Iron Deficiency Anemia

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Disclosure for Clara Camaschella

Vifor Pharma advisory board

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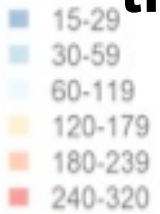
Global anemia prevalence

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

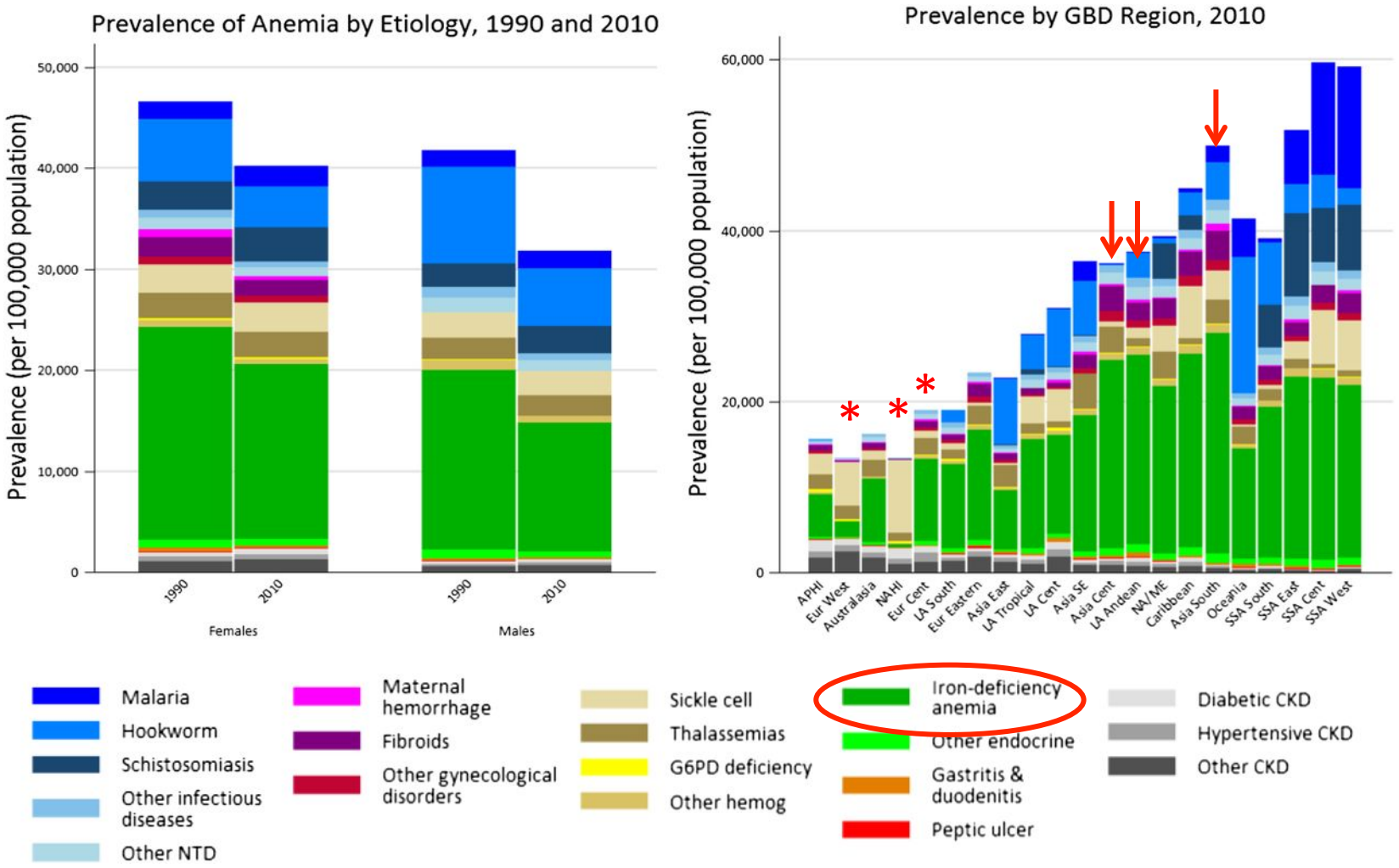
(Lancet. 2016 Oct 8)



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

ID = Iron deficiency
Decreased total body iron, especially iron stores, with preservation of erythroid iron
IDA = Iron deficiency anemia
Decreased total body iron and anemia

