

Iron Metabolism

Brenda Shinar, MD, FACP

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Case/Question 1.

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%)

CASE/ QUESTION 1.

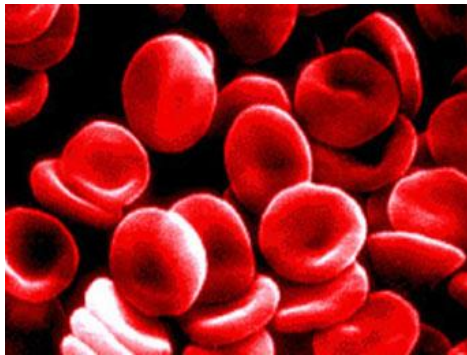
Which of the following statements accurately describes the cause of this patient's anemia?

- 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.

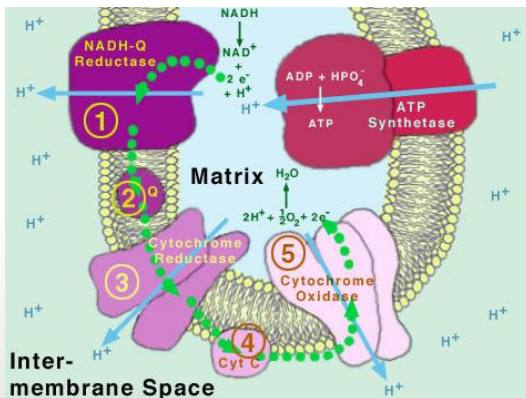
Objectives

- 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 in 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 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.

Iron Storage

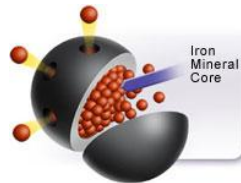
- Ferritin (tissue):

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

- Apo ferritin (or serum ferritin):

a **non-iron** containing molecule measured clinically in the plasma that reflects the overall iron storage.

(1 ng/mL of apo ferritin 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

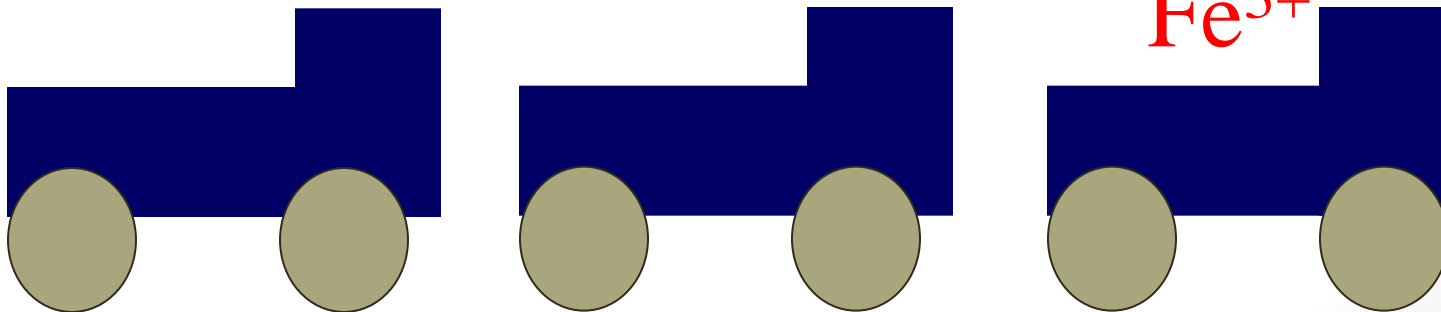
- Total Iron Binding Capacity (TIBC):

total transferrin available for binding Fe^{3+}

33% = normal

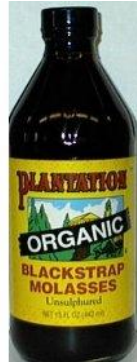
- Percent saturation:

