Iron Deficiency Anemia in the Pediatric Population

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OBJECTIVES

- Identify risk factors for iron deficiency in children
- Recognize symptoms of anemia
- Review an approach to treating iron deficiency in children

Case: Jackie

- 14 yo competitive skier presents to ER after a presyncopal episode
- Recent onset of occasional light-headedness, fatigue and decreased endurance
- Otherwise well, no significant past medical history
- Labs in ER showed **hemoglobin 66, MCV 62**
  - rest of CBC normal

Initial Management

- **Transfused** in ER
- Started on oral iron supplementation
- Referred to Pediatric Hematology

DIAGNOSIS: MICROCYTIC ANEMIA

Causes → "TAILS"

- Thalassemia
- Anemia of chronic disease
- Iron deficiency
- Lead poisoning
- Sideroblastic anemia

Jackie's History

- Good diet with adequate meat and veggies
- Normal growth/development
- Negative review of symptoms
  - No excessive bleeding/bruising, no menorrhagia
  - No concerns with abdominal pain/diarrhea/constipation
- No family history of anemia, bleeding or GI diseases

Investigations at first heme visit

- Hemoglobin up to 84, MCV still low at 68
- Smear: dual population post transfusion
- Iron studies:
  - Ferritin 10 (23-400 ug/L)
  - Iron 4 (9-30 umol/L)
  - IBC 88 (40-80 umol/L)
  - Transferrin 3.96 (2.20-3.37 g/L)
  - Transferrin Sat 0.05 (0.20-0.50)
- CRP slightly high at 2.7

"Iron lacks the glitter of gold and the sparkle of silver but outshines both in biologic importance"

Dr. Mark Fleming

Nathan and Oski's Hematology and Oncology of Infancy and Childhood

INTRODUCTION TO IRON

- Iron is the essential element of the **heme complex**, but is also vital to the function of a wide variety of critical **enzymes**

- The key to its biologic utility is its ability to exist in either of 2 stable oxidation states: **Fe^{+2}** & **Fe^{+3}**

IRON DISTRIBUTION

- Total body content of elemental iron ranges from **2 to 5 g**

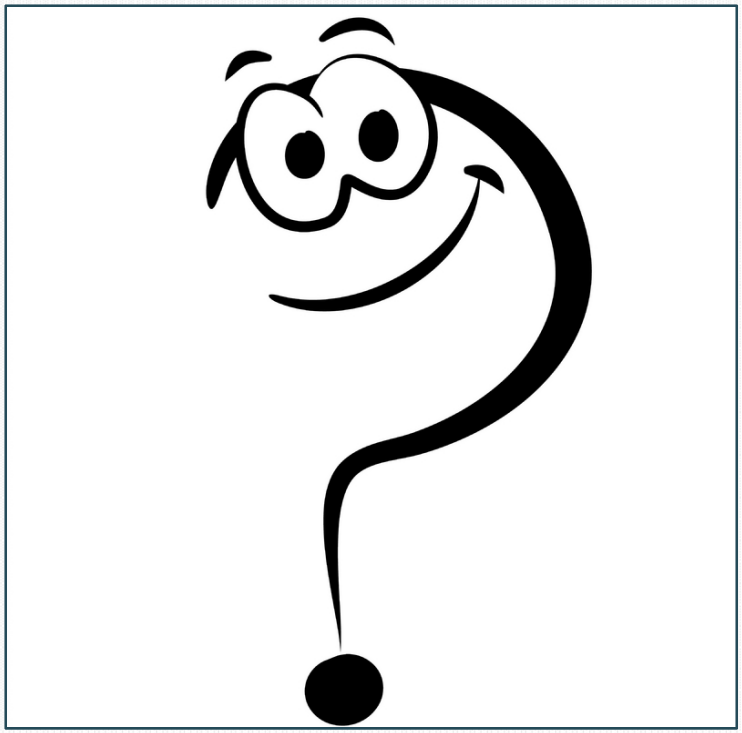
  ≈40 mg/kg in adult females

  ≈50 mg/kg in adult males

  ≈75 mg/kg in term newborns

  - 2/3 in Hemoglobin
  - 1/3 in tissue and transport forms:
    - Ferritin/Hemosiderin: 6-12 mg/kg
    - Transport iron in transferrin: <0.1 mg/kg
    - Heme and non-heme iron-containing enzymes

How much iron do we need?



- The average adult produces 200 billion red cells per day
- Each red cell contains > 1 billion atoms of iron?

Daily need for 2×10^{20} atoms of elemental iron (20mg)

Where does that iron come from?