Relative

FID = 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

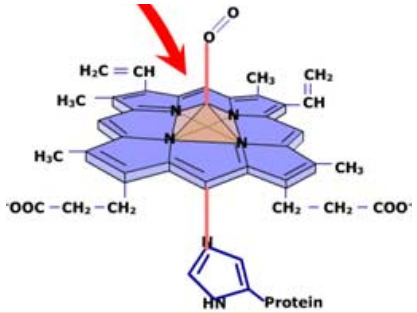
The two phases of erythropoiesis

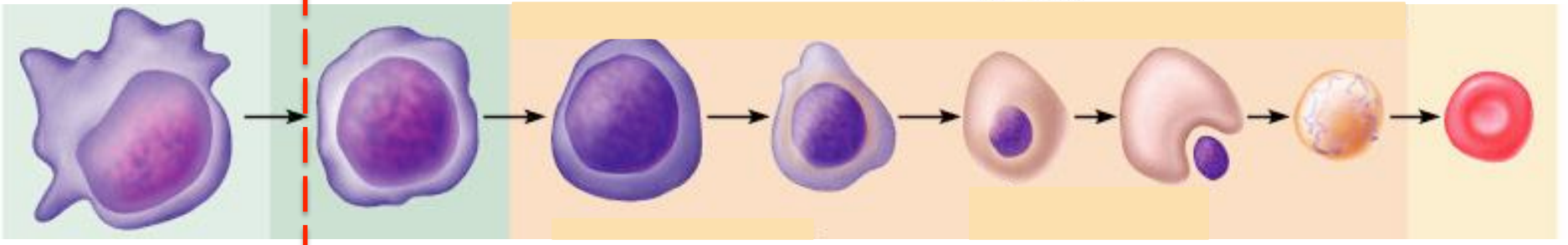
Multipotent stem cell

Erythroid Progenitors (BFU-E CFU-E)

Terminal erythropoiesis

Heme



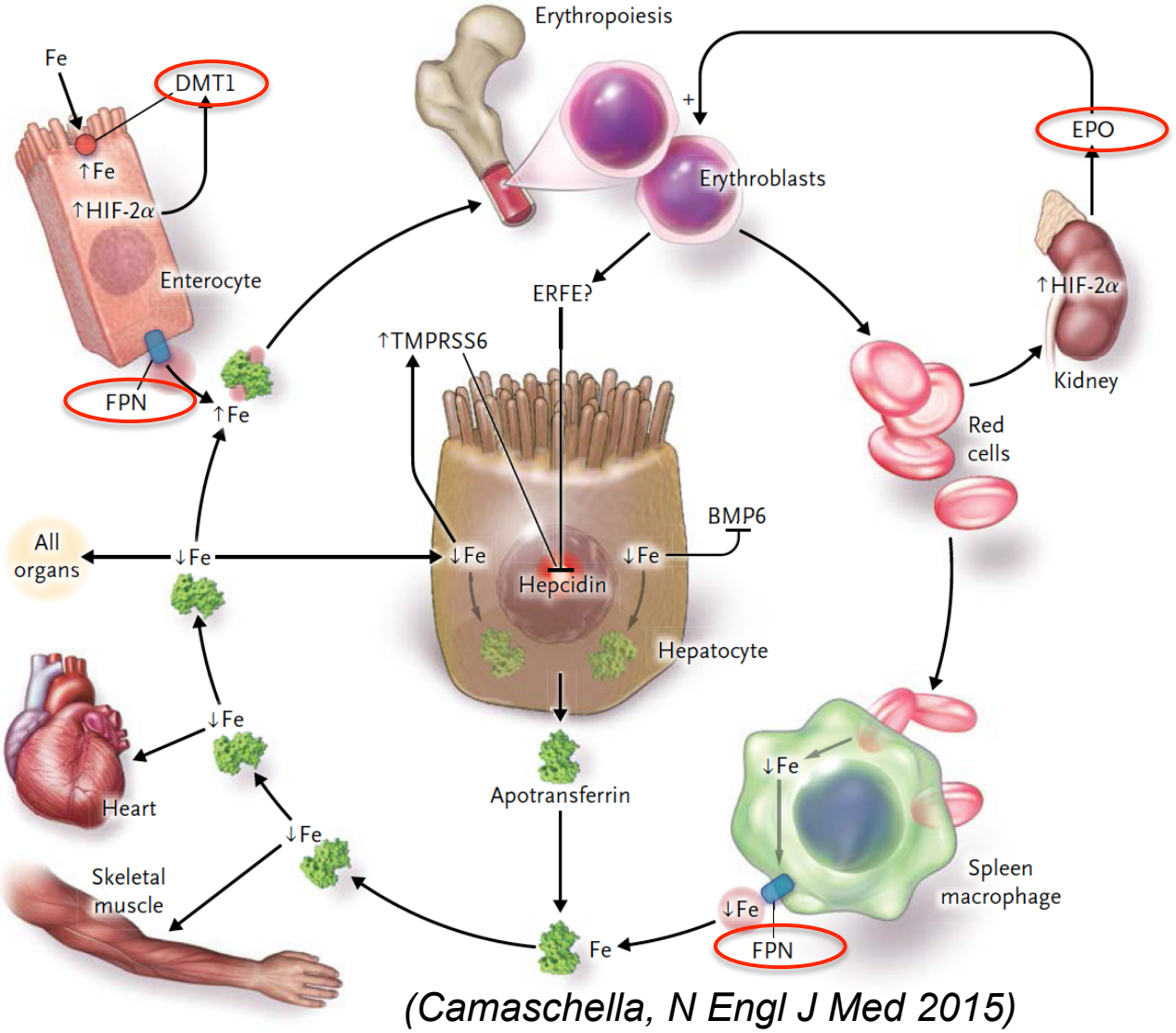


EPO

IRON

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

IDA: mechanisms of adaptation



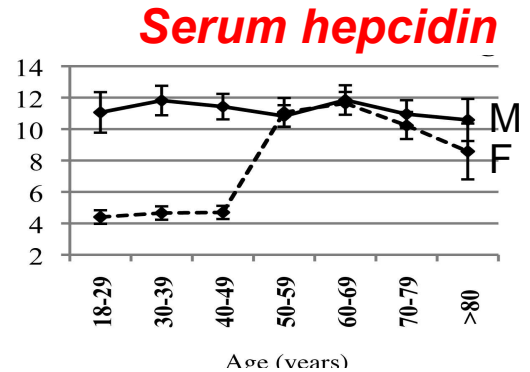
(Camaschella, N Engl J Med 2015)

