Iron Metabolism

Brenda Shinar, MD, FACP

September 22, 2020

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%)

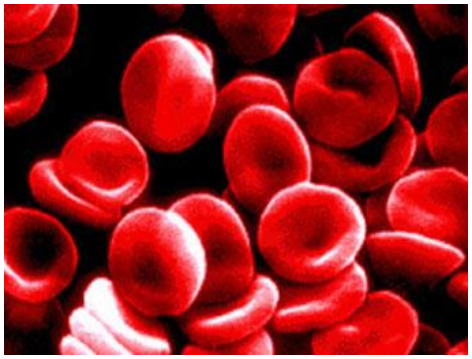
Which of the following statements accurately describes the cause of this patient's anemia?

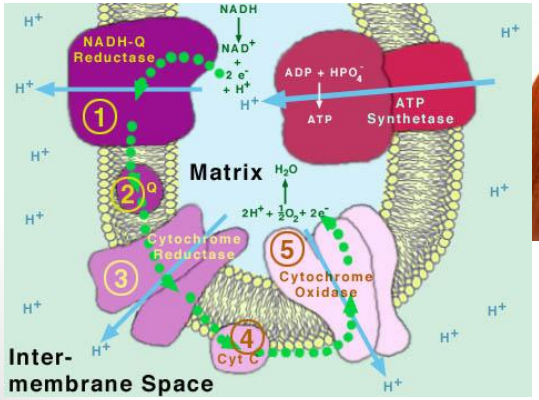
- A. This patient is iron deficient and the elevated ferritin is due to his infection.
- B. This patient is not iron deficient and his anemia is due to chronic disease/inflammation.
- C. The amount of information given is not enough to determine whether or not the patient is iron deficient.

Objectives

- Define the following terms: ferritin, hemosiderin, transferrin, total iron binding capacity, and percent saturation.
- Describe the **hepcidin iron exporter regulator** and know 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.
- **Distinguish between iron deficiency anemia and anemia of inflammation by correctly interpreting iron studies.**
- 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 and common!**

Iron Storage

- **Ferritin (tissue):**

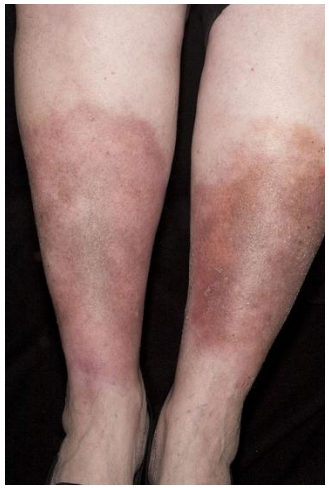
  a huge protein consisting of light and heavy chains which can store up to 4500 atoms of iron within its spherical cavity

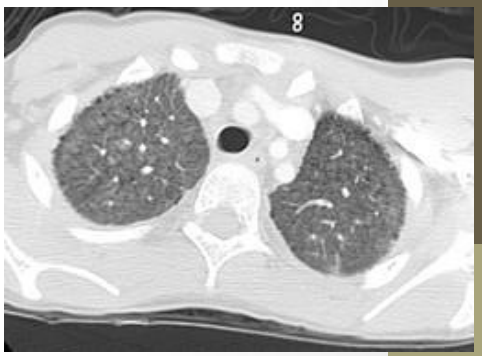
- **Apoferritin (or *serum* ferritin):**

  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

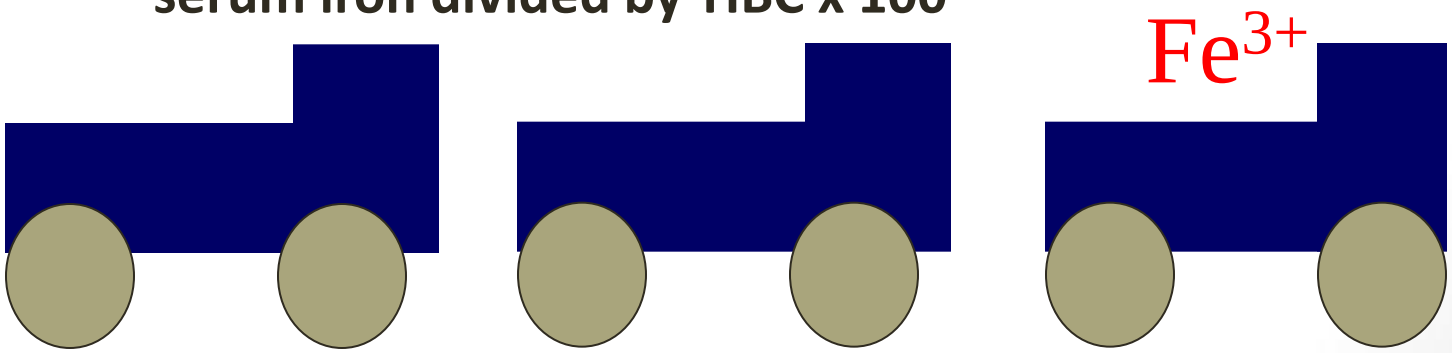
  - **Total Iron Binding Capacity (TIBC):**

