Patient Blood Management

dalla teoria alla pratica

PATIENT BLOOD MANAGEMENT
ASST OVEST MILANESE

Fisiopatologia del metabolismo del ferro e implicazioni terapeutiche

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Iron: essential but potentially dangerous

easily exchange electrons
$Fe^{3+} \leftrightarrow Fe^{2+}$
useful redox properties

free radicals generation
($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \underline{OH\bullet}$)

key-component of enzymes crucial for O_2 transport and energy production (Hb, cytochromes…)

strict regulation of body iron content needed

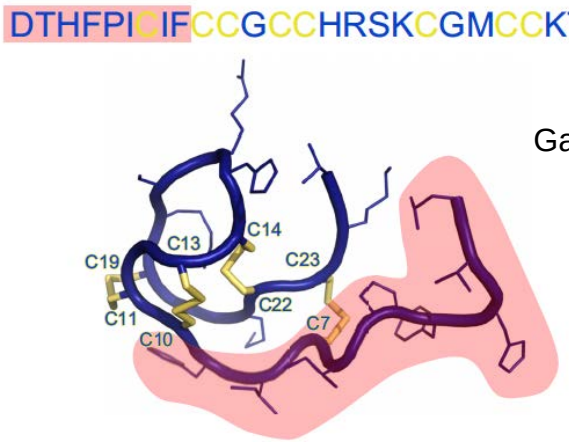
low
anemia
neuromuscolar impairment

excess
iron overload
toxic organ damage

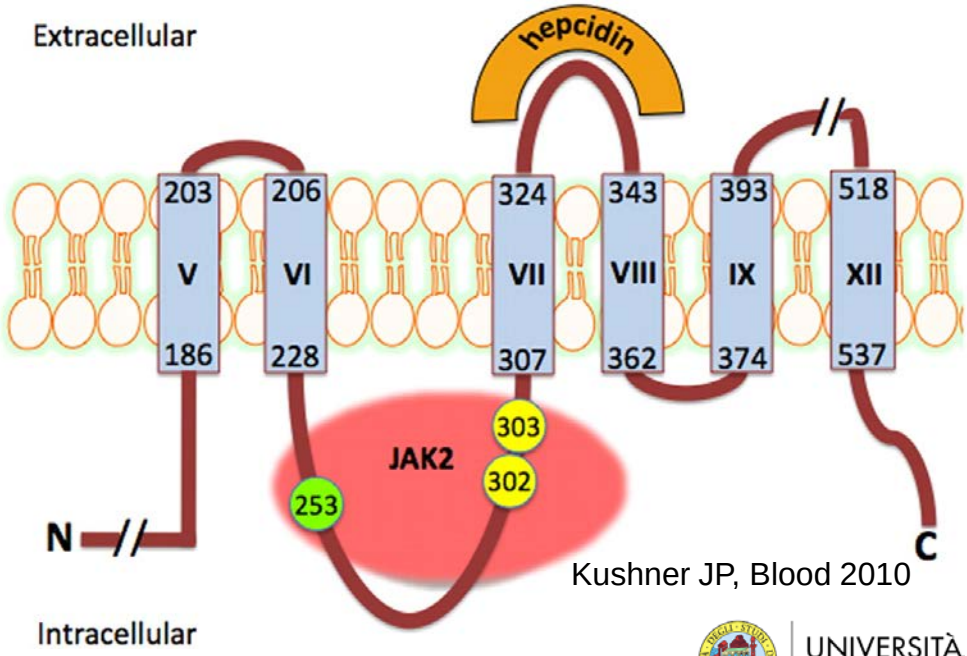
THE HEPCIDIN-FERROPORTIN AXIS

- **Hepcidin**: small peptide mainly produced by the **liver**

- interact with **its receptor** (**Ferroportin**, the only known iron exporter from the cells, ubiquitous but highly expressed in **duodenal cells**, **macrophages**, **hepatocytes**)



Ganz T, Physiol Rev 2013



Kushner JP, Blood 2010

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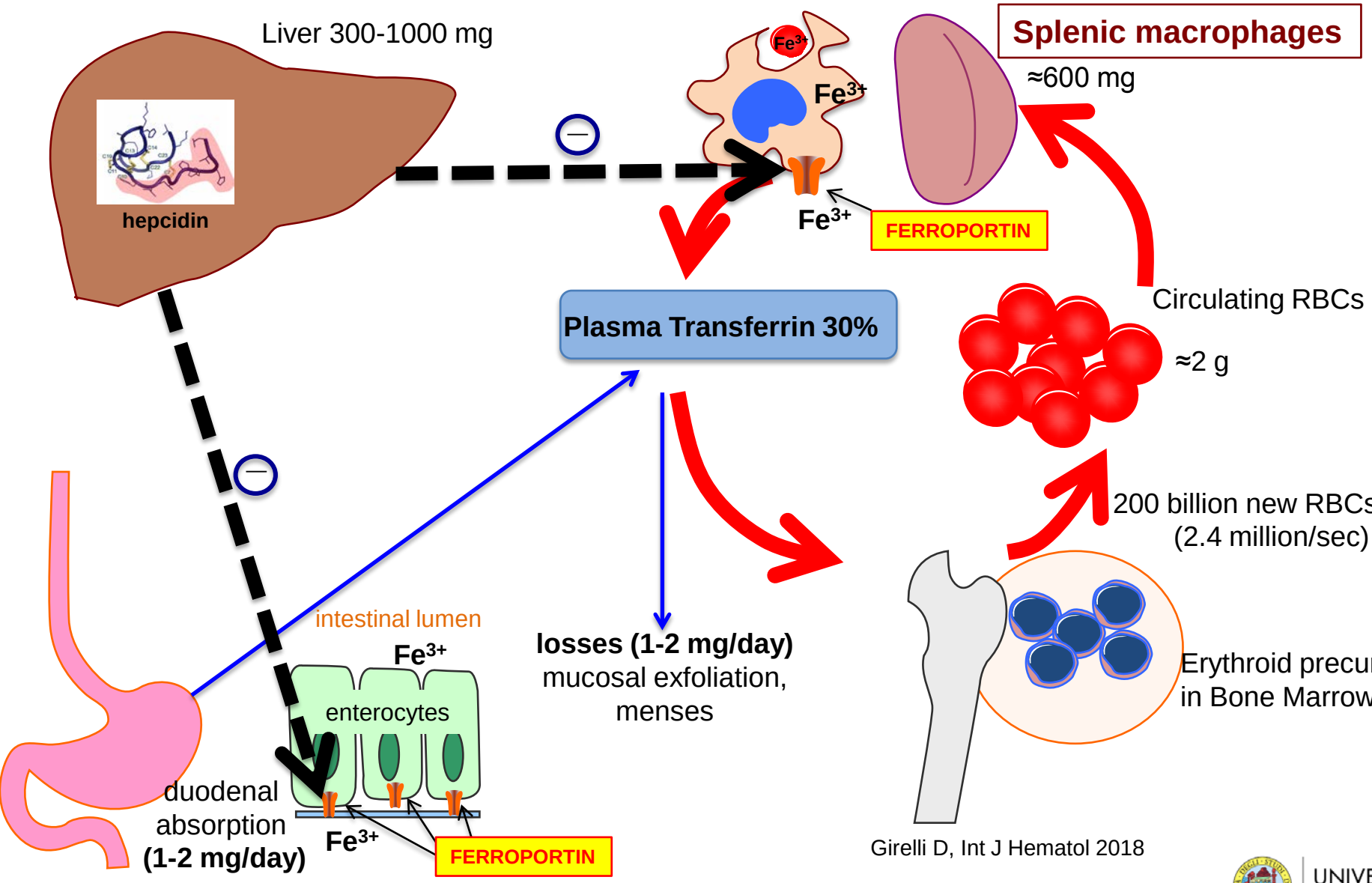
Systemic “ecological” iron homeostasis



