Anemia Management in Dialysis Patients

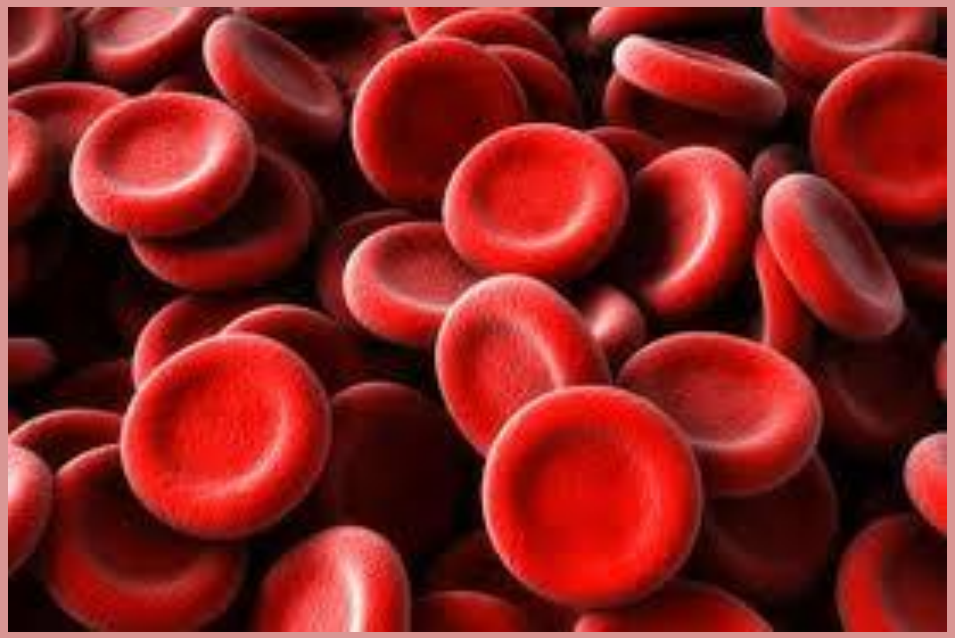
Northwest Kidney Center

Narrated by Andy Brockenbrough

Objectives

1. Define anemia.
2. Review causes of anemia among dialysis patients
3. Be familiar with management of anemia.
4. Recognize potential side-effects of erythropoietin.

Anemia Background



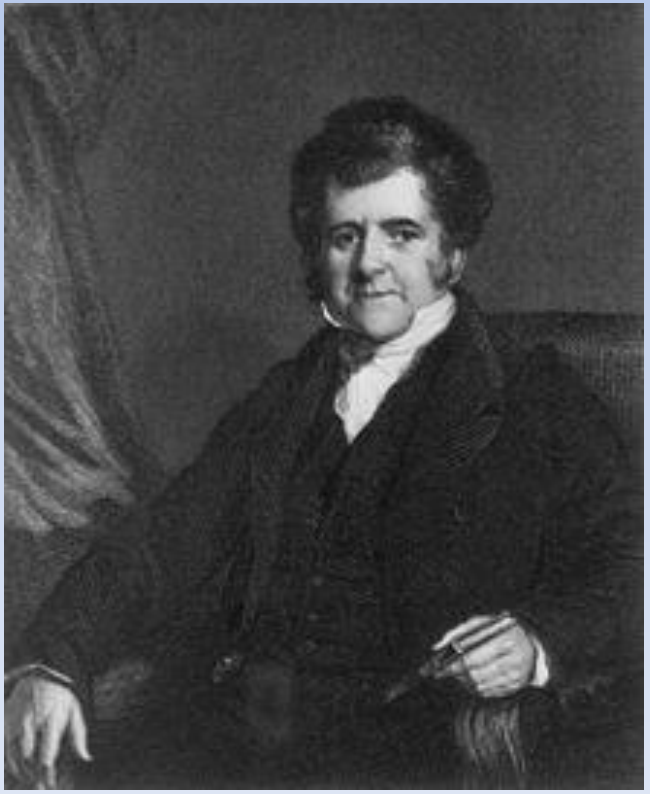
Definition

- Anemia is a reduction in hemoglobin or a reduction in the number of circulating red blood cells.
- Defined by the World Health Organization (WHO) as a hemoglobin (Hb) <13 g/dL for adult males and postmenopausal women and <12 g/dL for premenopausal women.
- Not specifically defined for dialysis patients, although the generally accepted goal is to keep hemoglobin above 10 g/dL.

