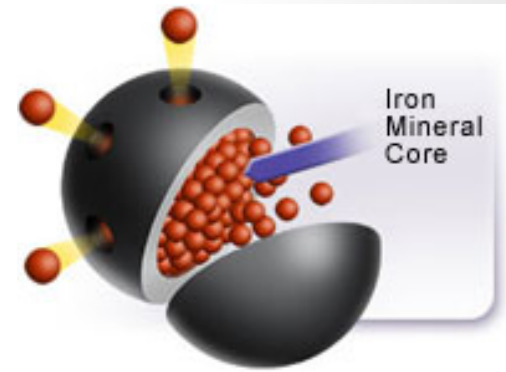
- Define the following terms: ferritin, hemosiderin, transferrin, total iron binding capacity, and percent saturation.
- Describe the hepcidin iron exporter regulator and how it is involved in hereditary hemochromatosis and anemia of chronic disease.
- Describe the symptoms of iron deficiency, the lab values (ferritin, hemoglobin and MCV) as they change with progressively more severe iron depletion, and list five conditions associated with iron deficiency.
- Describe the clinical manifestations of iron overload, name the organs involved in iron overload conditions, and know the appropriate lab tests indicated for the screening and diagnosis of hereditary hemochromatosis.
- Know the difference in the interpretation of iron studies in a patient with end-stage renal disease and the indication for iron supplementation.
- Know the indications and methods of treatment for iron overload.

Iron (Fe)



- Iron is the fourth most abundant element in the earth's crust.
- Biologically, it is a part of hemoglobin, myoglobin, and cytochromes.
- It readily converts from ferric (3+) to ferrous (2+) forms by donating and accepting electrons.
- **Iron homeostasis is tenuous; both states of deficiency and overload are harmful.**

Iron Storage



- **Ferritin (tissue):**
a huge protein consisting of light and heavy chains which can store up to 4500 atoms of iron within its spherical cavity
- **Apoferritin (or serum ferritin):**
a non-iron containing molecule measured clinically in the plasma that reflects the overall iron storage. (1 ng/mL of apoferritin indicates 10 mg of total iron stores)
- **Hemosiderin (skin, lungs):**
an insoluble intracellular protein that contains iron and is formed by the phagocytic digestion of blood



Iron Transport

- Transferrin:

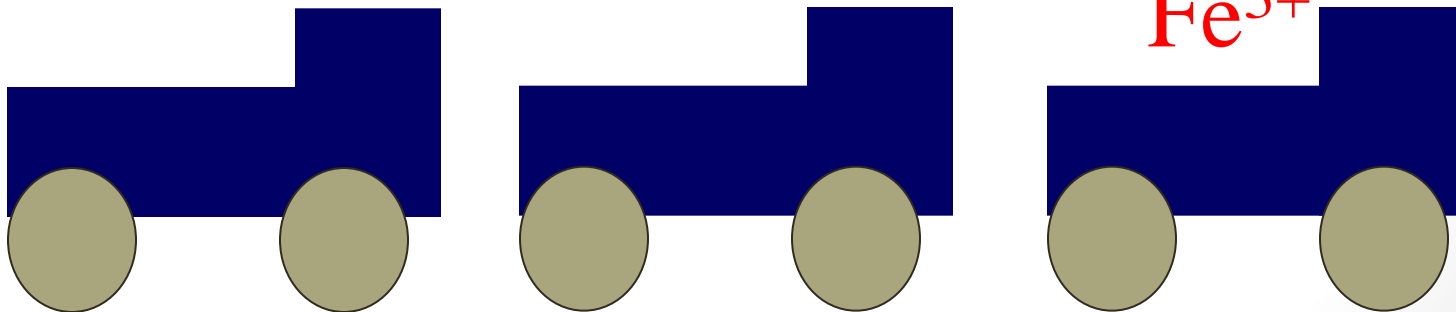
a protein that tightly binds one or two ferric (Fe^{3+}) molecules and transports the iron through the plasma

- Total Iron Binding Capacity (TIBC):

total transferrin available for binding Fe^{3+}

- Percent saturation:

serum iron divided by TIBC x 100



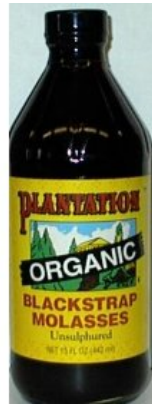
Iron Content and Distribution in Men and Women

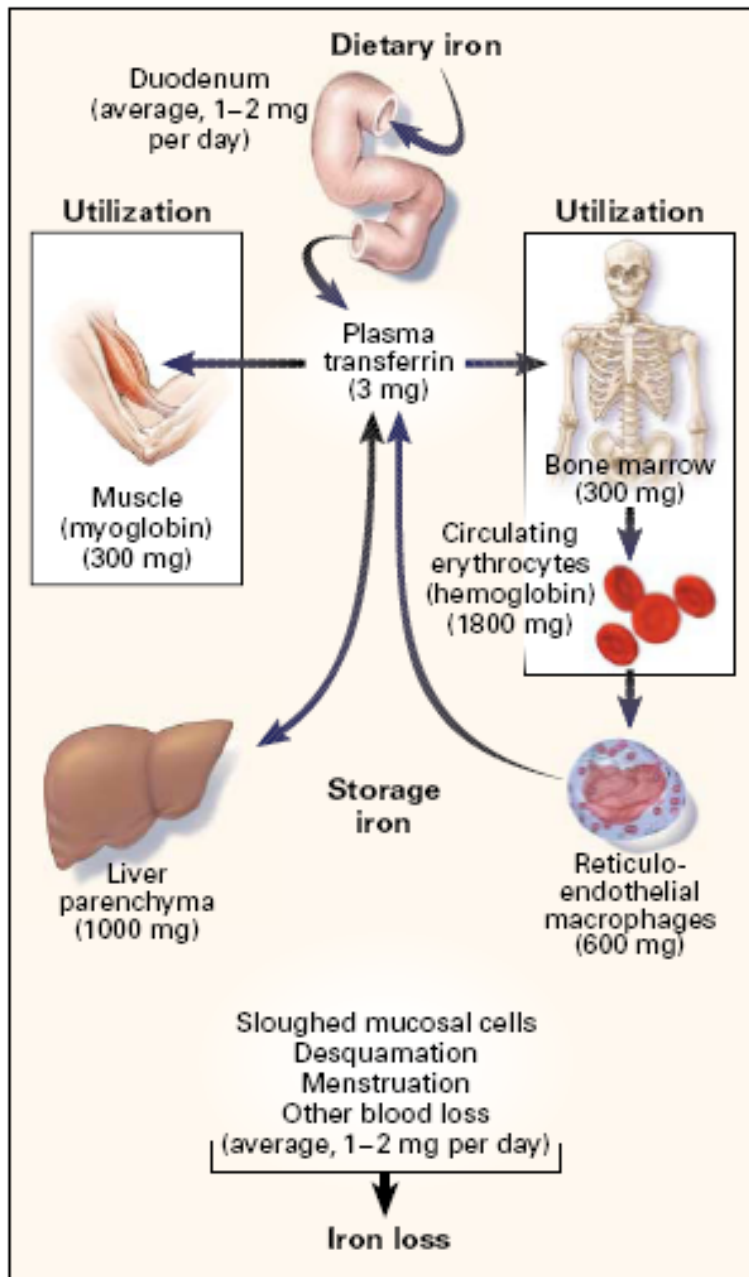
	70 kg man	60 kg woman
Iron stores - transferrin, ferritin, hemosiderin	1.4 g	0.3 g*
Hemoglobin	2.5 g	1.9 g
Myoglobin	0.14 g	0.13 g
Heme enzymes	0.01 g	0.01 g
TOTAL	4.05 g	2.34 g