Girelli D, Int J Hematol 2018

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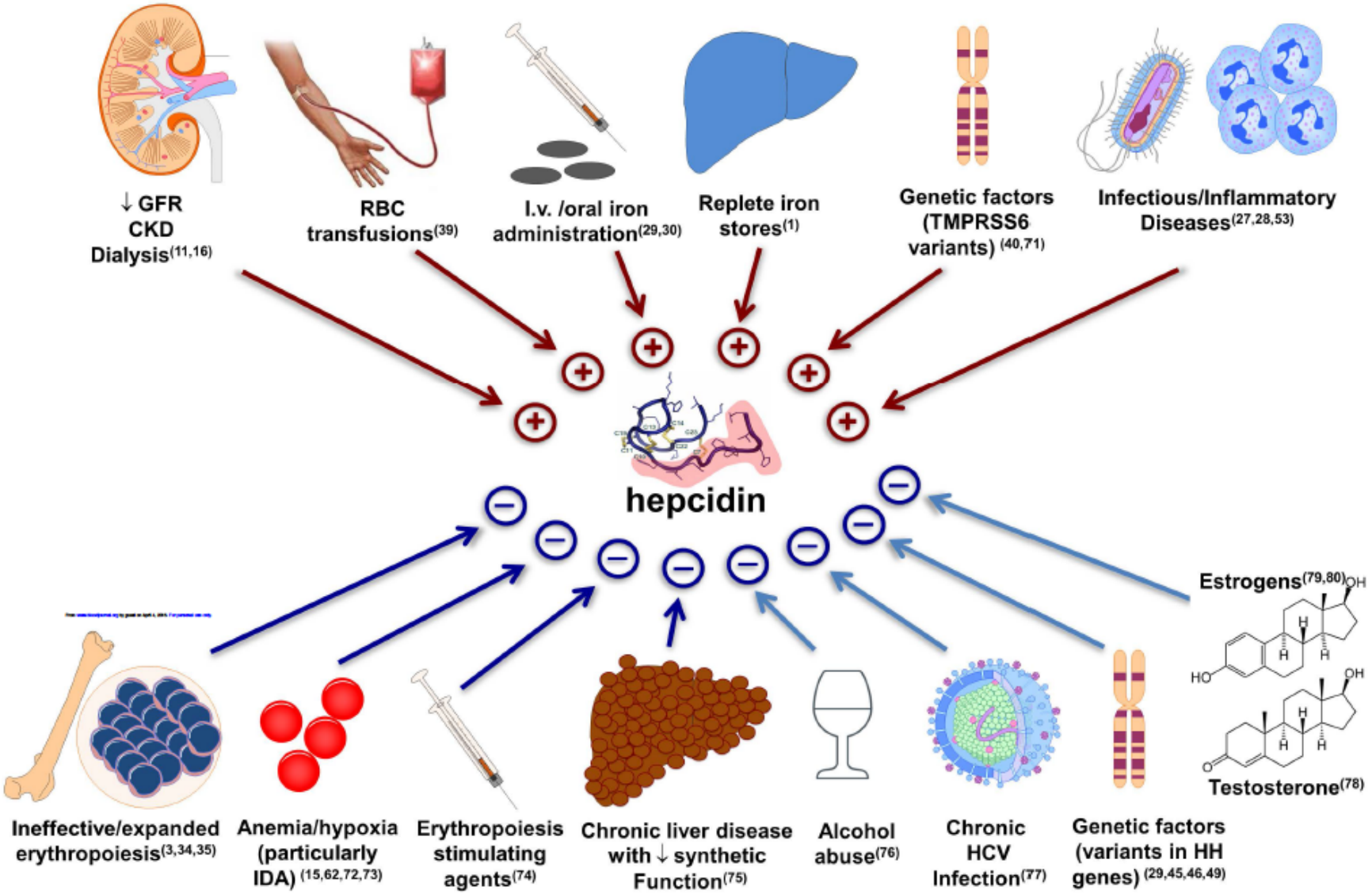
Clinical conditions influencing serum hepcidin levels



