Iron metabolism and medical needs: a view from Academia

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Iron therapy Master Class
Zürich, Switzerland, 13-15 October 2009
Classification of anemias

Regenerative
1. loss of blood (acute)
2. hemolysis

Hyporegeneratives
1. quantitatively insufficient erythropoiesis
   - erythroblastenia *
   - medullar aplasia (e.g., after ceratin drugs)
   - medullar "invasion" (leukaemia…)
2. qualitatively insufficient erythropoiesis
   - insufficient hemoglobin synthesis
     • iron deficiency or chronic blood losses
     • troubles of iron utilization *
   - insufficient DNA synthesis
     • vitamin B$_{12}$ deficiency
     • folates deficiency

* observed in infectious diseases, inflammation, and cancer (chronic situations)
What does the doctor need to look for in patients?

**TABLE 2 Some symptoms of anaemia**

<table>
<thead>
<tr>
<th>Part of body affected</th>
<th>Compensatory mechanism</th>
<th>Dysfunction^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td></td>
<td>Fatigue/tiredness, headaches, dizziness, difficulty thinking/concentrating, depressed mood</td>
</tr>
<tr>
<td>Eyes</td>
<td></td>
<td>Retinal damage</td>
</tr>
<tr>
<td>Heart</td>
<td>Rapid pulse, palpitations</td>
<td>Angina</td>
</tr>
<tr>
<td>Lungs</td>
<td>Rapid breathing, breathlessness</td>
<td>In severe cases, worsened breathlessness from pulmonary oedema secondary to heart failure</td>
</tr>
<tr>
<td>Kidneys</td>
<td></td>
<td>Water retention</td>
</tr>
<tr>
<td>Gut</td>
<td>Loss of appetite</td>
<td>Indigestion, irregular bowel movements, failure to absorb nutrients from food</td>
</tr>
<tr>
<td>Muscles/legs</td>
<td></td>
<td>Fatigue, reduced exercise capacity, swelling secondary to water retention (due in turn to kidney and heart failure)</td>
</tr>
<tr>
<td>Skin</td>
<td>Pallor, feeling cold</td>
<td>Brittle/broken nails</td>
</tr>
<tr>
<td>Reproductive organs</td>
<td></td>
<td>Increased menstrual bleeding, loss of periods, impotence, decreased libido</td>
</tr>
</tbody>
</table>

^a The clinically important effects are magnified if anaemia develops rapidly or organs are compromised and unable to work at increased capacity, e.g. coronary artery disease for symptoms associated with dysfunction of the heart.
Where is iron stored, and what for?

<table>
<thead>
<tr>
<th>Organ / Cells</th>
<th>amount</th>
<th>function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cells</td>
<td>1.8 g</td>
<td>$O_2$ transport</td>
</tr>
<tr>
<td>RES macrophages</td>
<td>0.6 g</td>
<td>iron storage</td>
</tr>
<tr>
<td>Liver</td>
<td>1.0 g</td>
<td>$O_2$ metabolism / storage</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>0.3 g</td>
<td>$O_2$ metabolism / storage</td>
</tr>
<tr>
<td>Muscles (myoglobin)</td>
<td>0.3 g</td>
<td>$O_2$ metabolism</td>
</tr>
<tr>
<td>Other tissues$^8$</td>
<td>0.1 g</td>
<td>$O_2$ metabolism</td>
</tr>
<tr>
<td>Transferrin</td>
<td>0.003 g</td>
<td>iron transport</td>
</tr>
</tbody>
</table>

- Iron stores are **low** compared to functional iron hemoglobin / myoglobin …
- Circulating iron is **very low** in quantity …
Where is iron stored, and what for?

<table>
<thead>
<tr>
<th>Organ / Cells</th>
<th>Iron</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cells</td>
<td></td>
<td>Oxygen transport</td>
</tr>
<tr>
<td>RES macrophages</td>
<td></td>
<td>Storage and metabolism</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td>Metabolism / Storage</td>
</tr>
<tr>
<td>Bone marrow</td>
<td></td>
<td>Metabolism</td>
</tr>
<tr>
<td>Muscles (myoglobin)</td>
<td></td>
<td>Metabolism</td>
</tr>
<tr>
<td>Other tissues</td>
<td></td>
<td>Metabolism</td>
</tr>
<tr>
<td>Transferrin</td>
<td></td>
<td>Transport</td>
</tr>
</tbody>
</table>

- Iron stores are **low** compared to functional iron hemoglobin / myoglobin …
- Circulating iron is **very low** in quantity …
Movements of iron into, within, and out of the body...