Most iron is recycled from the breakdown of old red cells by macrophages of the reticuloendothelial system

- In adults, only **5%** of daily iron needs (approx 1 mg) comes from dietary sources (equals losses from the GI tract
- In infants and children, **30% of daily iron needs must come from diet** because of the growth spurt and increase in body mass

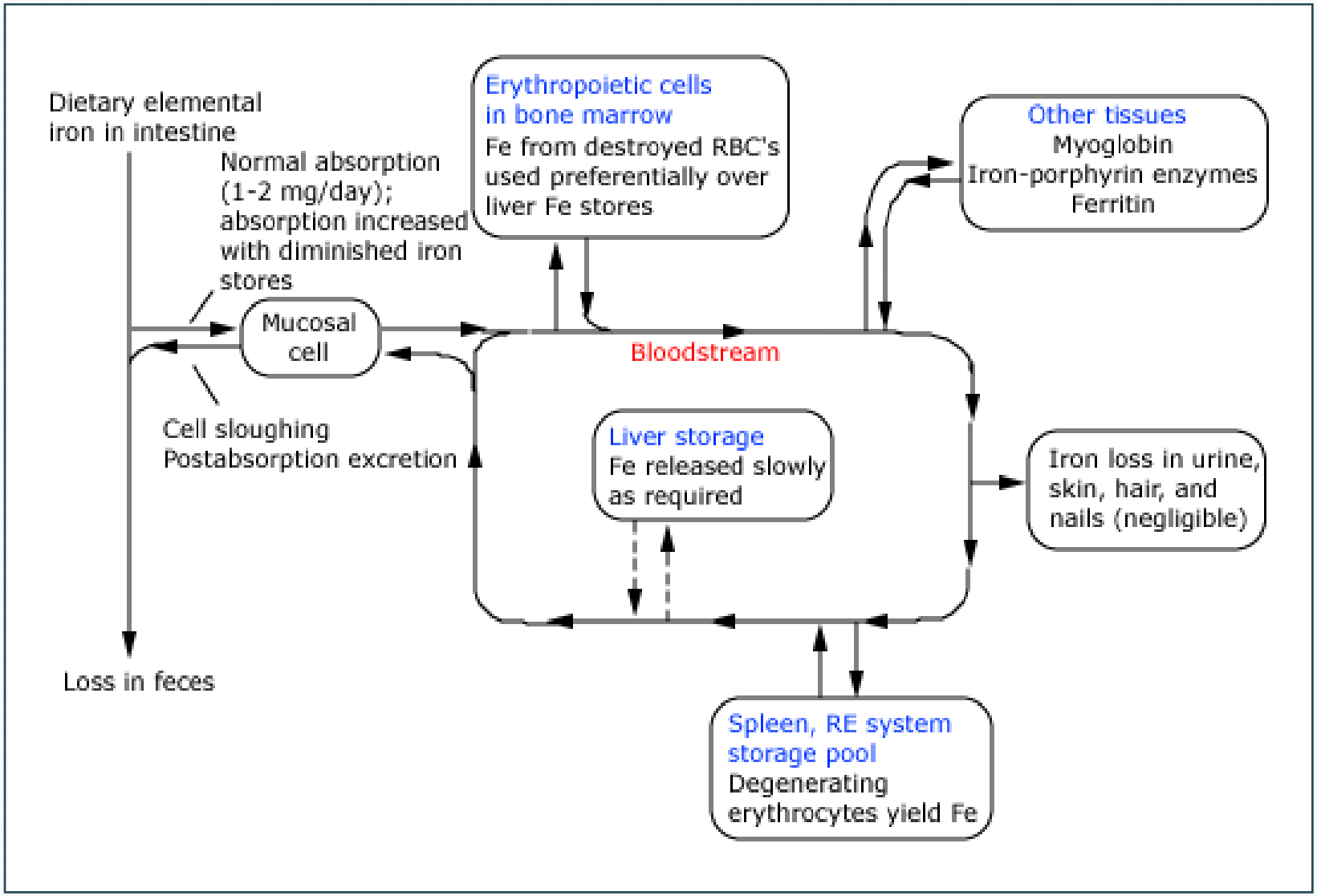
IRON REGULATION

- **There is <u>no normal mechanism of regulated iron loss</u>**
  - Neither the liver nor the kidney has a significant capability to excrete iron in humans