Girelli D, Blood 2016

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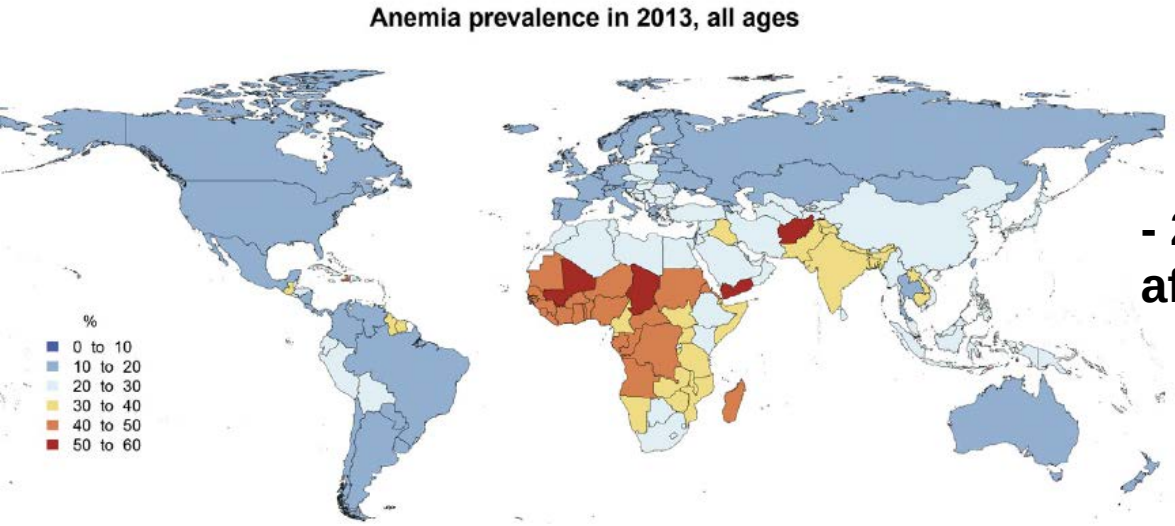
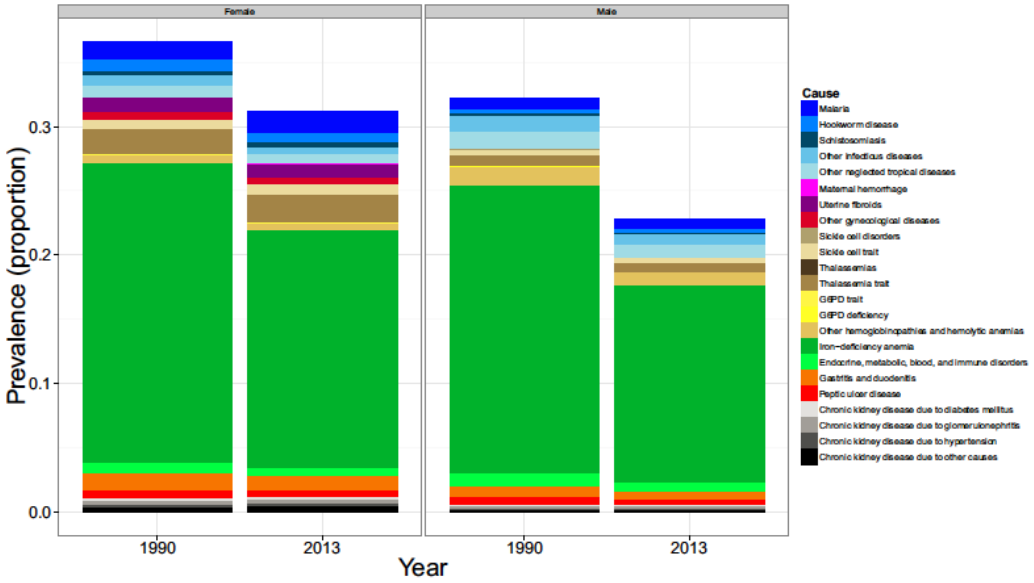
Anemia (and Iron Deficiency): one of most frequent disease worldwide





- 27% of world's population is affected by anemia

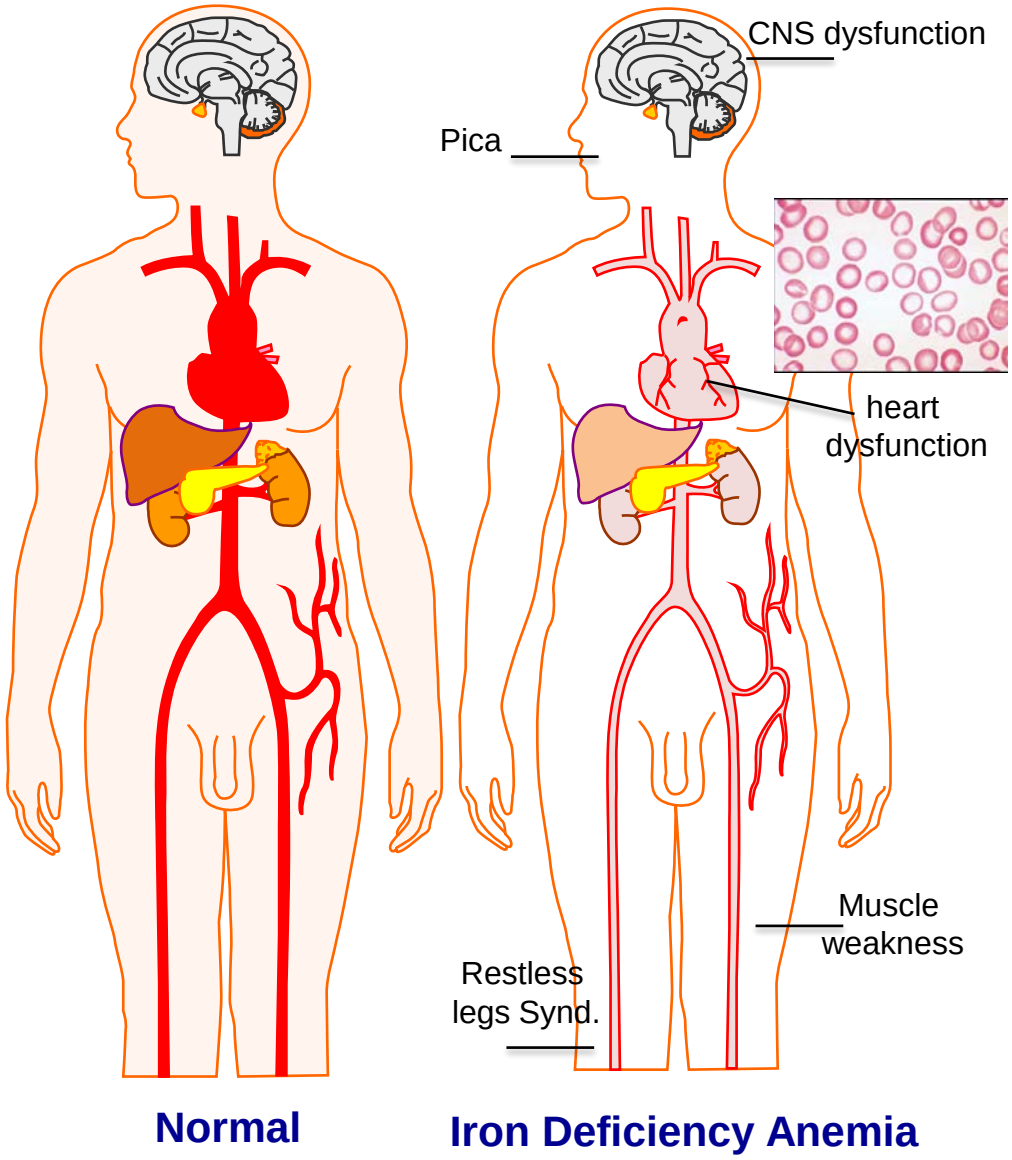
- Iron Deficiency ( ) = dominant cause (≥60%)