The in and out movements of iron are very limited compared "in body" turnover …
Movements of iron into, within, and out of the body...

The in and out movements of iron are very limited compared "in body" turnover ...
Absorption of iron: 1. intestinal control

- Iron homeostasis is regulated at the level of intestinal absorption
- Iron is absorbed by villus enterocytes in the proximal duodenum
- Efficient absorption requires an acidic environment (antacids or other conditions that interfere with gastric acid secretion can interfere with iron absorption)
- Ferric iron (Fe^{+++}) in the duodenal lumen is reduced to Fe^{++} * through the action of a brush border ferrireductase, and is cotransported with a proton into the enterocyte via the divalent metal transporter DMT-1 (which also transports many divalent metal ions).

- Inside the enterocyte, iron follows one of two major pathways
  - Iron abundance states: iron within the enterocyte is trapped by incorporation into ferritin and hence, not transported into blood. When the enterocyte dies and is shed, this iron is lost.
  - Iron limiting states: iron is exported out of the enterocyte via a transporter (ferroportin) located in the basolateral membrane

* favored by co-administration of ascorbic acid (vitamin C)

http://arbl.cvmbs.colostate.edu/hbooks/pathphys/digestion/smallgut/absorb_minerals.html
Iron absorption and mobilization:
2. role of hepcidin

Systemic iron homeostasis:

- Hepcidin controls the transferrin iron saturation by inhibiting iron efflux mainly from duodenal enterocytes and macrophages but also from hepatocytes.

- Hepcidin synthesis is positively regulated by the iron stores and negatively regulated by erythropoietic activity.

Note: the signal that regulates hepcidin expression through erythropoiesis, anemia and hypoxia is still unknown, but inflammation may increase its production.

Hepcidin "turn off" * the iron export system

A. before hepcidin treatment.
B. after hepcidin treatment: the ferroportin has been internalized leading to decreased cellular iron efflux.

Ganz & Nemeth, Biochim Biophys Acta. 2006;1763:690-9
Why do inflammation cause anemia?

Effects of inflammation on erythropoiesis and iron homeostasis in mammals.

(-): Negative effect; (+): Positive effect.

Why do inflammation cause anemia?

Effects of inflammation on erythropoiesis and iron homeostasis in mammals.


(-): Negative effect; (+): Positive effect.
Why do inflammation cause anemia?

Effects of inflammation on erythropoiesis and iron homeostasis in mammals.

(-): Negative effect; (+): Positive effect.

When do erythrocytes need iron?

Figure 1  Major stages of human erythropoiesis showing the point of commitment, the period of EPO dependence and the requirements for essential nutrients. BFU-E: Burst-forming unit-erythroid; CFU-E: Colony-forming unit-erythroid; EPO: Erythropoietin.
Anemia is a condition characterized by a bodily insufficiency of red blood cells, hemoglobin, or a combination of the two. **A most common form is iron deficiency anemia**, related to a paucity of the mineral iron, which the body requires to produce hemoglobin and transport oxygen.

Without enough oxygen circulating in the body, symptoms such as **extreme fatigue, pallor, weakness, lightheadedness, shortness of breath, and cold extremities** may develop. Other possible signs of iron deficiency anemia include brittle nails, poor appetite, increased susceptibility to infection, headache, swelling and soreness of the tongue, and cracking of the sides of the mouth, though mild cases are sometimes asymptomatic.

Iron deficiency anemia: who is at risk?

- nutrition deficiencies
  - lack of animal iron or "poor" quality nutrition
- pregnant women
  - fetal reserves building
- children
  - growth (young children)
  - ill-adapted nutrition (adolescents; young women)
- aged patients with decreased
  - medullar reserve
  - hormonal response to erythropoietic stimulants
  - alimentary supply
- acute blood loss
  - surgery
- cancer / inflammation / infections
  - "resistance" to erythropoietic stimuli

→ improve nutritional status

→ intervene!
Alimentary supplies

Absorption of iron from vegetable and meat foods in human subjects; 11–137 subjects used in each test

This guy is wrong!
Alimentary supplies

Absorption of iron from vegetable and meat foods in human subjects; 11-137 subjects used in each test

