Iron Metabolism

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September 13, 2022

Case

ID and CC:

- 45-year-old man
- Septic shock
- 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 (80-100 fL)

Question 1.

What do you think the PRE-TEST probability is that this patient is iron deficient and WHY?

A. Low

B. Intermediate

C. High

Question 2:

Which of the following test(s) would you order to determine whether he is iron deficient?

A. Ferritin

B. Transferrin

C. Total iron binding capacity

D. Serum iron

E. Percent saturation

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- 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%)

Question 3.

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.

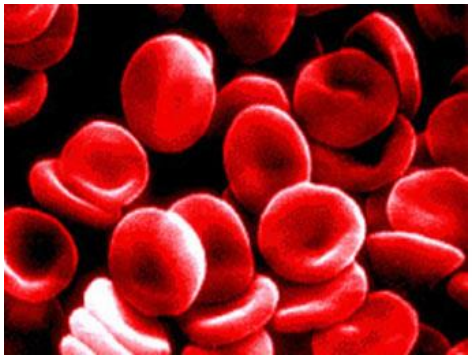
B. This patient is not iron deficient and his anemia is due to chronic disease/inflammation.

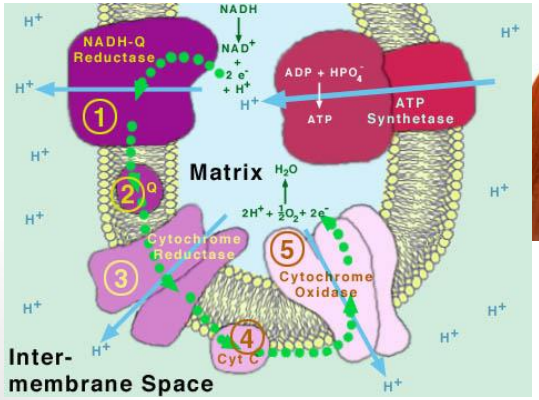
C. The amount of information given is not enough to determine whether or not the patient is iron deficient.

Learning Objectives

- Understand the importance of iron in the human body and that conditions of iron deficiency and iron overload are common.
  - Describe the **hepcidin iron exporter regulator** and understand how it is involved the regulation of iron absorption. Describe how **hepcidin** relates to hereditary hemochromatosis and anemia of chronic disease.
- Know how the lab values (ferritin, hemoglobin and MCV) change with progressively more severe iron depletion.
  - Distinguish between iron deficiency anemia and anemia of inflammation by correctly interpreting iron studies.
  - 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)





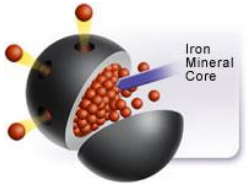
- Iron is the fourth most abundant element in the earth's crust.
- Biologically, it is a part of hemoglobin, myoglobin, and cytochromes.
- It readily converts from ferric (3+) to ferrous (2+) forms by donating and accepting electrons.
- **Iron homeostasis is tenuous; both states of deficiency and overload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

Iron Content and Distribution: 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.

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

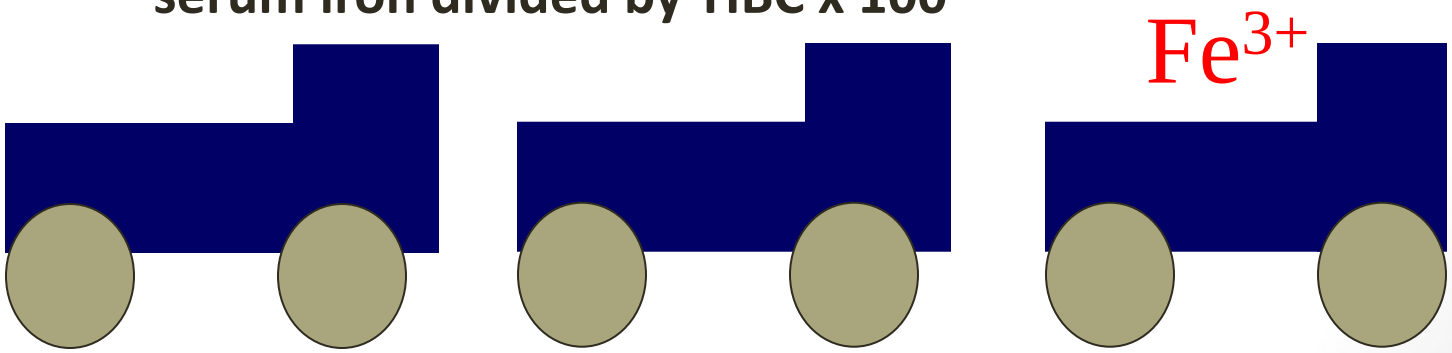
  - **Total Iron Binding Capacity (TIBC):**