- Mainly due to socio-economic reasons

(but iron replacement therapy not always easy as it seems)

Kassebaum N, Hematol Oncol Clin N Am 2016

Oral iron therapy: the frontline of IDA treatment



Effective
Inexpensive

BUT
LESS THAN IDEAL:

- GI AEs (35-59%) → non-adherence common

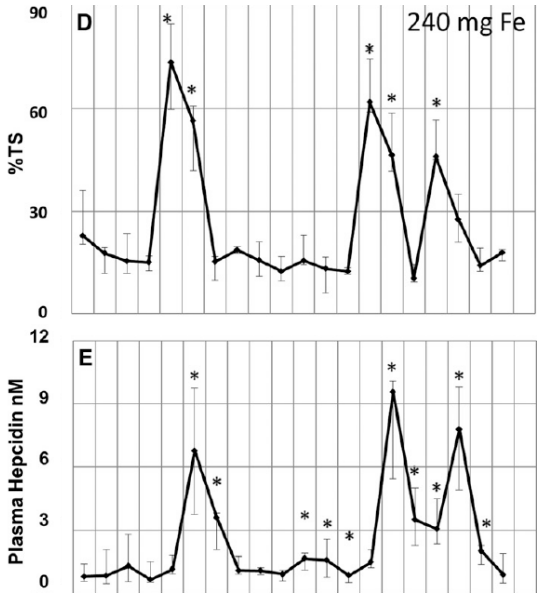
Regular Article

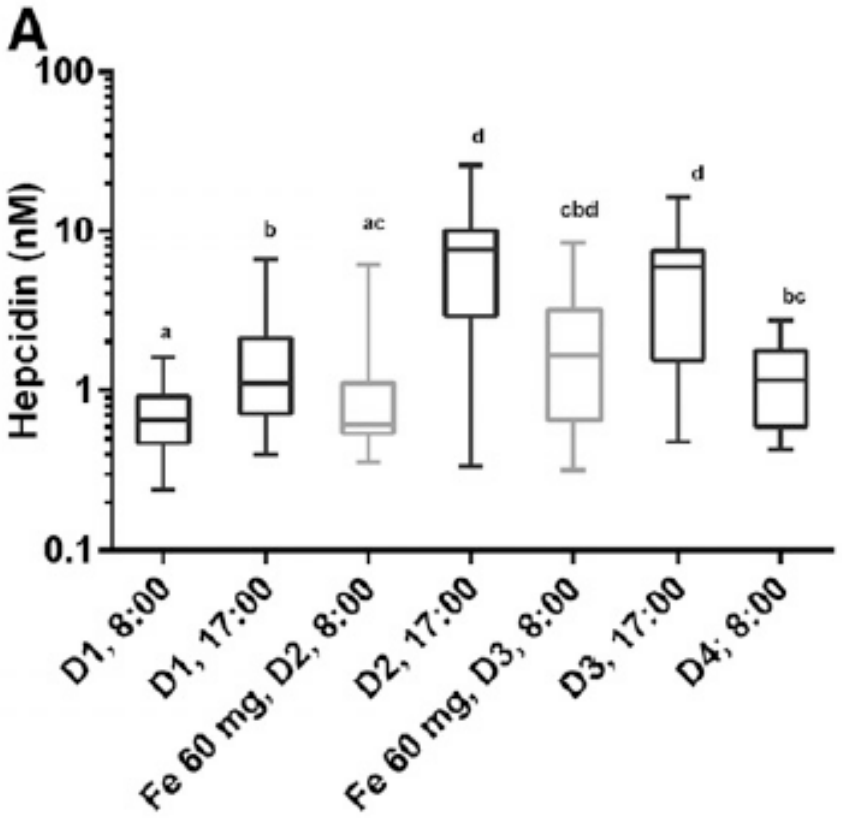
CLINICAL TRIALS AND OBSERVATIONS

Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women

Key Points

- Iron supplements at doses of 60 mg Fe as $FeSO_4$ or higher increase hepcidin for up to 24 hours and are associated with lower iron absorption on the following day.