* This value is an average. Approximately 20 percent of menstruant women may have no iron stores.
Data from Schrier, SL, Scientific American Medicine, Scientific American, New York, 1995.

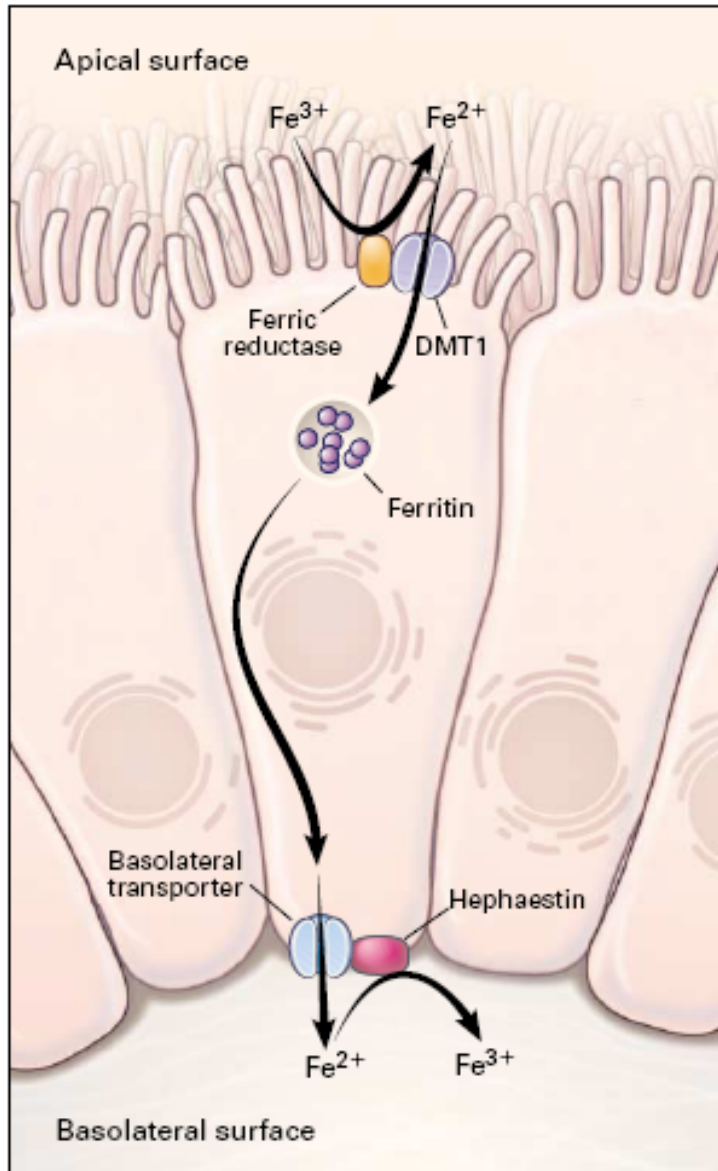


- The average western diet consumes 15-25 mg of iron per day

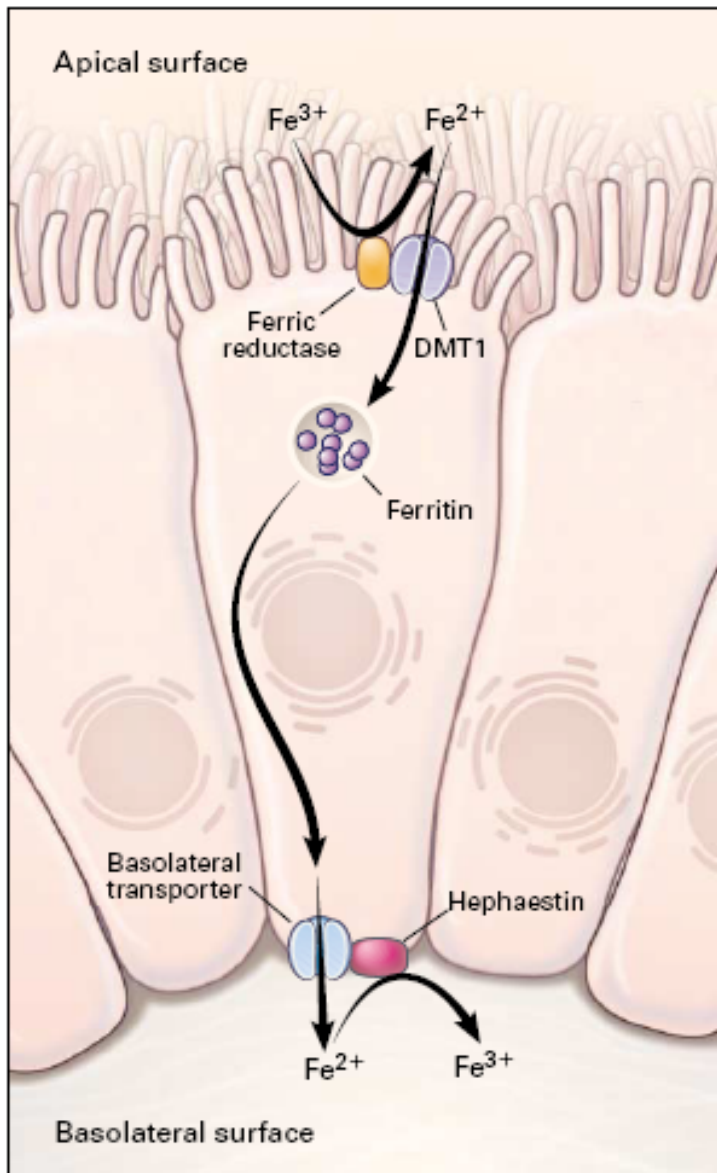




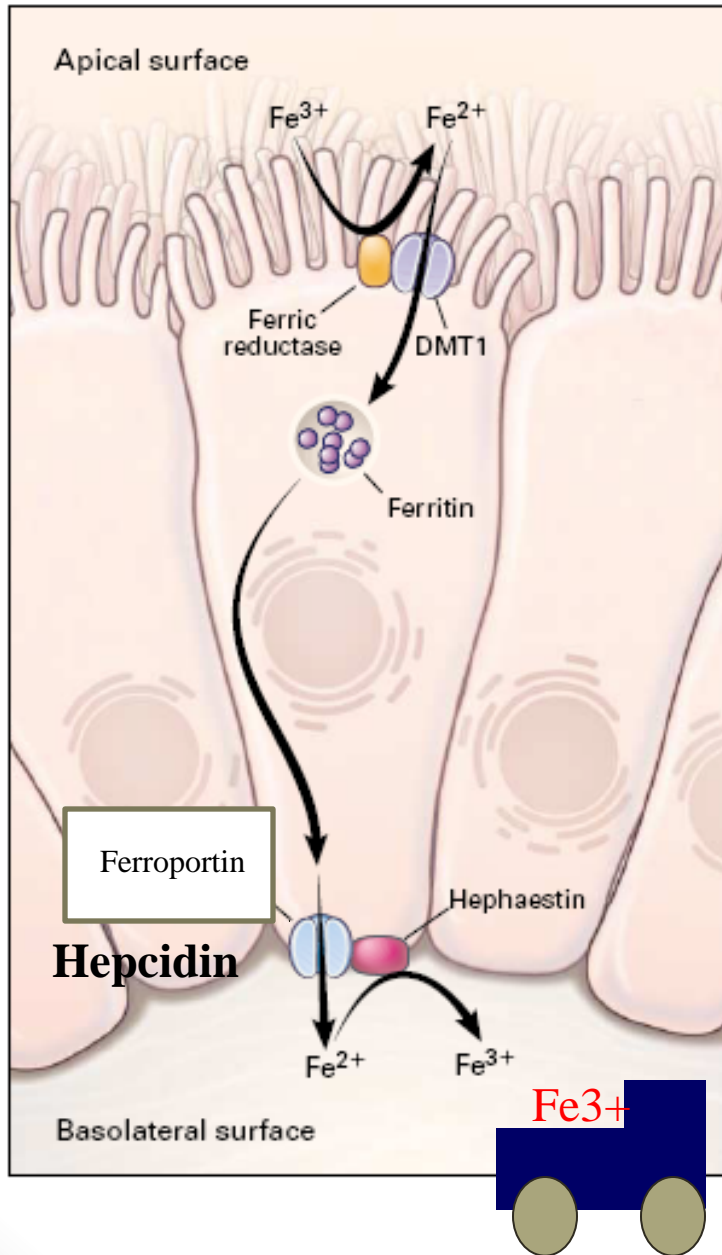
- **Iron is absorbed in the duodenum.**
- In a balanced state, 1-2 mg of ingested iron is absorbed and lost from the body each day.
- **Regulation of the intestinal absorption of iron is critical—humans have no physiologic pathway for excretion!**
- Iron circulates in plasma bound to a carrier protein called **transferrin**.
- Iron is stored in the liver, reticuloendothelial macrophages, and enterocytes as **ferritin**.



- In the stomach, the low pH of the gastric juices helps to dissolve ingested iron.
- Iron must pass from the gut lumen through the apical and basolateral membranes of the enterocyte to reach the plasma.
- The ferric iron (3+) is reduced to ferrous iron (2+) by a brush-border ferrireductase that is coupled to a transporter protein.



- This transporter protein, called “divalent metal transporter 1” (DMT 1) is a protein that transfers iron across the apical membrane and into the cell through a proton-coupled process.
- DMT 1 is not specific to iron; it also transports manganese, cobalt, copper, zinc, cadmium, and lead.
- How could this be important, clinically?