History

- Anemia was first linked to kidney disease over 170 years ago by Dr. Richard Bright.
  - English physician
  - “Father of nephrology”
  - “Bright’s disease”

- Nearly all patients who start dialysis today are anemic.



Richard Bright, 1789 - 1858

Complications of Anemia in ESRD

- **Definite**: Fatigue, shortness of breath, need for blood transfusions
- **Probable**: Reduced quality of life.
- **Possible**: Increased cardiac events (heart attacks, thickening of the heart muscle)

Causes of Anemia in Dialysis Patients

Causes

1. Blood loss (access, circuit, gastrointestinal)
2. Nutritional deficiency (iron, other)
3. Inflammation.
4. Erythropoietin deficiency.

Many Causes!!!

1. Blood Loss

- Dialysis circuit
- Frequent phlebotomy
- Gastrointestinal bleeding
- Menstruation

2. Nutritional Deficiency

- Iron
- Folate
- B12

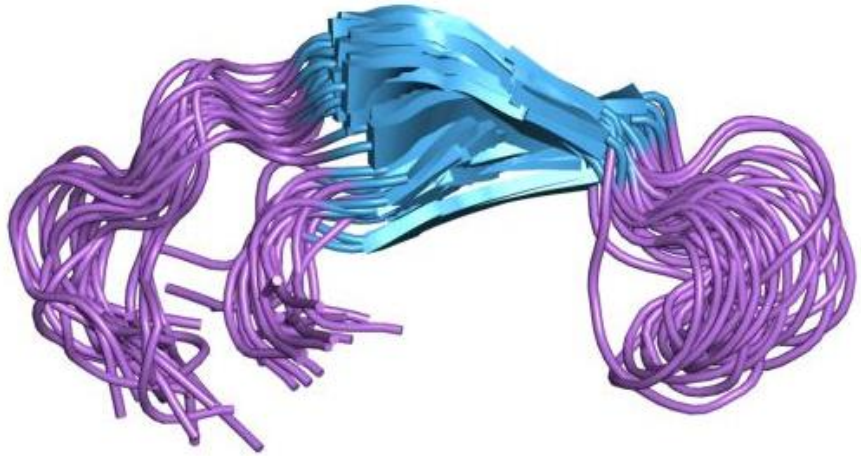
Markowitz GS, Kahn GA, Feingold RE, Coco M, Lynn RI: An evaluation of the effectiveness of oral iron therapy in hemodialysis patients receiving recombinant human erythropoietin. Clin Nephrol 48: 34–40, 1997

3. Inflammatory Block

- Illness → **inflammation**.
- Uremia: Suspected that circulating uremic-induced inhibitors of erythropoiesis contribute to the anemia.
- Excess of a hormone called **hepcidin**.

