

# Iron Overload in Bone Marrow Failure

Patient Education Day

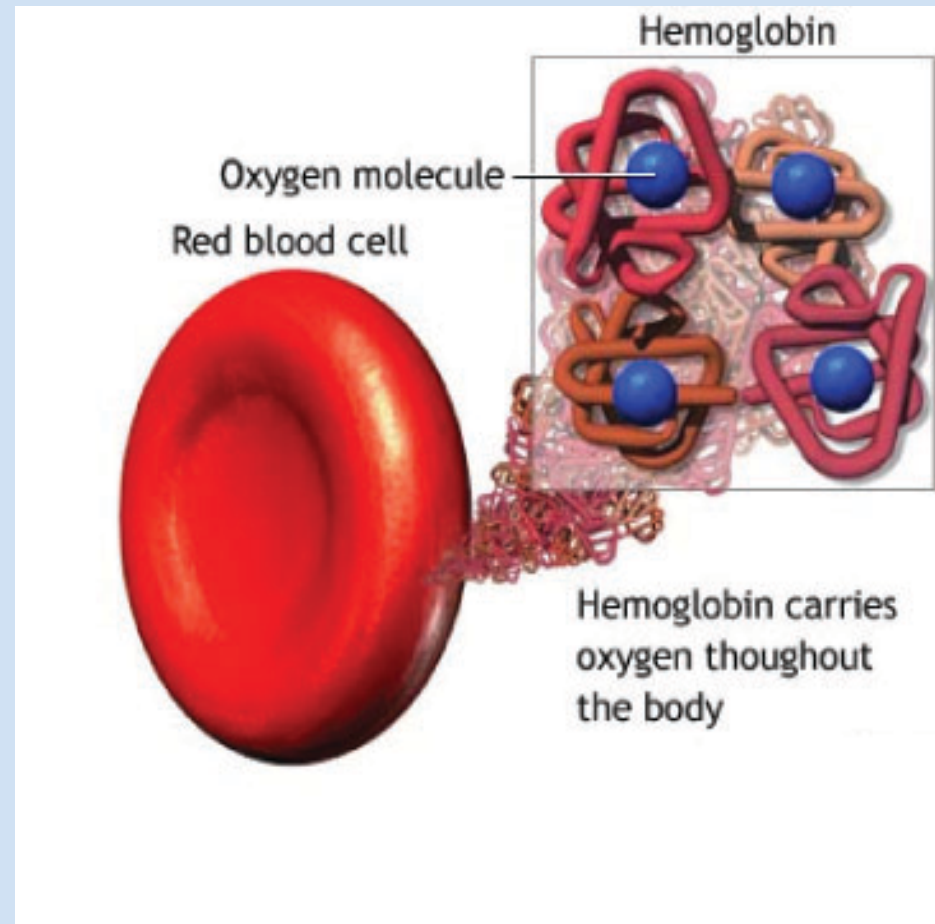
Oct 4, 2014

# Objectives

- Describe the role of iron in the body
- Review the sources of iron in the body
- Examine the potential complications of iron overload
- Review different ways to prevent and reduce iron overload

# What does iron do in the body?

- All body cells need iron
  - oxygen transport, energy production, and cellular growth and proliferation
- Important part of hemoglobin
- Muscle cells use it to make myoglobin
- Enzymes in other cells i.e. catalases



# Iron content in the body

- Women average 3g, men average 4g
  - Hemoglobin in red cells 2.5g
  - Other iron-containing proteins i.e. myoglobin 400mg
  - Iron bound to transferrin in plasma 3-7mg
  - Remainder is storage iron
- Women generally less storage iron due to increased losses
  - Menses, pregnancy, deliveries, lactation, iron intake may be less
  - Blood donations (either gender)