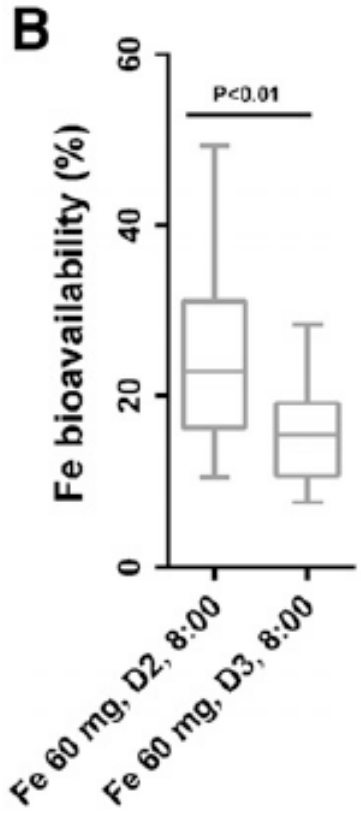
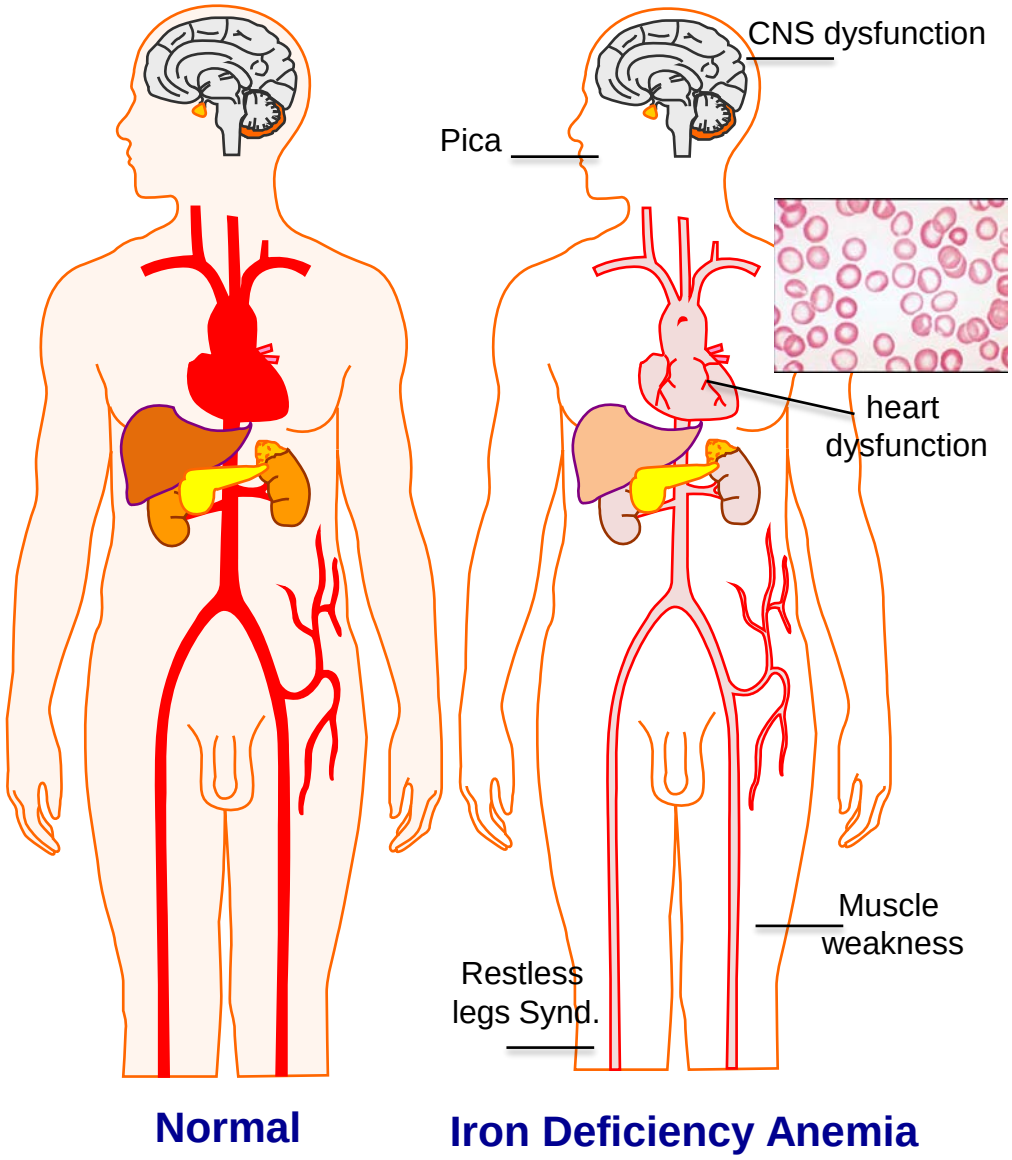


Figure 3. A supplemental iron dose of 60 mg Fe results in an increase in hepcidin after 24 hours and in a decreased iron absorption from the consecutive dose

Moretti D, Blood 2015

Oral iron therapy: the frontline of IDA treatment



Effective
Inexpensive

BUT
LESS THAN IDEAL:

- GI AEs (35-59%) → non-adherence common
- **Need of prolonged administration (3 months for replacing iron stores)**
- **Poorly absorbed in certain conditions**

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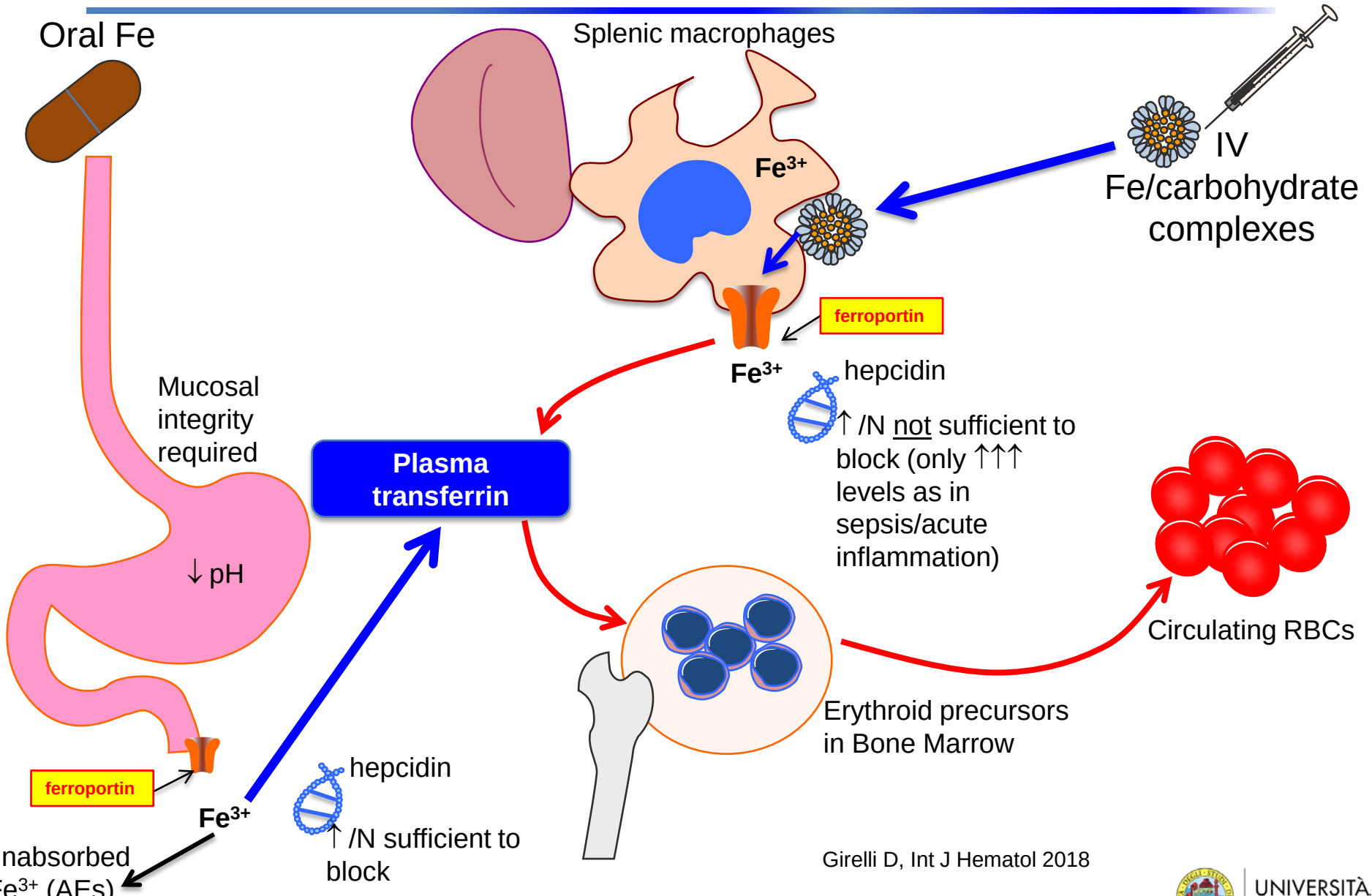
Different pharmacokinetic between oral and IV iron, revisited in the hepcidin era