    total transferrin available for binding Fe+3

    33% = normal

  - **Percent saturation:**

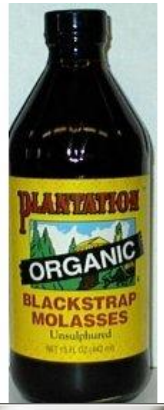
    serum iron divided by TIBC x 100



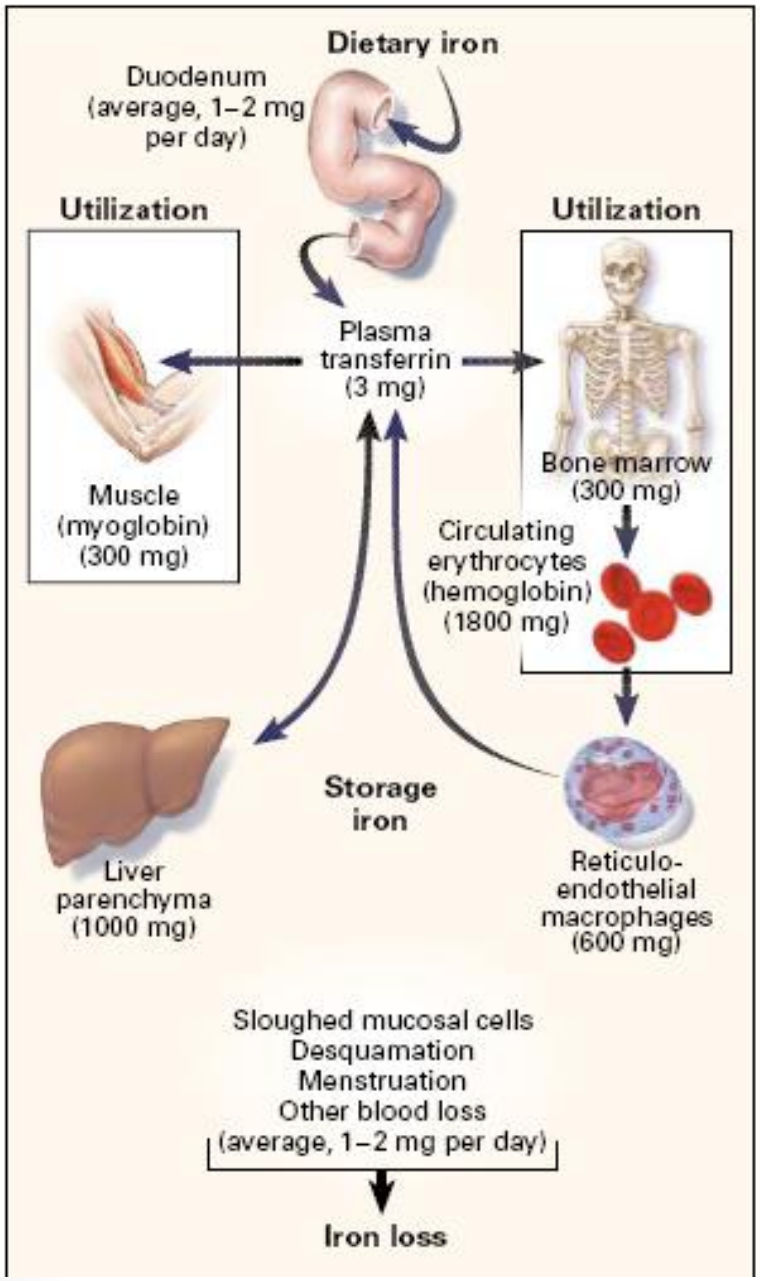
Iron Content and Distribution in Men and Women

	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 _____.