Table 28.5 Iron content of alcoholic beverages

<table>
<thead>
<tr>
<th>Beverage</th>
<th>Iron content (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US beer</td>
<td>0.1</td>
</tr>
<tr>
<td>Gin, whisky</td>
<td>0.6</td>
</tr>
<tr>
<td>US wines</td>
<td>2.3-2.6</td>
</tr>
<tr>
<td>Red and white French wines</td>
<td>6.2</td>
</tr>
<tr>
<td>Cider and wine from Rennes (France)</td>
<td>10-16</td>
</tr>
</tbody>
</table>

Alimentary supplies

What you need (for optimal bioavailability) is this:

"vegetal" iron

hemic iron

old but useful publication ➔

Food Iron Absorption: A Comparison of Vegetable and Animal Foods

By M. Layrisse, J. D. Cook, C. Martinez, M. Roche, J. N. Kuhn, R. B. Walker and C. A. Finch

Iron absorption measurements have been made in 131 individuals relating the absorption of nine different foods tagged biosynthetically with radioiron. Relatively low absorption, ranging from 1.7-7.9, was found with wheat, corn, black beans, lettuce and spinach. Higher values of from 15.6-20.3 were observed with soybeans, fish, veal and hemoglobin.

Blood, Vol. 33, No. 3 (March) 1969, 430
Why is hemic iron more bioavailable?

because of the presence of a specific heme-transporter at the level of the intestinal cell villi

Dunn et al. Trends in Cell Biol 2006; 17: 93-100
Oral iron with pharmaceutical preparations …

All have a **poor bioavailability** (non hemic iron…)
- May help if … you have a lot of time *
  thus, not in acute situations
  (ascorbic acid may help …)
- treatment is ALWAYS long (3-6 months!!)

All have **several undesirable effects** (you MUST warn the patient !!) due to presence of **large amounts of free iron** (that will not be reabsorbed)
- irreversible teeth staining
- diarrhea or constipation,
- blackened stools (with persistent stains on clothes)
- risk of ulcers (Iron sulfate) **

Do **NOT** administer with drugs that may be **complexed** by dicationic or tricationic iron
(diphosphonates, levodopa, fluroquinolones, tetracyclines, …) or which can reduce iron
bioavailability (antacids, phosphates, calcium salts, …)

* typical time to recover from a 300 ml blood loss: 1-2 months
** see next slides
Iron sulfate and gastric ulcers…

Figs. 1–6. 1. Esophagastroduodenoscopy: pale, villous appearing flat lesion along the lesser curvature of gastric body. 2. Gastric biopsy: crystalline iron deposition overlying gastric mucosa with fibrosis and chronic inflammation (H&E, 200 ×). 3. Gastric biopsy: Prussian blue stain highlights the crystalline iron deposition (Prussian blue, 200 ×). 4. Gastric biopsy: iron deposition in gastric glands (Prussian blue, 400 ×). 5. Ferrous sulfate tablet: iron tablet material shows crystalline appearance (HE, 400 ×). 6. Ferrous sulfate tablet: Prussian blue stain of iron tablet material (Prussian blue, 400 ×) (for interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).
Iron sulfate and esophageal ulcers…

Iron-induced esophageal ulceration

Fig. 1 Upper endoscopy at day 1 revealed a black-brown, ulcerated and necrotic lesion, just below the upper esophageal sphincter.

Fig. 2 Granulation tissue from the area with ulcerated esophagitis containing abundant brown crystalline material (hematoxylin and eosin, ×400).

Fig. 3 Positive blue staining of the crystalline material with Perl's iron stain (×400).

Fig. 4 Upper endoscopy at day 8 showing the progressive resolution of the lesion, with a brown pigmentation and no necrosis.

Areia et al., Endoscopy. 2007; 39 Suppl 1:E326
Oral Iron preparations

**Fer gluconate**

<table>
<thead>
<tr>
<th>Lodeiron (Grüenthal)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>comp. effervescent (p.c.)</td>
<td></td>
</tr>
<tr>
<td>30 x 655 mg</td>
<td>Rb</td>
</tr>
<tr>
<td>60 x 655 mg</td>
<td>Rb</td>
</tr>
</tbody>
</table>

**Polyaccharate ferrique**

<table>
<thead>
<tr>
<th>FerriOne (Trenker)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>comp. polyaccharate ferrique complexe</td>
<td></td>
</tr>
<tr>
<td>20 x 326 mg</td>
<td>Rb</td>
</tr>
<tr>
<td>56 x 226 mg</td>
<td>Rb</td>
</tr>
<tr>
<td>(150 mg Fe³⁺)</td>
<td></td>
</tr>
<tr>
<td>sol. 60 ml 255 mg/5 ml</td>
<td>Rb</td>
</tr>
<tr>
<td>250 ml 225 mg/5 ml</td>
<td>Rb</td>
</tr>
<tr>
<td>(150 mg Fe³⁺)</td>
<td></td>
</tr>
</tbody>
</table>

