Iron Deficiency Anemia

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Global anemia prevalence

Anemia is a public health problem

Global Disease Burden (GBD 2015) estimates 2.36 billion people affected with anemia, more than half due to iron deficiency

(Lancet. 2016 Oct 8)

Among consequences:
- cognitive impairment in children
- increased morbidity/mortality of mothers
- decreased physical performance in workers
- worse outcome of concomitant disorders
Decrease of anemia prevalence (1990-2010)

(Kassebaum et al. Blood 2014;123:615-624)
Classification of iron deficiency

**Absolute**

\[ \text{ID} = \text{Iron deficiency} \]
Decreased total body iron, especially iron stores, with preservation of erythroid iron

\[ \text{IDA} = \text{Iron deficiency anemia} \]
Decreased total body iron and anemia

**Relative**

\[ \text{FID} = \text{functional iron deficiency} \]
Iron insufficient for increased erythroid demands:
e.g. after ESA treatment

**Iron-restricted erythropoiesis**
Reduced iron supply to erythropoiesis irrespective of the stores. Includes ACD/AI

**Tissue ID without anemia**
e.g.: ID in chronic heart failure
The two phases of erythropoiesis

Multipotent stem cell → Erythroid Progenitors (BFU-E CFU-E) → Terminal erythropoiesis

Iron needs for Hb synthesis of 200 billions erythrocytes: about 20-25 mg/day
IDA: mechanisms of adaptation

(Camachella, N Engl J Med 2015)
Physiological conditions at risk for ID (increased iron requirements)

- Children (< 2 yrs)
- Adolescent girls
- Young women
- Pregnant women

Regular blood donors

Usually no specific cause
→ no extensive workup needed

(Traglia et al, J Med Genet 2011)
Pathological causes

Insufficient intake
Malnutrition, vegetarians, vegans, iron poor-foods

Decreased absorption
Gastrectomy, duodenal by pass, bariatric surgery
*H. pylori* infection, celiac sprue, atrophic gastritis, IBD
drugs (proton pump inhibitors, H2 blockers)
Genetic IRIDA

Chronic blood loss
*Gastrointestinal tract*: any benign or malignant lesion, hookworm
Drugs (salicylates, corticosteroids, NSAID)
*Genitourinary system*: heavy uterine bleeding, hemolysis (PNH)
Bleeding defects (hereditary hemorrhagic telangiectasia)
GI-related causes

Surgical procedures
- Gastrectomy
- Gastric by pass (Bariatric surgery)

Malnutrition
Inadequate dietary iron intake

Upper GI blood losses
- Esophagitis, gastritis, ulcers, cancer or pre-malignant lesions, angiodysplasia, (antithrombotic drugs)

Malabsorption
- HP infection, AAG, CD, IBD, drugs (PPI).

Lower GI blood losses
- Colon-rectal cancer or pre-malignant polyps, IBD, ano-rectal lesions (e.g. hemorrhoids), angiodysplasia (antithrombotic drugs)

(modified from Busti F et al, Front Pharmacol 2014)

Refractory IDA: < 1g Hb increase after 4 weeks of oral iron therapy
(Hershko and Camaschella Blood 2014)
Main pathogenic mechanisms proposed to explain the association between *H. pylori* infection and IDA

- Uses iron for own growth and proliferation
- Reduced intragastric content of vitamin C
- Microerosions and chronic bleeding

Iron depletion

Iron deficiency anaemia

Iron refractory iron deficiency anemia
(IRIDA - OMIM #206200)

Rare recessive disorder due to *TMPRSS6* mutations
Iron deficiency anemia – normal/high hepcidin
Moderate anemia, severe microcytosis
Very low transferrin saturation - Normal high ferritin
Refractory to oral and partially refractory to iv iron

(Wang et al, Frontiers Pharmacol, 2015)
TMPRSS6 mutations in IRIDA strengthen the relevance of low hepcidin for iron absorption

(adapted from Hentze et al Cell, 2010)
Do *TMPRSS6* SNPs confer susceptibility to IDA?