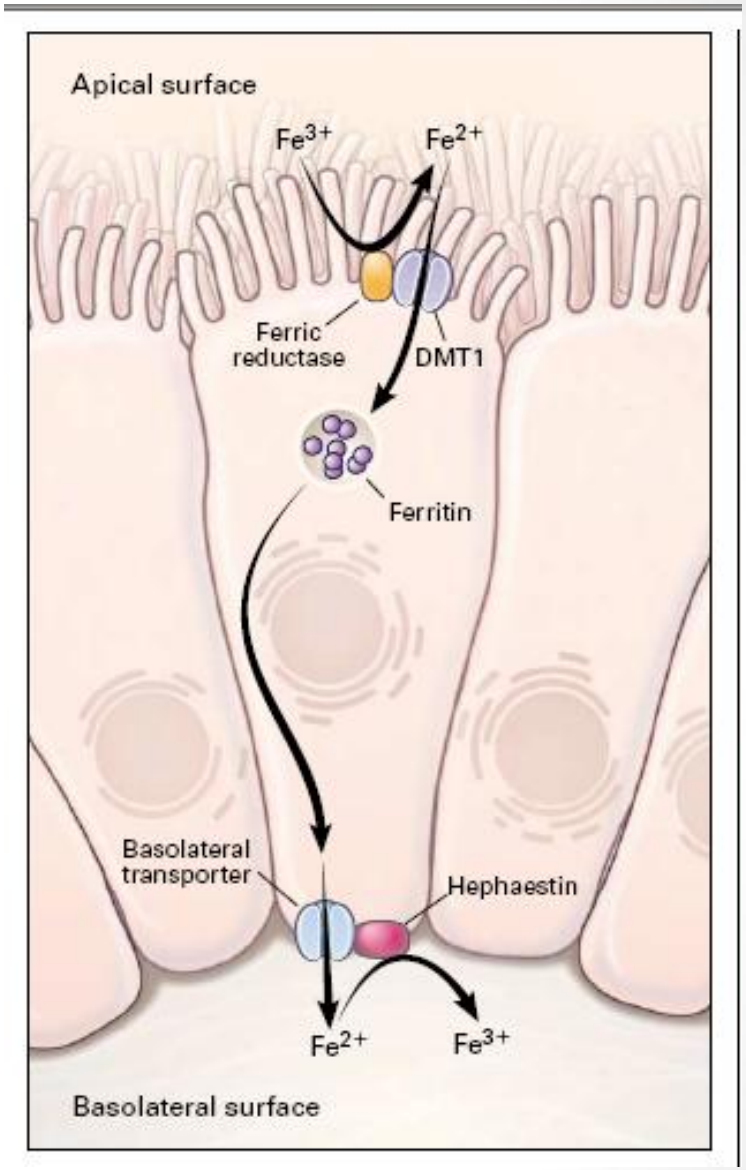
  Transferrin

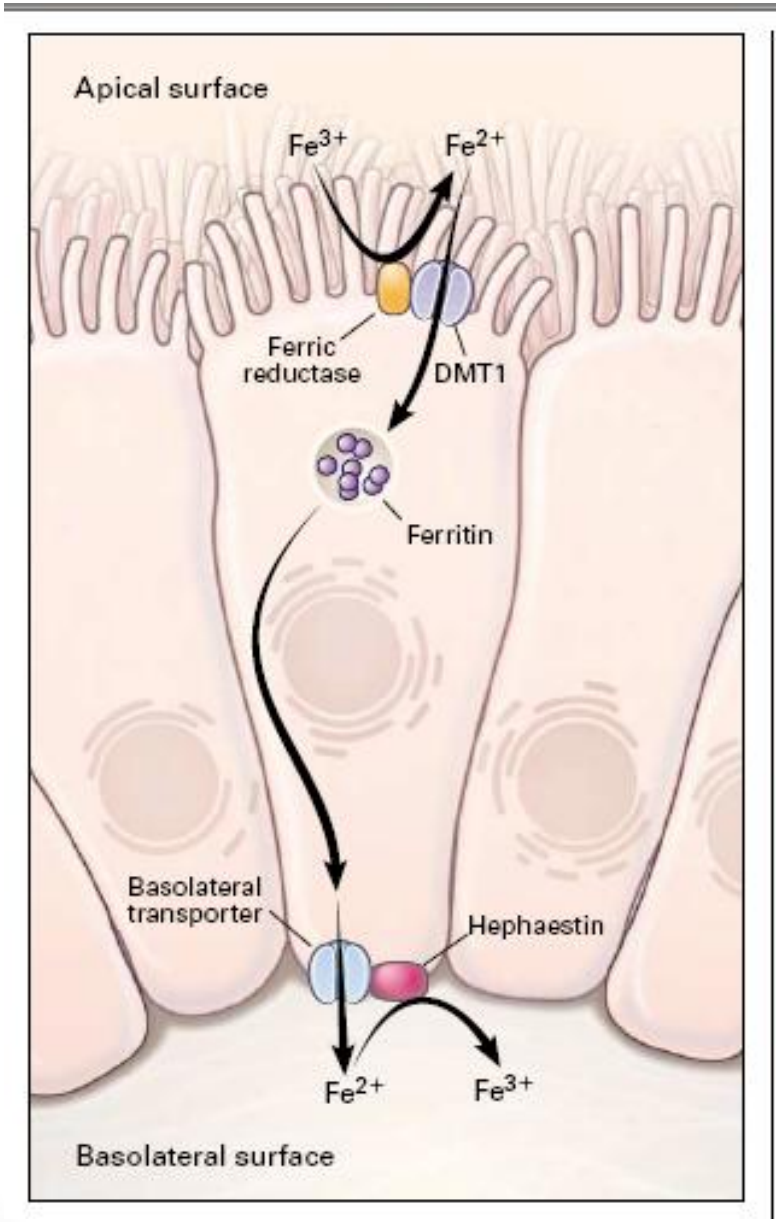
- Iron is stored in the liver, reticuloendothelial macrophages, and enterocytes as _____.

  Ferritin

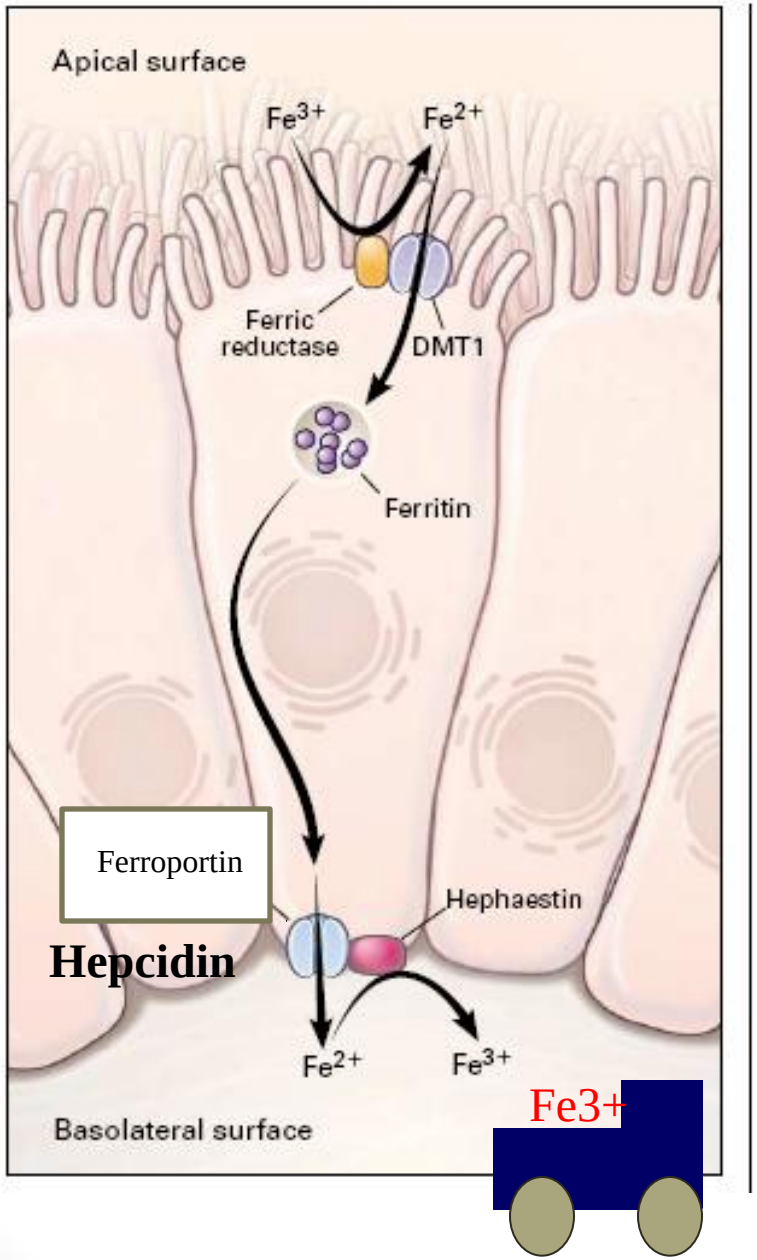
Iron Absorption

- 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 called “divalent metal transporter-1”. (DMT1)





- 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?