# Where do we get dietary iron?



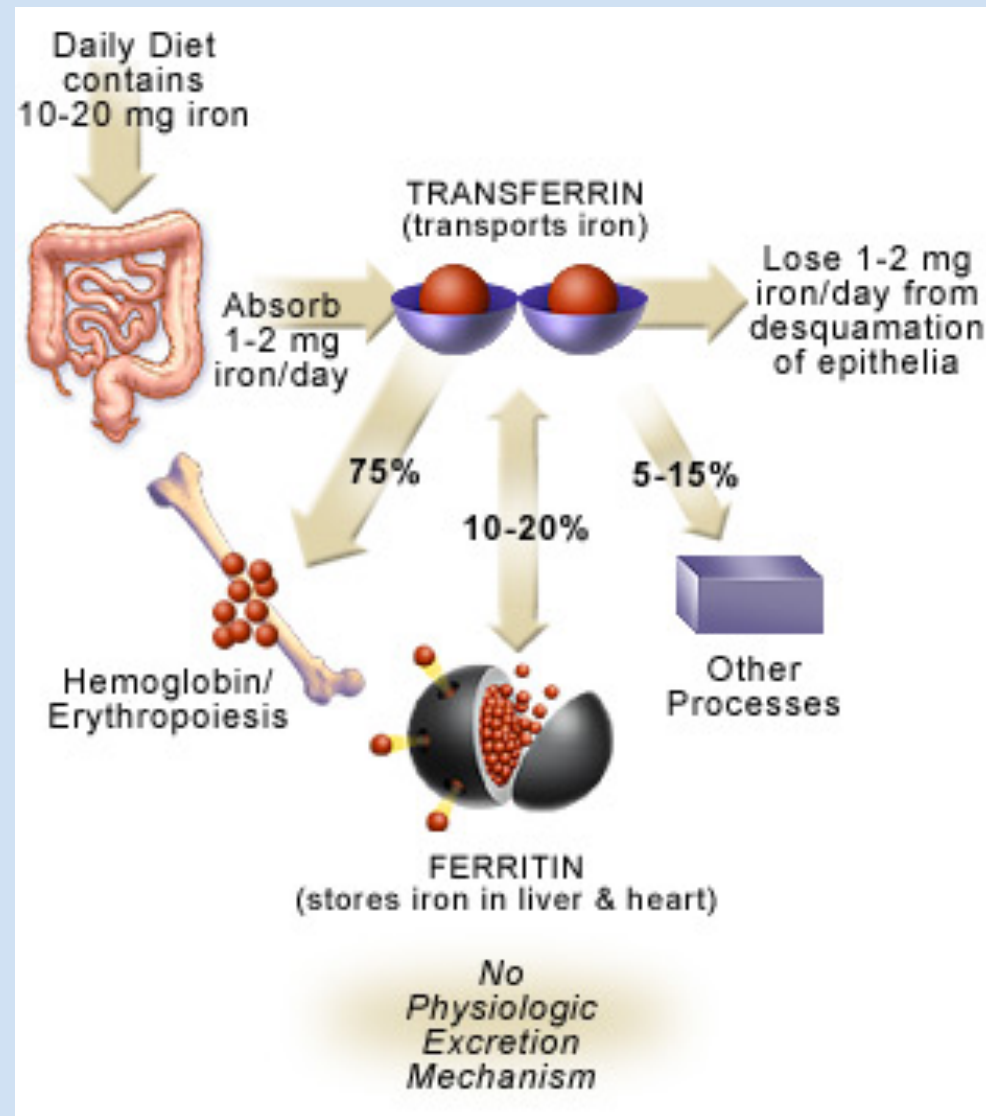
- Food
  - Heme iron – meat, poultry, fish – easily absorbed
  - Non-heme iron – dried beans, lentils, peas
  - Fortified foods – flour, cereals, pasta
  - Absorption increased if taken with vit C
    - citrus fruits and juices, cantaloupe, strawberries, broccoli, tomatoes and peppers.
- Vitamin supplements
  - Multivitamins without iron are available

# Inhibitors of iron absorption

- Absorption impaired by tea, coffee, cereals, eggs, milk, certain antibiotics, antacids



# The iron cycle



Iron is carefully balanced in the body





# Causes of iron overload

## 1) excessive iron intake

- Iron supplements

- Red blood cell transfusions (200 mg/unit)

## 2) increased iron absorption from the GI tract

- Hereditary hemochromatosis

- Ineffective red blood cell production

## 3) decreased iron excretion

- Generally fixed iron excretion

- Increased iron excretion if blood donor, blood loss

# What happens if we get too much iron?



Many of these symptoms are found in bone marrow failure syndromes that require blood transfusion