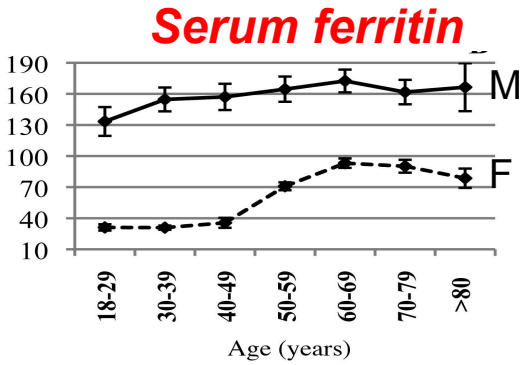
Physiological conditions at risk for ID
(increased iron requirements)

- 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

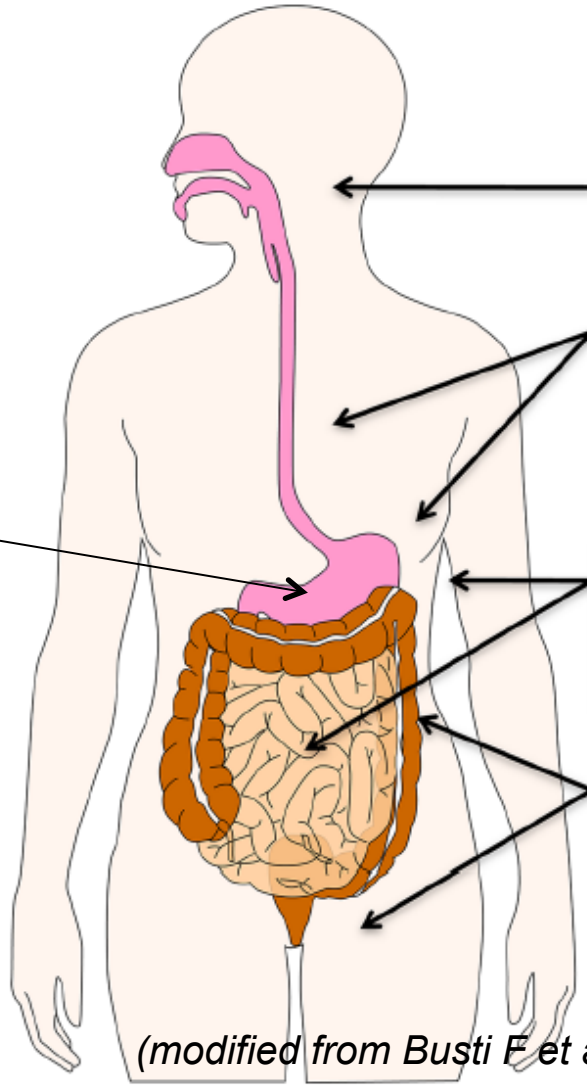
Gastrointestinal tract: any benign or malignant lesion, hookworm

Drugs (salycilates, corticosteroids, NSAID)

Genitourinary system: heavy uterine bleeding, hemolysis (PNH)

Bleeding defects (hereditary hemorrhagic telangiectasia)

GI-related causes



Malnutrition
Inadequate dietary iron intake

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

Surgical procedures
Gastrectomy
Gastric by pass
(Bariatric surgery)