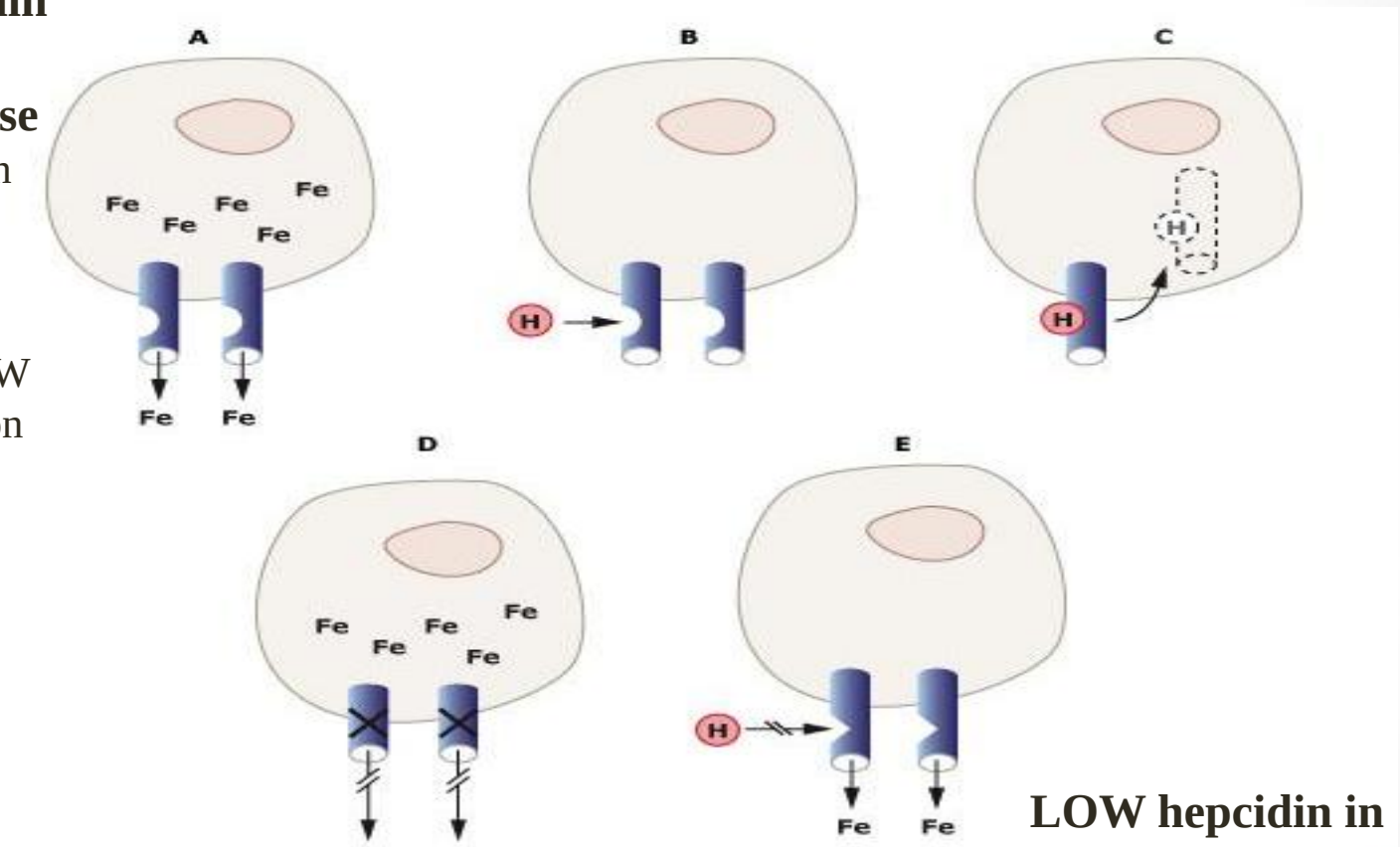
- Iron within the enterocyte is stored as **ferritin**. This iron may be lost with desquamation of the enterocyte.
- On the basolateral surface, the exporter is called ferroportin.
- Ferroportin requires a molecule to oxidize the ferrous iron back into ferric iron for loading onto _____.

  Transferrin
- **HEPCIDIN is the regulator of ferroportin that determines how much iron enters the circulation.**

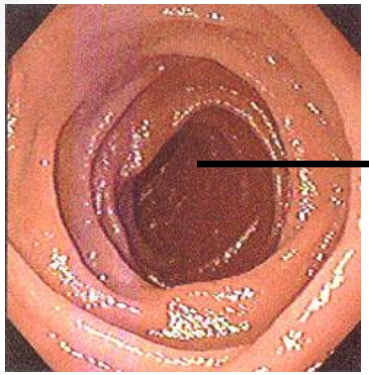
Hepcidin: iron export regulator

HIGH hepcidin in anemia of chronic disease
= decreased iron release out of enterocytes and macrophages resulting in LOW iron % saturation

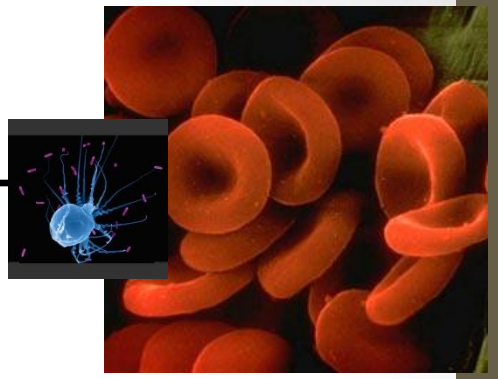
(A,B,C,and D)

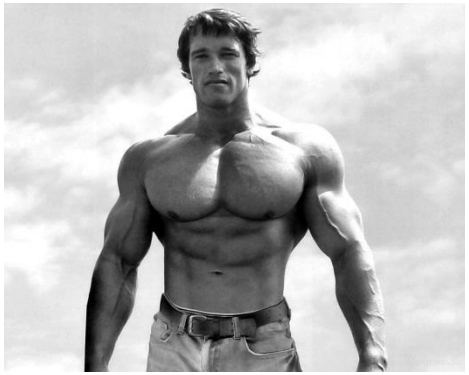


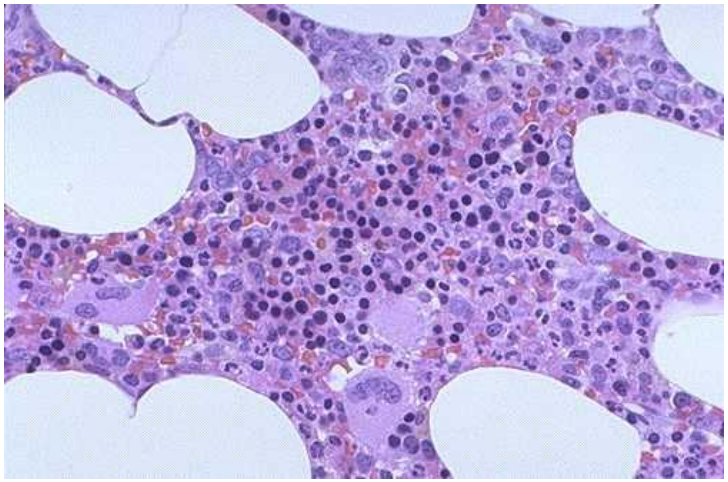
LOW hepcidin in hereditary hemochromatosis
=increased iron absorption (E)