serum iron divided by TIBC x 100

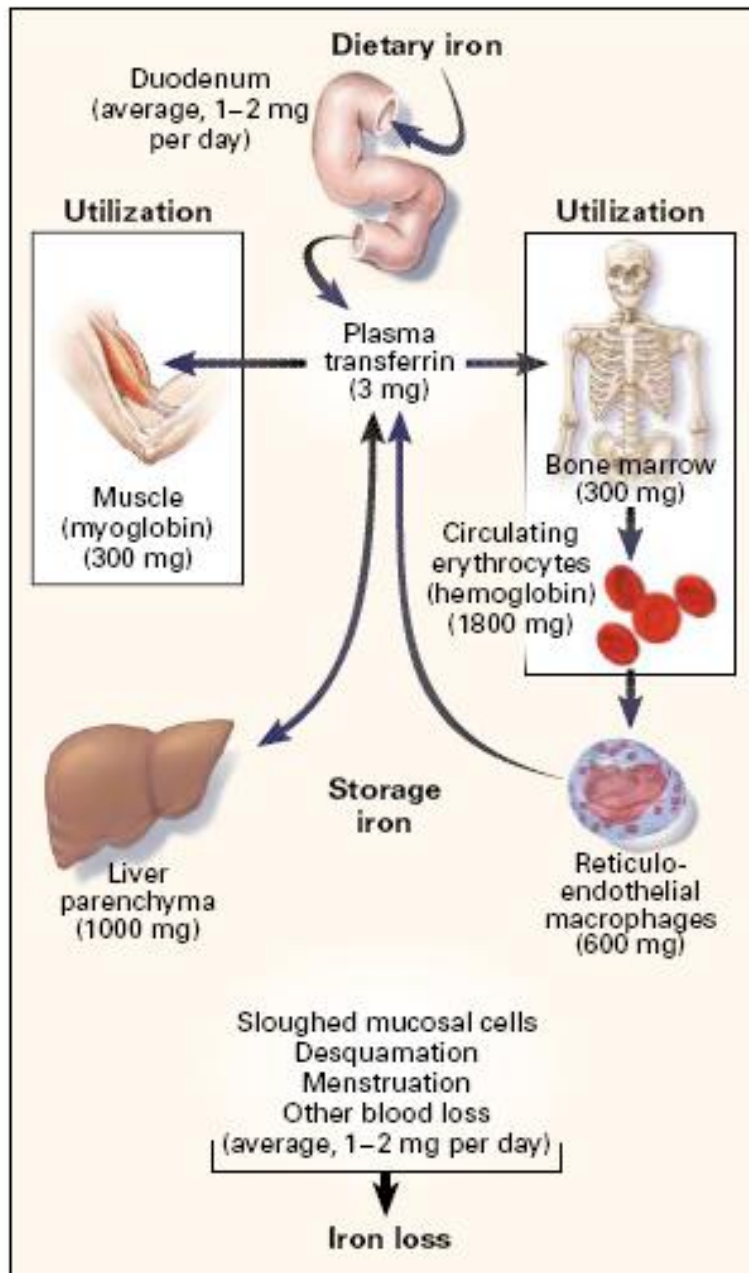


Iron Absorption

- 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!*



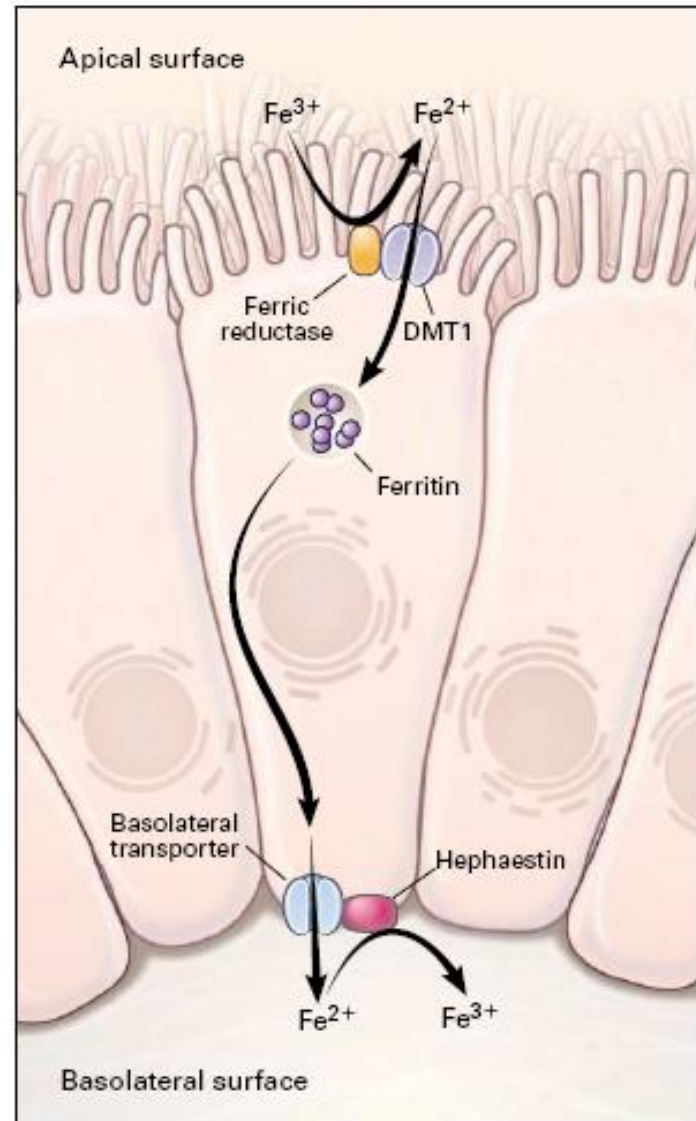
Iron Absorption



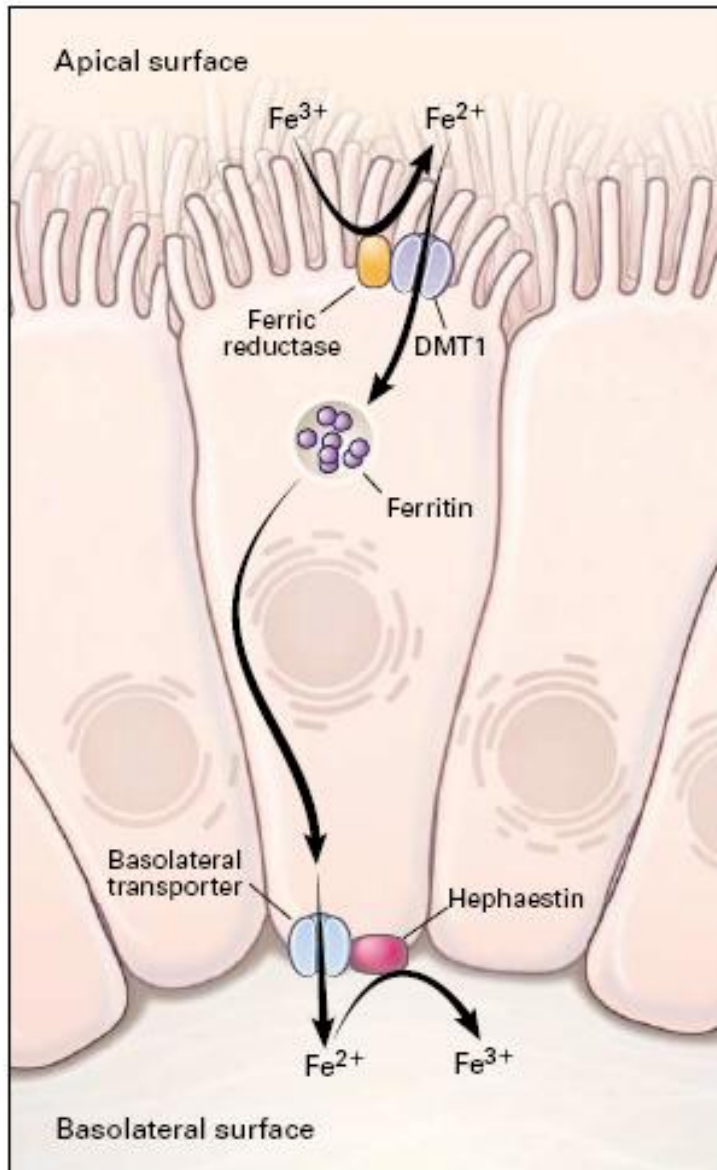
- Iron is absorbed in the _____.
 - A. Duodenum**
 - B. Jejunum**
 - C. Ileum**
- In a balanced state, 1-2 mg of ingested iron is absorbed and lost from the body each day.
- Iron circulates bound to transferrin with a normal TIBC % saturation of: _____.
 - A. 10%**
 - B. 33%**
 - C. 45%**
- Iron is stored as ferritin in all of the following places EXCEPT:
 - A. Enterocyte**
 - B. Macrophage**
 - C. Liver**
 - D. Skin**

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)