Hepcidin

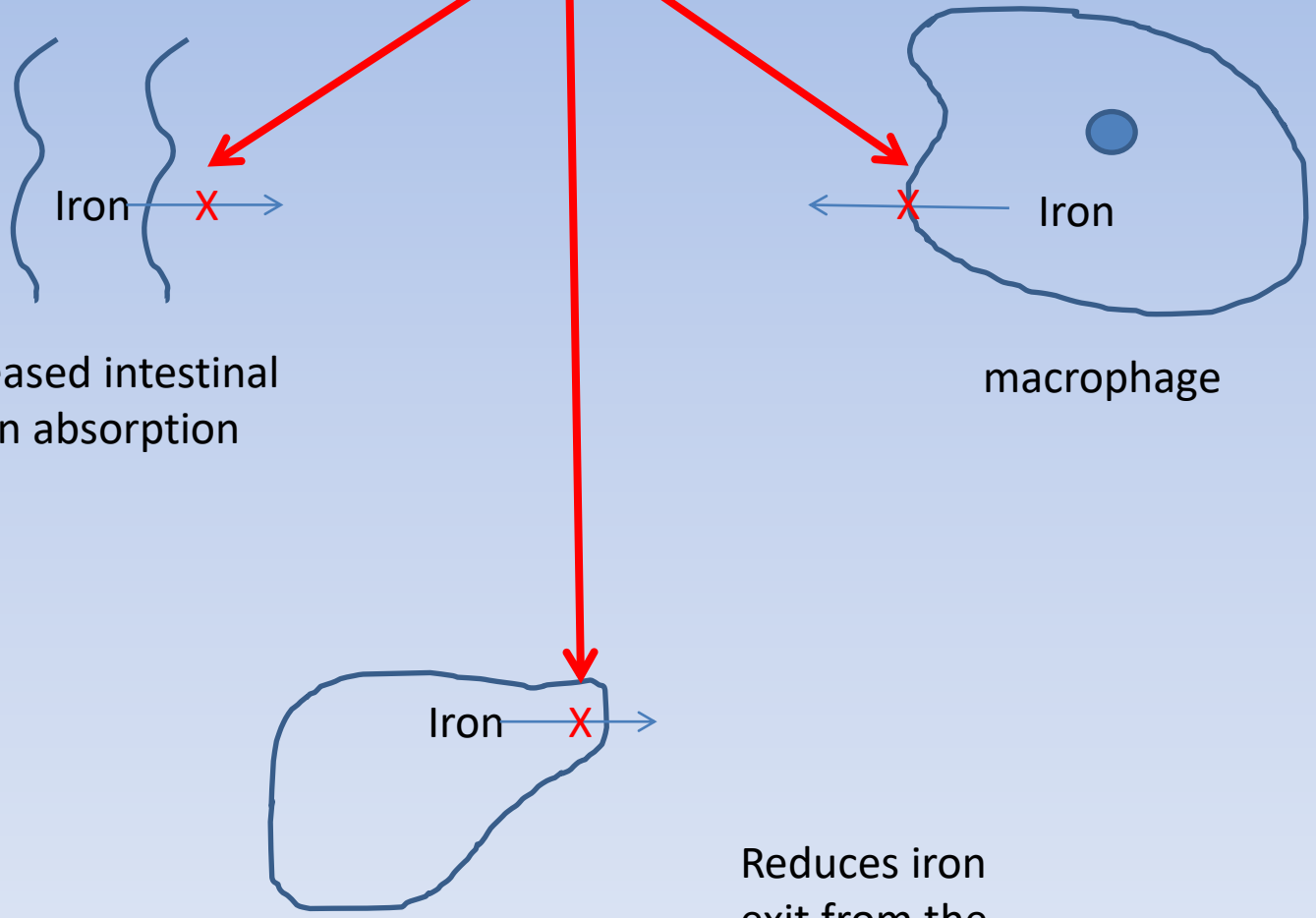
- Discovered in 2000
- Protein in humans synthesized by the liver
- Key regulator of entry of iron into circulation (blood stream) in mammals.
- Reduces iron in the blood stream by several mechanisms.



Hepcidin

Decreases dietary iron absorption by reducing iron transport across gut mucosal cells.

Reduces iron exit from macrophages



Decreased intestinal iron absorption

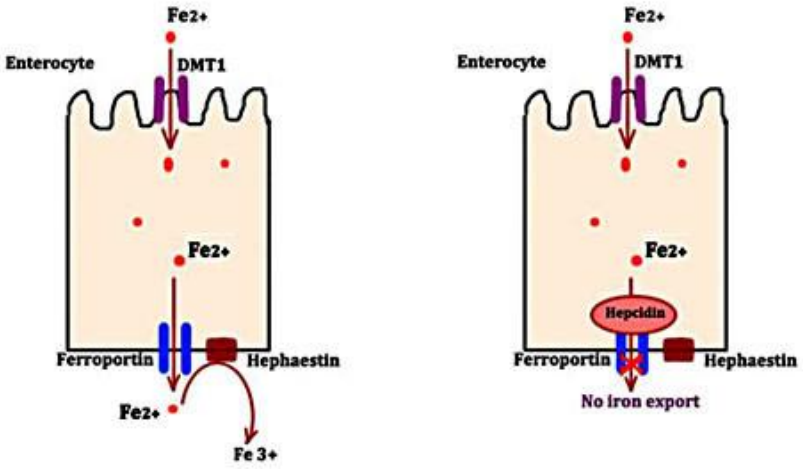
macrophage

Liver

Reduces iron exit from the liver

How does Hepcidin do this?

- Inflammation → high hepcidin levels →
  - Binds ferroportin → internalization and degradation of both.
  - This prevents iron being exported and the iron is sequestered in the cells.

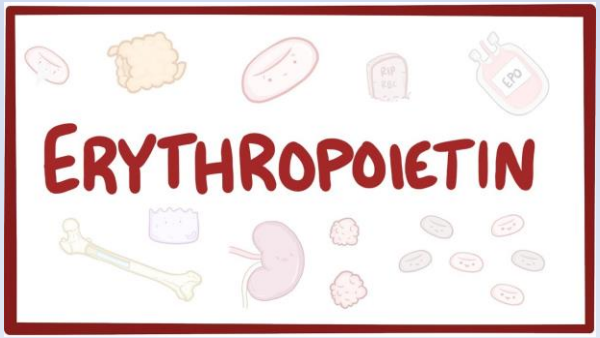


Why learn about Hepcidin?