    total transferrin available for binding Fe+3

    33% = normal

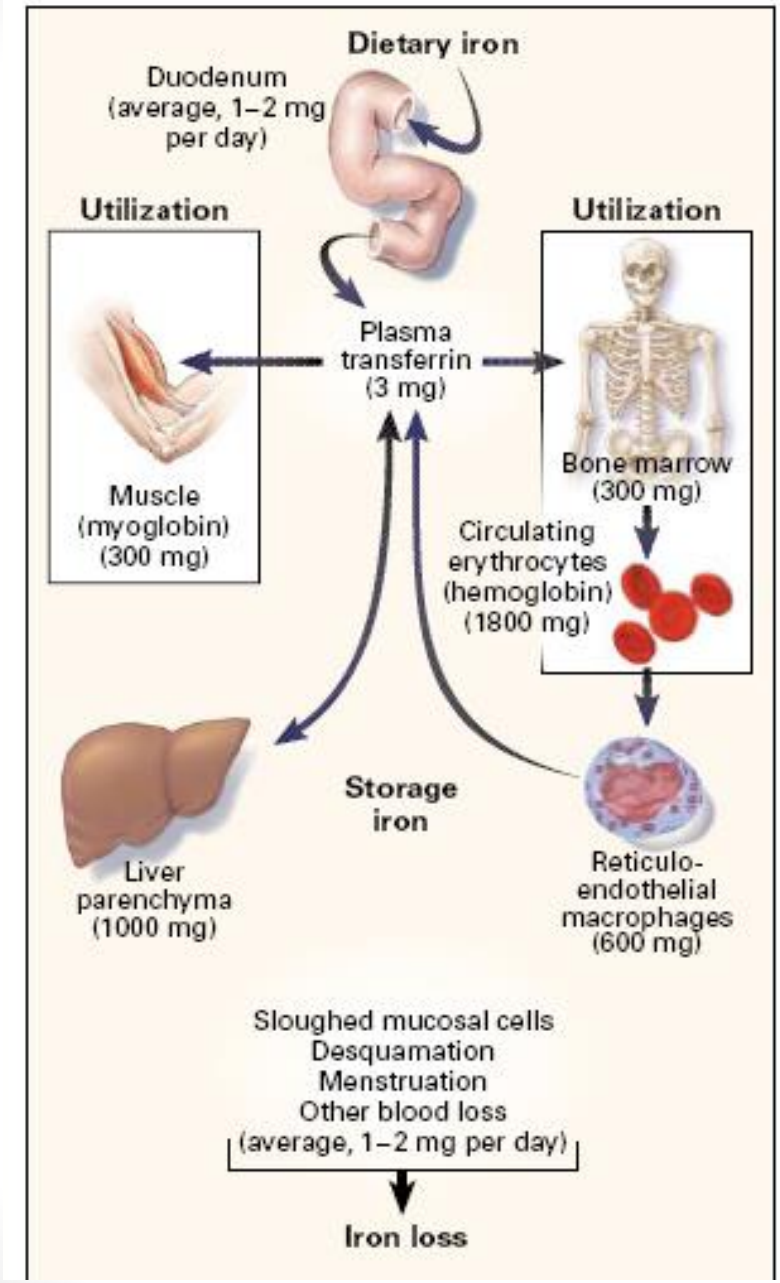
  - **Percent saturation:**

    serum iron divided by TIBC x 100



Iron Absorption

- **The average western diet consumes 15-25 mg of iron per day**
- **Regulation of the intestinal absorption of iron is critical—humans have *no physiologic pathway for excretion*!**

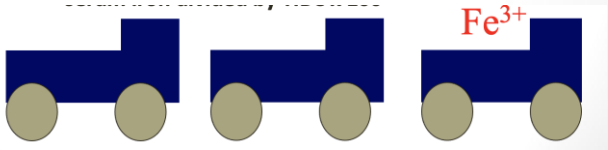


Iron Absorption:

Questions 4.

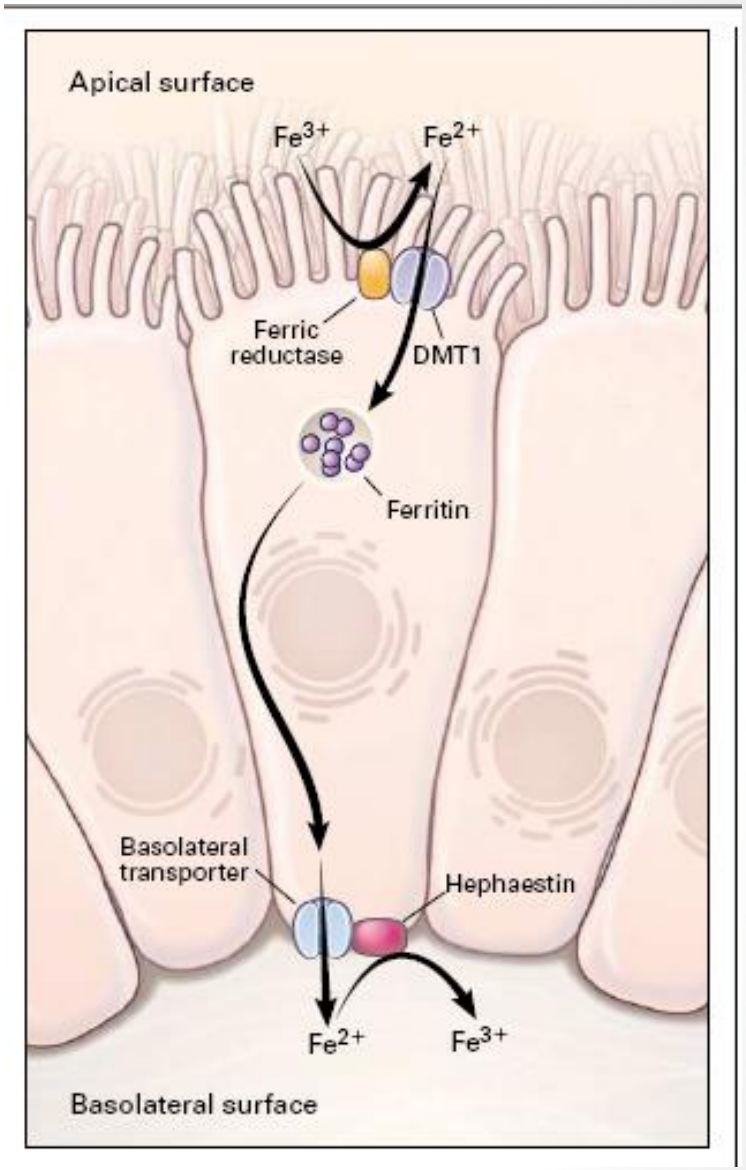
- **Iron is absorbed in the _____.**
  - **A. Duodenum**
  - **B. Jejunum**
  - **C. Ileum**