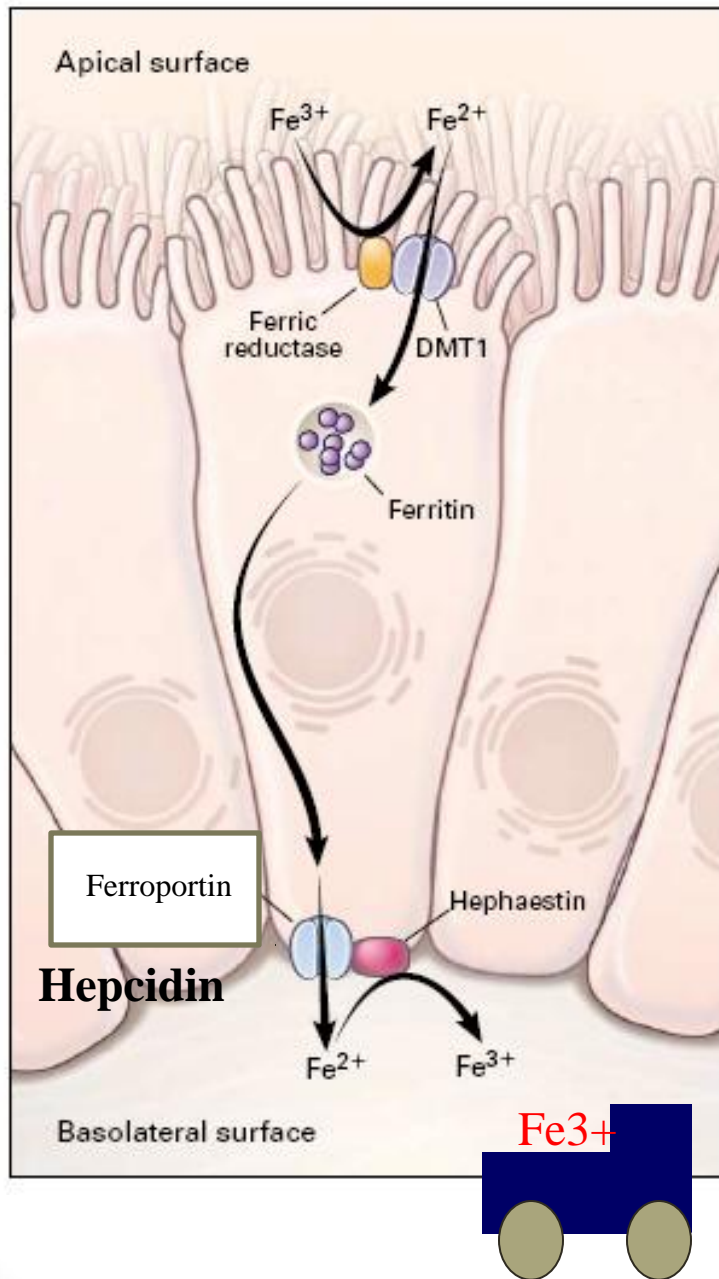


Iron Absorption



- 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.
- How could this be important, clinically?

Iron Absorption



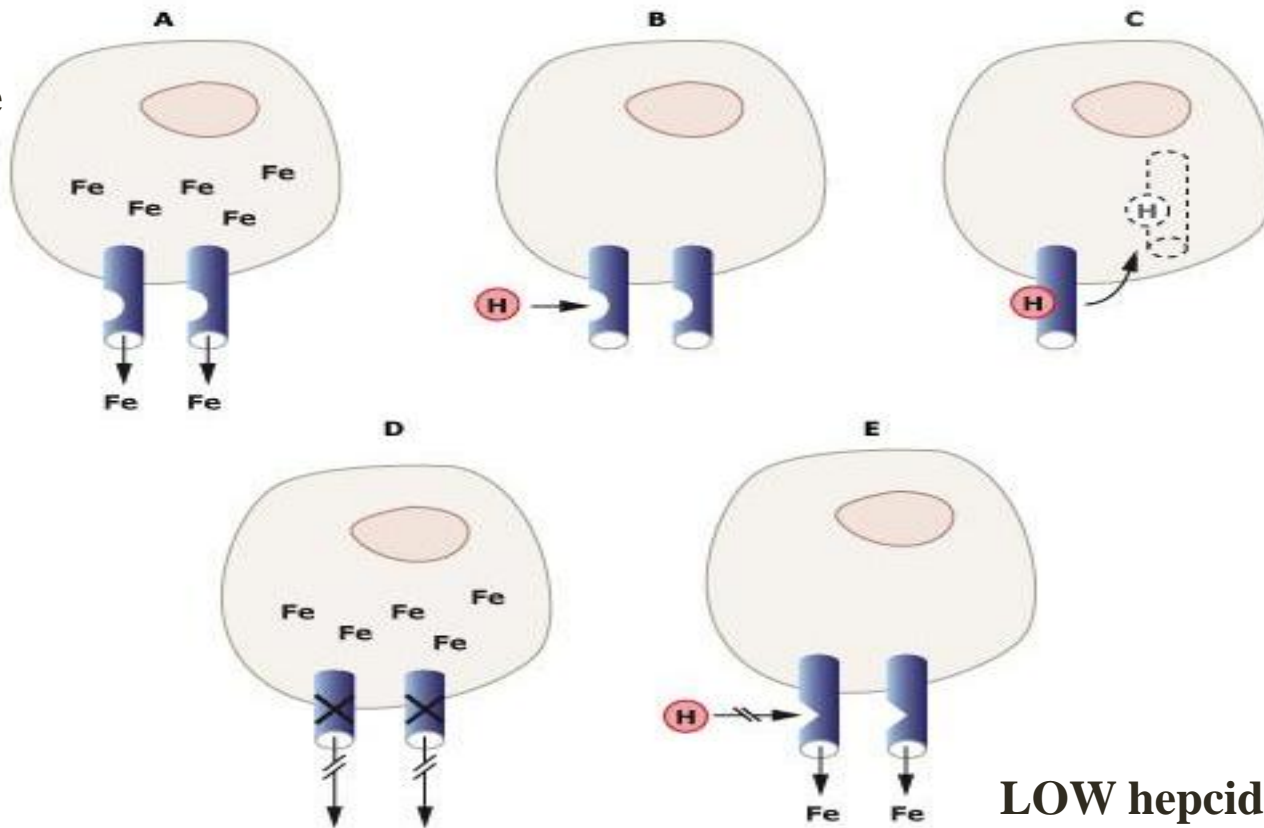
- Iron within the enterocyte is stored as **ferritin**.
- On the basolateral surface, the exporter is called ferroportin.
- Ferroportin requires a molecule to oxidize the ferrous iron back into ferric iron for loading onto Transferrin Trucks.
- **HEPCIDIN is the regulator of ferroportin that determines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