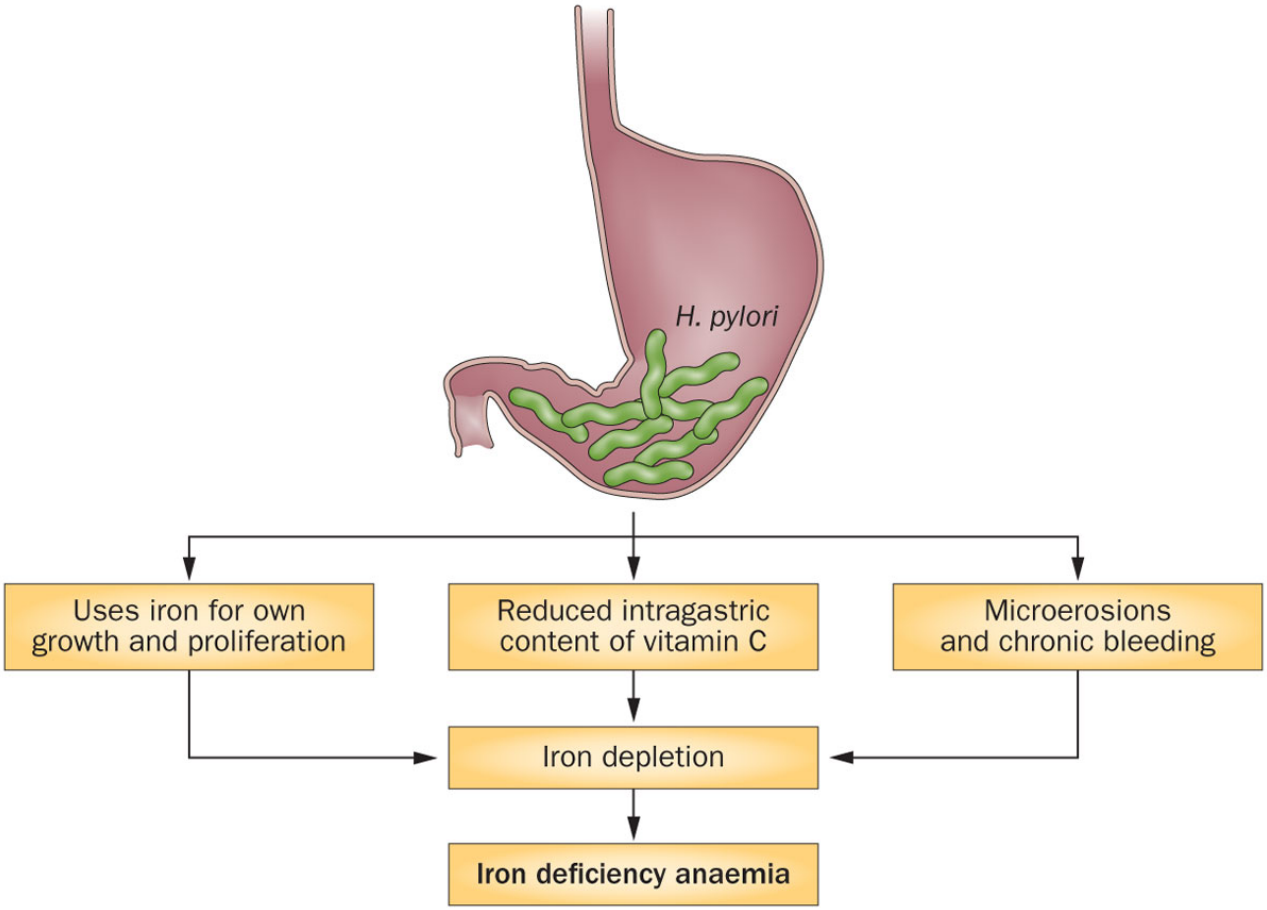
Malabsorption
HP infection, AAG, CD, IBD, drugs (PPI).

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



Franceschi, F. *et al.* Clinical effects of *Helicobacter pylori* outside the stomach *Nat. Rev. Gastroenterol. Hepatol.* 2013

nature REVIEWS GASTROENTEROLOGY & HEPATOLOGY

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

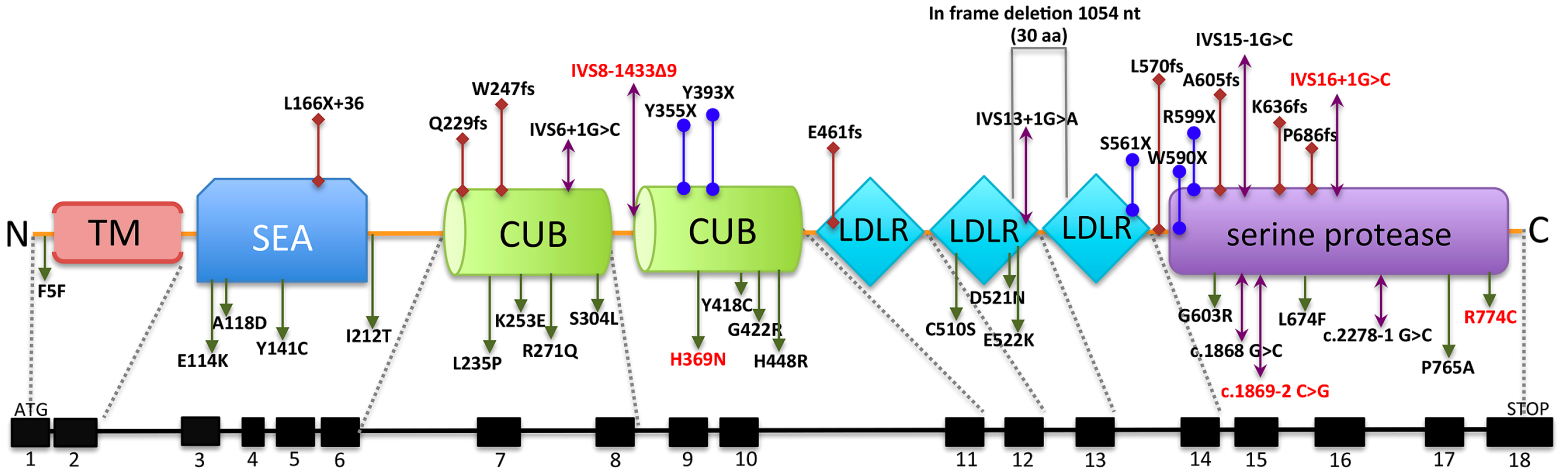
Rare recessive disorder due to *TMPRSS6* mutations