Girelli D, Int J Hematol 2018

Established indications to i.v. iron

condition	examples/comments
Failure of oral iron	non-adherence, AEs
Malabsorption	**celiac** disease, **gastritis** (atrophic, autoimmune, Hp+), bariatric surgery, genetic **IRIDA**
Severe IDA	generally accepted threshold: **Hb < 8 g/dl**
End-stage Chronic Kidney Disease (CKD)	**(+ ESAs)**
Inflammatory Bowel Diseases	IDA in **active** disease
Pregnancy	**severe** IDA in **II-III trimester**
Heart Failure (HF)*	Systolic HF (LVEF ≤ 45%)

*Iron deficiency (even without anemia): serum ferritin <100 µg/L or <300 µg/L, if TSAT ≤20%

Camaschella C, NEJM 2015 (adapted)

i.v. iron: historical (and chemical perspective)

History of i.v. iron

1947: Fe-Saccharide

1954: Fe-Dextran(HMW)

risk

1991: Fe-Dextran(LMW)

risk

1999: Fe-Gluconate

2000: Fe-Sucrose

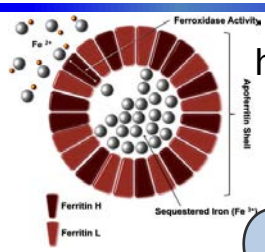
"New"

>2009: Ferumoxytol

Fe-isomaltoside

Fe-Carboymaltose

risk



human ferritin

Fe^{3+} oxyhydroxide

(polynuclear **CORE**)

8-25 nm

carbohydrate shell
(stabilizer)

unique for each compound

Key differences in:
- ✓ **Immunogenicity**
- ✓ **Strength of stabilization**

Girelli D, Int J Hematol 2018

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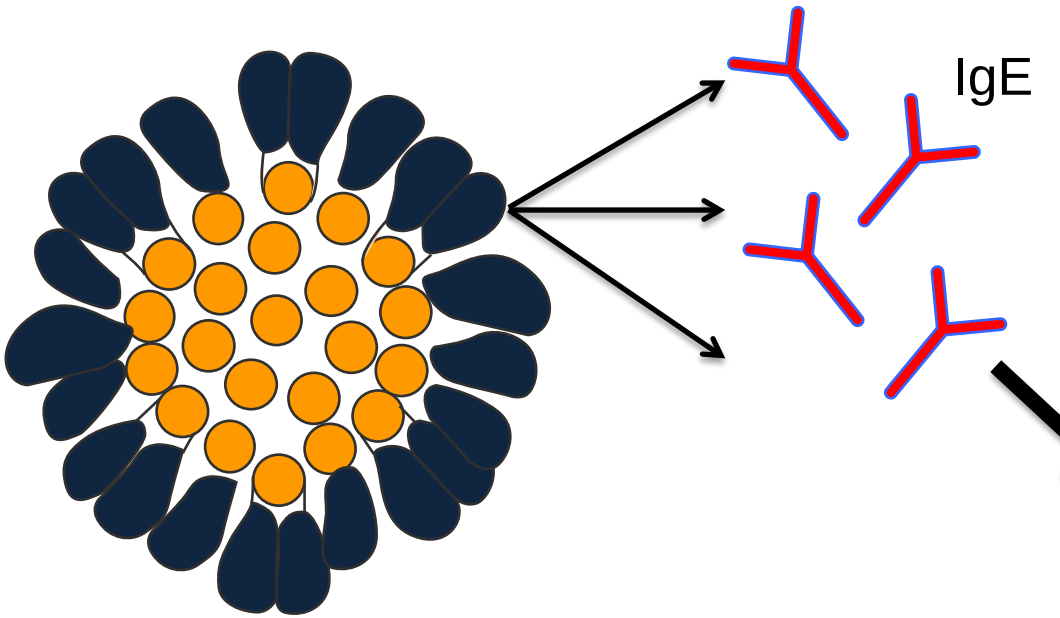
HMW dextran: the only truly immunogenic i.v. iron drug



Anaphylaxis

1954: Fe-Dextran(HMW)

Retrospective analysis of > 30 million doses of i.v. iron:

virtually <u>all</u> <u>life-threatening</u> AEs by i.v. iron are due to HMW-dextran