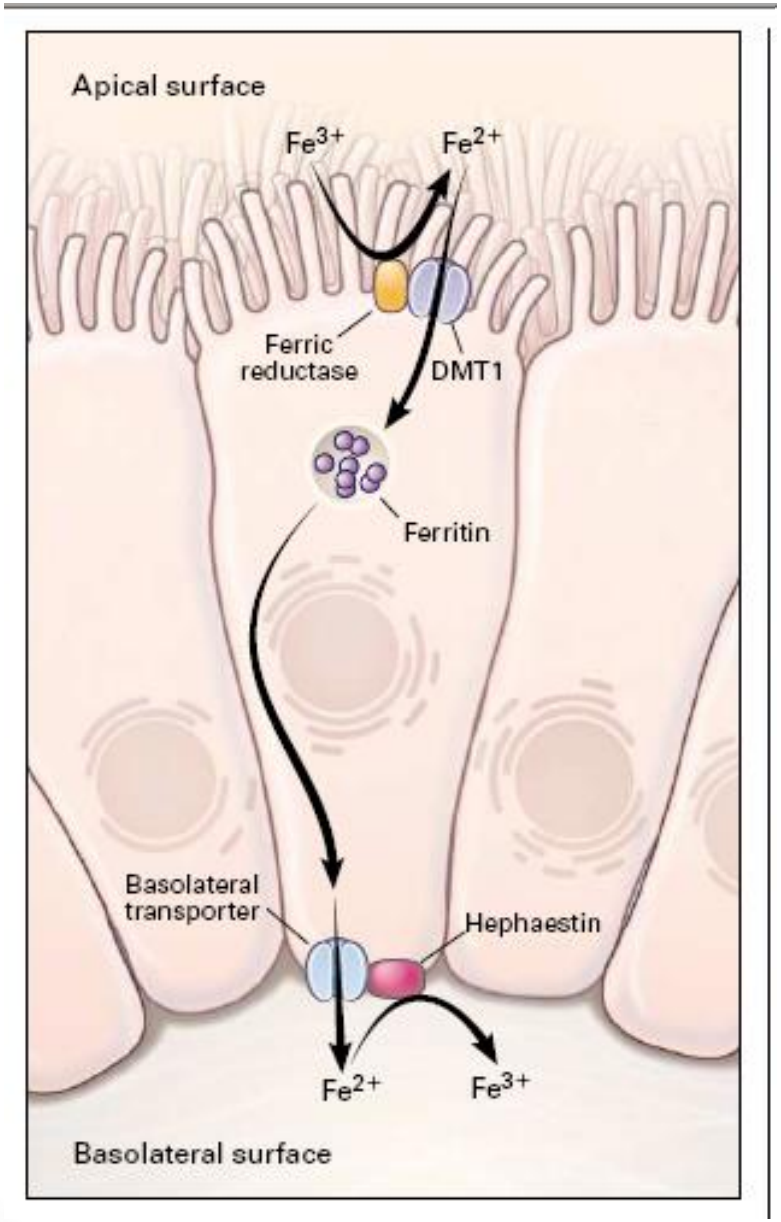
- **Iron circulates bound to transferrin with a normal TIBC % saturation of: _____.**
  - **A. 10%**
  - **B. 33%**
  - **C. 45%**



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 ferric-reductase that is coupled to a transporter protein called “divalent metal transporter-1”. (DMT1)