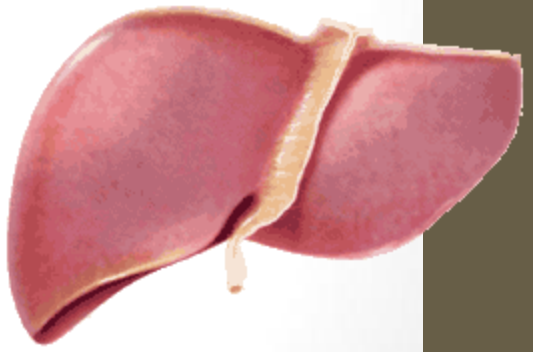


Fe 3+









Iron Deficiency

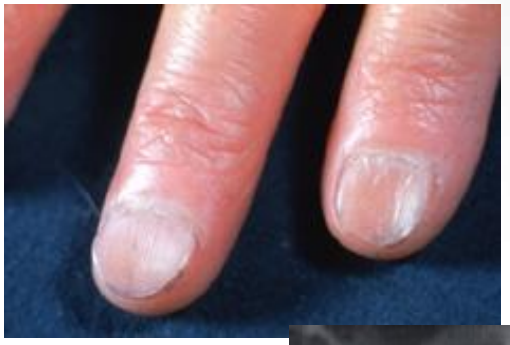
TABLE 1. Prevalence of iron deficiency — United States, National Health and Nutrition Examination surveys, 1988–1994 and 1999–2000*

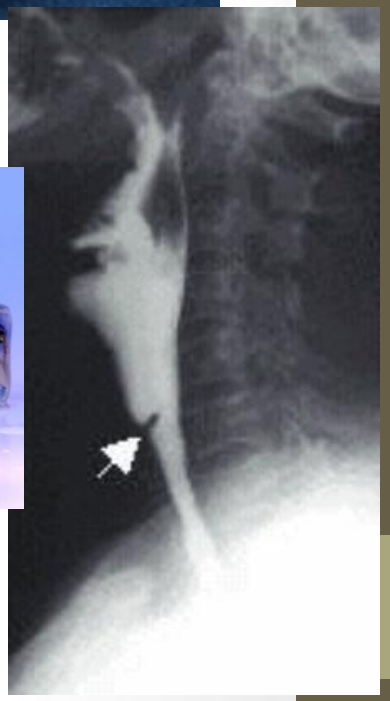
Sex/Age group (yrs)	1988–1994 No.	%	(95% CI†)	1999–2000 No.	%	(95% CI)
Both sexes						
1– 2	1,339	9	(6 –11)	319	7	(3 –11)
3– 5	2,334	3	(2 – 4)	363	5	(2 – 7)
6–11	2,813	2	(1 – 3)	882	4	(1 – 7)
Males						
12–15	691	1§¶	(0.1 – 2)	547	5¶	(2 – 8)
16–69	6,635	1¶	(0.6 – 1)	2,084	2¶	(1 – 3)
≥70	1,437	4	(2 – 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 ≤ 30 ng/dL = Iron deficient (PPV 83%, PLR= 11)
Serum ferritin ≥ 100 ng/dL = Iron sufficient (NLR .08)

What about a ferritin value between 30 and 100?

Best tests to help distinguish IDA from ACD…

- Transferrin: (TRUCKS)
  - High in iron deficiency anemia
  - Low in ACD

Retic %		1.4
Retic #		51
Immature Retic Fraction (IRF)		21.2 * H
Retic Hgb Equivalent [RET-He]		21.0 * L
Iron		23 L
Transferrin		185 L
Trans % Sat		9.8 L

- Low reticulocyte-hemoglobin concentration (RET-He) that improves with IV iron

  Low RET-He concentration does not distinguish between ACD and IDA but IF it increases 2-3 days after IV iron is administered, it is likely contributing to anemia

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

Differential Diagnosis for Iron Deficiency due to GI process

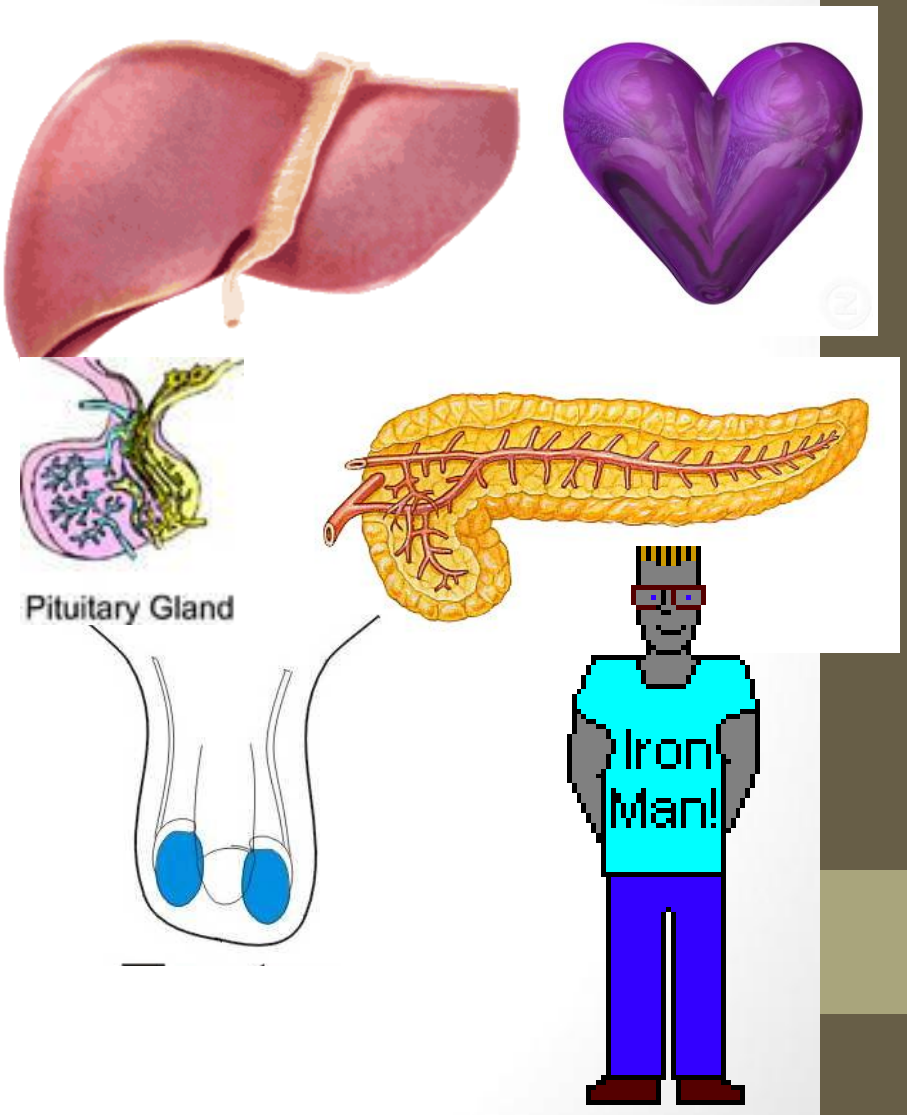
- Malabsorption
  - Total or partial gastrectomy
  - Antacid
  - H. pylori
  - Celiac disease
  - IBD
- Loss
  - -Itis of the GI tract
  - Neoplasm (polyp/CA)
  - Peptic ulcer
  - AVM
  - Parasites (hookworm)
  - Other…