Iron deficiency anemia – normal/high hepcidin

Moderate anemia, severe microcytosis

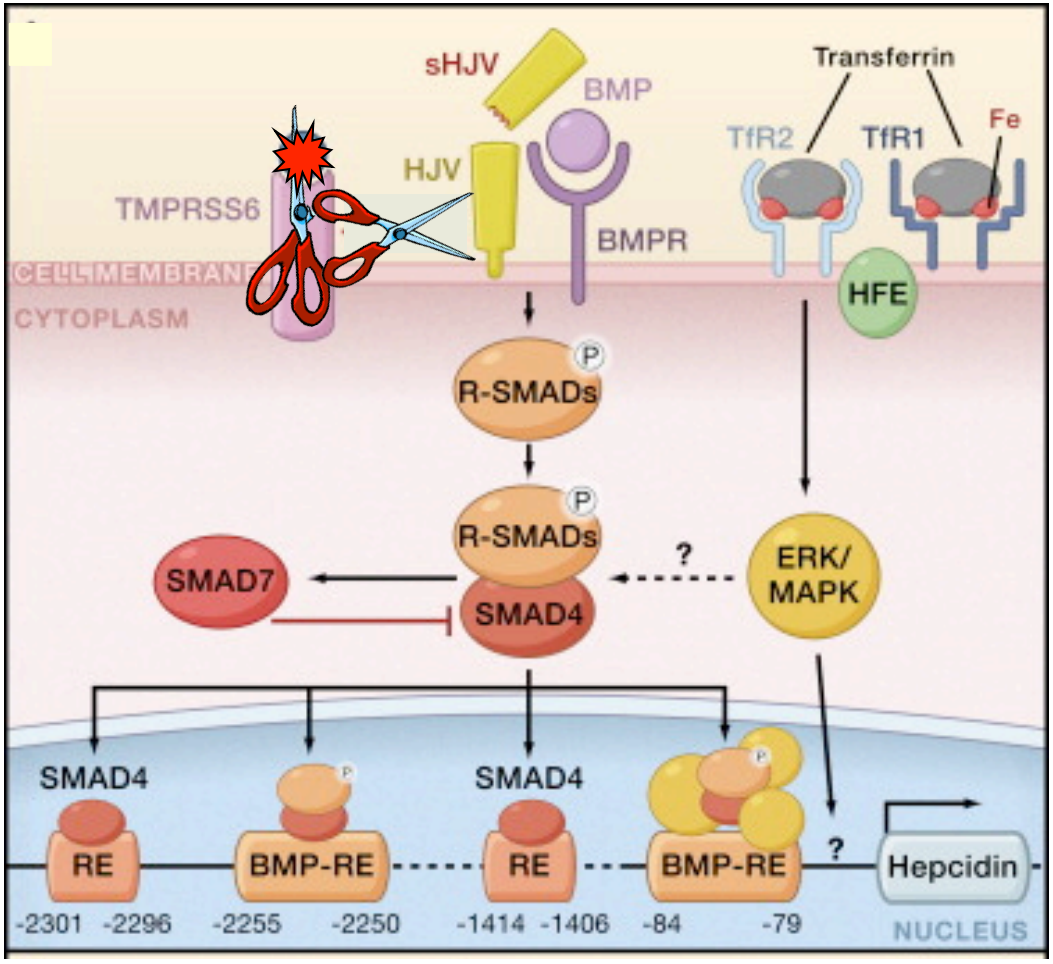
Very low transferrin saturation - Normal high ferritin

Refractory to oral and partially refractory to iv iron



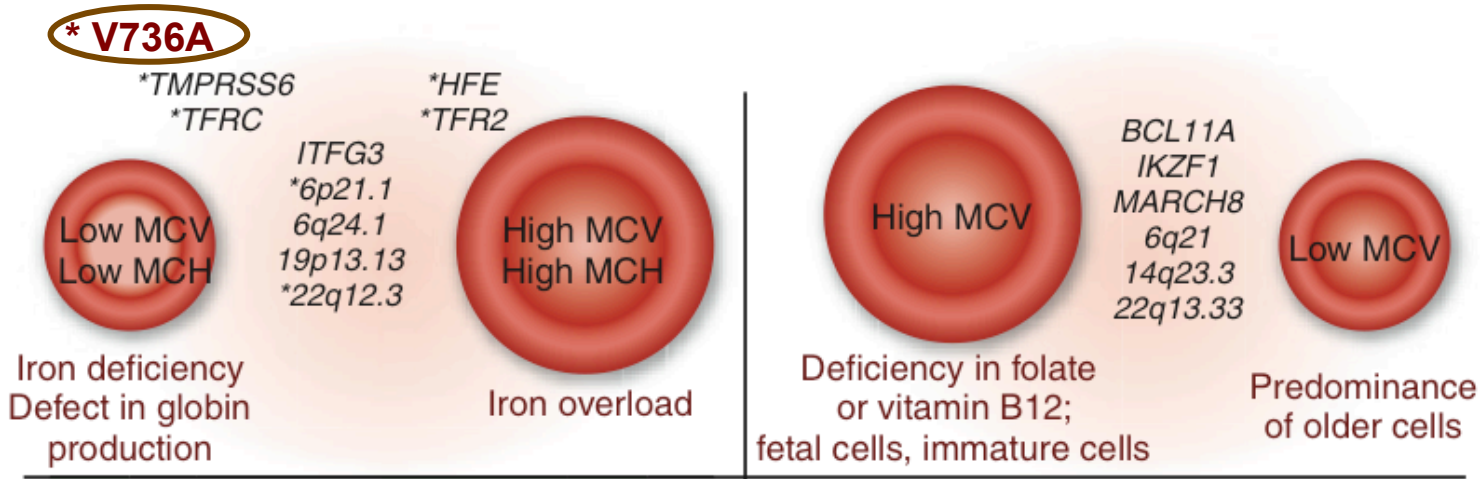
(Wang et al, Frontiers Pharmacol, 2015)

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?