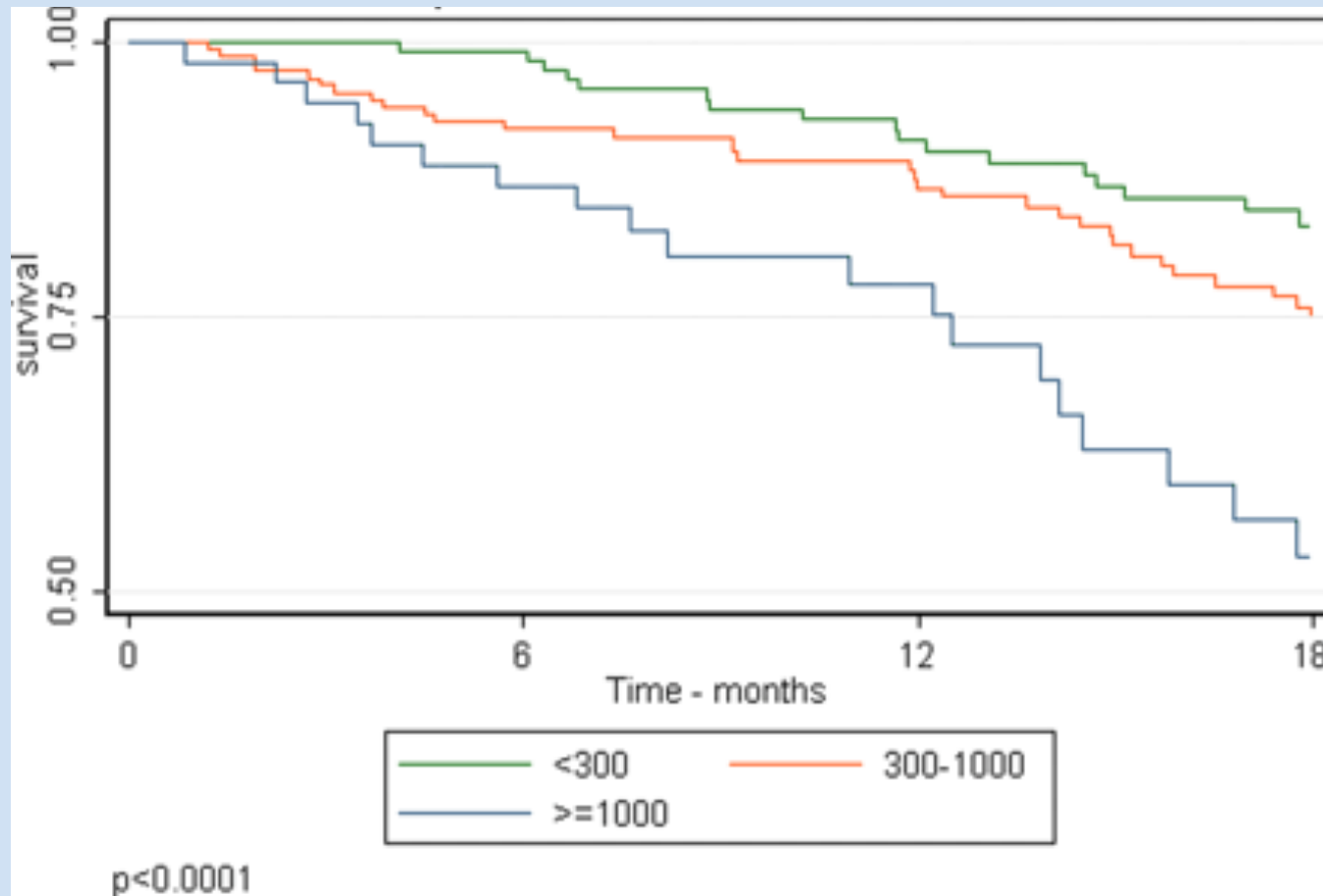
# How do we measure iron in the body?