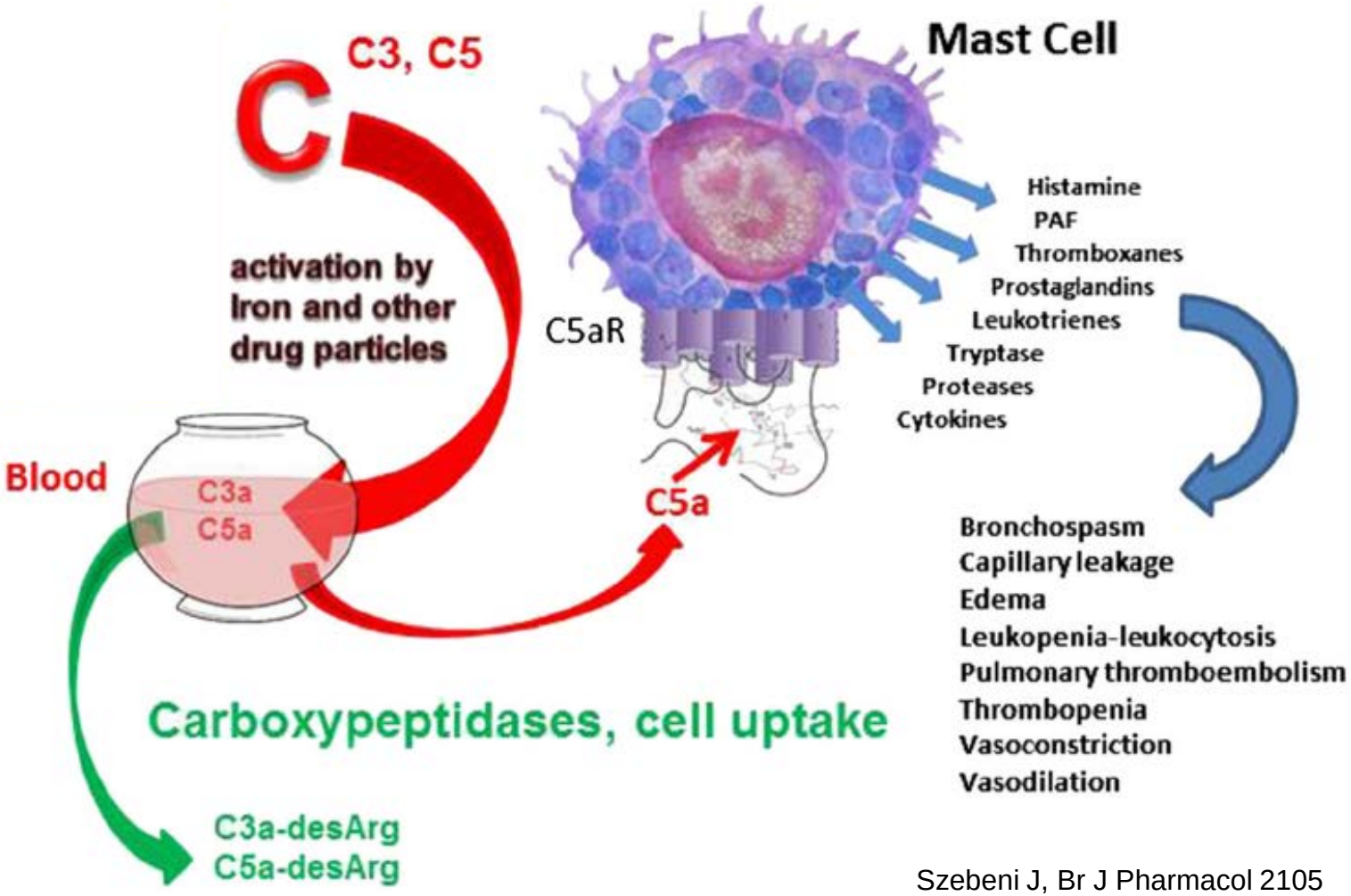
Certhow GM, Nephrol Dial Transplant 2006

↓

definitively removed form the market

Other mechanism(s) for i.v. iron SAEs

Complement activation-related pseudo-allergy



Szebeni J, Br J Pharmacol 2105

Meta-analysis of 103 trials using non-HMW-dextran iron

The Safety of Intravenous Iron Preparations: Systematic Review and Meta-analysis

MAYO CLINIC

Table 2. Severe adverse events reported with IV iron relative to any comparator (placebo, no iron, oral iron)

Severe adverse events	RR (95%)
All iron studies	1.04 (0.93-1.17)
SAE by compound	
Ferric carboxymaltose	0.82 (0.64-1.06)
Ferric gluconate	1.12 (0.96-1.30)
Ferumoxytol	1.04 (0.71-1.53)
Iron dextran (LMW)	1.05 (0.77-1.45)
Iron isomaltose/polymaltose	1.09 (0.43-2.80)
Iron sucrose	1.33 (0.96-1.83)
Infusion reactions	2.47 (1.43-4.28)*
Mortality	1.06 (0.81-1.39)
Infections	1.17 (0.83-1.65)
Gastrointestinal	0.55 (0.51-0.61)*

No fatal reactions or anaphylaxis reported in 103 trials composing 10 390 treated with IV iron. Adapted from Avni et al[26] with permission.
*Significant.

Serious AEs **can occur with any preparation** but are no more frequent than comparators, and **extremely rare <1:200,000 doses** (major transfusional reactions = 1:21,000).

Only **minor infusion reactions** consistently reported

Avni T, Mayo Clin Proc 2015

Minor infusion reactions

5 min, no intervention

Auerbach M, Hematology 2016

≈1:200

Flushing ± myalgias (chest or lumbar) ± nausea ± nasal congestion without sustained hypotension

Almost invariably self-limited

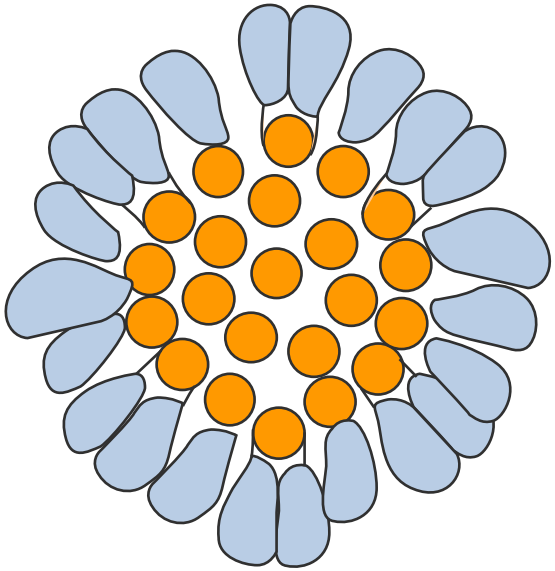
Can be aggravated by treatment with antihistamines (do not treat)