(Andrews N, Nat Genet 2009)

Val736Ala influences red cell and iron traits *(Benjamin et al Nat Genet 2009)*

…..serum hepcidin levels *(Nai et al, Blood 2012)*

…..and shows inter-ethnic differences *(Gichohi et al, Genes Nutr 2015)*

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 BioIron 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 tes, 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)

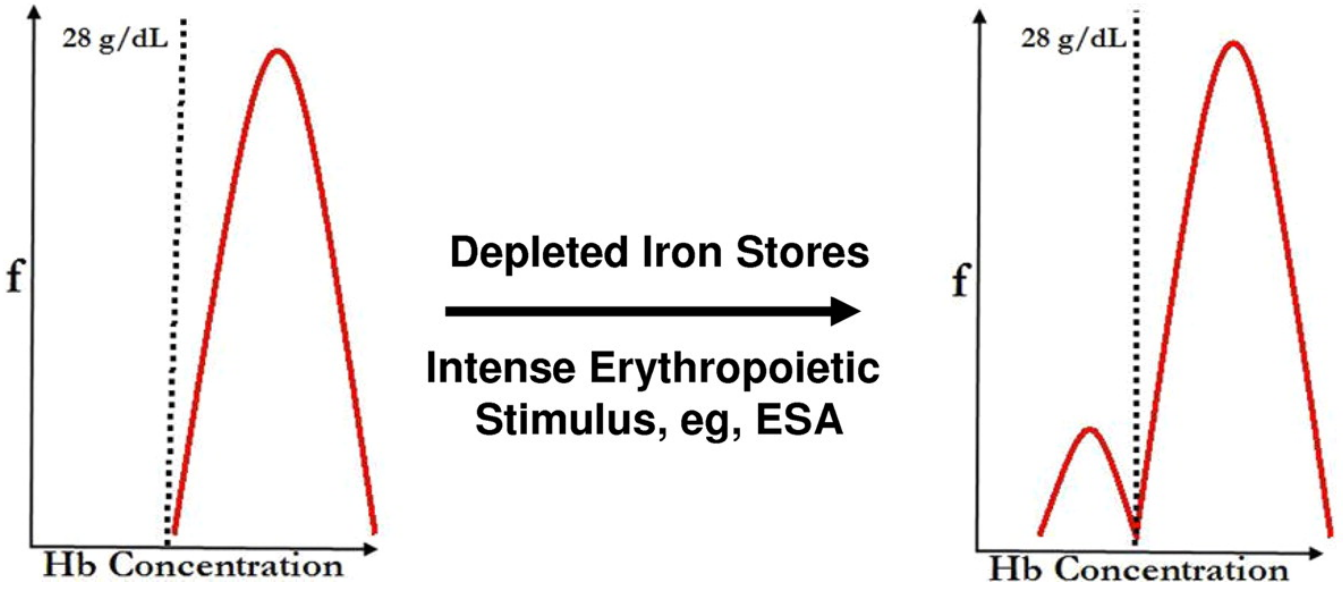
best-established variable for **FID:**
% HRC (percent hypochromic red cells):
6% cut off in CKD

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**



Lawrence Tim Goodnough et al. Blood 2010;116:4754-4761

THERAPY

IDA: oral iron supplementation. I

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

THERAPY

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

THERAPY

Improving oral iron dosing schedule

In non-anemic young women with ferritin ≤20µg/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

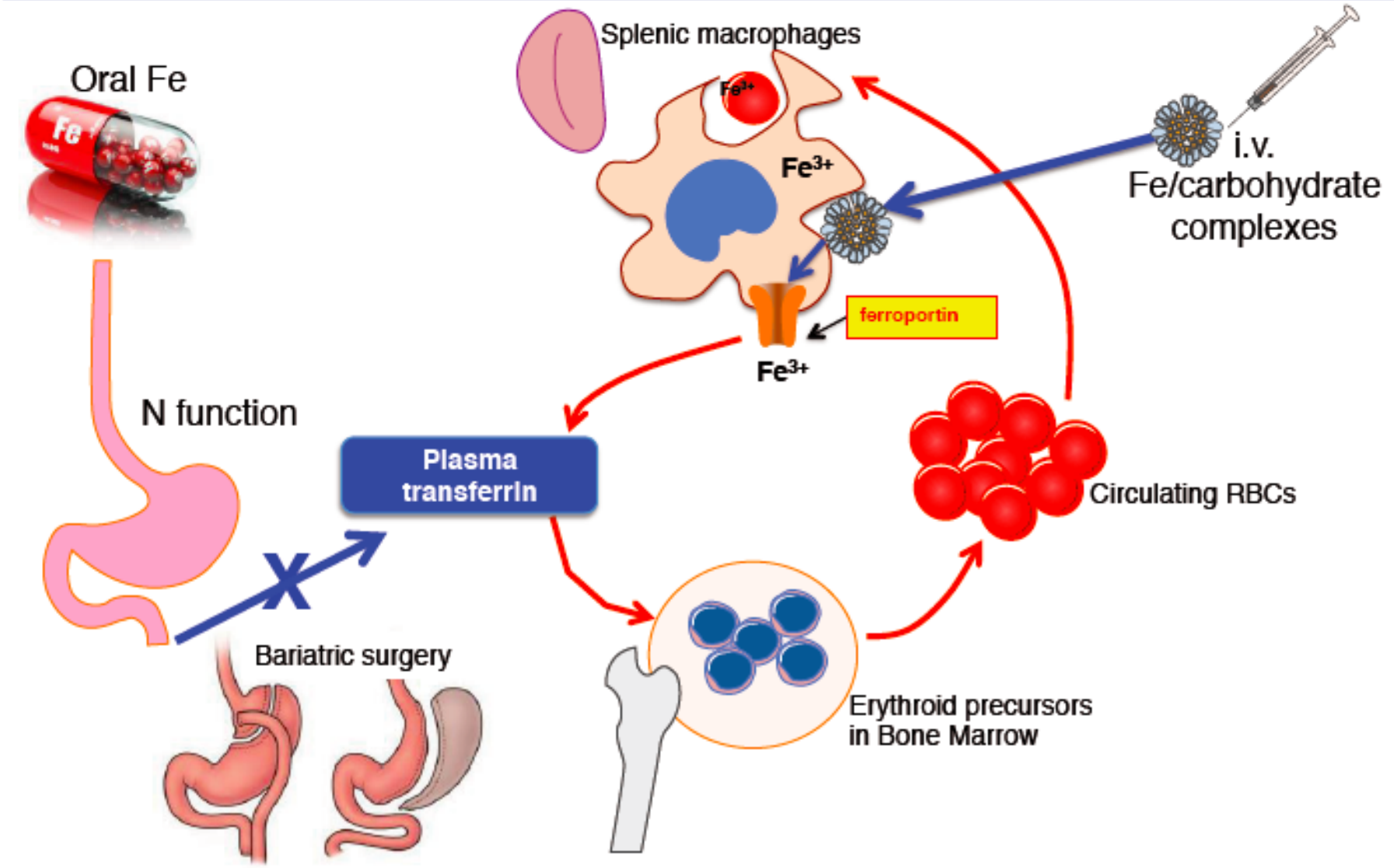
- Oral iron intolerance or refractoriness
- GI disorders (IBD, acute flares)
- Need for a quick recovery: eg severe anemia in pregnancy
- Chronic bleeding not manageable with oral iron
- ESA treatment in CKD
- Substitution for blood transfusions when not accepted by patient
- Genetic IRIDA