- Ferritin (storage iron)
  - Ferritin is an acute phase reactant and is high in inflammation, infection, acute illness as well
- Iron saturation in blood
  - May reflect recent iron in meal or transfusion
- Liver biopsy
  - Accurate, invasive
- MRI – ferriscan of liver or cardiac T\*MRI
  - Noninvasive, expensive, not always available

# How much iron is too much iron?

- Depends:
  - In hemochromatosis, ferritin >1000ug/L associated with increased risk of liver fibrosis and cirrhosis
  - In thalassemia major, sustained values >2500 ug/L predict long term heart risk
  - Low values, <1000 ug/L increase risk of deferoxamine (an iron chelator) toxicity

# LeukemiaNet Prospective Registry: Independent Survival Impact of Ferritin



# Risk of transfusional iron overload without treatment in thalassemia

- Cardiomyopathy – 8-15y
- Hypogonadism – 5-10y
- Diabetes – 5-10y
- Liver fibrosis and dysfunction – 5y
- Cirrhosis – 20-30y
- Liver cancer – 30-50y
- Infection – 2<sup>nd</sup> most common death in thalassemia major

# Risk of Iron Overload in MDS

Transfusion dependency associated with complications of iron overload (2.9x risk) in a retrospective study

- Conduction/rhythm disturbance (4x risk)
- Diabetes (5x risk)
- Liver dysfunction (3x risk)
- Retrospective review of ferritin >1000 µg/l significantly affected overall survival
  - Hazard ratio 1.36 for every 500 µg/L rise in ferritin >1000 µg/L.
  - ferritin level 1000 µg/L after a median 21u RBCs

# Percent of patients with cardiac iron deposits at post-mortem prior to chelation era

Number of units transfused	% patients with cardiac iron
0-25	1.4%
26-50	11%
51-75	28%
76-100	60%
101-200	60%
201-300	100%
>300	50%



# Cardiac MRI

- T2\* MRI <20 ms – increased cardiac iron and decreased heart contraction
- T2\* MRI <10 – increased risk of heart failure
- Target is >20ms (normal)
- Yearly screen in heavily transfused patients

# Principles of iron chelation therapy

- Prevention
  - Balance iron intake and output
- Rescue
  - Patients with high levels of body iron, high levels of cardiac iron, patients with heart dysfunction

# Strategies to reduce iron overload

- 1) Decrease iron load by decreasing transfusions
- 2) Chelation therapy – bind iron out of the body and help the body excrete it
  - iv/subcutaneous continuous infusion or oral
- 3) Phlebotomies in some patients where bone marrow failure is no longer a problem
  - l.e. post bone marrow transplant, treated aplastic anemia

# Decrease iron by decreasing transfusions

- Choose threshold for transfusion based on symptoms
- Erythropoietin in MDS to reduce transfusions based on risk factors:

- 1)  $\geq 2$  units RBCs/month
- 2) Erythropoietin level  $>500$

#Risk Factors	Response rate
0	74%
1	23%
2	7%

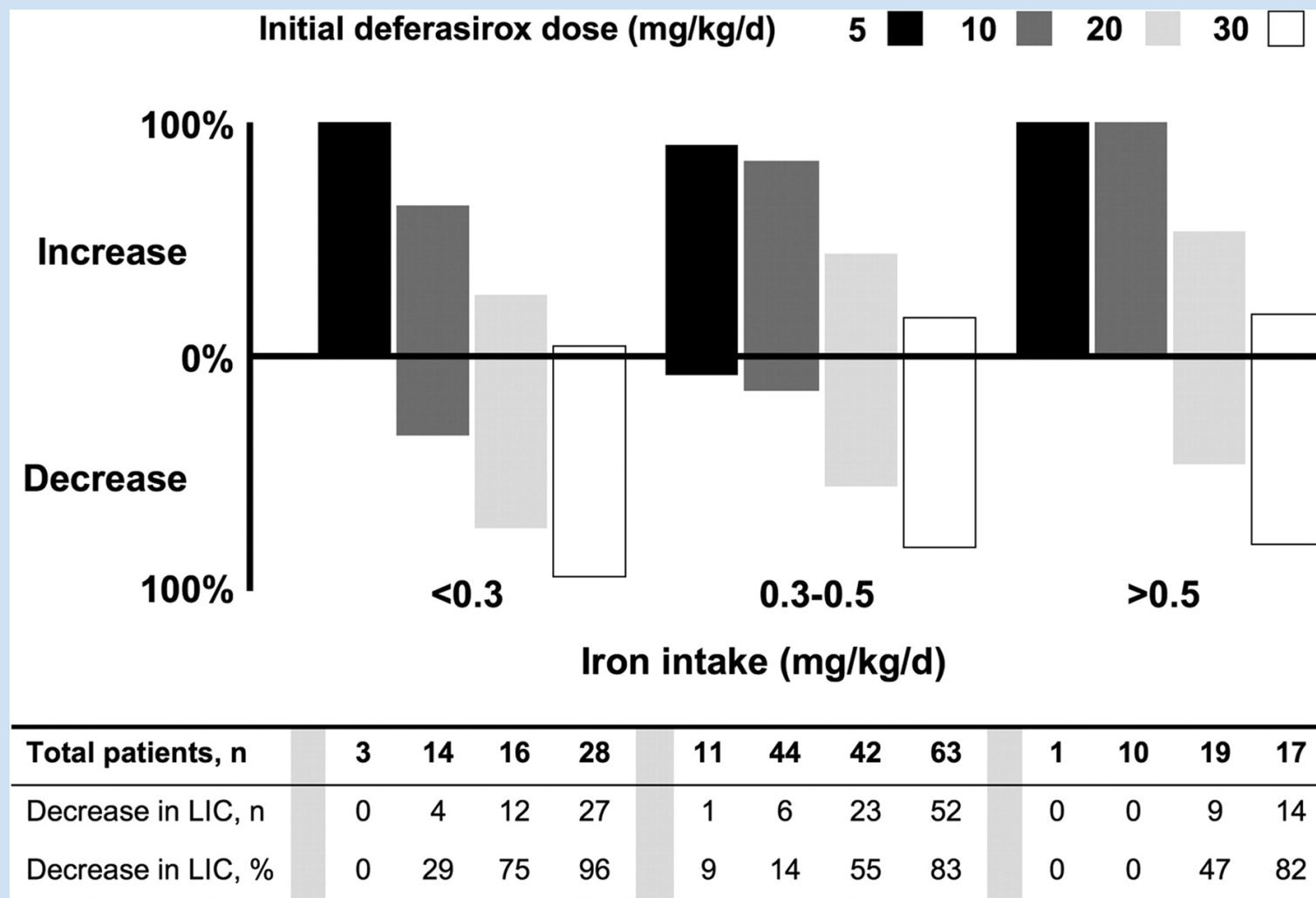
Improvement in global QOL ( $p < 0.001$ ) with borderline significance for fatigue