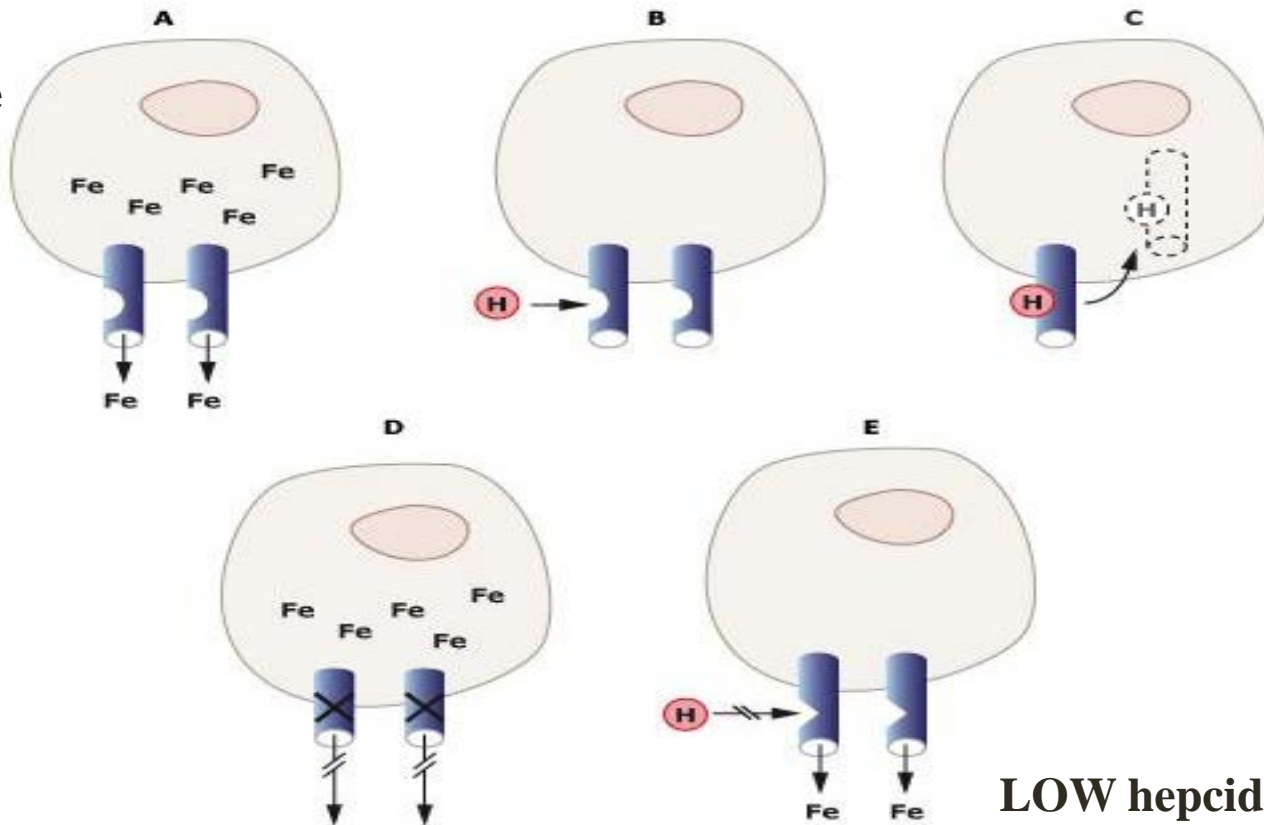
- Iron within the enterocyte is stored as **ferritin**. This iron may be lost with desquamation of the enterocyte.
- On the basolateral surface, the exporter is called ferroportin.
- Ferroportin requires a molecule to oxidize the ferrous iron back into ferric iron for loading onto **transferrin**.
- **HEPCIDIN** is the regulator of ferroportin that determines how much iron enters the circulation.

Hepcidin: iron export regulator

HIGH hepcidin in anemia of chronic disease

= decreased iron
release out of
enterocytes and
macrophages
resulting in LOW
iron % saturation

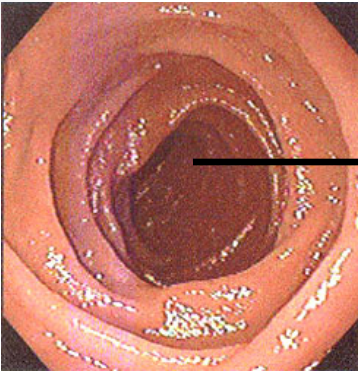
(A,B,C,and D)



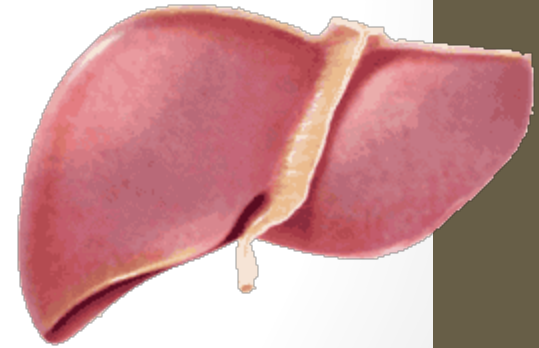
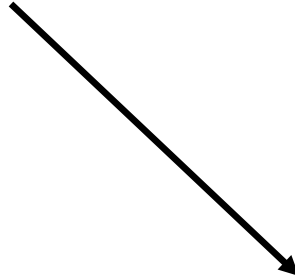
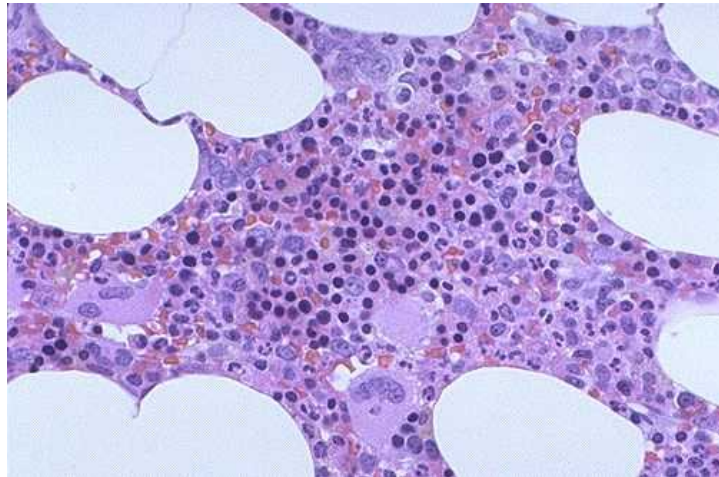
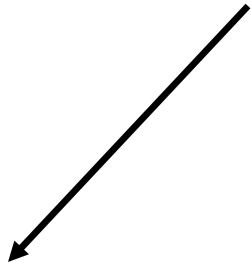
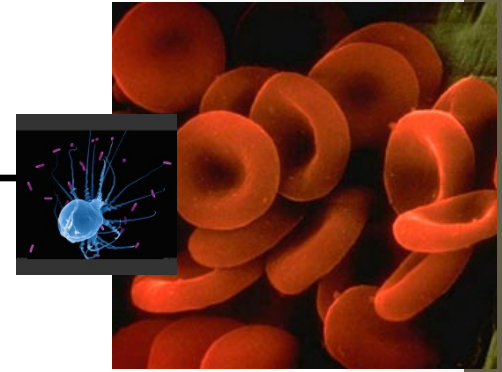
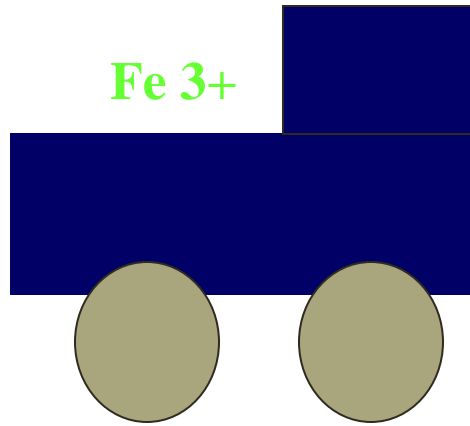
LOW hepcidin in hereditary

hemochromatosis

=increased iron
absorption (E)