Do not recur with re-challenge

Macdougall IC, Kidney Int 2016

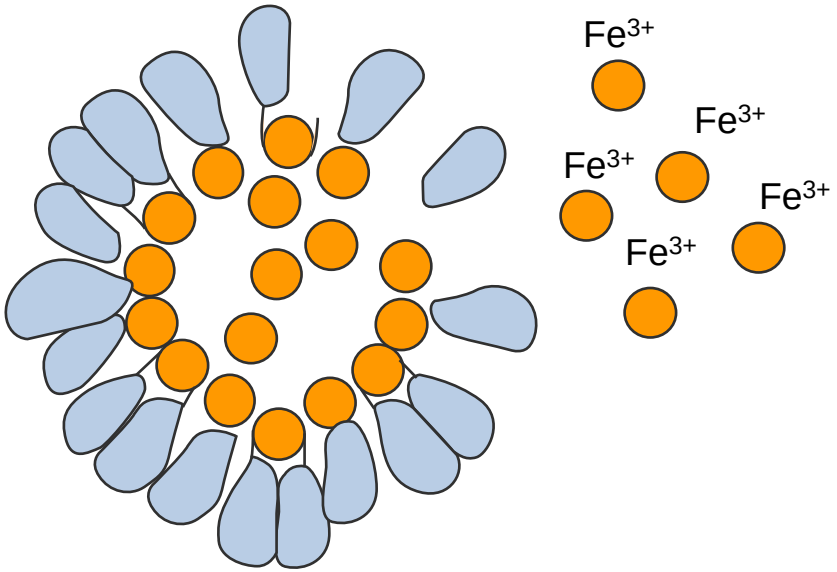
Stability of i.v. iron/complex is crucial for infusion reactions

Stable complex



Stability of i.v. iron/complex is crucial for infusion reactions

Unstable complex



Release of free iron in plasma before phagocytosis

Acute hemodynamic toxicity

Amount of released free iron is dose-dependent → poor stability limits the total dose of elemental iron that can be safely administered per single infusion

Erythema
Flushing
Hypotension
(not sustained)

Auerbach M, Hematology 2016

Currently used i.v. iron preparations

Drug	Brand name	Stability	Maximum single dose	Total replacement dose in single infusion (1-1,5 g)	Minimun administration time
Fe-Gluconate 	Ferlixit®	low	125 mg	no (repeated access needed)	30-60 min
Fe-Sucrose 	Venofer®	low-moderate	200 mg	no (idem)	30 min

Ganzoni's formula and simplified schemes

Ganzoni formula:

Total body iron deficit/cumulative iron dose (mg) =

body weight* (kg) x (target Hb – actual Hb in g/L) x 0.24** + iron depot (mg)***

*Use ideal body weight in overweight patients. If underweight, use actual body weight

**The factor 0.24= 0.0034 x 0.07 x 1,000:

For this calculation the iron content of haemoglobin = 0.34%,

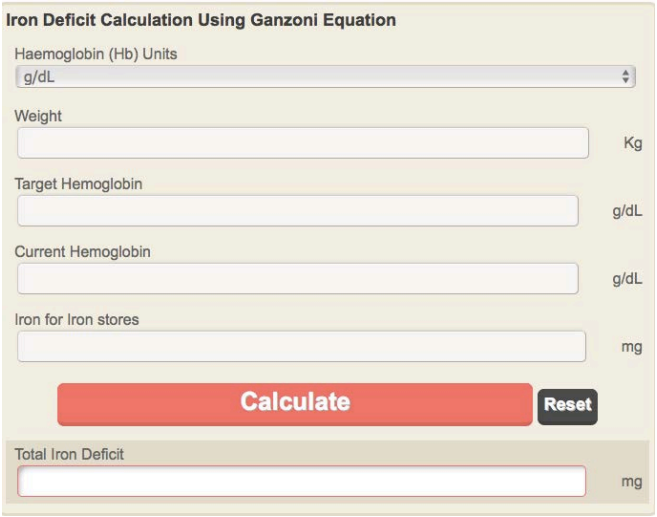
blood volume = 7% of the bodyweight, and

1,000 is the conversion from g to mg

***Iron depot:

<35 kg body weight: iron depot = 15 mg/kg body weight

≥35 kg body weight: iron depot = 500 mg



https://www.easycalculation.com/medical/iron-deficit-calculator.php

For example a 70 kg female with Hb 80 g/L has an iron deficit of:

70 x (150 – 80) x 0.24 + 500 = 1676 mg i.e. approx. 1700 mg

When using FCM →

Estimated cumulative iron dose

Hb g/L	Body weight 35 kg to <70 kg*	Body weight ≥70 kg*
<100 g/L	1,500 mg	2,000 mg
≥100 g/L	1,000 mg	1,500 mg

*Use ideal body weight in overweight patients. If underweight, use actual body weight

validated on Evstatiev R, Gastroenterology 2011

Extended indications for i.v. iron

condition	examples/comments
ID/IDA in elderly	If comorbidities/polypharmacy (including PPI) prevent adherence to (or effectiveness of) long-term oral iron
Perioperative anemia	Patient Blood Management strategies to prevent RBCs transfusions
IDA in cancer	± ESAs
Restless leg syndrome*	
Mountain Sickness*	(prevention)
Heavy Uterine Bleeding*	

* Auerbach M, Hematology 2016 (adapted)

Take-home messages

- ✓ **New (“third generation”) i.v. iron drugs are characterized by higher stability of the carbohydrate shell and by improved safety profiles**
- ✓ **They allow easy and convenient schedules, with complete replacement of iron in 1 or 2 administrations.**
- ✓ **This drives a paradigm shift in the treatment of one of the most common disease worldwide, with extending indications (to be confirmed).**

The Verona Interdisciplinary Group on Iron Disorders

Participants Units

1. Internal Medicine
2. Clinical Chemistry & Molecular Biology
3. Blood Bank / Transfusional Service
4. Radiology
5. Pathology
6. Gastroenterology

Fabiana Busti, Paola Capelli, Annalisa Castagna, Michela Corbella, Massimo Delledonne, Giorgio Gandini, Alejandro Giorgetti, Giacomo Marchi, Oliviero Olivieri, Roberto Pozzi-Mucelli, Monica Rizzi, Alice Vianello, Luciano Xumerle.

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