**Fer sulfate 7H₂O**

<table>
<thead>
<tr>
<th>Fero-Grad 500 (Pharma Logistics)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>comp. (acide ascorbique 500 mg + fer sulfate 7H₂O 525 mg)</td>
<td></td>
</tr>
<tr>
<td>30 x 525 mg</td>
<td>Rb</td>
</tr>
<tr>
<td>(105 mg Fe³⁺)</td>
<td></td>
</tr>
<tr>
<td>60 x 525 mg</td>
<td>Rb</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fero-Gradunet (Pharma Logistics)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>comp. (fer sulfate 7H₂O)</td>
<td></td>
</tr>
<tr>
<td>30 x 525 mg</td>
<td>Rb</td>
</tr>
<tr>
<td>60 x 525 mg</td>
<td>Rb</td>
</tr>
<tr>
<td>(105 mg Fe³⁺)</td>
<td></td>
</tr>
</tbody>
</table>

**Association fer-acide folique**

<table>
<thead>
<tr>
<th>Gembarrol (Keia)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>comp. (acide folique 0.5 mg + fer fumarate 200 mg)</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>Rb</td>
</tr>
</tbody>
</table>
When iron is more urgently needed than can be obtained by oral route?

- **intolerance or low adherence to oral preparations**
  (up 1/5 of all patients [Kulliggs et al. Alim. PharM; Ther. 2006; 24:1507-1523])

- **acute blood loss**
  - surgical interventions and accidental hemorrhagea
  - post-partum

- **diseases associated with disturbance of iron absorption and/or utilization**
  - inflammatory bowel disease
  - congestive heart failure
  - chronic kidney disease
  - cancer-related anemia in association with erythropoietin
Why more iron after administration of erythropoietin?

Conditions where endogenous EPO is insufficient:
- renal insufficiency
- cancer (overproduction of cytokines)

Erythropoiesis-stimulating agents should be used to target hemoglobin 11-12 g/dl in patients with chronic kidney disease (or tumors). Intravenous iron may be beneficial for patients with hemoglobin less than 11 g/dl and transferrin saturation less than 25% despite elevated ferritin (500-1200 ng/ml).

What is the link between EPO and need of iron?

Figure 1  Major stages of human erythropoiesis showing the point of commitment, the period of EPO dependence and the requirements for essential nutrients. BFU-E: Burst-forming unit-erythroid; CFU-E: Colony-forming unit-erythroid; EPO: Erythropoietin.
Why do some patients "resist" to EPO?

Figure 1. Causes of rHuEpo resistance has many causes including inflammation, iron-restricted erythropoiesis, and marrow suppression. Sometimes, various diseases and conditions share all 3 conditions. For example, patients with uremia may have blood losses, inflammation, and marrow suppression. rHuEpo, recombinant human erythropoietin; PTFE, polytetrafluoroethylene.

Elliott et al., Advances in Chronic Kidney Disease, 2009; 16:94-100
# Diagnostic and handling of EPO-resistance

## Table 1. Etiology, Diagnosis, and Treatment of Erythropoietin Resistance

<table>
<thead>
<tr>
<th>Cause</th>
<th>Findings</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron-restricted erythropoiesis</td>
<td>TSAT &lt;20%</td>
<td>Maintenance IV iron</td>
</tr>
<tr>
<td></td>
<td>Ferritin &lt;1,200 ng/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High rHuEpo dose</td>
<td></td>
</tr>
<tr>
<td>Dialysis dose</td>
<td>URR &lt;65%</td>
<td>Improve dialysis delivery</td>
</tr>
<tr>
<td>Volume overload, congestive heart failure</td>
<td>Rales, peripheral edema, elevated blood pressure</td>
<td>Challenge dry weight</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Low serum albumin</td>
<td>Treat underlying disease</td>
</tr>
<tr>
<td></td>
<td>Micronutrient depletion</td>
<td>Correction of malnutrition</td>
</tr>
<tr>
<td>Access infection/Inflammation</td>
<td>Elevated C-reactive protein in the setting of a catheter or graft</td>
<td>Removal of access and transition to native fistula if possible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treat underlying disease</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Elevated PTH</td>
<td>Treat hyperparathyroidism</td>
</tr>
<tr>
<td>Aluminum intoxication</td>
<td>Dialysate or oral aluminum, Citrate coadministered with aluminum, hypochromic microcytic anemia</td>
<td>Desferrioxamine for aluminum intoxication and removal of offending agent</td>
</tr>
<tr>
<td>Dialysate contamination</td>
<td>Anemia in large percentage of patients at single dialysis unit</td>
<td>Improve dialysate water quality, ultrapure dialysate</td>
</tr>
<tr>
<td>Periodontal disease</td>
<td>Poor dentition, gum swelling, tenderness, and bleeding on physical examination</td>
<td>Referral to a dentist</td>
</tr>
</tbody>
</table>