# Chelation therapy

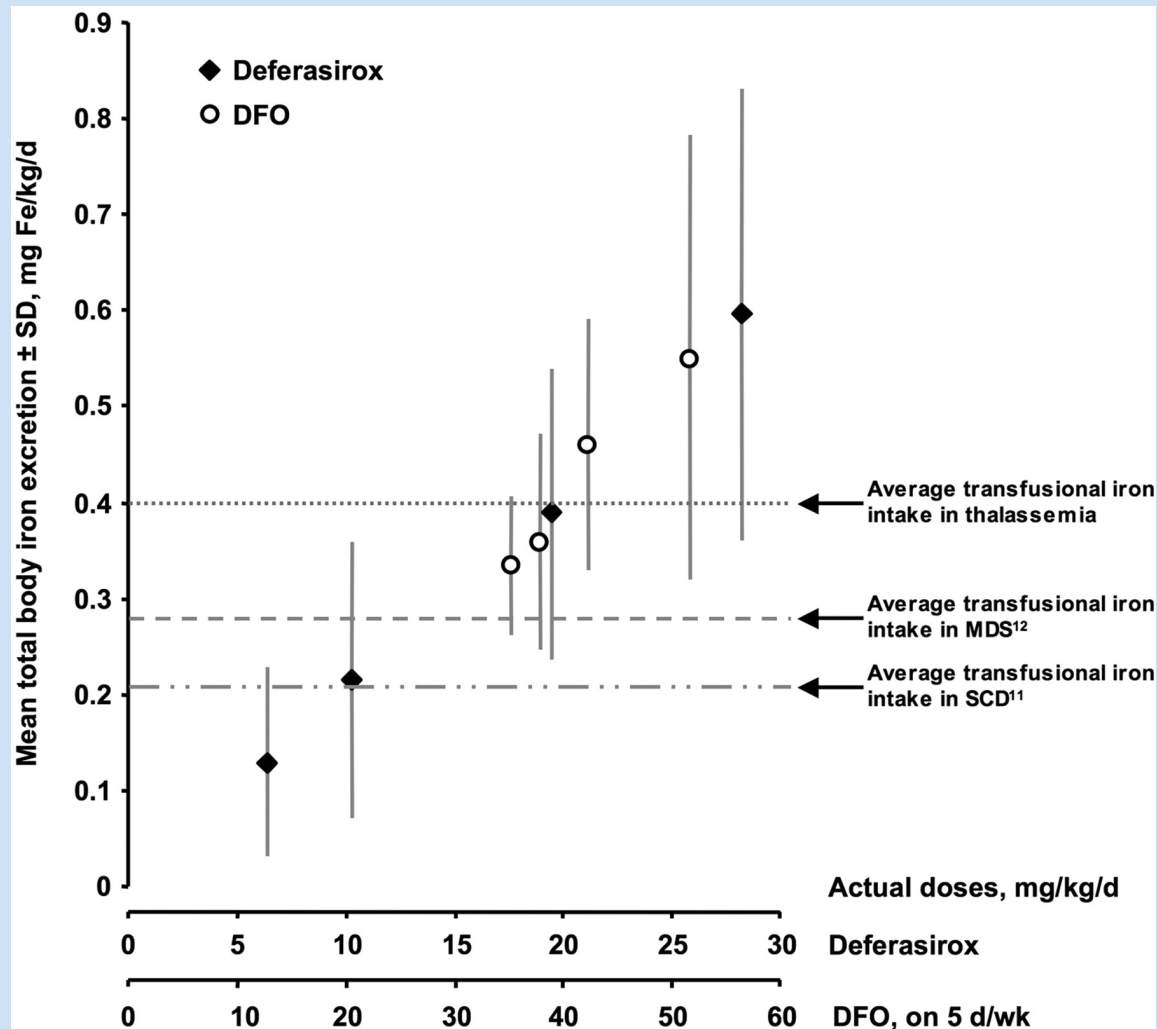
	Deferoxamine	Deferasirox
Dose (mg/kg/d)	25-60	20-30
Route	Sc, IV (8-12h, 5d per week) continuous infusion	Oral once daily
Half-life	20-30 mins	8-16h
Side Effects	Local reactions, ophthalmologic, hearing, allergy, growth retardation in children	GI upset, rash, elevated creatinine, elevated liver enzymes, ophthalmologic, hearing