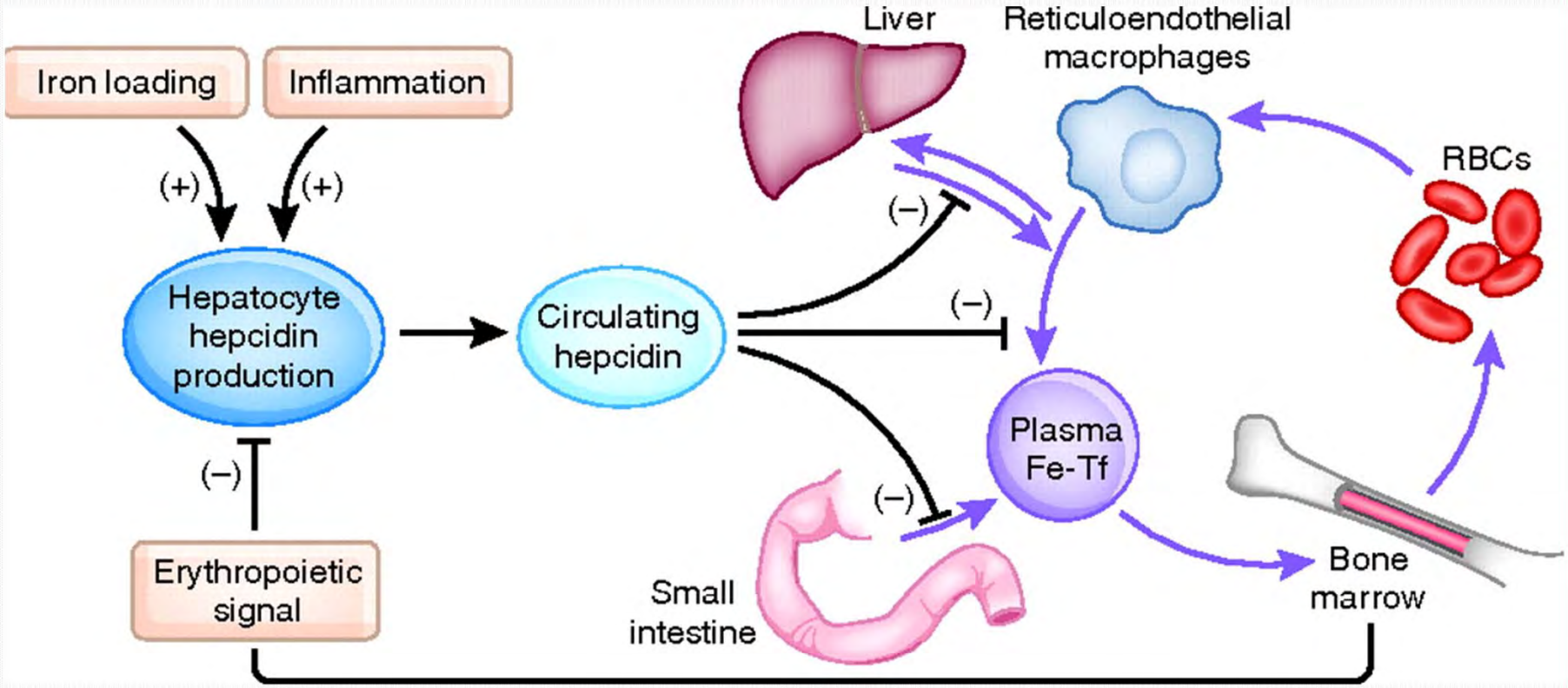
- **Consequently, <u>the primary regulator</u> of iron homeostasis is <u>intestinal iron absorption</u>**

IRON ABSORPTION

- An adequate diet contains about **15 mg/day** of iron, of which **only 10% is absorbed**
  - 20-30% of dietary iron present in heme is absorbed from the gut
  - 5% of dietary non-heme iron is absorbed
- Iron absorption occurs predominantly in the **proximal duodenum**