Fe^{3+}



Iron Deficiency

TABLE 1. Prevalence of iron deficiency — United States, National Health and Nutrition Examination surveys, 1988–1994 and 1999–2000*

Sex/Age group (yrs)	1988–1994			1999–2000		
	No.	%	(95% CI) [†]	No.	%	(95% CI)
Both sexes						
1–2	1,339	9	(6 –11)	319	7	(3–11)
3–5	2,334	3	(2 – 4)	363	5	(2 – 7)
6–11	2,813	2	(1 – 3)	882	4	(1 – 7)
Males						
12–15	691	1 ^{§¶}	(0.1– 2)	547	5 [¶]	(2 – 8)
16–69	6,635	1 [¶]	(0.6– 1)	2,084	2 [¶]	(1 – 3)
≥70	1,437	4	(2 – 3)	381	3 [§]	(2 – 7)
Females**						
12–49	5,982	11	(10 –12)	1,950	12	(10–14)
12–15	786	9	(6 –12)	535	9	(5–12)
16–19	700	11	(7 –14)	466	16	(10–22)
20–49	4,495	11	(10 –13)	949	12	(10–16)
White, non-Hispanic	1,827	8	(7 – 9)	573	10	(7–13)
Black, non-Hispanic	2,021	15	(13 –17)	498	19	(14–24)
Mexican American	1,845	19	(17 –21)	709	22	(17–27)
50–69	2,034	5 [¶]	(4 – 7)	611	9 [¶]	(5–12)
≥70	1,630	7	(5 – 8)	394	6	(4 – 9)

* All racial/ethnic groups except where noted.

[†] Confidence interval.

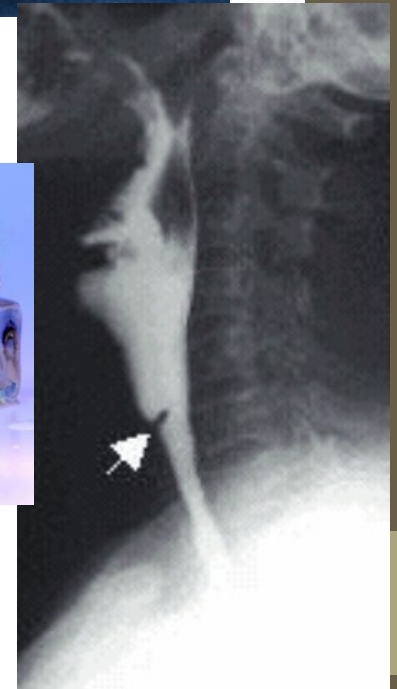
[§] Unreliable; relative standard error (i.e., standard error/prevalence estimate) is >30%.

[¶] p<0.05 for comparison between surveys within age and sex category.

** Nonpregnant only.

Iron Deficiency Signs & Symptoms

- Anemia
- Fatigue
- Pallor
- Poor exercise tolerance
- Pica or Pagophagia
- Restless leg syndrome
- Koilonychia
- Plummer-Vinson syndrome



Laboratory Tests in Iron Deficiency of Increasing Severity

	Normal	Fe deficiency without anemia	Fe deficiency with mild anemia	Severe Fe deficiency with severe anemia
Marrow reticulo- endothelial iron	2+ to 3+	None	None	None
Serum iron, µg/dL	60 to 150	60 to 150	<60	<40
Iron binding capacity (transferrin), µg/dL	300 to 360	300 to 390	350 to 400	>410
Saturation (SI/TIBC), percent	20 to 50	30	<15	<10
Hemoglobin, g/dL	Normal	Normal	9 to 12	6 to 7
Red cell morphology	Normal	Normal	Normal or slight hypochromia	Hypochromia and microcytosis
Plasma or serum ferritin, ng/mL	40 to 200	<40	<20	<10

Serum ferritin \leq 30 ng/dL = Iron deficient (PPV 83%, PLR= 11)

Serum ferritin \geq 100 ng/dL = Iron sufficient (NLR .08)

What about in between 30 and 100?

Other Tests to help distinguish IDA from ACD...

- Transferrin:
 - Low or low normal in ACD
- Increased soluble transferrin receptor (sTfR)
- Specificity 84% and PPV 58%
- Soluble transferrin receptor – ferritin index
- Still need inflammatory markers/ acute phase reactants for interpretation

- Low reticulocyte-hemoglobin concentration (RET-He)
 - Does not distinguish between ACD and IDA but can improve in 2-3 days after IV iron supplementation to prove response to iron therapy

<input type="checkbox"/> Retic %	1.4
<input type="checkbox"/> Retic #	51
<input type="checkbox"/> Immature Retic Fraction (IRF)	21.2 * H
<input type="checkbox"/> Retic Hgb Equivalent [RET-He]	21.0 * L
<input type="checkbox"/> Iron	23 L
<input type="checkbox"/> Transferrin	185 L
<input type="checkbox"/> Trans % Sat	9.8 L

What about ESRD patients?

- **Functional Iron deficiency:**
 - a fall in iron saturation after giving epogen (which increases demand for iron)
- **KDOQI Guidelines:**
 - Goal hemoglobin
 - 10-11.5 g/dL
- **Absolute iron deficiency =**
 - TIBC % sat < 20%
 - Ferritin < 100 ng/mL
- **May still benefit from IV iron with epogen**
 - TIBC % sat < 30%
 - Ferritin < 500 ng/mL

TABLE 1. CAUSES OF IRON DEFICIENCY.