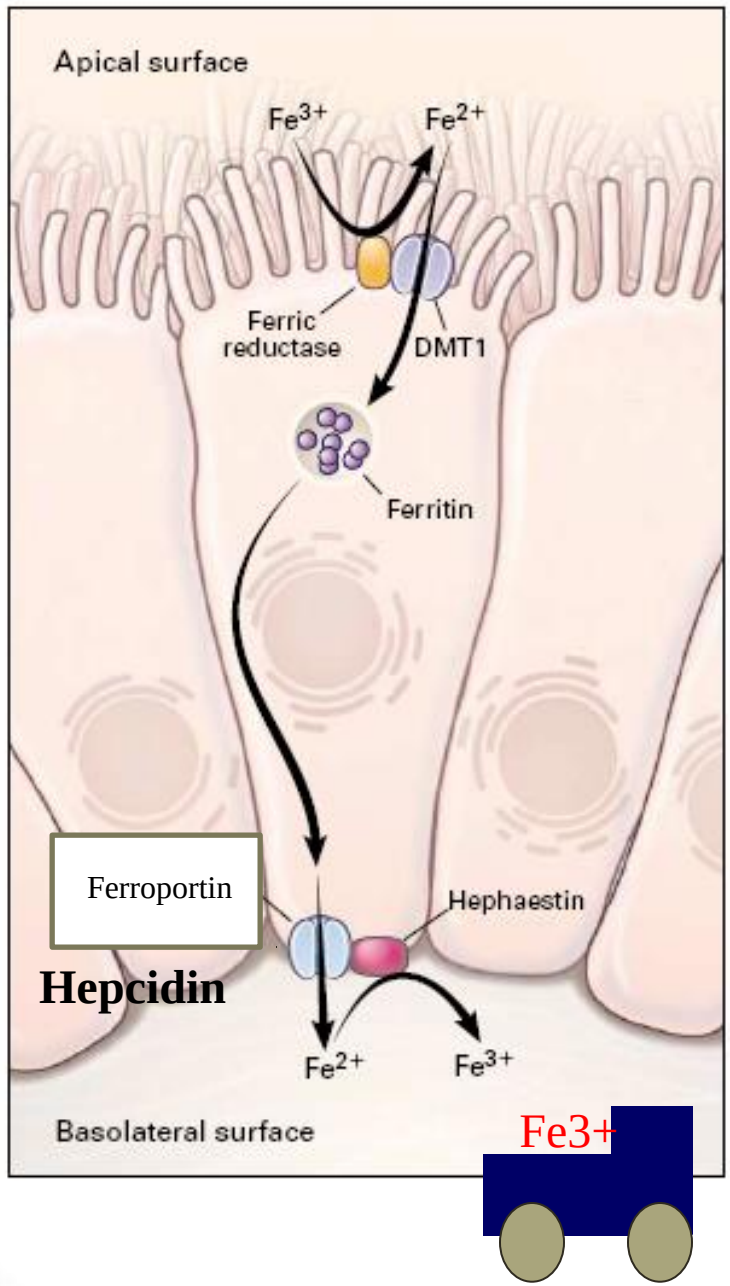




Iron Absorption

- 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.
- Question 5:
- How could this be important, clinically?

Iron Absorption

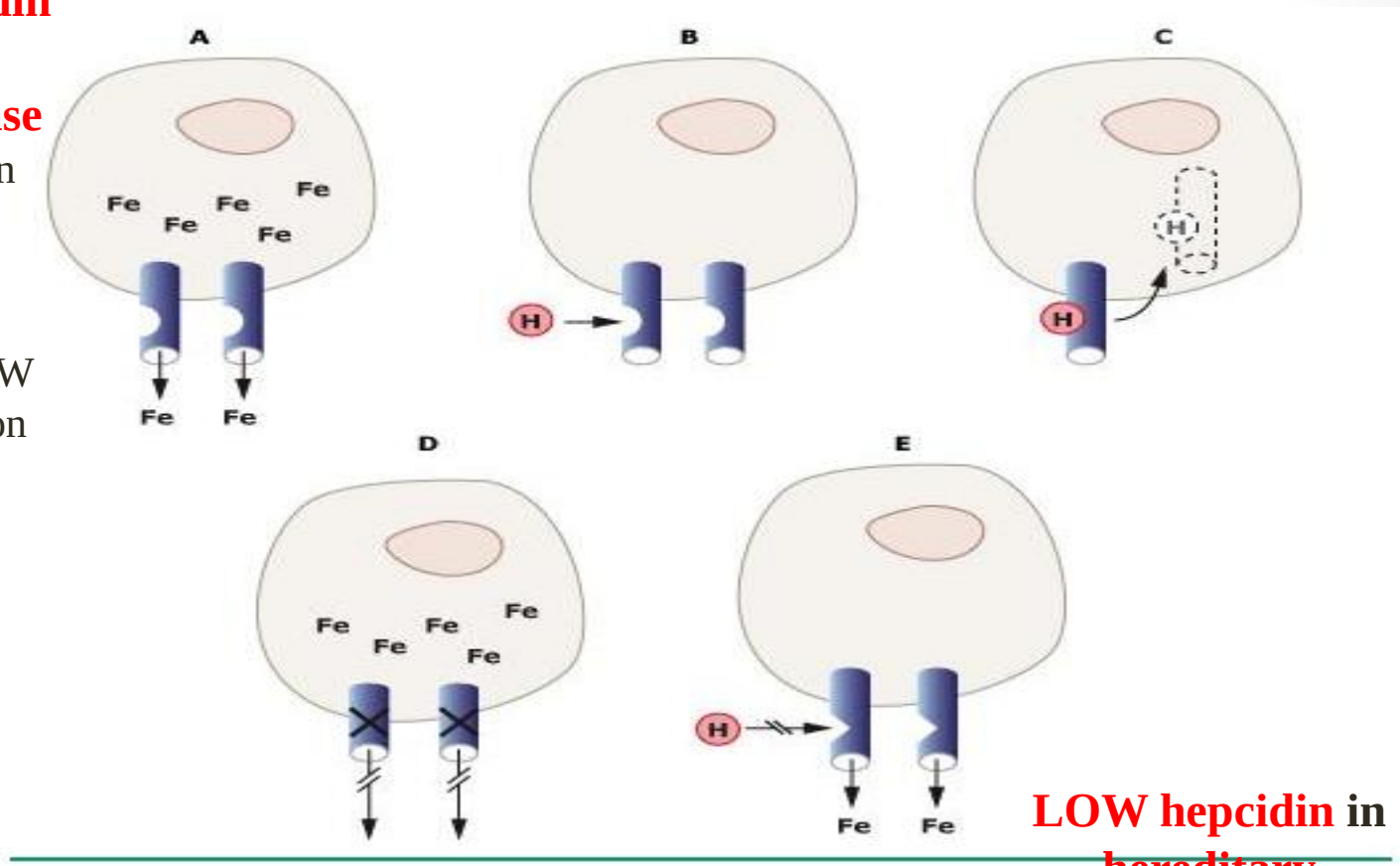


- Iron within the enterocyte is stored as **ferritin**.
- On the basolateral surface, the exporter is called ferroportin.
- Ferroportin requires a molecule to oxidize the ferrous iron back into ferric iron for loading onto Transferrin Trucks.
- **HEPCIDIN is the regulator of ferroportin that determines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