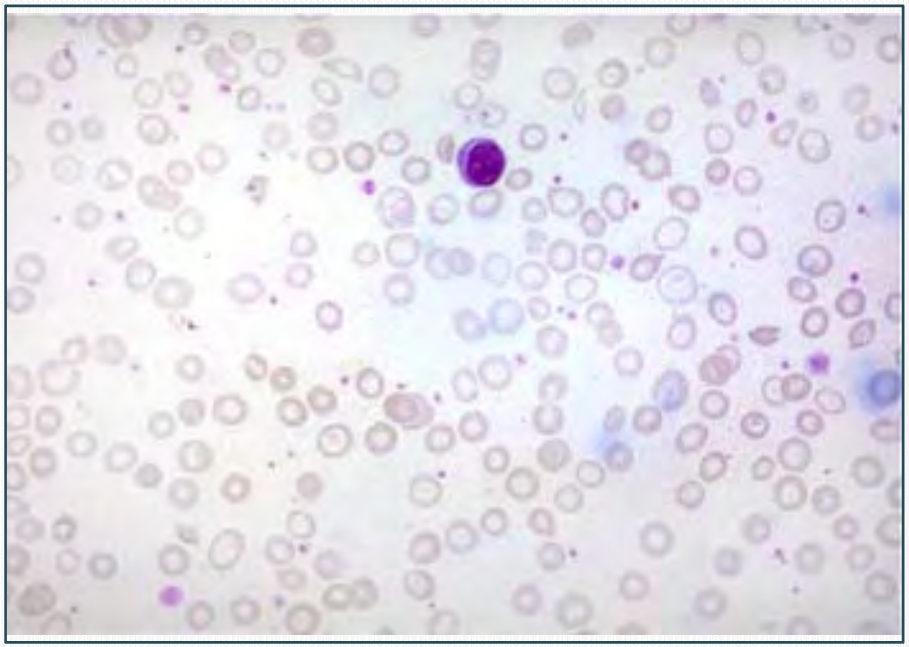

Dietary elemental iron in intestine
Normal absorption (1-2 mg/day); absorption increased with diminished iron stores
Erythropoietic cells in bone marrow
Fe from destroyed RBC's used preferentially over liver Fe stores
Other tissues
Myoglobin
Iron-porphyrin enzymes
Ferritin
Mucosal cell
Bloodstream
Cell sloughing
Postabsorption excretion
Liver storage
Fe released slowly as required
Iron loss in urine, skin, hair, and nails (negligible)
Loss in feces
Spleen, RE system storage pool
Degenerating erythrocytes yield Fe

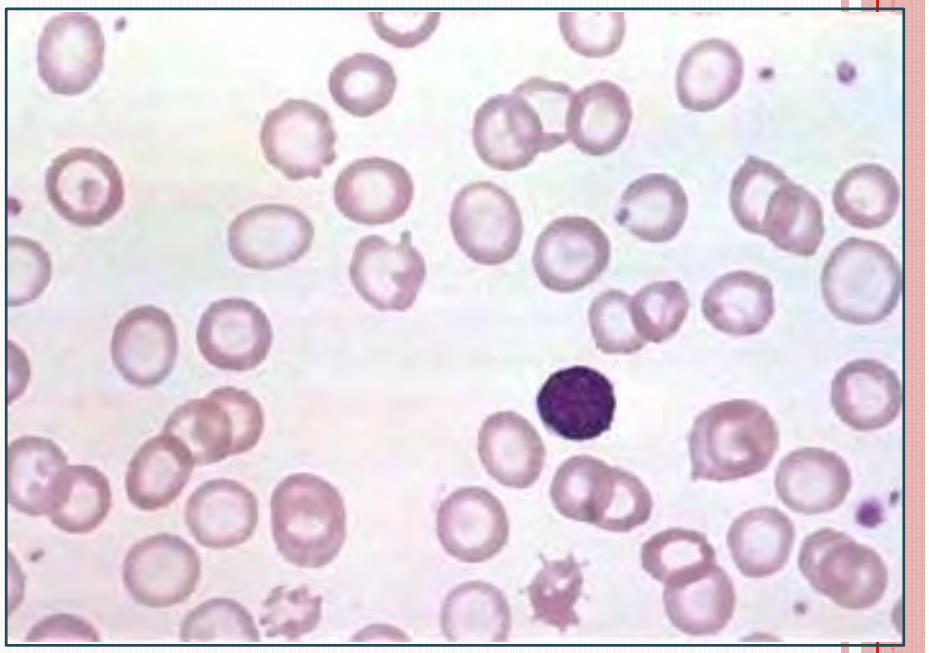
HEPCIDIN



Young and Zaritsky, 2009

IRON DEFICIENCY ANEMIA (IDA)





Iron deficiency Anemia

- IDA is the **most frequent and widespread nutritional deficiency in the world**

- Phases of development of iron deficiency:
  1. Prelatent iron deficiency (storage iron deficiency)
  2. Latent iron deficiency (iron-limited erythropoiesis)
  3. **Iron deficiency anemia**
     - hemoglobin concentration is >2 SD below the mean for same sex/age

Table 1. Causes of Iron Deficiency.

Cause	Example
Physiologic	
Increased demand	Infancy, rapid growth (adolescence), menstrual blood loss, pregnancy (second and third trimesters), blood donation
Environmental	Insufficient intake, resulting from poverty, malnutrition, diet (e.g., vegetarian, vegan, iron-poor)
Pathologic	
Decreased absorption	Gastrectomy, duodenal bypass, bariatric surgery, *Helicobacter pylori* infection, celiac sprue, atrophic gastritis, inflammatory bowel diseases (e.g., ulcerative colitis, Crohn's disease)*
Chronic blood loss	Gastrointestinal tract, including esophagitis, erosive gastritis, peptic ulcer, diverticulitis, benign tumors, intestinal cancer, inflammatory bowel diseases, angiodysplasia, hemorrhoids, hookworm infestation, obscure source Genitourinary system, including heavy menses, menorrhagia, intravascular hemolysis (e.g., paroxysmal nocturnal hemoglobinuria, autoimmune hemolytic anemia with cold antibodies, march hemoglobinuria, damaged heart valves, microangiopathic hemolysis) Systemic bleeding, including hemorrhagic telangiectasia, chronic schistosomiasis, Munchausen's syndrome (e.g, self-induced hemorrhages)
Drug-related	Glucocorticoids, salicylates, NSAIDs, proton-pump inhibitors
Genetic	Iron-refractory iron-deficiency anemia
Iron-restricted erythropoietic	Treatment with erythropoiesis-stimulating agents, anemia of chronic disease, chronic kidney disease*