Parenteral iron therapy. II

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…….

Pharmacokinetic differences: oral *vs* i.v. iron



Intravenous iron preparations

Dose calculation, rapid effect (store repletion)

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

*) black box warning for hypersensitivity reactions

The issue of safety

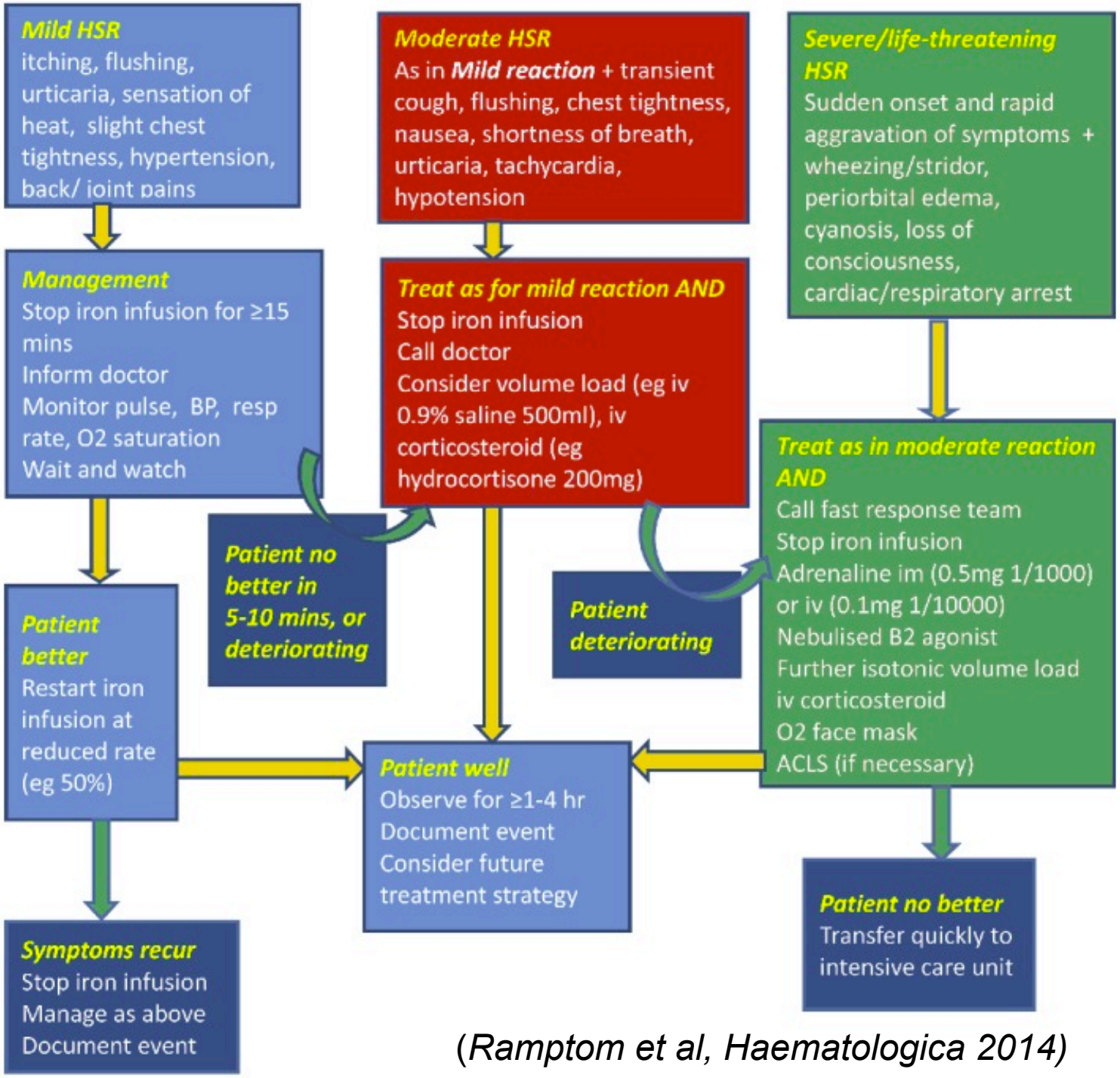
IV iron **is not** associated with increased risk of severe AE or infections in a meta-analysis of >10.000 patients