- Hepcidin inhibitors are being studied as a possible treatment for anemia in dialysis patients.
- Hereditary hemochromatosis: genetic condition.
  - Hepcidin production by liver is LOW.
  - Iron overload occurs due to increased iron efflux from storage and increased gut iron absorption

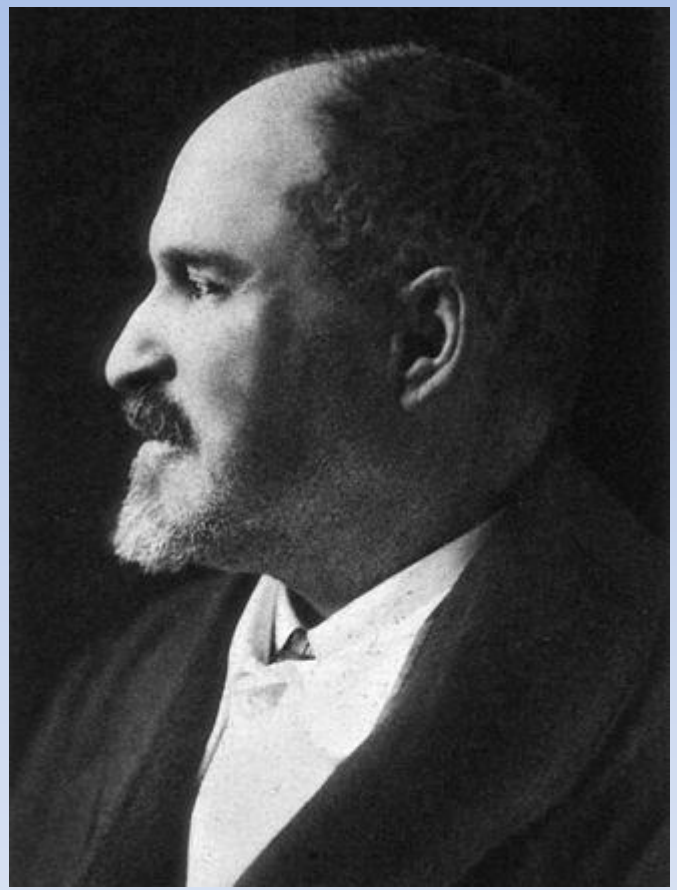
5. Erythropoietin Deficiency

- Erythropoietin = a hormone produced by the kidney which stimulates red blood cell production.
- Levels in dialysis patients are typically only 1-10% of normal.
- Responsible for most (about 80%) of anemia in the dialysis population.



Erythropoietin History

- 1904: Paul Carnot (professor of medicine in Paris) proposed the idea that hormone regulate the production of red blood cells. He called it "*hemopoietine*."
  - Subjected rabbits to bloodletting, then infused their blood into other rabbits, who then developed polycythemia.



Erythropoietin History

- 1977: Miyake *et al* isolated erythropoietin from 2500 liters of urine from patients with aplastic anemia
- **1985**: Human gene encoding for erythropoietin was characterized; allowed for industrial production of recombinant human erythropoietin.
- **1987**: Joseph Eschbach et al published the first clinical trial of erythropoietin at the Northwest Kidney Center.
- **1989**: Epogen received FDA approval.

ORIGINAL ARTICLE FREE PREVIEW ARCHIVE

Correction of the Anemia of End-Stage Renal Disease with Recombinant Human Erythropoietin

Joseph W. Eschbach, M.D., Joan C. Egrie, Ph.D., Michael R. Downing, Ph.D., Jeffrey K. Browne, Ph.D., and John W. Adamson, M.D.

- N Engl J Med 1987; 316:73-78
- N=25 patients at the Northwest Kidney Center given recombinant erythropoietin.
- No further transfusions needed.

Phase III Trial

- Annals of Internal Medicine. 1989 Dec 15;111(12):992-1000.
- n=333 hemodialysis patients with hematocrit < 30%, given Epogen.
- Mean hematocrit increased from 22.3% → 35%.
- Transfusion decreased from 1030 in previous 6 months to virtually none (!).