* Inflammatory conditions may be associated with iron deficiency. NSAIDs denotes nonsteroidal antiinflammatory drugs.

Camishella, NEJM 2015

Epidemiology of IDA in Kids

- IDA affects 750 MILLION children around the world
- 30-40% of children and pregnant women in industrialized countries are iron deficient
- Canadian children: 3.5-10.5%, but higher is some populations

Abdullah *et al.* IDA in Children, CPS 2011

Why are Children at risk for IDA?

Multifactorial…

- Increased needs due to rapid growth
- Inadequate intake of iron-containing foods
- Malabsorption
- Exacerbated in preterm babies (dec stores)

Abdullah *et al.* IDA in Children, CPS 2011

Dietary sources of Iron

https://www.uhs.uga.edu/nutrition/iron

Risk Factors of IDA

- Race/ethnicity
- Low socioeconomic status
- Prematurity/low birth weight
- Excessive milk intake
- Early introduction of cow's milk
- Prolonged bottle feeding
- Prolonged exclusive breast feeding
- Overweight/obesity
- Non-attendance to daycare

Abdullah *et al.* IDA in Children, CPS 2011

Iron deficiency: clinical manifestations

- Common Symptoms:
  - Pallor
  - Fatigue
  - Presyncope/syncope
  - Palpitations
- Less Common:
  - Pica (geophagia,pagophagia)
  - Epithelial changes: angular stomatitis, glossitis, koilonychia
  - Decreased immunity
  - Thrombosis
  - Neurocognitive defects

Long-term Issues related to IDA in Kids

- IDA is a systemic condition→ impairs physical functioning, infant growth and development and immune function
- Clear association between IDA and impaired neurocognitive development
- Unknown if impact of ID is reversible with iron therapy → more research needed
- **Prevention is important!**