**Can use combination therapy for severe iron overload**

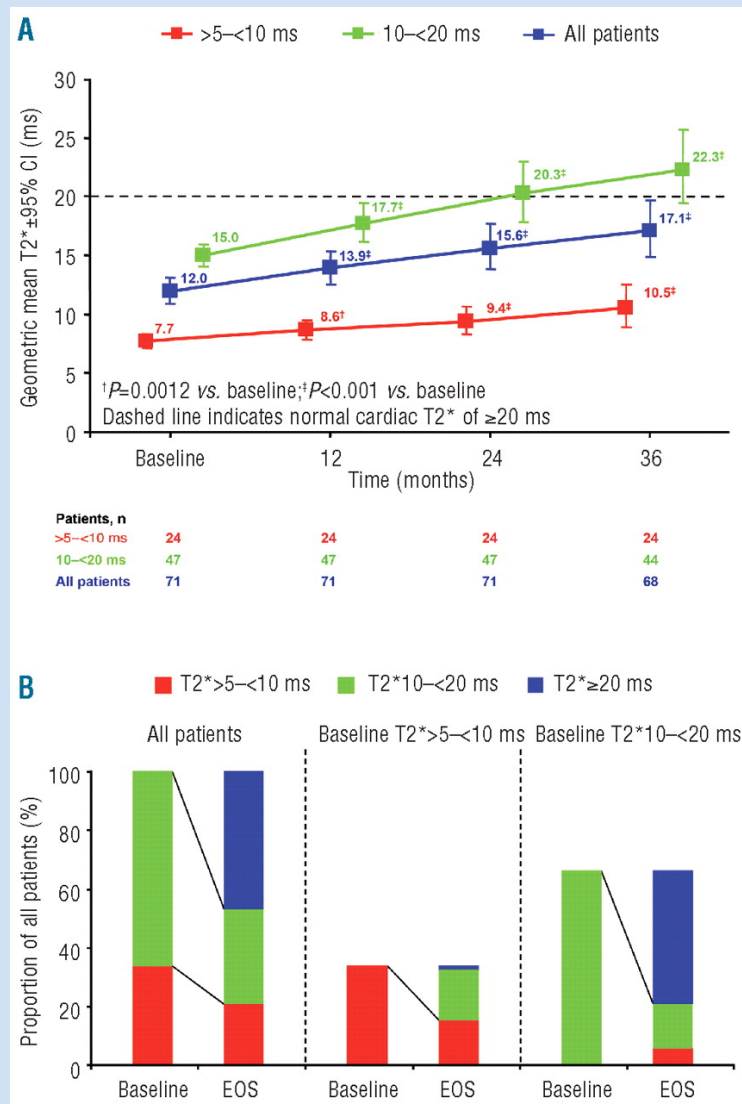
## Proportion of patients with increased or decreased liver iron concentration (LIC), according to iron intake and deferasirox dose.