Blood Transfusions

Downsides

- Infection
  - Hepatitis B, other blood borne viral infections
- Decrease transplant success
  - Sensitization of the patient to possible kidney transplants
- Iron Overload Syndrome:
  - Deposition of iron in major organs, including liver, pancreas, heart, and pituitary.

Other Effects of Erythropoietin

- Wound healing
- Brain's response to neuronal injury
- Vasoconstriction
- Stimulates blood vessel growth (angiogenesis)
- Stimulates proliferation of smooth muscle fibers
- Increases intestinal iron absorption.
- Probably improves memory
- May have effects on mood.

Erythropoietin Blood Levels

- Very low in the absence of anemia
- Can increase 1000 – 10K fold under hypoxic stress (low blood oxygen levels).
- This is why patients with lung disease often have very high hemoglobin levels.
- Very low in patients with kidney failure
  - Some exceptions: Polycystic kidney disease. Patients with renal tumors.

Epoetin alpha

- Single greatest drug expenditure paid by the U.S. Medicare system
  - In 2010, the program paid $2 billion for the drug

Management of Anemia in Dialysis Patients

Screening

- We screen all patients for anemia upon initiation of maintenance dialysis with a complete blood count (CBC).
- Hemoglobin is then monitored at least monthly.
  - Also check hemoglobin whenever clinically indicated (e.g. after major surgical procedures, hospitalization, or bleeding).
- Start erythropoietin when hemoglobin < 10, and target range 10-11 (consensus opinion).

How do we treat anemia in dialysis patients?

- Recombinant human erythropoietin (rHuEPO) and Iron

IV iron

- Will be discussed in a separate talk in greater detail.
- In general, it is important to administer intravenous iron either before or along with the Epogen.
- Indications for iv iron: TSAT < 20%, Ferritin < 200 ng/mL.

Goal of Therapy

- Reduce the need for transfusion
- Improve quality-of-life symptoms, exercise tolerance, and reduce need for transfusions.

Currently available ESAs

- Recombinant human erythropoietin (rHuEPO)
  - Epoetin alpha (Procrit, Epogen, Retacrit)
  - Epoetin beta (Epogin, NeoRecormon, Recormon)
  - Epoetin theta (Biopoin, Eporatio)
- Biosimilars
  - HX575 (Sandoz)
  - SB309 (Hospira)
- Longer-acting ESA
  - Darbepoetin alpha (Aranesp)
  - **Methoxy polyethylene glycol-epoetin beta (Mircera**)

Mircera

- Long-acting erythropoiesis-stimulating agent or “ESA” (Roche)
- FDA approved in November 2007; available in the US since 2015.
- Made by linking erythropoietin-beta with methoxy polyethylene glycol butanoic acid
- Decreased affinity for the erythropoietin receptor but longer half-life.

Plasma Half-lives of Erythropoietin Analogues (hours)

	IV	SQ
Epoetin Alpha	**6.8**	**19.4**
Darbepoetin alpha	25.3	48.8
Methoxy polyethylene glycol-epoetin beta (Mircera)	130	133

Sports Fact

- July 17, 2008: Italian bicycle racer Riccardo Riccò was disqualified from the Tour de France because urine sample tested positive for Mircera.

Target Hemoglobin

Target Hemoglobin

- 1989: Treat hemoglobin from about 7 up to 10 g/dL.
- 1990s-2009: Interest in normalizing hemoglobin (hemoglobin 13+).
  - Problem: Multiple studies in kidney disease population link treating with Epogen to Hb 13-16 g/dL associated with cancer, heart disease, stroke, access thrombosis.

Normal Hematocrit Trial (NHT)

Besareb et al. N Engl J Med 1998 Aug 27;339(9):584-90.

- N=1233 hemodialysis patients with cardiac disease (heart failure, heart attacks) with baseline Hb values of 9 to 11 g/dL on an Epogen.
- Randomly assigned to achieve and maintain a Hb of either 14 or 10 g/dL.
- Results: Study terminated after 29 months because of more adverse events in the high hemoglobin group.
  - Higher risk of the death or nonfatal heart attacks
  - 7% higher 1&2 year mortality rates
  - Greater risk of access thrombosis (39% vs 29%)
  - Greater risk of hospitalization.

RCTs on “normalizing” Hb

- **Parfrey** et al (n=596): Hemodialysis patients. Increased stroke risk.
- **Drueke** et al (n=600): Chronic kidney disease population. Trend towards increased mortality.
- **Singh** et al (n=1432): Chronic kidney disease population. No benefit, increased cardiovascular risk.
- **Pfeffer** et al (n=4032): Chronic kidney disease population. No clear benefit, increased risk stroke, cancer deaths.