Abdullah *et al.* IDA in Children, CPS 2011

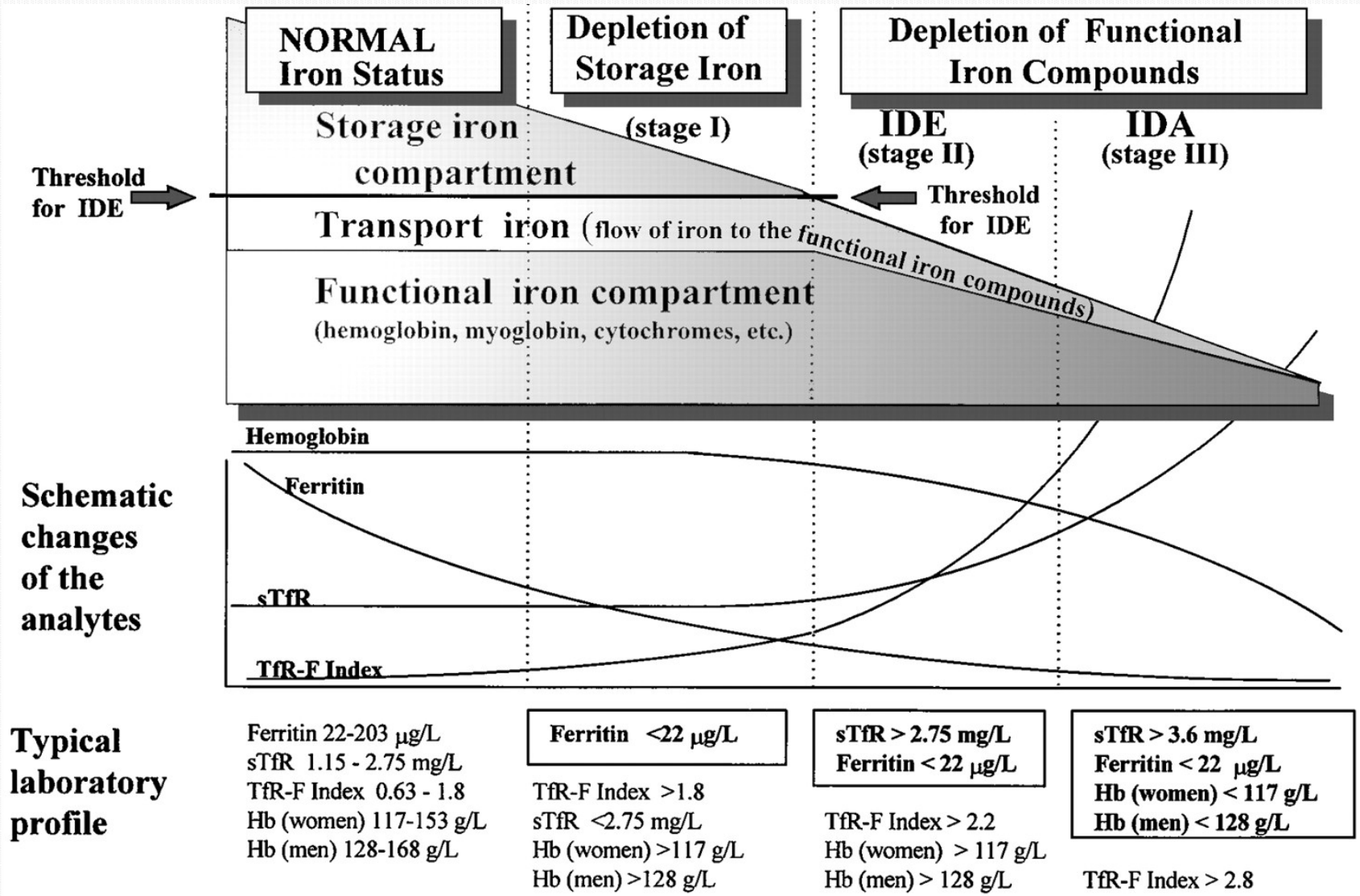
Iron Indices

- **Ferritin**
  - Cellular storage protein for iron→ measure of iron stores
  - Acute phase reactant
- **Serum iron**
  - Measure of transferrin-bound iron
- **TIBC**
  - The sum of all iron binding sites on Tf constitutes the Total Iron-Binding Capacity
  - Circulating Tf normally is about 1/3 saturated with iron
- **Transferrin saturation: Fe/TIBC**
  - Normal: approx 33%

Comparing disorders of iron

iron panel	IRON PANEL TESTS					
	Serum Iron	Serum Ferritin	Transferrin Iron Saturation Percentage	Total Iron Binding Capacity (TIBC)	Transferrin	Hemoglobin
Hemochromatosis	↑	↑	↑	↓	↓	NORMAL
Iron Deficiency Anemia	↓	↓	↓	↑	↑	↓
Sideroblastic Anemia	↑	↑	↑	↓	↓	↓
Thalassemia	↑	↑	↑	↓	↓	↓
Porphyria Cutanea Tarda (PCT)	↑	↑	↑	↓	↓	NORMAL
Anemia of Chronic Disease (ACD)	↓	↑ OR NORMAL	↓	↓	↓	↓
African Siderosis (AS)	↑	↑	↑	↓	↓	NORMAL
Vitamin B12 Deficiency (pernicious anemia)	↑ OR NORMAL	↑ OR NORMAL	↑ OR NORMAL	↓ OR NORMAL	↓ OR NORMAL	↓

www.irondisorders.org



Suominen et al. Blood 1998

CASE 1: JACKIE (CONTINUED)

Iron indices consistent with IDA…but why?

Additional testing:

- Hemoglobinopathy screen→ normal
- Bleeding screen→ normal
- GI testing→ TTG IgA 18.5
  - suggestive of Celiac disease

Celiac Disease and Iron Deficiency

- Many patients with Celiac disease have anemia at the time of diagnosis
- Anemia secondary to malabsorption of iron, folic acid, and/or vitamin B12
- Celiac disease may also be associated with thrombocytosis, thrombocytopenia, leukopenia, venous thromboembolism, hyposplenism and IgA deficiency

Journal of Pediatric Gastroenterology and Nutrition
40:1–19 © January 2005 Lippincott Williams & Wilkins, Philadelphia

Clinical Guideline

Guideline for the Diagnosis and Treatment of Celiac Disease in Children: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

Celiac testing is recommended for all "children with iron-deficiency anemia resistant to oral iron"

TABLE 1. *Non-gastrointestinal manifestations of celiac disease*

A) Manifestations for which there is strong to moderate evidence
Dermatitis herpetiformis
Dental enamel hypoplasia of permanent teeth
Osteopenia/Osteoporosis
Short stature
Delayed puberty
Iron-deficient anemia unresponsive to treatment with oral iron (*well documented in adults only*)
B) Manifestations for which the evidence is less strong
Hepatitis (elevated liver enzymes)
Arthritis
Epilepsy with occipital calcifications