TSAT, transferrin saturation; rHuEpo, recombinant human erythropoietin; URR, urea reduction ratio; PTH, parathyroid hormone.
Can iron be administered by the parenteral route?

A few milestones:


- IV solutions with saccharose (sucrose) were found more acceptable (Lancet 1947; i:49-51)

- Fisons introduced iron dextran in 1954, first for intramuscular (Lancet 1954; ii: 942) and later on for intravenous administration

- Several other preparations of complexed iron have since then been introduced, with large variations between countries for commercialization

Example for Belgium:

<table>
<thead>
<tr>
<th>Spécialités à usage parentéral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noms de spécialité</td>
</tr>
</tbody>
</table>

- **Fercyl (Sterop)**
  - [for dextran]
  - amp. 1 ml
  - 5 x 100 mg Fe²⁺/2 ml
  - Rx
  - € 6.00

- **Venéfer (Fresenius)**
  - [for saccharose]
  - amp. 1 ml
  - 5 x 100 mg Fe²⁺/2 ml
  - U.H.
But what are (some of) the problems?

- Complexation is often insufficiently stable leading to liberation of free, toxic ionic iron, causing oxidative stress …
  - iron gluconate (Venofer®) needs to be administered by small doses (100-200 mg) over several days

- The complexing agent may cause severe adverse reactions
  - formation of anti-dextran antibodies
  - Iron-dextran needs to be administered very slowly (50 mg/min max.) and often over several hours

- Anaphylactic-type reactions, including deaths
- Use only in those patients with iron deficiency:
  - Verified with lab tests
  - Not amenable to oral iron therapy.

- Resuscitation techniques and treatment of anaphylaxis and anaphylactoid shock must be readily available.

- Most preparations do not fully take into account the way iron should be delivered to cells!
Pharmacological properties

<table>
<thead>
<tr>
<th></th>
<th>Iron dextran</th>
<th>Iron sucrose</th>
<th>Ferric gluconate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>$t_{1/2}$ elimination (hr)</td>
<td>6</td>
<td>5–6</td>
<td>1</td>
</tr>
<tr>
<td>Clearance (1,000-mg dose)</td>
<td>10–20 mg/hr$^a$</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>$V_d$ (L)$^b$</td>
<td>Not reported</td>
<td>7.9</td>
<td>6</td>
</tr>
<tr>
<td>Dialyzed Safety profile</td>
<td>Negligible</td>
<td>Negligible</td>
<td>Negligible</td>
</tr>
<tr>
<td>Pregnancy category$^c$</td>
<td>C</td>
<td>B</td>
<td>B</td>
</tr>
</tbody>
</table>

$^a$ Cleared by the reticuloendothelial system.
$^b$ $V_d$ (L), volume of distribution in liters.
$^c$ B and C denote pregnancy risk factors established by the FDA.