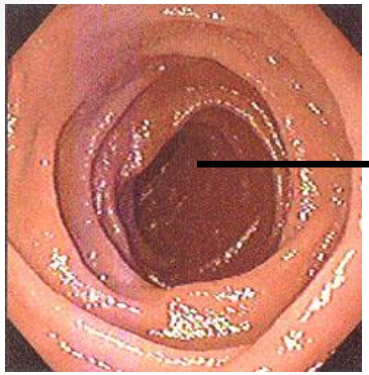
Hepcidin: iron export regulator

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

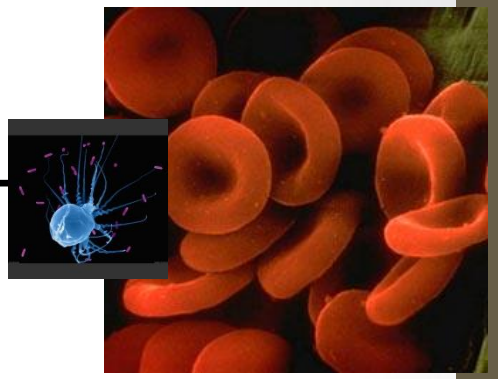
(A,B,C,and D)

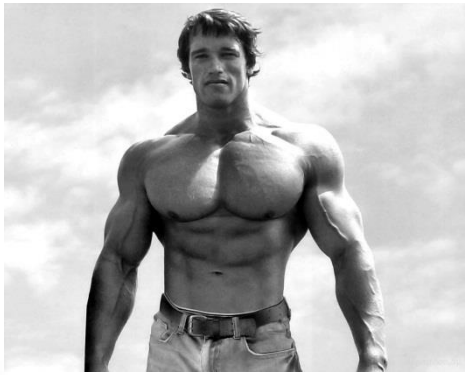


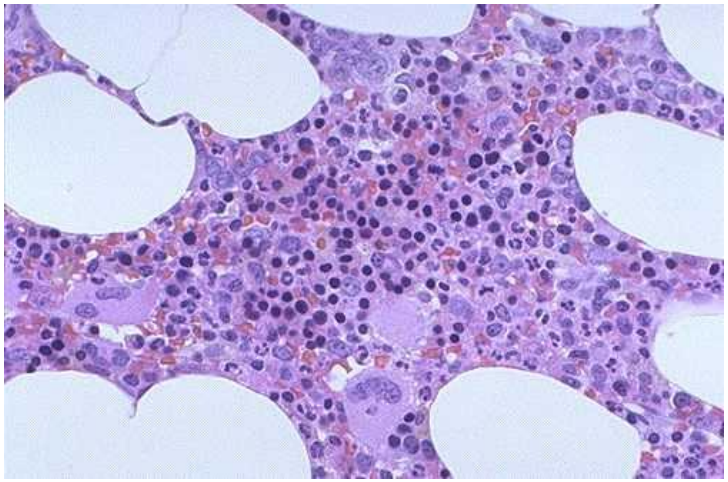
LOW hepcidin in hereditary hemochromatosis
=increased iron absorption (E)

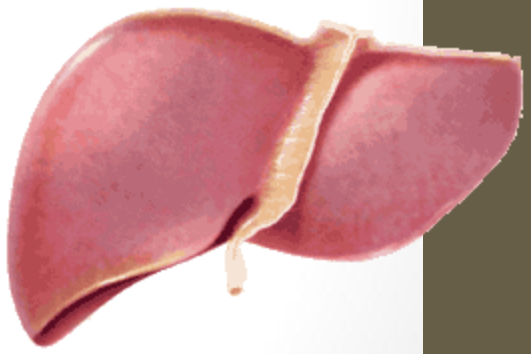


Fe 3+









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)

Question 6: How do you interpret the following?

- 28-year-old female who compulsively chews on ice:

- Hemoglobin 10 g/dL
- MCV 70 fL
- Ferritin < 2

- Her identical twin sister:

- Hemoglobin 14 g/dL
- MCV 82
- Ferritin 7

What if the ferritin value is between 30 and 100?