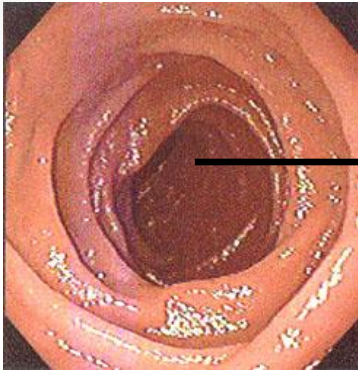
(A,B,C,and D)



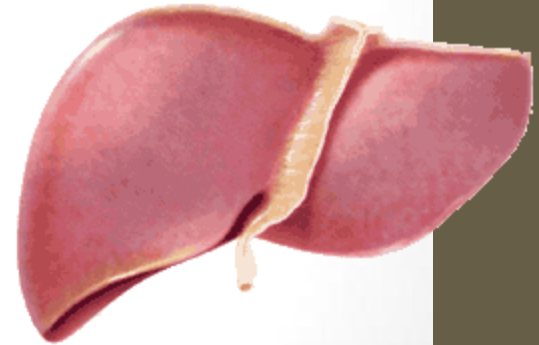
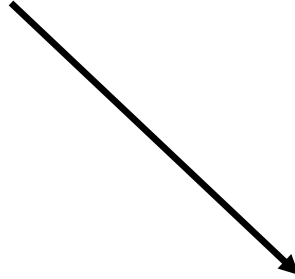
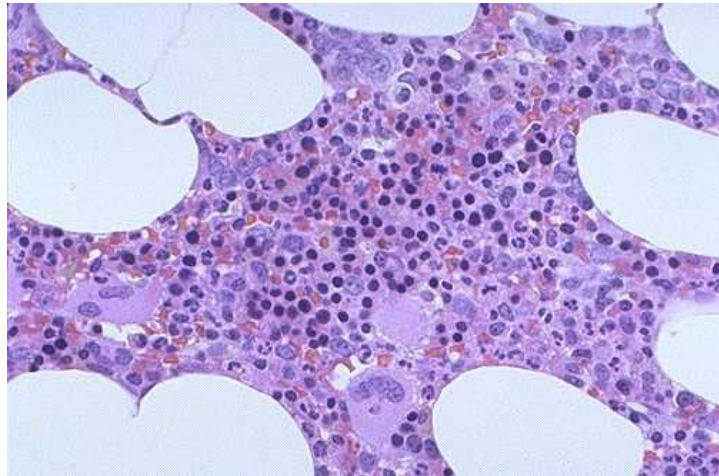
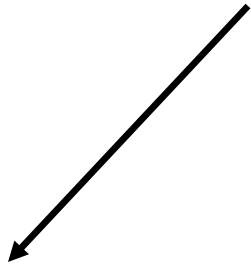
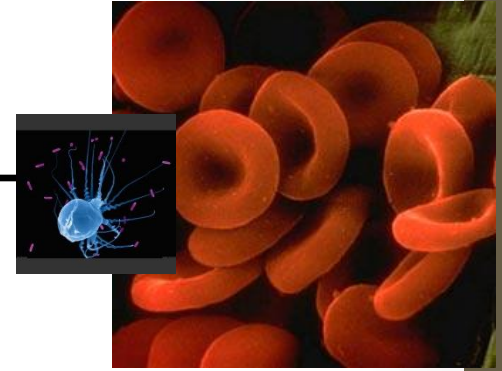
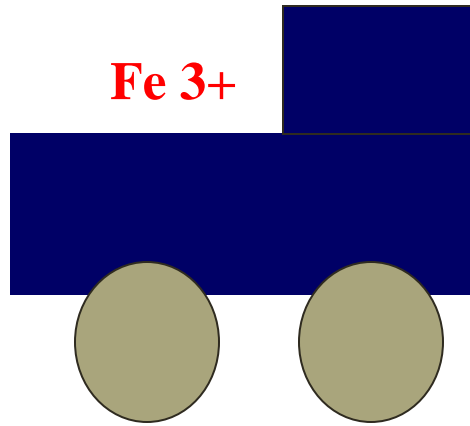
LOW hepcidin in hereditary