**Guidelines**

**TABLE III. Administration Guidelines for Parenteral Iron Products**

<table>
<thead>
<tr>
<th></th>
<th>Iron dextran</th>
<th>Iron sucrose</th>
<th>Ferric gluconate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td>50 mg/mL (2-mL vial)</td>
<td>20 mg/mL (5-mL vial)</td>
<td>12.5 mg/mL (5-mL ampule)</td>
</tr>
<tr>
<td>IV injection</td>
<td>NTE 50 mg/min</td>
<td>NTE 20 mg/min</td>
<td>NTE 12.5 mg/min</td>
</tr>
<tr>
<td>(maximum rate)</td>
<td></td>
<td>Physician discretion</td>
<td>Physician discretion</td>
</tr>
<tr>
<td>Test dose</td>
<td>Required on first infusion</td>
<td>25-mg IV slow push</td>
<td>25-mg IV slow push or 25 mg</td>
</tr>
<tr>
<td>Test dose</td>
<td>25-mg IV slow IV push</td>
<td></td>
<td>in 50 mL of NS IV over 60 min</td>
</tr>
<tr>
<td>Dosing</td>
<td>100 mg</td>
<td>100 mg</td>
<td>125 mg</td>
</tr>
<tr>
<td>IV injection</td>
<td>100 mg over 2-5 min</td>
<td>100 mg IV over 5 min</td>
<td>125 mg IV over 10 min</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>Daily until calculated total</td>
<td>1-3 times week</td>
<td>1,000 mg over 8 dialysis sessions</td>
</tr>
<tr>
<td>amount required</td>
<td>based on iron replacement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum cumulative dose</td>
<td>Based on iron replacement</td>
<td>1,000 mg</td>
<td>1,000 mg</td>
</tr>
<tr>
<td>Stability</td>
<td>Not reported</td>
<td>48 hr (concentration of 0.5-2 mg/mL)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Diluent</td>
<td>0.9% sodium chloride</td>
<td>0.9% sodium chloride</td>
<td>0.9% sodium chloride</td>
</tr>
<tr>
<td>Total dose infusion</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Infusion</td>
<td>Dilute dose in 250-1,000 mL of 0.9%</td>
<td>100 mL 0.9% NS IV over 15 min</td>
<td>125 mg in 100 mL of NS IV over 1 hr</td>
</tr>
<tr>
<td>Routes</td>
<td>IM (INFed) IV infusion</td>
<td>IV injection IV infusion</td>
<td>IV injection IV infusion</td>
</tr>
</tbody>
</table>

*Abbreviations: NTE, not to exceed; NS, normal saline.

How is iron delivered to cells?

Figure 31.33
Endocytic pathway for transferrin. Iron is released in acidic endosomes. Apotransferrin and the receptor are recycled. [After A. Dautry-Varsat and H. F. Lodish. How receptors bring proteins and particles into cells. Copyright © 1984 by Scientific American, Inc. All rights reserved.]
How is iron delivered to cells?

Iron is never free in plasma but VERY tightly bound to transferrin as Fe$^{3+}$

Figure 31.33
Endocytic pathway for transferrin. Iron is released in acidic endosomes. Apotransferrin and the receptor are recycled. [After A. Dautry-Varsat and H. F. Lodish. How receptors bring proteins and particles into cells. Copyright © 1984 by Scientific American, Inc. All rights reserved.]
How is iron delivered to cells?

Fe$^{3+}$-loaded transferrin binds to a surface receptor...

Figure 31-33
Endocytic pathway for transferrin. Iron is released in acidic endosomes. Apotransferrin and the receptor are recycled. [After A. Dautry-Varsat and H. F. Lodish. How receptors bring proteins and particles into cells. Copyright © 1984 by Scientific American, Inc. All rights reserved.]
How is iron delivered to cells?

The Fe^{3+}-loaded transferrin – receptor complex is internalized by adsorbative pinocytosis.
How is iron delivered to cells?

Thanks to acid pH (~ 5), Fe$^{3+}$ is reduced to Fe$^{2+}$, unloaded from the transferrin – receptor complex, and reaches the cytosol (to be used or stored).
How is iron delivered to cells?

The free-transferrin - receptor complex recycles to the cell surface... where free transferrin is liberated ...

to capture any free iron and do its job again ...
Why could Ferinject® be more "physiological"?

It mimics what transferrin would do … and it helps reloading transferrin with Fe³⁺

Geisser P, 1992
Proposed use of intravenous iron in surgical patients

<table>
<thead>
<tr>
<th>Preoperative Hb</th>
<th>Hb 10–12 g/dl</th>
<th>Hb 12–14 g/dl</th>
<th>Hb &gt; 14 g/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>-21</td>
<td>200 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-14</td>
<td>200 mg</td>
<td>200 mg</td>
<td></td>
</tr>
<tr>
<td>-7</td>
<td>200 mg</td>
<td>200 mg</td>
<td></td>
</tr>
<tr>
<td>*Only if Hb &lt; 13 g/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Surgery

| +2              | 200 mg        | 200 mg        | 200 mg      |

+7

**Day**

| Total dose     | 1000–1200 mg | 600–1000 mg | 400–600 mg |

Fig. 2 A tentative algorithm for the use of intravenous iron sucrose in a 70-kg patient scheduled for major orthopaedic surgery with an expected haemoglobin drop of 4 g/dl. Total iron dose (mg), total iron deficiency (TID) + surgical iron loss (SIL); TID = [target Hb (g/dl) – actual Hb (g/dl)] × weight (kg) × 2.4; where target Hb is 14 g/dl and 2.4 is a factor (Hb iron content × blood volume × 1000); SIL = expected Hb drop (g/dl) × 165; assuming that 165 mg of iron are needed to raise Hb by 1 g/dl; day, perioperative day (+preoperative, +postoperative); Ft, ferritin; CRP, C-reactive protein.