- 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

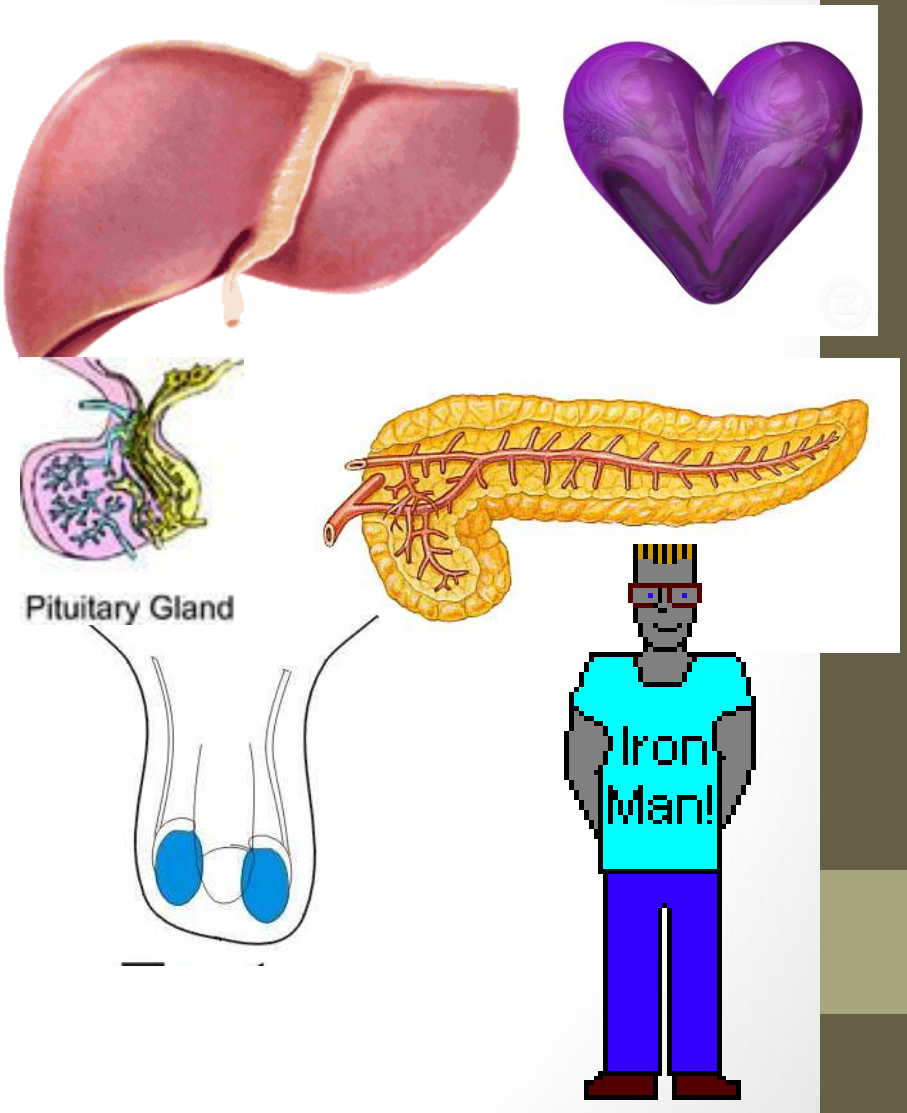
- Malabsorption
  - Total or partial gastrectomy
  - Antacid
  - H. pylori
  - Celiac disease
  - IBD
- Loss
  - -Itis of the GI tract
  - Neoplasm (polyp/CA)
  - Peptic ulcer
  - AVM
  - Parasites (hookworm)
  - Other…

Iron Overload

- Think of 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.

- Question 8.
- Give several organs that may be affected by iron overload states.