hemochromatosis

=increased iron
absorption (E)



Fe³⁺



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 ≤ 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



<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

- **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

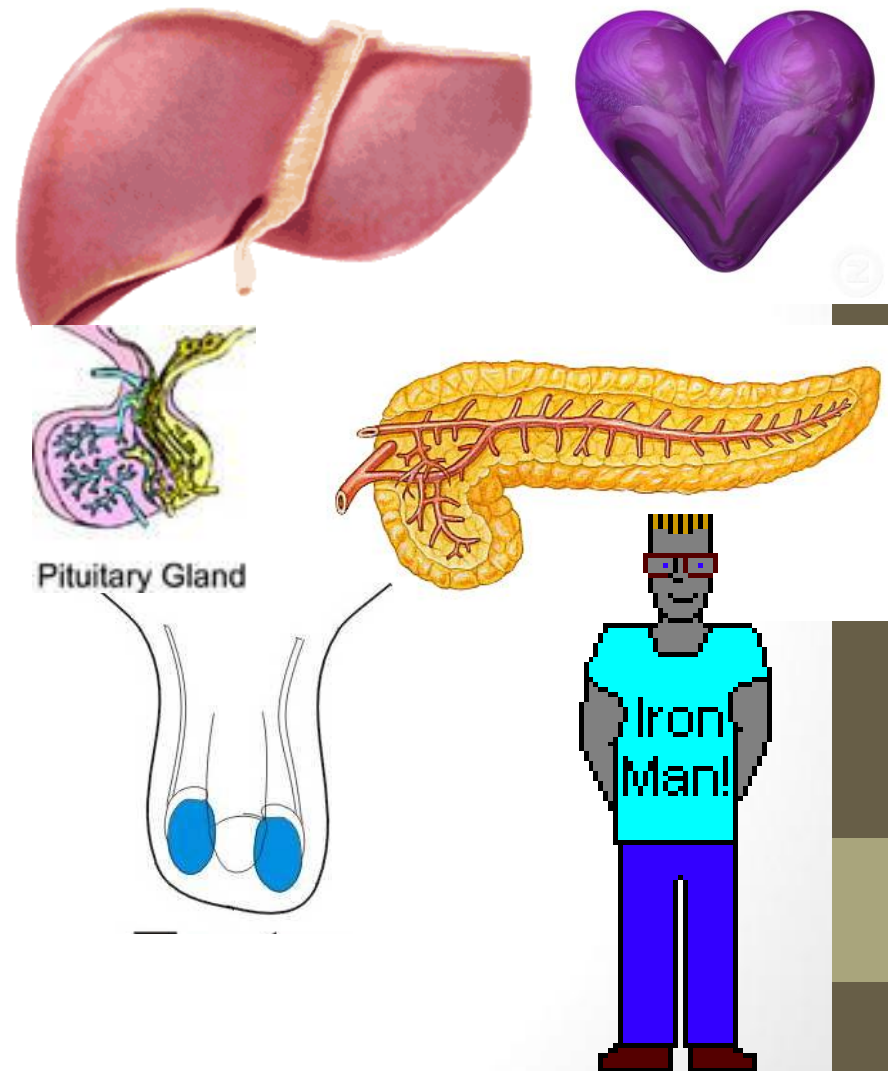
- Loss

- -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.