Proposed use of intravenous iron in cancer patients

Our institutional guidelines for the assessment of iron stores in patients with cancer- or treatment-related anemia and the administration of parenteral iron with ESAs in patients with non-myeloid malignancies with chemotherapy-induced anemia.


**Flowchart**

- **Hemoglobin (Hb)<12g/dl^a**
  - Assess iron, folate and B<sub>12</sub> levels as indicated by the red blood cell indices. Correct deficiencies per institutional guidelines before considering erythropoietin therapy.\(^b\)
  - **Hb < 10g/dl?**
    - **No.**
Proposed use of intravenous iron in cancer patients (2 of 3)

Yes. Measure serum ferritin (SF) and calculate transferrin saturation (TSAT) before starting darbepoetin alfa.
Start darbepoetin alfa 200mcg every 2 weeks or darbepoetin alfa 300mcg every 3 weeks.

TSAT < 20% and SF 100 to 500 ng/ml?

Yes. Administer INFeD as multiple intravenous infusions of 250mg in 100ml 0.9% sodium chloride over 30min every week for 4 weeks.

TSAT 20 – 35% or SF > 500 – 900 ng/ml?

Yes. Re-evaluate iron stores and consider INFeD if no response to darbepoetin alfa after 2 doses.

TSAT > 35% or SF > 900ng/ml?

Yes. Do not administer parenteral iron.
Proposed use of intravenous iron in cancer patients (3 of 3)

Measure Hb, SF and TSAT 2 weeks after starting darbepoetin alfa, then every 4 weeks (darbepoetin alfa every 2 weeks) or 6 weeks (darbepoetin every 3 weeks)

Adjust doses of darbepoetin alfa to maintain the lowest Hb level sufficient to reduce the number of red blood cell transfusions. Administer parenteral iron based on TSAT and SF.

These guidelines are strictly to guide the administration of ESA therapy and parenteral iron in patients with non-myeloid malignancies currently receiving chemotherapy.

Iron deficiency anemia is defined as a TSAT <20% or a serum ferritin <100 ng/ml. These guidelines are not intended to guide the administration of iron with this underlying diagnosis.
Is infection a risk of iron therapy?

• This has been a much controversial area... with suggestions and experimental evidence that iron supplementation
  – will increase host defenses (PMN use oxydant species to kill bacteria)
  – BUT will also promote microbes' growth because they may need iron...*

• Most evidences come from studies with oral administration in 3d world countries with undernourished populations (probably deficient in iron) and high incidence of malaria...

• No studies of oral iron supplementation clearly show deleterious effects in non-malarious areas...

• Milk fortification reduced morbidity due to respiratory disease in two very early studies in non-malarious regions, but this was not confirmed in three later fortification studies, (decreased morbidity rates could be achieved by breast-feeding alone).

• No systematic studies report oral iron supplementation and infectious morbidity in breast-fed infants in nonmalarious regions.

* unlikely to take place with S. aureus et S. pneumoniae because there is enough Hb where they live in humans...

Does oral iron supplementation increase infections *?


* in non-malarious areas...
Does oral iron supplementation increase infections *?