# Dosing according to transfusion requirements by diagnosis



# Improvement in T\*MRI and number of patients with severe iron overload over 3 years of deferasirox therapy

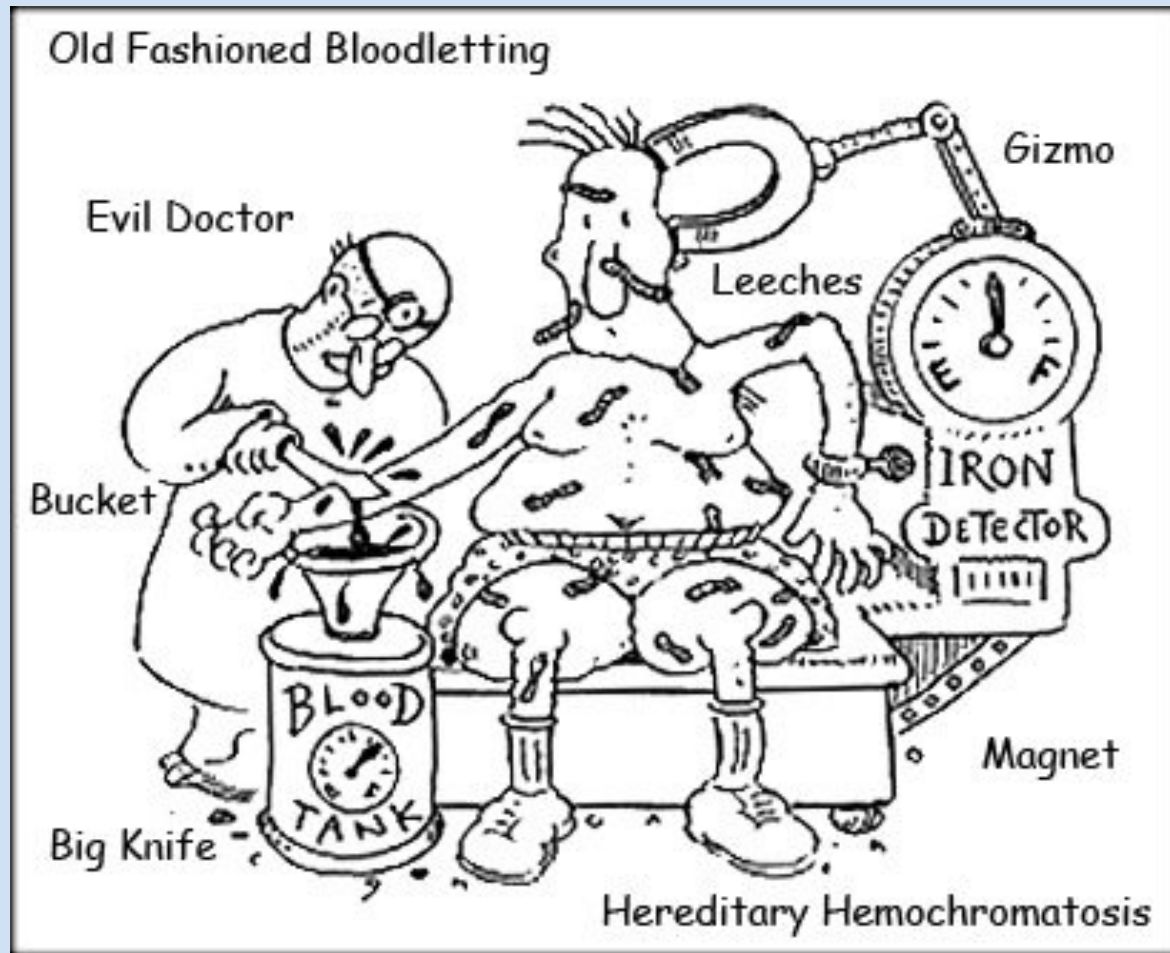




# Helping reduce side effects of oral deferasirox

- GI
  - Martini shaker (patient support program)
  - Imodium
  - Antinausea medications
- Renal
  - Stay well hydrated, avoid nephrotoxic medications
- Liver
  - Avoid other hepatotoxic medications

# Phlebotomies



# Does Iron Chelation Confer a Survival Benefit in MDS?

- Retrospective review from Vancouver of 178 MDS patients 1981 - 2006
- Predictors of survival were IPSS risk disease and iron chelation therapy
- Low/Intermediate-1 IPSS median overall survival for patients receiving iron chelation was 160 vs. 40 months for non-chelated patients.
- ?Selection bias where patients given chelation were more likely to have lower risk MDS

# Canadian Guidelines for MDS

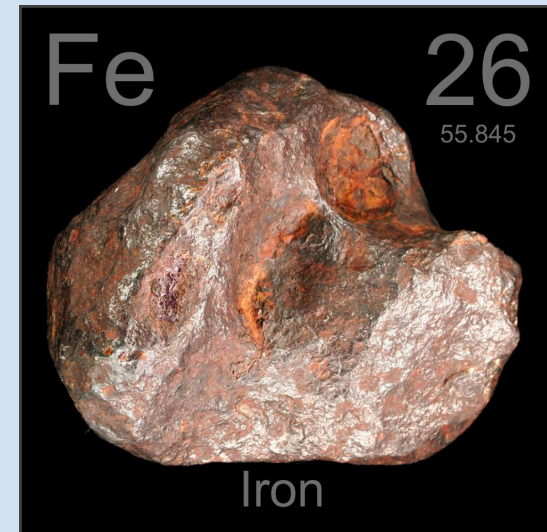
- Consider iron chelation:
  - In patients with expected survival at least one year
  - In patients with ferritin >1000, >20 units blood transfused, or documented iron overload
  - In patients with increased iron stores and planned allogeneic stem cell transplantation
- deferoxamine 20-50 mg/kg/day by subcutaneous or intravenous infusion over 12-15 hours 5 days/week
- Deferasirox orally daily
- Monitor for iron overload complications and complications of drug therapy

# Elevated serum ferritin is a risk factor for liver sinusoidal obstruction syndrome post HCT

ferritin	Odds Ratio of SOS
628	1.8
1000	2.49
1500	2.61
2000	2.28
3000	3.32
4000	4.10

# When do we stop chelation or phlebotomies?

- In hemochromatosis with phlebotomies goal is generally  $<50 \text{ ug/L}$
- In regularly transfused and chelated
  - $1000 \text{ ug/L}$  with DFO
  - $500 \text{ ug/L}$  with deferasirox
  - ? With combination therapies



# Questions?