Inadequate absorption

Poor bioavailability

Antacid therapy or high gastric pH

Excess dietary bran, tannin, phytates, or starch

Competition from other metals (e.g., copper or lead)

Loss or dysfunction of absorptive enterocytes

Bowel resection

Celiac disease

Inflammatory bowel disease

Intrinsic enterocyte defects

Increased loss

Gastrointestinal blood loss

Epistaxis

Varices

Gastritis

Ulcer

Tumor

Meckel's diverticulum

Parasitosis

Milk-induced enteropathy of early childhood

Vascular malformations

Inflammatory bowel disease

Diverticulosis

Hemorrhoids

Genitourinary blood loss

Menorrhagia

Cancer

Chronic infection

Pulmonary blood loss

Pulmonary hemosiderosis

Infection

Other blood loss

Trauma

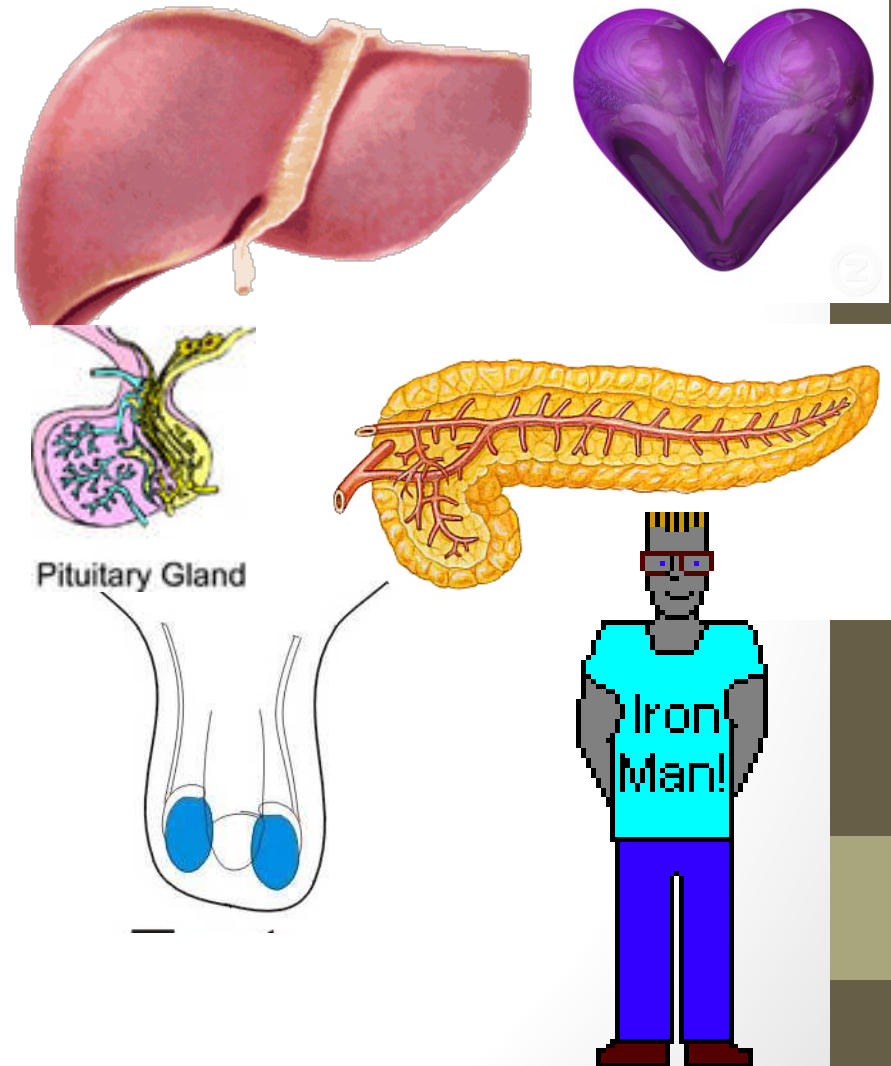
Excessive phlebotomy

Large vascular malformations

Iron Overload

Iron overload may occur because of:

- abnormal intestinal absorption of normal amounts of dietary iron,
- excesses of dietary iron, or
- parenteral sources of iron such as multiple blood transfusions.



Iron Overload: Signs and Symptoms

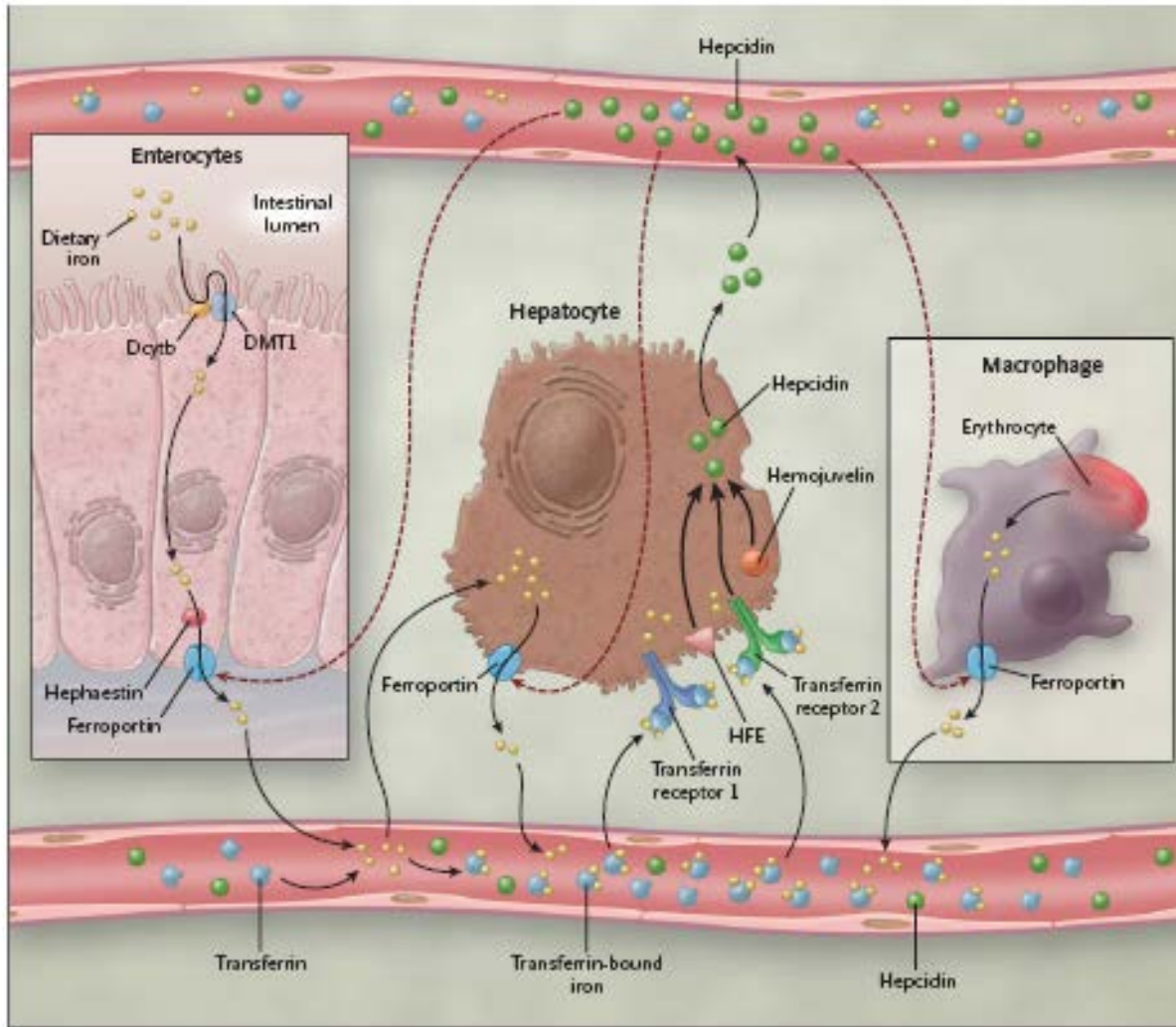
- Unexplained fatigue
- Joint pain
- Liver disease: elevated aminotransferase levels, hepatomegaly, cirrhosis, hepatocellular carcinoma
- Diabetes mellitus
- Impotence
- Hypothyroidism
- Heart failure
- Arrhythmias