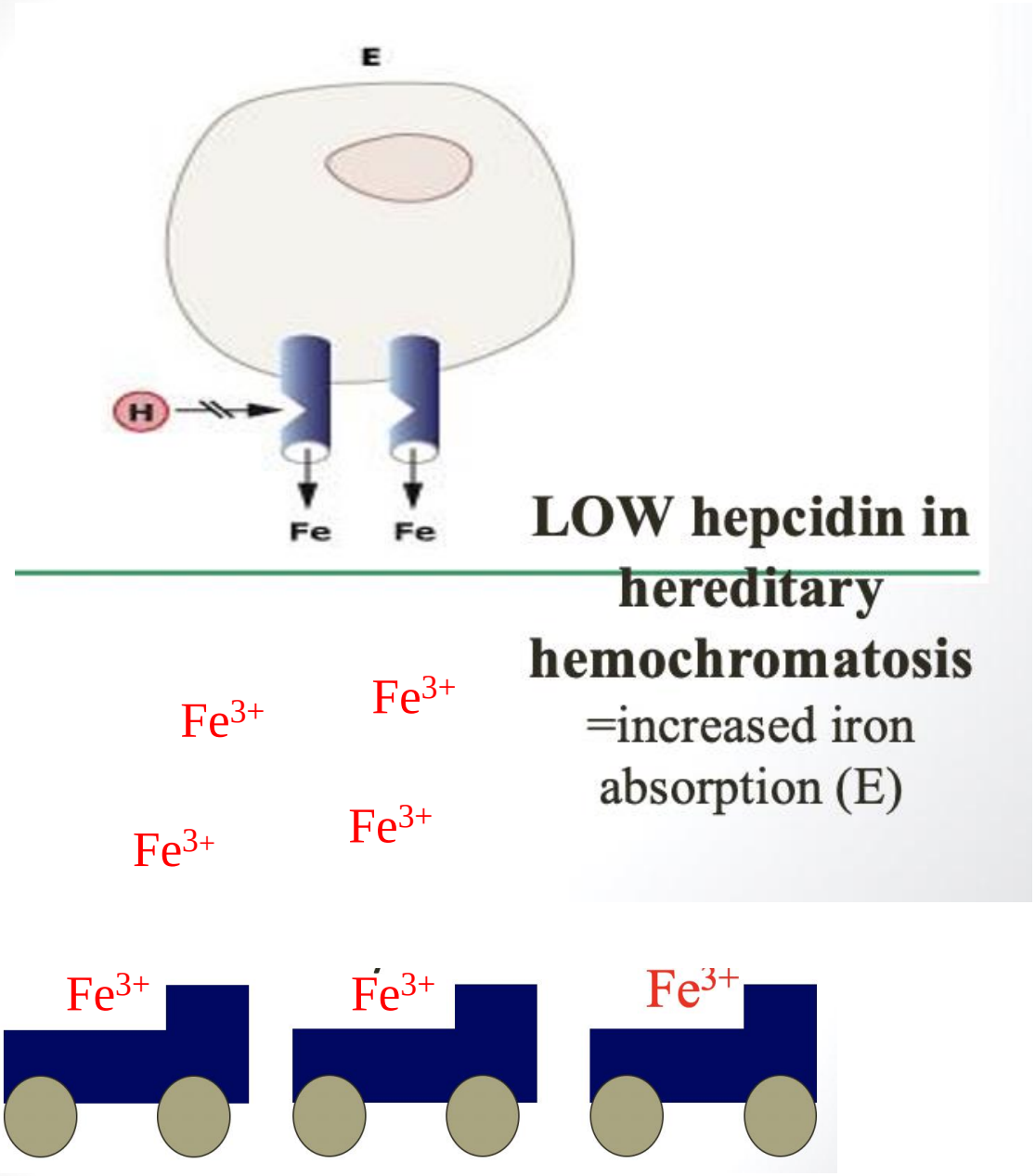
Iron Overload: Signs and Symptoms

- Unexplained fatigue
- Joint pain (CPPD) 2nd and 3rd MCP OA changes
- 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**

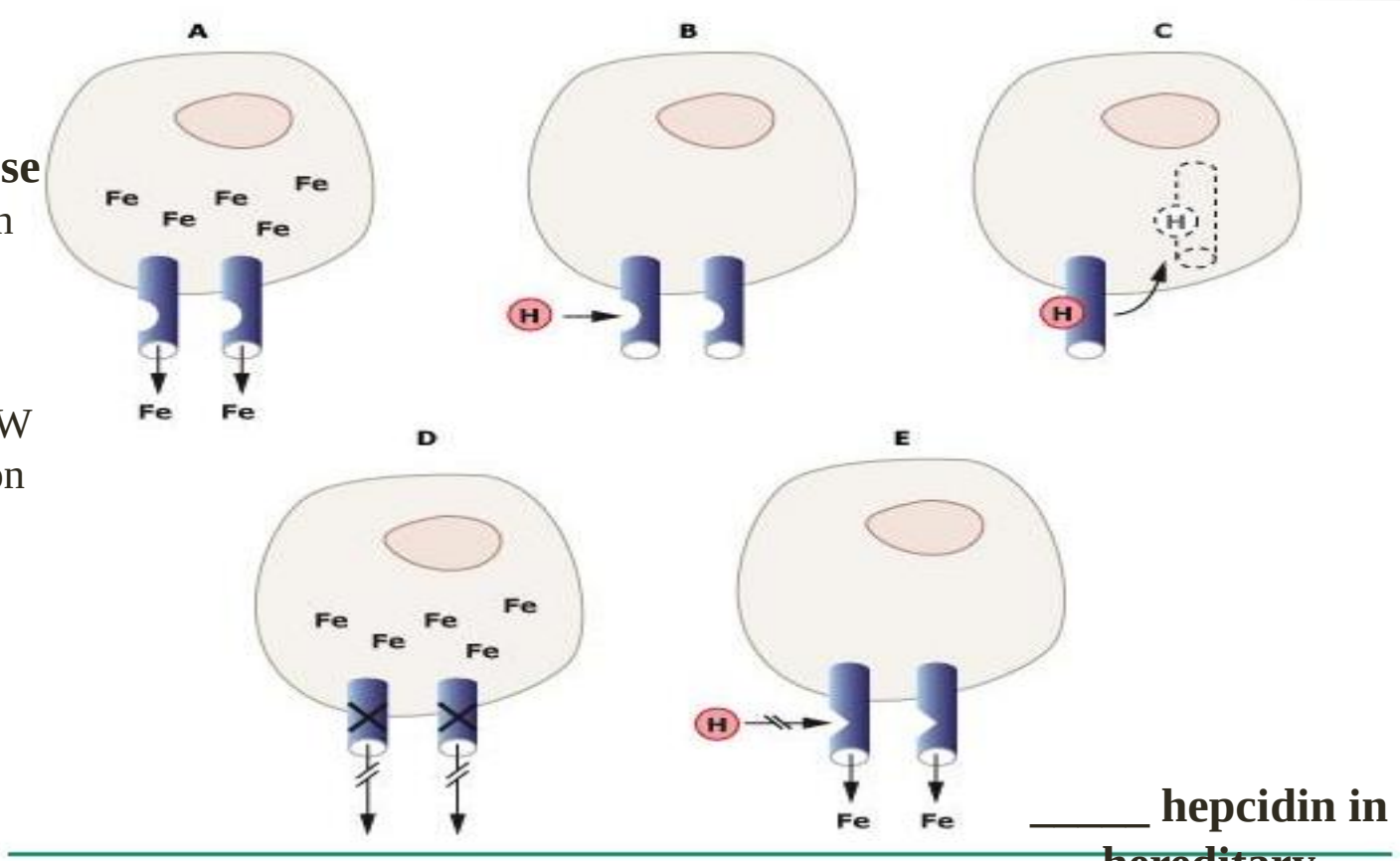


- **When the HFE protein is mutated as in HH**, there is **not enough hepcidin produced.**
- The export of iron from the basolateral side of the enterocyte, the macrophage, and the hepatocyte is allowed to continue **unhindered.**
- This overloads the transferrin binding capacity and **elevates the percent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