Val736Ala influences red cell and iron traits

.....serum hepcidin levels

.....and shows inter-ethnic differences
Genetic susceptibility to IDA

In > 2000 unrelated elderly Chinese women TMPRSS6 736Val, the variant with “high” hepcidin, was associated with increased risk of iron-deficiency anemia (low serum iron and Hb levels)

(An et al, Hum Mol Genet 2012)

Female blood donors, carriers of 736Ala, seem more resistant to develop ID after blood donation than carriers of the high-hepcidin associated variant

(Kiss JE. Clin Lab Med. 2015)

In >14,000 Swedish blood donors, 736Val was negatively associated with iron stores (based on ferritin levels) in males

(Sorensen, Transfusion 2016)
Other chapters
(in red those discussed at Biolron 2017)

ID in chronic inflammatory disorders (e.g. IBD)
ID in chronic kidney disease (CKD)
ID in the elderly

ID in chronic heart failure
ID in perioperative anemia
ID in obesity (and its surgical treatment)
ID in sport medicine
Diagnosing ID/IDA

Ferritin:  
< 12 ng/ml (specificity 98% sensitivity 25%)  
< 30 ng/ml (specificity 98%, sensitivity 92%)

Transferrin saturation:  < 16%

MCV, MCH: reduced (not early indices)

- Increased red cell zinc protoporphyrin (ZPP > 80 mg/dl): screening tests, scarcely available

- Negative bone marrow Perl’s staining: highly specific but invasive

- High sTfR and low serum hepcidin levels

Always search the cause!
Diagnosing ID in ACD/AI

Proposed tests:
sTfR/log ferritin ratio: low in ACD, high in ID and ID/ACD
Hepcidin levels: high in ACD, low in ID and ID/ACD

In practice:

Ferritin: < 100 ng/ml or
< 200 ng/ml (CKD, hemodialysis)
< 300 ng/ml (heart failure)

Transferrin saturation: < 20%
FID = functional iron deficiency

Erythroid iron supply insufficient for increased requirements (even with replete stores): e.g. increased endogenous (after acute bleeding) or exogenous erythropoietin (EPO)

best-established variable for FID: % HRC (percent hypochromic red cells): 6% cut off in CKD

next most established option: CHr (reticulocyte Hb content): <27.2 g/dL
The effect of depleted iron stores or ESA on flow cytometry detection of %HYPO

Percent Hypochromic Red Cells (%HYPO)

- Flow cytometry with 2 detectors
  - High angle for Hb content
  - Low angle for cell size
  - Allows construction of a histogram for Hb content

Treatment (traditional)
Iron salts: 100-200 mg elemental iron, divided doses, between meals.
Lower doses (60mg/daily) in the occurrence of side effects, in the elderly or for anemia prevention.

Problems
Variable and low absorption (10-20%)
Potential toxicity of non-absorbed iron on intestinal mucosa (ROS generation) - microbiota changes?
Slow response: > 2-3 months for store repletion
IDA: oral iron supplementation. II

GI side effects: nausea, vomiting, diarrhea, constipation, metallic taste … common (30-70%)
Higher than placebo or IV iron (recent metanalysis) → reduced compliance.

Other compounds?
New effective oral iron formulations with better absorption (limited studies)
Schedule of administration?
Alternate day treatment? (to be further explored!)

Session IX: Iron Deficiency and Inflammatory Iron Restriction
Improving oral iron dosing schedule

In non-anemic young women with ferritin $\leq 20\mu$g/l a study with 60 mg FeSO$_4$ on alternate day maximized fractional iron absorption, increased efficacy, reduced GI side effects, improving oral iron tolerance

Limits: small number of cases, short term (2 days) study, ID non-anemic subjects (iron absorption is higher in IDA)

(Moretti et al, Blood 2015)
When to move from oral to iv iron?

May **hepcidin** levels guide the choice of the type of treatment? *(Bregman DB, Am J Hematol 2013)*

Hepcidin was the most consistent predictor of erythrocyte iron incorporation in anemic children from malaria areas in Gambia *(Prentice et al, Blood 2013)*

Discussed also in *Girelli et al, Blood. 2016*

The analysis of 5 randomized trials suggests that **Hb increase >1 g/dL at 14 days** is the best predictor of sustained response *(Okam et al, Haematologica 2015)*

“**Controversies in iron supplementation**” on Tuesday morning
Parenteral iron therapy. I

Established indications

• Oral iron intolerance or refractoriness
• GI disorders (IBD, acute flares)
• Need for a quick recovery: eg severe anemia in pregnancy
• Chronic bleeding not manageable with oral iron
• ESA treatment in CKD
• Substitution for blood transfusions when not accepted by patient
• Genetic IRIDA
Potential indications (studies in progress)

- ID in chronic heart failure
- Perioperative anemia (Transfusion sparing strategy within Patient Blood Management)
- Anemia of CKD before ESA treatment
- Persistent anemia after ESA in cancer patients under CHT
- Restless leg syndrome……
Indications to intravenous iron

Oral iron intolerance/ineffectiveness
Need for rapid recovery (e.g. severe IDA in pregnancy)
Excessive bleeding
Gastrectomy, duodenal bypass
Substitute for unacceptable blood transfusions
ESA in CKD

Genetic IRIDA
Active IBD
CKD (irrespective of ESA)
Chronic heart failure (?)
Perioperative anemia (?)