- Name the organs involved in iron overload:



Iron Overload: Signs and Symptoms

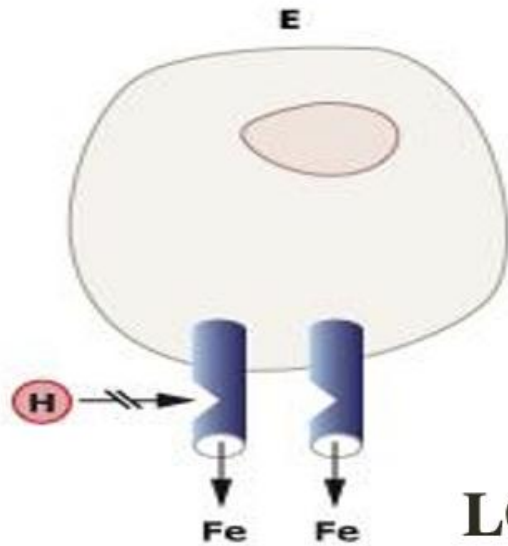
- Unexplained fatigue
- Joint pain (CPPD) 2nd and 3rd MCP OA changes
- Liver disease: elevated aminotransferase levels, hepatomegaly, cirrhosis, hepatocellular carcinoma
- Diabetes mellitus
- Impotence
- Hypothyroidism
- Heart failure
- Arrhythmias

Hereditary Hemochromatosis

- **A disease of inappropriate iron absorption resulting in the overload of iron in various organs**
- The majority of patients with HH are 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!

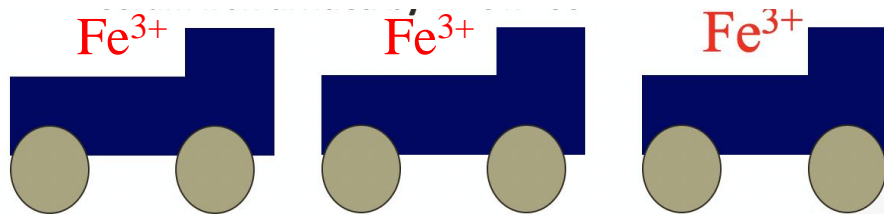


Celtic282Y



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

Fe^{3+} Fe^{3+}
 Fe^{3+} Fe^{3+}



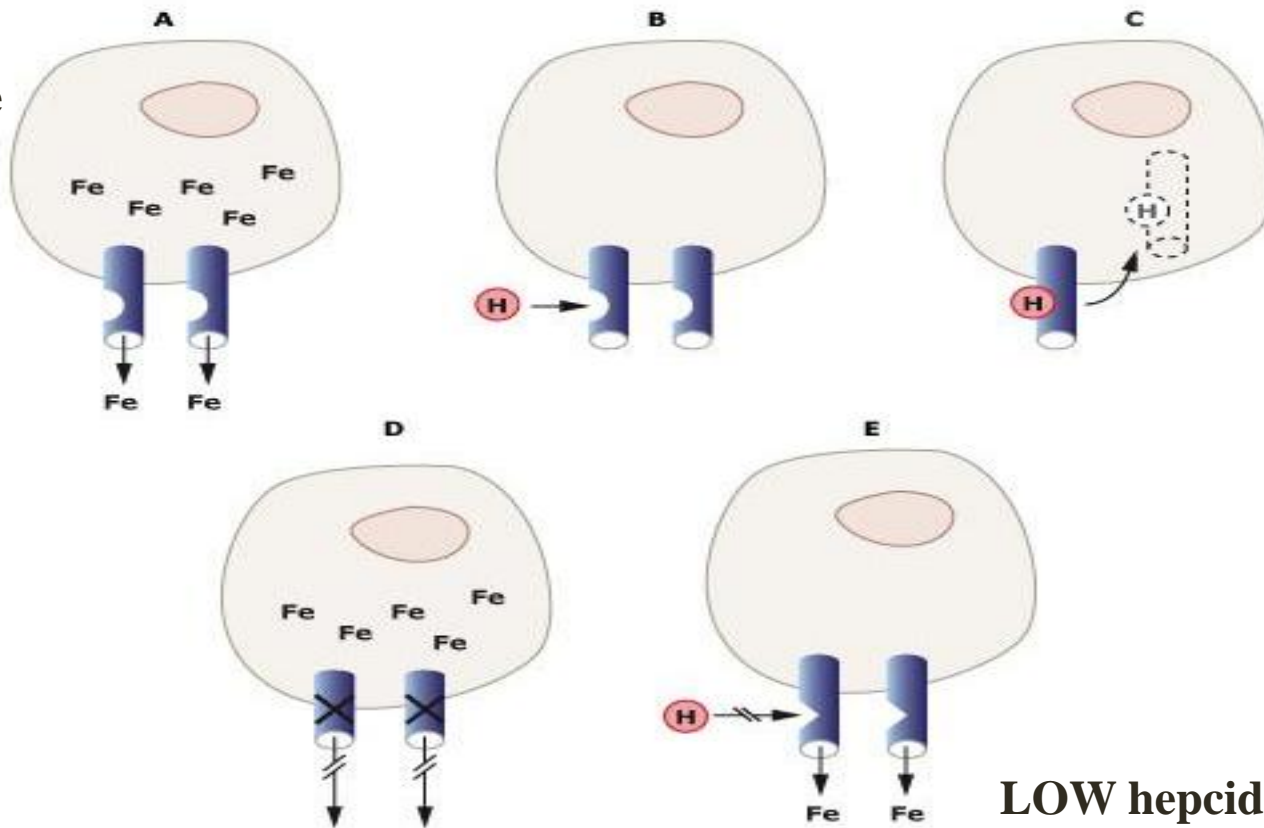
- When the HFE protein is mutated as in HH, there is not enough hepcidin produced.
- The export of iron from the basolateral side of the enterocyte, the macrophage, and the hepatocyte is allowed to continue **unhindered**.
- This overloads the transferrin binding capacity and **elevates the percent saturation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