(Avni et al, Mayo Clin Proc 2015)

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



(*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

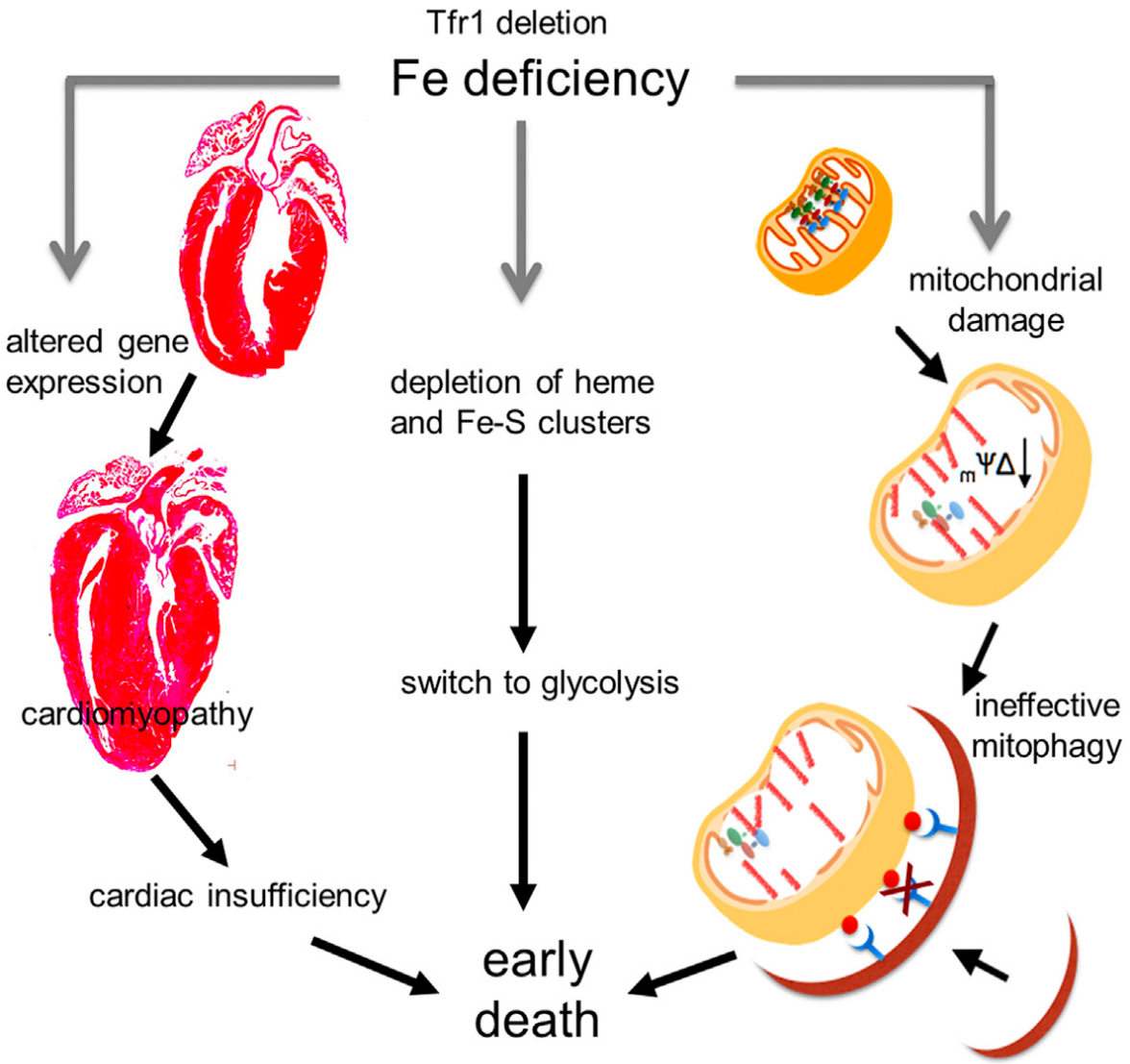
ID in heart failure reported about 37-50% using the "broad" definition:
Serum ferritin <100 ng/ml **or** <300 ng/ml **and** transferrin saturation <20%

(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 *Tfr1*$^{-/-}$ mice



A model for tissue ID in the absence of anemia? *(Xu et al., 2015, Cell Reports 13, 1–13)*

Thank you very much!

San Raffaele Hospital, Milano

Vita Salute University, Milano