Treatment of Iron deficiency

Oral replacement
whenever possible

IV replacement
in some circumstances

Transfusion
(almost) never

Oral replacement

- As long as the patient can absorb it
- Elemental iron: 3-6 mg/kg/day
- Ferrous sulfate:
  - Elixir: 44 mg/5 ml elemental iron
  - Drops (Fer-In-Sol®): 15 mg/0.6 ml elemental iron (125 mg/5 ml)
  - Tablet: 65 mg
- **Don't forget about education and compliance!!!**

IRON DEFICIENCY: RESPONSE TO TREATMENT

Time	Response
12-24 hrs	↓ irritability □ appetite
36-48 hrs	Initial BM response erythroid hyperplasia
48- 72 hrs	Reticulocytosis peak at 5-7 days
4- 30 days	↑ Hb level
1-3 months	Repletion of iron stores

Days on iron therapy

Fig. 2. Response to oral iron therapy in a child who has severe iron-deficiency anemia.

When is IV iron better?

Indications for IV Iron Therapy

Established indications:

- Failure of oral iron therapy
- Iron intolerance
- Need for quick recovery
- Use of EPO in chronic renal disease

Other potential indications: EPO non-responders, transfusion-sparing strategy in surgical patients, iron deficiency in heart failure

Camishella, NEJM 2015

Types of IV iron

Iron sucrose (VENOFER)

- most commonly used, superior safety profile

Iron dextran (DEXTRAN)

- More commonly associated with anaphylactic reactions

Ferric gluconate

- approved for use in pediatric patients >6yo receiving hemodialysis
- associated with hypotension (41%), headaches (24%) and hypersensitivity reactions

"The safety and effectiveness of VENOFER in pediatric patients has not been established."

****not for use in infants <1 month of age***

Use of IV Iron in Pediatrics

- Retrospective review of 38 children who received iron sucrose for non-renal indications:
  - 13 with iron deficiency refractory to oral iron therapy
  - 13 with iron malabsorption/dependence on TPN
  - 7 for chronic gastrointestinal blood loss
  - 5 “other”
- total of 510 doses of IV iron sucrose, there were only 6 adverse reactions (1.2%)
- Overall good response to the iron sucrose, with a median hemoglobin rise of 19 – 31 g/l depending on the indication

Shelley *et al*. 2011

Response to both oral iron and IV iron sucrose based on indication for IV iron therapy

Primary indication for IV iron sucrose	n	Median hemoglobin rise after oral iron, g/dl (range)*	Median hemoglobin rise after IV iron sucrose, g/dl (range)	
Non-adherent/intolerant to oral iron	13	0.05 (−1.0, 1.0)	3.1 (0.8, 7.6)	**62x better**
Malabsorption	13	0.4 (−0.4, 3.3)	1.9 (−2.7, 5.8)	5x better
Chronic blood loss	7	0.65 (−1.4, 5.7)	1.9 (0.2, 6.6)	3x better
Other†	5	1.1 (0, 2.2)	2.1 (0.6, 2.7)	2x better

*Oral iron therapy not previously administered to 8 patients

†Iron refractory iron deficiency anemia (n=2), anemia of inflammation (n=3)

Shelley *et al*. 2011

IV IRON SUCROSE TREATMENT REGIMEN

1. Calculate total iron deficit for initial repletion:

   Total cumulative dose (mg) =

   [target Hgb-actual Hgb] x wt(kg) x 0.24 + [15 x wt(kg)]

1. Dosing
   - Max daily dose 7mg/kg to max 300mg/dose.
   - Divide calculated dose and give every 3-7 daus until dose is administered

Test dose: not necessary

Shelley *et al*. 2011

WHY NOT IV IRON?