Question 7:
Hepcidin: iron export regulator

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

(A,B,C,and D)



_____ **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.

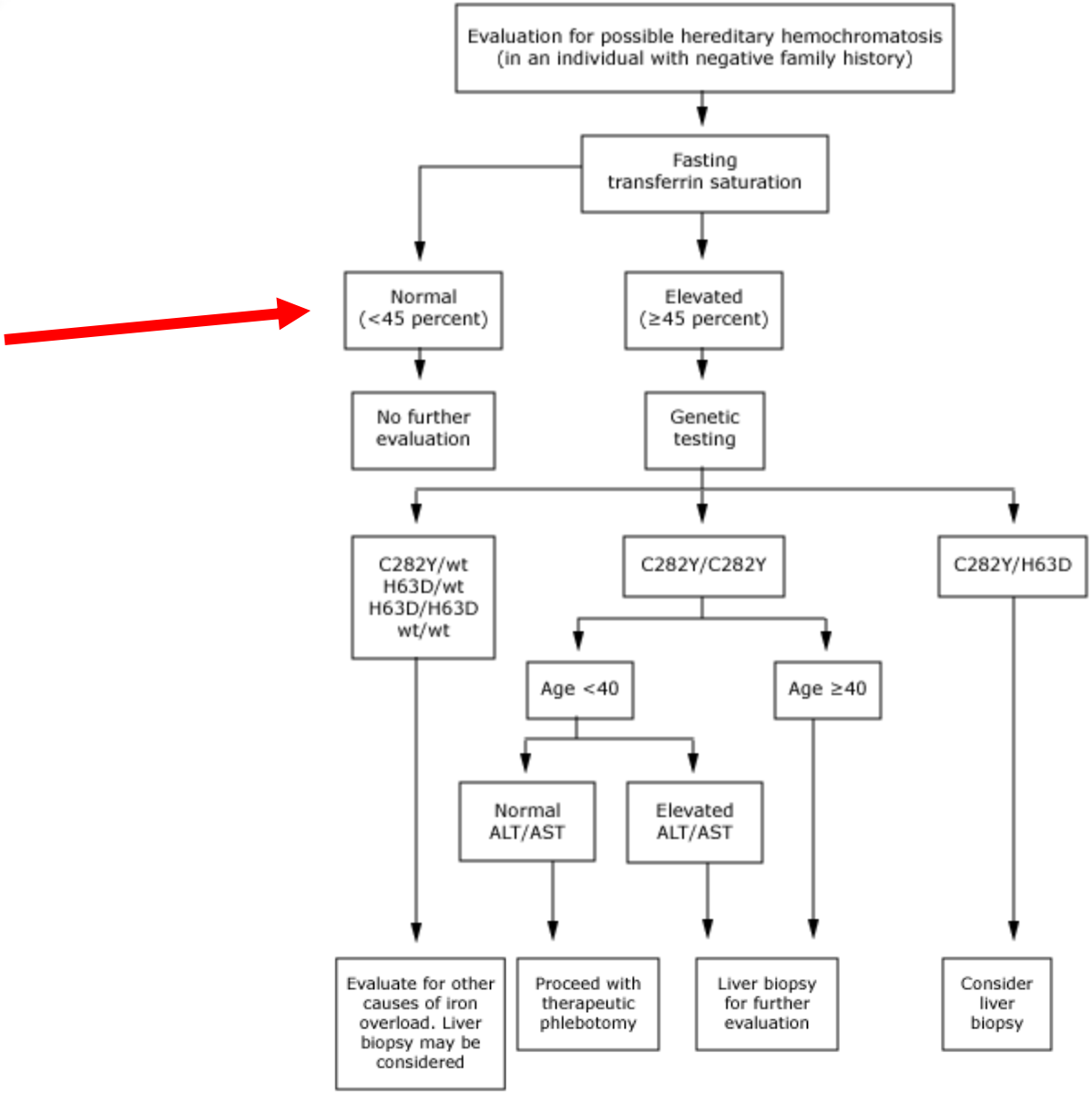
- Elevated ferritin is less sensitive than elevated transferrin saturation in screening for HH because a greater degree of iron overload is required to raise the ferritin concentration.

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)
- Transferrin 100 mg/dL (188-341 mg/dL)
- Percent saturation 8% (15-50%)

QUESTION 1.

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.

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 2

- 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 (188-341)
- % 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

Case 3

- Patient is a 27 yo white male
- 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
- Normal except for:
- **Gastrointestinal**: Soft, Non-distended, Normal bowel sounds, diffuse tenderness to palpation.

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...
Extract | Full Text | PDF
N Engl J Med 352:1741, April 28, 2005 *Perspective*
Related Searches: hepcidin | iron overload | iron deficiency anemia

Iron Deficiency Anemia: Evaluation and Management
MATTHEW W. SHORT, LTC, MC, USA, and JASON E. DOMAGALSKI, MAJ, MC, USA*Madigan Healthcare System, Tacoma, Washington*

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