Traditional

Novel

ESA = erythropoietic stimulating agents
IBD = inflammatory bowel diseases
CKD = chronic kidney disease

Pharmacokinetic differences: oral vs i.v. iron

Oral Fe

N function

Bariatric surgery

Plasma transferrin

Splenic macrophages

Fe³⁺

Ferroportin

Fe³⁺

Fe/carbohydrate complexes

Circulating RBCs

Erythroid precursors in Bone Marrow
## Intravenous iron preparations

**Dose calculation, rapid effect (store repletion)**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Approved dose (mg)</th>
<th>Maximum safe dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferric gluconate</td>
<td>125 (10-60 min)</td>
<td>250 (1 hour)</td>
</tr>
<tr>
<td>Iron sucrose</td>
<td>100-400 (2-90min)</td>
<td>300 (2 hours)</td>
</tr>
<tr>
<td>Iron dextran (LMW)</td>
<td>100 (2 min)</td>
<td>1000 (1-4 hours)</td>
</tr>
<tr>
<td>Ferric carboxymaltose</td>
<td>750-1000 (15 min)</td>
<td>750-1000 (15min)</td>
</tr>
<tr>
<td>Ferrumoxytol*</td>
<td>510 (15-60 min)</td>
<td>510 (15-60 min)</td>
</tr>
<tr>
<td>Iron isomaltoside</td>
<td>20/Kg (15 min)</td>
<td>20/Kg (15 min)</td>
</tr>
</tbody>
</table>

*) black box warning for hypersensitivity reactions
The issue of safety

IV iron is not associated with increased risk of severe AE or infections in a meta-analysis of >10,000 patients


To minimize the risk of severe reactions (EMA recommendations):
resuscitation facilities; trained staff; test dose useless; antihistamines useless, even dangerous

Contraindications: infections, history of drug allergy and severe atopy; 1st trimester of pregnancy

Infusion reactions (itching, abdominal pain, nausea, headache, flushing, myalgia, arthralgia) are common.
Lab tests: hypophosphatemia
Mild HSR
- itching, flushing, urticaria, sensation of heat, slight chest tightness, hypertension, back/joint pains

Management
- Stop iron infusion for ≥15 mins
- Inform doctor
- Monitor pulse, BP, resp rate, O2 saturation
- Wait and watch

Patient no better in 5-10 mins, or deteriorating
- Restart iron infusion at reduced rate (eg 50%)

Patient better
- Observe for ≥1-4 hr
- Document event
- Consider future treatment strategy

Patient no better
- Transfer quickly to intensive care unit

Moderate HSR
- As in Mild reaction + transient cough, flushing, chest tightness, nausea, shortness of breath, urticaria, tachycardia, hypotension

Treat as for mild reaction AND
- Stop iron infusion
- Call doctor
- Consider volume load (eg iv 0.9% saline 500ml), iv corticosteroid (eg hydrocortisone 200mg)

Patient deteriorating
- Call fast response team
- Stop iron infusion
- Adrenaline im (0.5mg 1/1000) or iv (0.1mg 1/10000)
- Nebulised B2 agonist
- Further isotonic volume load iv corticosteroid
- O2 face mask
- ACLS (if necessary)

Severe/life-threatening HSR
- Sudden onset and rapid aggravation of symptoms + wheezing/stridor, periorbital edema, cyanosis, loss of consciousness, cardiac/respiratory arrest

Treat as in moderate reaction AND
- Call fast response team
- Stop iron infusion
- Adrenaline im (0.5mg 1/1000) or iv (0.1mg 1/10000)
- Nebulised B2 agonist
- Further isotonic volume load iv corticosteroid
- O2 face mask
- ACLS (if necessary)

(Ramptom et al, Haematologica 2014)
Treating ID without anemia

Young females with ID: especially when symptomatic or planning a pregnancy!

ID in blood donors!

Prevention of anemia of surgery

Chronic systolic heart failure

Plenary Session II and Panel discussion on Tuesday morning
Iron and heart failure

ID in heart failure reported about 37-50% using the “broad” definition: Serum ferritin <100 ng/ml or <300 ng/ml and transferrin saturation <20%

(Jankoska et al, Eur Heart J 2010)

FAIR-HF and CONFIRM-HF trials of IV iron vs placebo: better response in 6 min walking test, NYHA class, QOL and risk of hospitalization (in CONFIRM-HF) in iron-treated patients vs controls, even independently of anemia correction.

Why a failing heart would need iron?
Isolated cardiomyocyte iron deficiency in \textit{Tfr1}^{-/-} mice

A model for tissue ID in the absence of anemia? \textit{(Xu et al., 2015, Cell Reports 13, 1–13)}
Thank you very much!

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