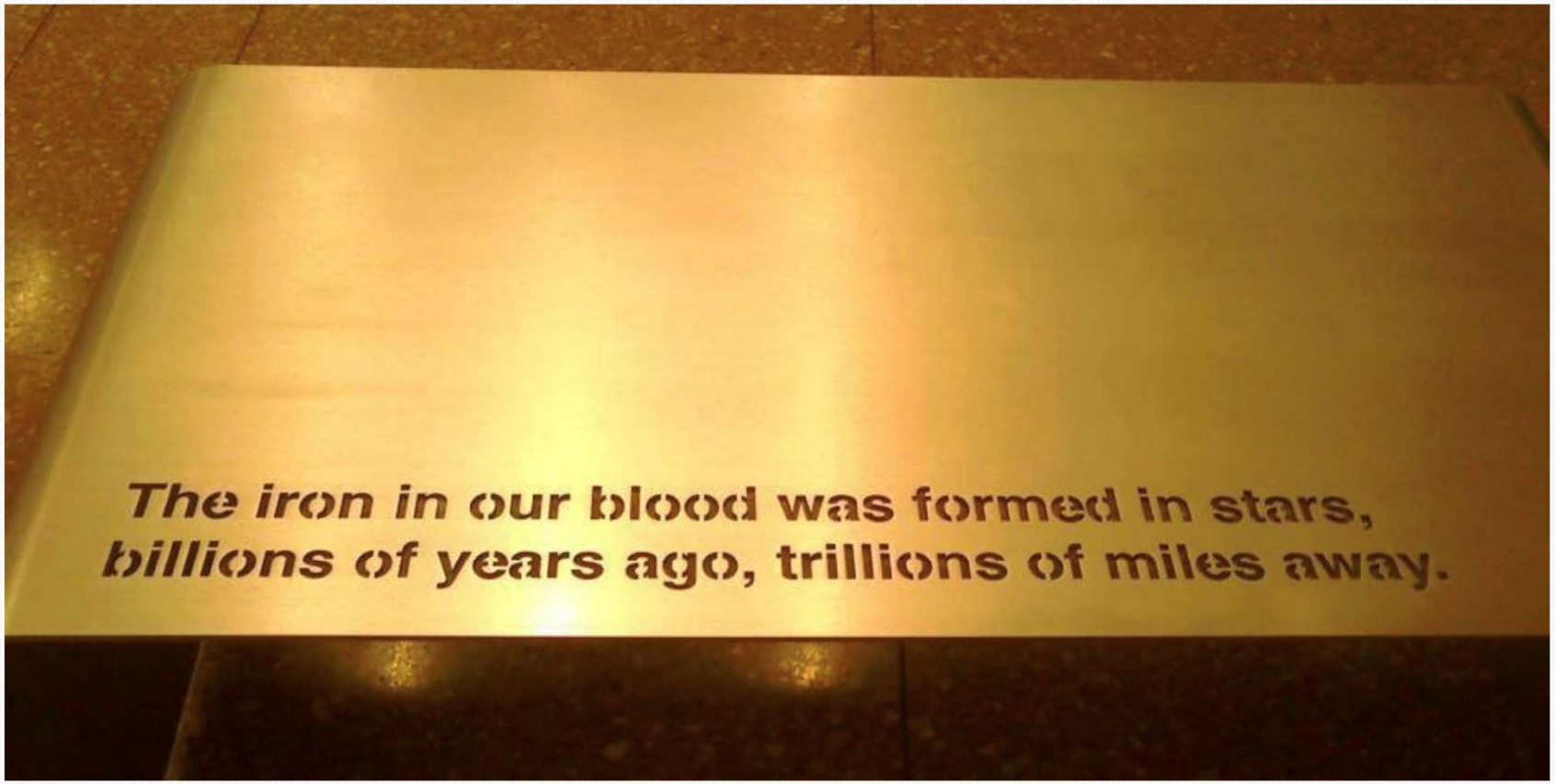
- **Anaphylaxis (rare)**
- **Expensive**
  - Venofer (iron sucrose):
    - $240 for a dose of 500 mg, $0.48 per mg of Fe
    - oral iron preparations:
      - Ferrous sulfate $10 for 500mg ($0.02 per mg)
      - Ferrous gluconate $7 for 500mg ($0.014 per mg)
      - Ferrous fumarate $8-9 for 500mg ($0.016 per mg)

Transfusion for Iron Deficiency

- **Only if the patient is hemodynamically unstable!!!!!!**
- Give slowly if anemia is chronic→ monitor for volume overload
- Each unit of blood has 250mg of iron

SUMMARY

- A good history will usually tell you why a patient is iron deficient
- Treating iron deficiency is usually easy and IV iron is helpful in challenging situations
- NEVER treat iron deficiency with transfusion unless your patient is unstable



Royal Tyrell Museum Bench

QUESTION 1

Iron deficiency anemia (IDA) is defined as:

A. A hemoglobin >2 SD above the mean for age/sex with a high ferritin
B. A hemoglobin <2 SD below the mean for age/sex with a low ferritin
C. A normal hemoglobin for age/sex with a low ferritin
D. A normal hemoglobin with a low serum iron and normal ferritin
E. None of the above

QUESTION 2

Risk factors for iron deficiency in children, include all EXCEPT:

A) Prematurity and low birth weight
B) Low socioeconomic status
C) Early introduction of solids
D) Excessive milk intake
E) Prolonged bottle feeding

QUESTION 3

IDA in a toddler is optimally treated with:

A) Oral iron therapy, elemental iron 6mg/kg/day for 3-4 weeks
B) Red blood cell transfusion, 10-15mL/kg
C) Oral iron therapy, elemental iron 6mg/kg/day for 3-4 months
D) Dietary counseling and modification to include iron-rich foods
E) B and D