Hereditary Hemochromatosis

- **A disease of inappropriate iron absorption resulting in the overload of iron in various organs**
- The majority of patients with HH are descended from a common Celtic ancestor who lived 60-70 generations ago!
- 85% of HH patients carry a missense mutation of the HFE gene on chromosome 6
- In most cases, the mutation is a single base change that substitutes tyrosine for cysteine at position 282 of the HFE protein (C282Y)
- Homozygosity for the C282Y mutation is found in 5 of every 1000 persons of North European descent— a prevalence 10 x that of cystic fibrosis genotypes!



Celtic282Y



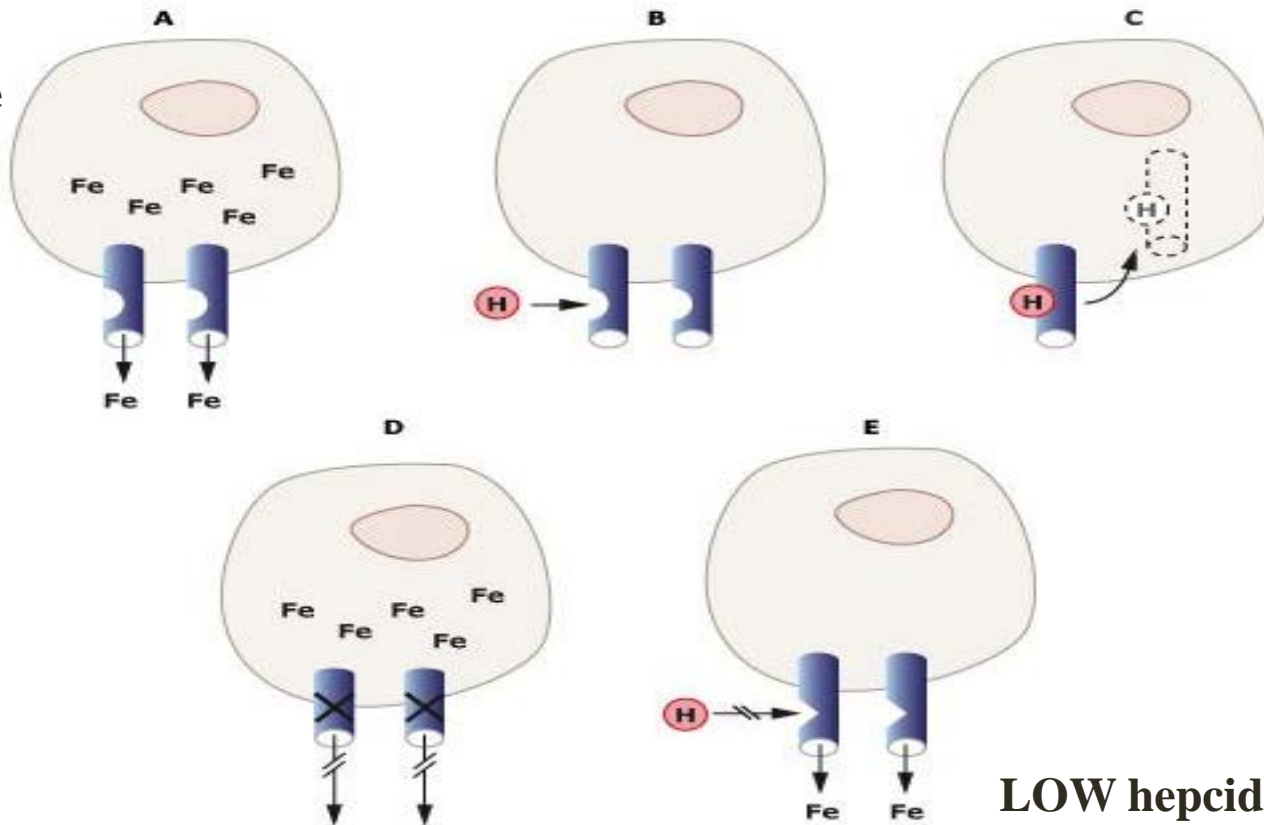
- **When the HFE protein is mutated as in HH, there is not enough hepcidin produced.**
- **The export of iron from the basolateral side of the enterocyte, the macrophage, and the hepatocyte is allowed to continue unimpeded.**
- **This overloads the transferrin binding capacity and elevates the percent saturation in the plasma.**

Hepcidin: iron export regulator

HIGH hepcidin in anemia of chronic disease

= decreased iron
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(A,B,C,and D)



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Laboratory Diagnosis of Iron Overload

- A fasting transferrin saturation $> 60\%$ in men or $> 50\%$ in women will detect about 90% of patients with homozygous HH.
- An elevated ferritin above 300 ng/mL in men and above 200 ng/mL in women suggests an iron overload state in the absence of inflammatory conditions.
- Elevated ferritin is less sensitive than elevated transferrin saturation in screening for HH because a greater degree of iron overload is required to raise the ferritin concentration.