Iron Overload

- What are the 3 main categories of iron overload?

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

- Name the organs involved in iron overload:



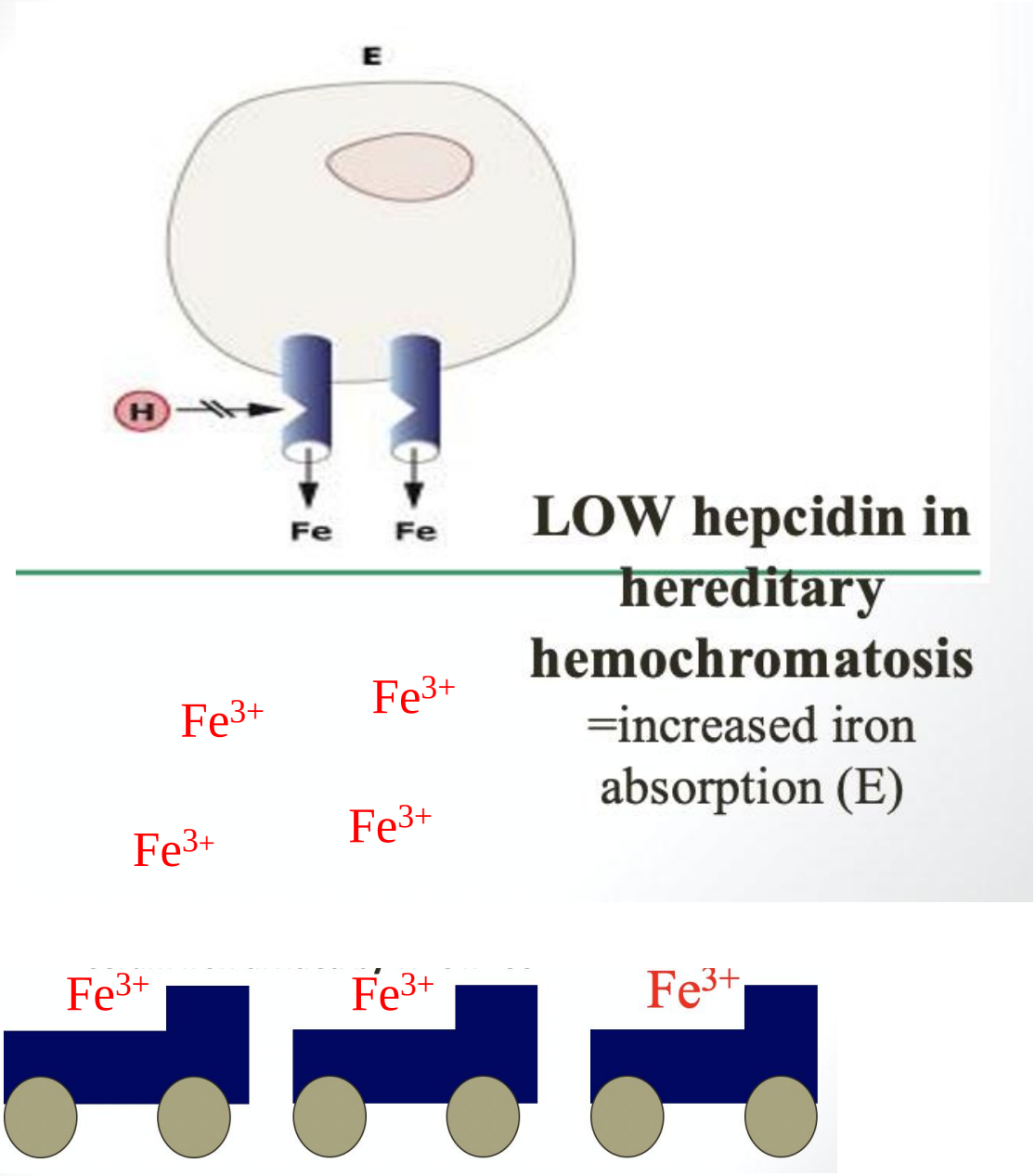
Iron Overload: Signs and Symptoms

- 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 decended 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 decent– a prevalence 10 x that of cystic fibrosis genotypes!