Hepcidin: iron export regulator

HIGH hepcidin in anemia of chronic disease

= decreased iron
release out of
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resulting in LOW
iron % saturation

(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.

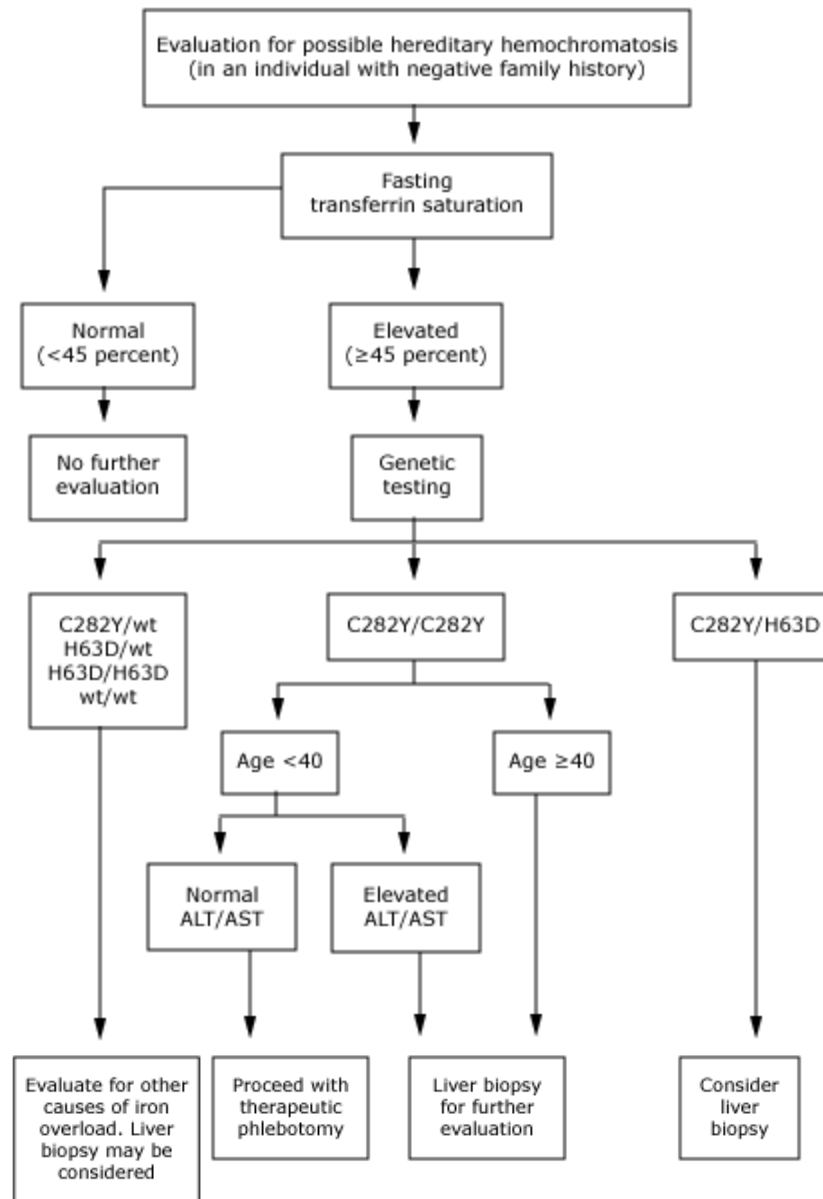
Other Tests for Iron Overload

- 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.
- 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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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 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.**

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

MISC HEMO

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

<input type="checkbox"/> Hgb A			95.2 %
<input type="checkbox"/> 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 hemoglobins 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, USAMadigan Healthcare System,
Tacoma, Washington

January 15, 2013 ◆ *Volume 87, Number 2* www.aafp.org/afp