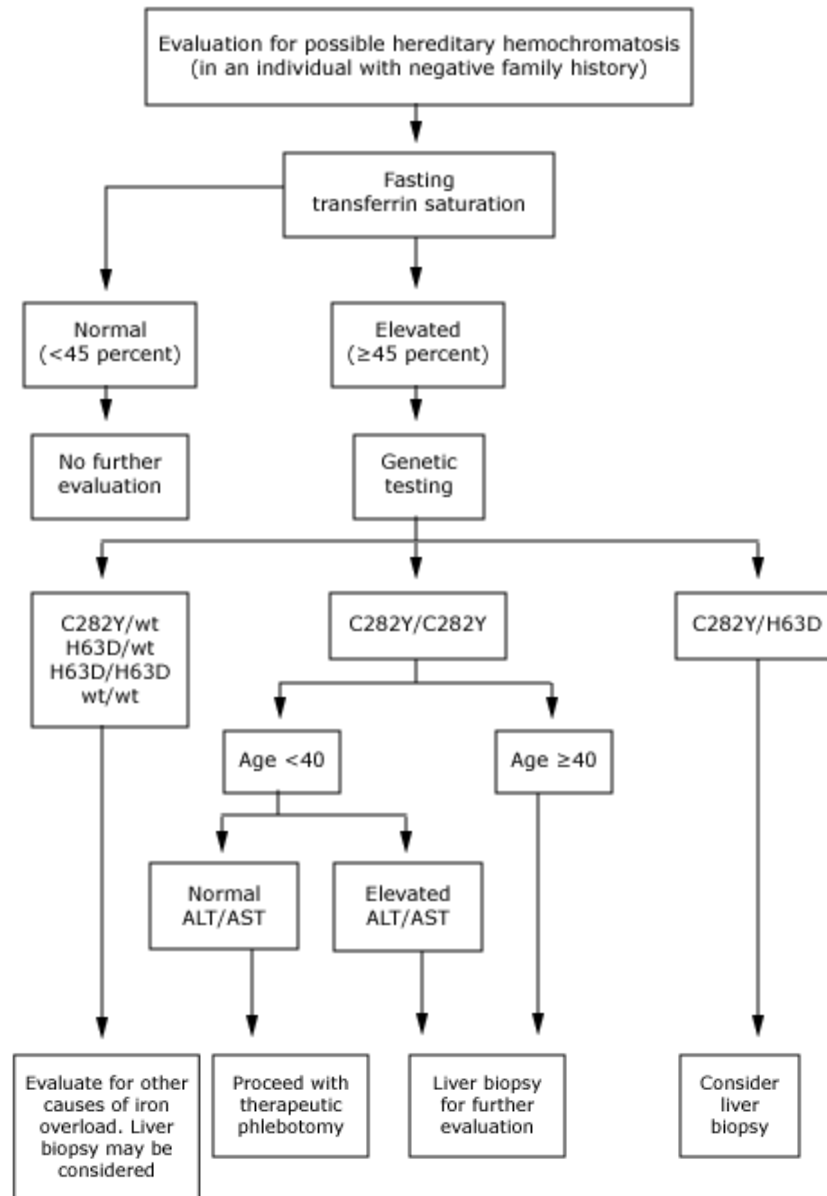
Other Tests for Iron Overload

- Liver biopsy for hepatic iron content
- CT and T2 MRI measurements of liver or heart
- Quantitative phlebotomy

Hemochromatosis of the liver



CT scan through the upper abdomen shows high attenuation throughout the liver (L), which normally has a similar attenuation to the spleen (white arrow). Other deposition diseases producing this appearance include amiodarone toxicity. *Courtesy of Jonathan Kruskal, MD.*



Treatment of Iron Overload

- Iron overload due to multiple transfusions in sickle cell disease, thalassemia's, and possibly myelodysplastic syndrome.
- Criteria for chelation therapy: Ferritin > 1000 ng/mL
- Deferoxamine (IV infusion); vision, hearing, renal SEs
- Deferiprone (oral therapy); neutropenia, agranulocytosis SEs
- Deferasirox (oral therapy); abdominal pain, N/V, diarrhea, skin rash
- Iron overload due to Hereditary Hemochromatosis is phlebotomy.

Summary

- Iron homeostasis is regulated mostly by degree of absorption by the HEPCIDIN exporter regulator because the body lacks efficient excretion mechanisms.
- Iron deficiency and excess are both deleterious and common.
- In clinical practice, low ferritin (<30) indicates iron deficiency and high TIBC (>45%) percent saturation indicates overload.
- Anemia of inflammation and iron deficiency anemia are distinguished by ferritin (>100 unlikely to be iron deficient) and transferrin (LOW, not likely to be iron deficient)

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- Hemodynamic compromise
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Case

- 49 year old woman
- PMH:
- Cystic fibrosis
- Pancreatic insufficiency
- Chronic sinusitis
- Anemia
- Hgb 8.4
- Hct 28.0
- MCV 78
- RDW 15.6
- Retic 2.1
- Serum iron 23
- Transferrin 187
- % saturation 9.7
- Ferritin 165

Case

- 40 year old woman
- PMH:
- Infected pancreatic pseudocyst
- Gallstone pancreatitis
- DM 2
- Anemia
- Hgb 7.9
- Hct 26.8
- MCV 72
- RDW 17.1
- Retic 1.7
- Serum iron 14
- Transferrin 295
- % saturation 3.7
- Ferritin 6

Case

- 66 year-old man
- PMH:
- Hypoxemic respiratory failure
- Endocarditis
- Sternal wound dehiscence
- DM type 2
- Anemia
- Hgb 8.0
- Hct 26.2
- MCV 73
- RDW 17.2
- Retic 1.3
- Serum iron 24
- Transferrin 207
- % saturation 9.1
- Ferritin 100

Case

- 28 year old woman

PMH:

- Cystic fibrosis
- Pancreatic insufficiency
- GERD
- Depression
- Anemia

- Hgb 8.4
- Hct 26.3
- MCV 82
- RDW 17.2
- Retic 1.7
- Serum iron 19
- Transferrin 288
- % saturation
- Ferritin 24

Recommended Reading

Orchestration of Iron Homeostasis

Fleming RE, Bacon BR

...of inflammation, iron retention by duodenal enterocytes and reticuloendothelial macrophages leads to markedly low transferrin saturation, iron-restricted erythropoiesis, and mild-to-moderate anemia. Thus, hepcidin offers a unifying explanation for the abnormalities in iron metabolism observed in these...

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N Engl J Med 352:1741, April 28, 2005 *Perspective*

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