Celtic**282Y**

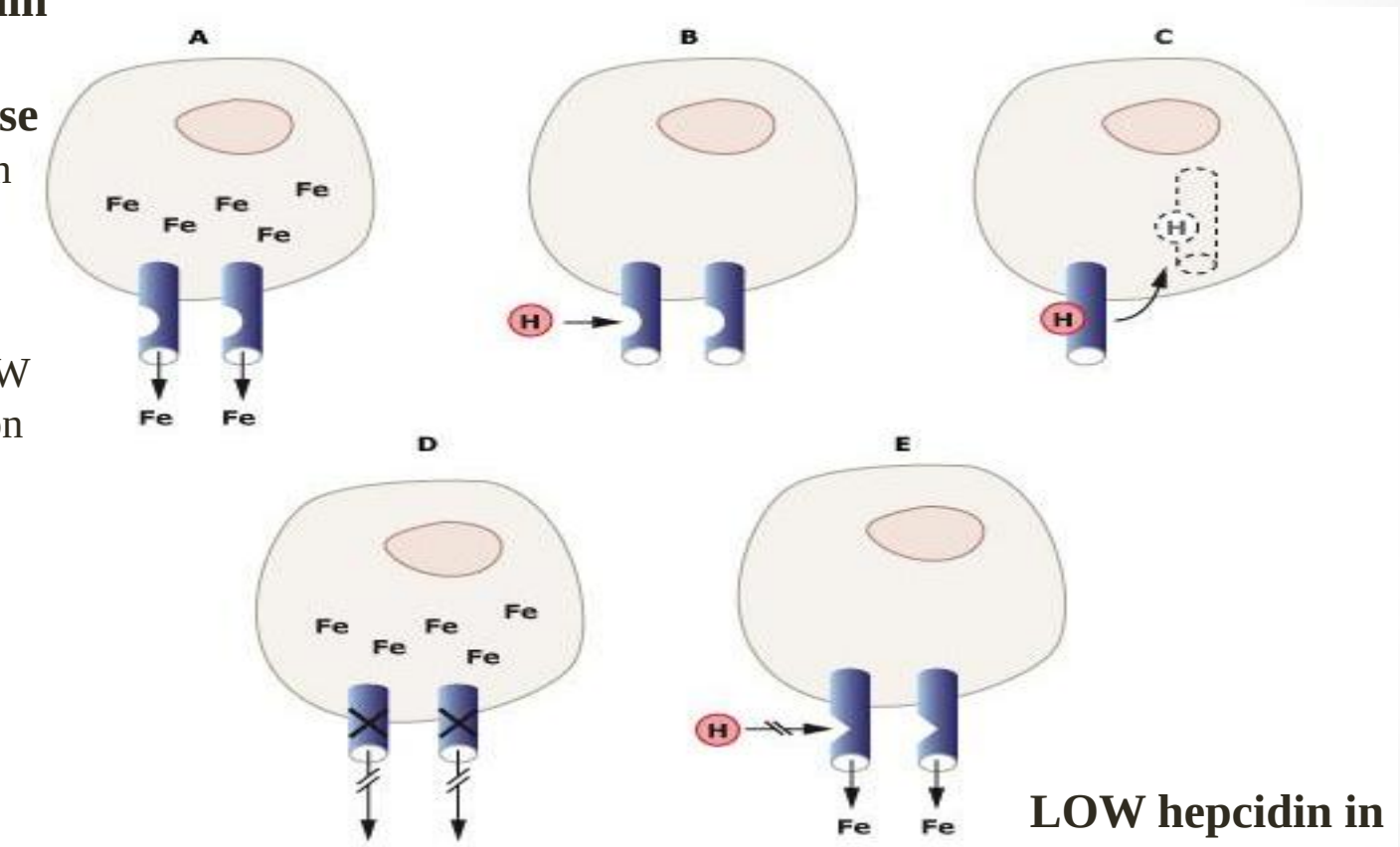


- **When the HFE protein is mutated as in HH**, there is **not enough hepcidin produced.**
- The export of iron from the basolateral side of the enterocyte, the macrophage, and the hepatocyte is allowed to continue **unhindered.**
- This overloads the transferrin binding capacity and **elevates the percent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

Hepcidin: iron export regulator

HIGH hepcidin in anemia of chronic disease
= decreased iron 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)

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.

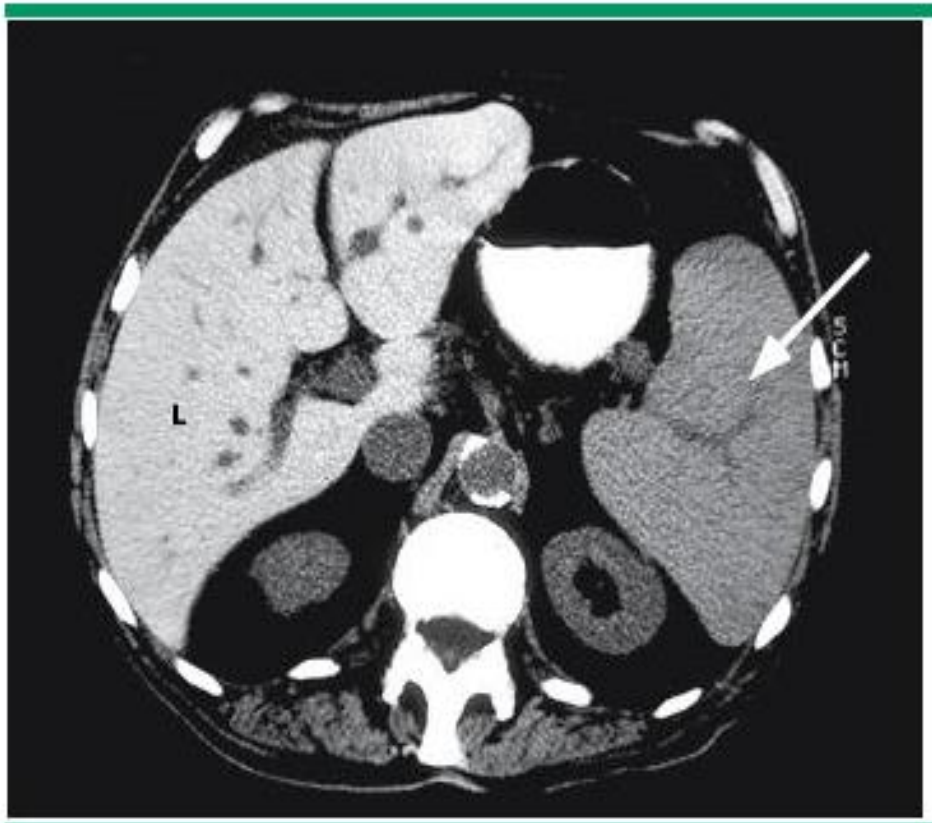
- An elevated ferritin above 300 ng/mL in men and above 200 ng/mL in women suggests an iron overload state in the absence of inflammatory conditions.

- 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.