Why the adverse side-effects?

- It seems likely that supraphysiologic doses of ESAs, especially at very high doses or in patients resistant to treatment, have effects in other tissues.
- Findings have renewed interest in finding alternatives to Epogen.

Current Understanding

- Targeting Hb > 13: Harmful
- Hb < 10: Associated with diminished quality of life
- Hb 9.5 – 11.5: Likely to be beneficial and safe for most patients.

Summary

- Anemia contributes to many of the symptoms associated with reduced kidney function.
  - Partial correction of anemia provides benefit.
- We routinely monitor all hemodialysis patients for anemia and iron deficiency.
- Treatment of anemia includes erythropoiesis-stimulating agents (ESAs) and/or intravenous (IV) iron.
- Target hemoglobin levels range from 10 to 11 g/dL, rather than higher levels.
  - Levels > 13 are associated with adverse outcomes.

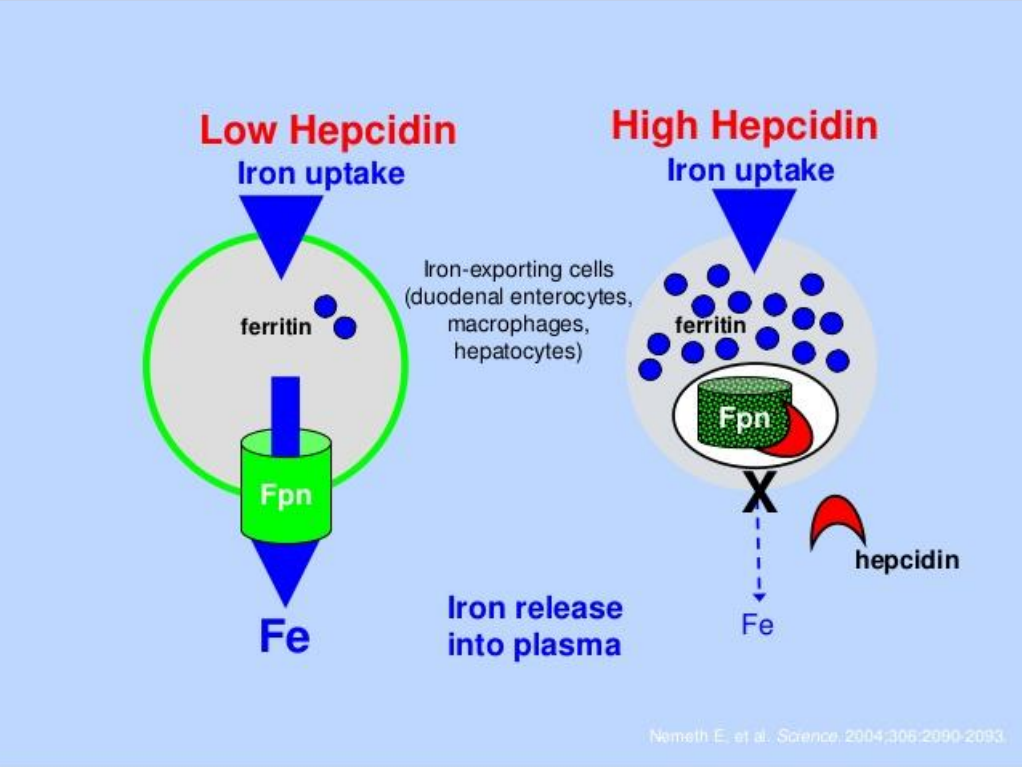
Quiz Time!

Name three causes of Anemia in ESRD

- Erythropoietin deficiency
- Blood loss
- Nutritional deficiency
- Inflammatory block

High levels of this molecule cause "inflammatory block" anemia

Hepcidin



What are some advantages to treating anemia in the dialysis population?

- Improved energy.
- Better quality of life
- Decreased need for transfusion.

Why is it good to avoid transfusion in dialysis patients?

- Avoid the risk of infection
- Avoid triggering antibody production to foreign proteins (antibodies make transplant more challenging).
- Risk of iron overload.
- Cost

What are some problems associated with raising hemoglobin to 13 g/dL?

- Increased risk of cancer, mortality, heart disease, hospitalization, access thrombosis, blood clots.


THANK
YOU