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>OR [95%CI Fixed]</th>
<th>OR [95%CI Fixed]</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Neonatal parenteral iron 250 mg 2y outcome</td>
<td>Cartwell Dunn Adult</td>
<td>1 / 63</td>
<td>6 / 138</td>
<td>0.34[0.03, 2.02]</td>
<td>1972</td>
</tr>
<tr>
<td>James Koembe Adult</td>
<td>7 / 65</td>
<td>5 / 74</td>
<td>1.84[0.49, 6.43]</td>
<td>1980</td>
<td></td>
</tr>
<tr>
<td>James Koembe OPD</td>
<td>5 / 65</td>
<td>20 / 74</td>
<td>0.43[0.10, 1.62]</td>
<td>1980</td>
<td></td>
</tr>
<tr>
<td>02 Milk fortification to infants aged 3 mo-18mo with Fe 60-100 mg/d for 1y</td>
<td>MacKay Summer Dunn</td>
<td>12 / 52</td>
<td>26 / 100</td>
<td>0.73[0.34, 1.60]</td>
<td>1978</td>
</tr>
<tr>
<td>MacKay Winter Dunn</td>
<td>6 / 35</td>
<td>45 / 135</td>
<td>0.41[0.16, 1.07]</td>
<td>1978</td>
<td></td>
</tr>
<tr>
<td>03 Cereal fortification Fe 4.1-5.1 mg/d from 4-8mo age</td>
<td>Javalid et al.</td>
<td>25 / 29</td>
<td>50 / 57</td>
<td>0.69[0.23, 2.27]</td>
<td>1981</td>
</tr>
<tr>
<td>04 Oral iron supplementation Fe 30 mg/d to anemic malnourished preschoolers</td>
<td>Angeles et al.</td>
<td>2 / 36</td>
<td>6 / 37</td>
<td>0.28[0.06, 1.45]</td>
<td>1993</td>
</tr>
</tbody>
</table>

**FIGURE 3** Iron trials in nonmalarious regions. Outcome: diarrheal infections (all types). Method of administration: parenteral iron: infants (1: Cartwell 1972, James and Combes 1960); food fortification: infants (2: MacKay 1978 and 3: Javalid et al. 1991); oral supplementation: preschoolers (4: Angeles et al. 1993). Methods of morbidity quantification: hospital based clinical assessment of serious infections (1); unblinded oral recall with historical controls (2); field clinical assessment (3 and 4); prospective passive case detection (1); prospective active case detection (2–4). OPD, outpatient detection.

* in non-malarious areas...
What about infections in "Western" patients?


Randomized, double-blind, placebo-controlled trial of effects of enteral iron supplementation on anemia and risk of infection during surgical critical illness.

Pieracci et al. Department of Surgery, Weill Cornell Medical College, New York, New York 10021, USA.

**BACKGROUND:** Critical illness is characterized by hypoferremia, iron-deficient erythropoiesis (IDE), and anemia.

**SETTING:** Enteral iron supplementation (ferrous sulfate 325 mg three times daily) or placebo until hospital discharge (97 vs. 103) in surgical patients

**OUTCOMES:** hematocrit, iron markers (i.e., serum concentrations of iron, ferritin, and erythrocyte zinc protoporphyrin [eZPP]), red blood cell (RBC) transfusion, transfusion rate (mL RBC/study day), nosocomial infection, antibiotic days, study length of stay (LOS), and death.

**RESULTS:** No difference with respect to incidence of infection (46.8% vs. 48.9%; p = 0.98), antibiotic days (14 vs. 16; p = 0.45), LOS (14 vs. 16 days; p = 0.24) or mortality rate (9.4% vs. 9.9%; p = 0.62).

**CONCLUSION:** Enteral iron supplementation of anemic, critically ill surgical patients does not increase the risk of infection and may benefit those with baseline IDE by decreasing the risk of RBC transfusion.
What about the infection risk for parenteral iron?

- much of the evidence is from *in vitro* studies

Authors’ discussion: The clinical implications of our finding… are currently unknown and require further studies.
What you will learn in the next days about iron therapy

• Clinical studies of available formulations (as registered)
• Medical education
• Science now and in the near future
• Patient Management
• Use in Oncology (future indication ?)

• My wish list for the future of iron therapy
  – further clinical data in treatment of anemia in chronic diseases (cancer, chronic heart failure, inflammatory diseases)
  – impact of intravenous iron on (i) cytokines and inflammation-related markers in vitro and in vivo, (ii) atherotic plaques peroxidation (cardiovascular disease); (iii) infections (in vitro [comparison with iron-sucrose] and in vivo) …
  – nephrotoxicity of new formulations in comparison with iron-sucrose
Where is Louvain?

Where we are now, in the outskirts of Brussels for the Faculty of Medicine of the French speaking Catholic University of Louvain (*Université catholique de Louvain*)

original place of the University (founded in 1425), and present place of the Flemish-speaking Catholic University of Louvain (*Katholieke Universiteit Leuven*)

Where the other Faculties of the French-speaking *Université catholique de Louvain* are located (in a place called Louvain-la-Neuve)
And here is how it will look when you come and visit us …

the Cellular and Molecular Pharmacology team