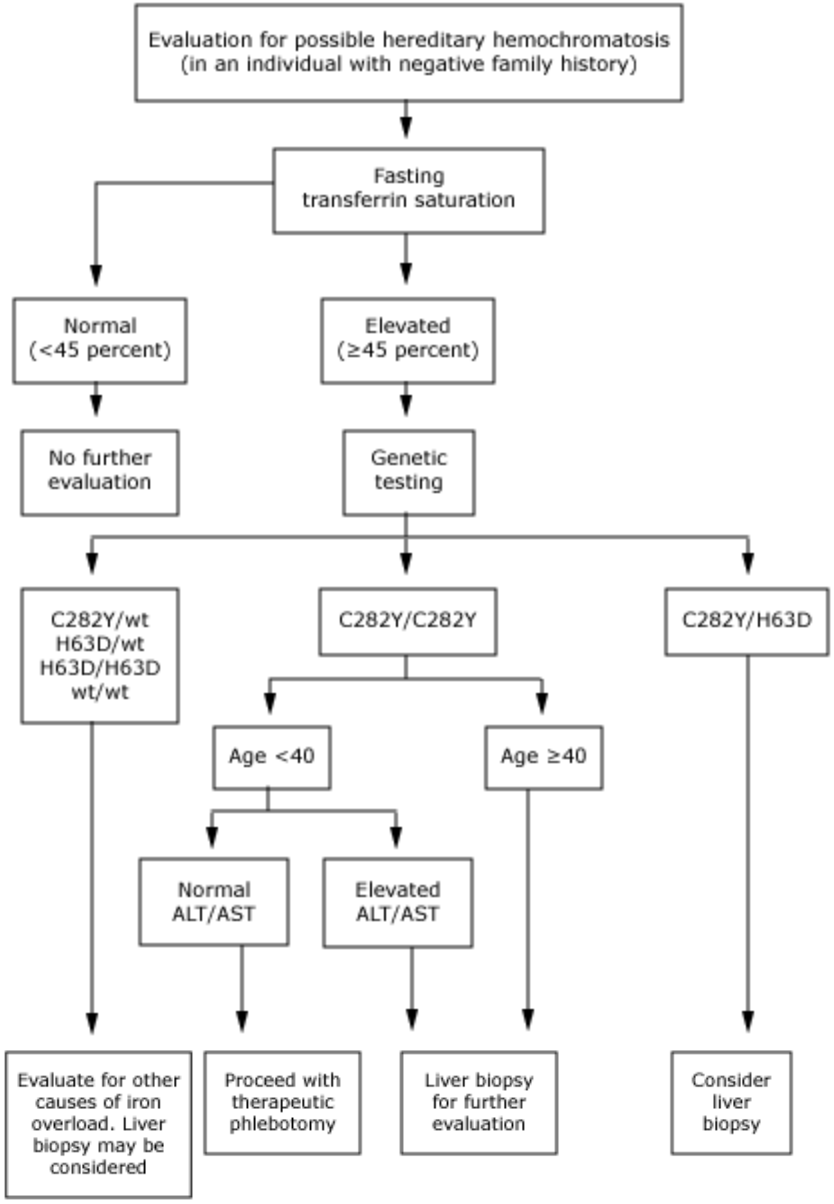
Other Tests for Iron Overload

- 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.*


Evaluation for possible hereditary hemochromatosis (in an individual with negative family history)
Fasting transferrin saturation
Normal (<45 percent)
Elevated (≥45 percent)
No further evaluation
Genetic testing
C282Y/wt H63D/wt H63D/H63D wt/wt
C282Y/C282Y
C282Y/H63D
Age <40
Age ≥40
Normal ALT/AST
Elevated ALT/AST
Evaluate for other causes of iron overload. Liver biopsy may be considered
Proceed with therapeutic phlebotomy
Liver biopsy for further evaluation
Consider liver biopsy

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.

- 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)

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)
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- Percent saturation 8% (15-50%)

Which of the following statements accurately describes the cause of this patients 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.

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Patient is a 27 yo male with a history of abdominal pain and diarrhea x 6 months associated with 40 lb weight loss. He was diagnosed with C diff in May and failed flagyl treatment. He presents with increasing abdominal pain and diarrhea with new symptoms of vomiting. He presents with continued chronic diarrhea with bloody stools.

Physical Examination
VS: 136/78 HR 84 RR 14 T 98.1 95% RA
General: Alert and oriented, No acute distress.
Eye: Pupils are equal, round and reactive to light, Normal conjunctiva.
HENT: Normocephalic, Normal hearing, Oral mucosa is moist.
Respiratory: Lungs are clear to auscultation, Respirations are non-labored, Breath sounds are equal, Symmetrical chest wall expansion.
Cardiovascular: Normal rate, Regular rhythm, No murmur, No edema.
Gastrointestinal: Soft, Non-distended, Normal bowel sounds, diffuse tenderness to palpation.
Genitourinary: No costovertebral angle tenderness, No urethral discharge.
Integumentary: Warm, Dry, No rash.
Neurologic: Alert, Oriented, No focal deficits.
Psychiatric: Cooperative, Appropriate mood & affect.

WBC	13.3 K/MM3 H
RBC	6.44 M/MM3 H
HGB	13.0 g/dL L
HCT	41.5 %
MCV	64 fL L
MCH	20.2 pg L
MCHC	31.3 g/dL
RDW-CV	17.2 % H
RDW-SD	35.0 fL L
Nucleated RBCs, Automated	0 %
Platelet	303 K/MM3
MPV	10.3 fL

MISC HEMO		
Retic %		1.6 %
Retic #		85 K/ul
Immature Retic Fraction (IRF)		27.9 % * H
Retic Hgb Equivalent [RET-He]		18.7 pg * L
Sed Rate		43 mm/hr H
Iron		53 ug/dL
Transferrin		142 mg/dL L
Trans % Sat		29.4 %
Ferritin		222 ng/mL

Hgb A				95.2 %
Hgb A2				4.8 % H
Helec Interp				Helec Interp

Result type:	Helec Interp
Date/Time of Service:	July 23, 2017 17:15 MST
Result status:	Auth (Verified)
Performed By:	ZHOU MD PhD, WENDI on July 25, 2017 14:39 MST
Verified by:	ZHOU MD PhD, WENDI on July 25, 2017 14:39 MST
Encounter info:	36902559, BEMC, Observation, 07/23/2017 - 07/25/2017

*** Final Report ***

Elevation of Hemoglobin A2, consistent with beta thalassemia trait.

Reviewed by Dr. Wendi Zhou at Banner -- University Medical Center Phoenix.

Hemoglobinopathy evaluation involves interpretation of high performance liquid chromatography (HPLC) results in the context of red cell indices. Variant hemogolobins such as S, C, E, and others are detected. Some, but not all thalassemic disorders are detected. Consultative assistance is sought when necessary.

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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