Approccio pratico all'anziano anemico

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Summary

1) Anemia in the elderly: definition, prevalence, etiology and prognostic implications.

2) The central role of iron (and hepcidin) in the two most frequent forms of anemia in elderly: iron deficiency anemia (IDA) and the “anemia of chronic diseases” (ACD).

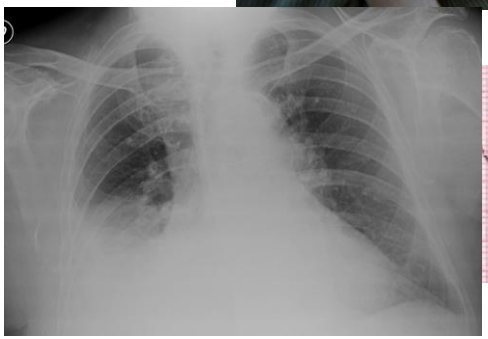
3) Possible novel approaches to diagnosis and management of IDA-ACD in the elderly in light of the recent discoveries on iron metabolism.

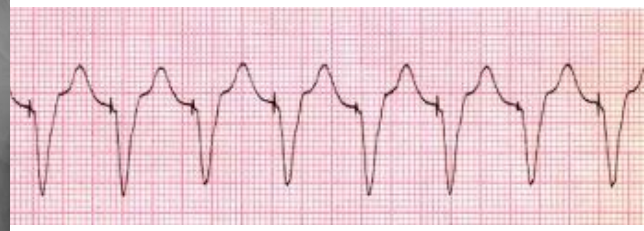
Caso Clinico

G.R., anni 83, in P.S. per dispnea.

APP: dimesso 30 gg. prima per scompenso cardiaco.

APR: cardiopatia ischemico-ipertensiva in compenso labile, portatore di PM, T2DM, dislipidemia, aterosclerosi carotidea non critica, artrosi polidistrettuale, ipertrofia prostatica.





In P.S.: Sat O2 89%, TnT 0.16 ng/mL, NT-pro-BNP 3150 pg/mL, PCR < 3 mg/L, Hb 11.9 g/dL, MCV 88 fL, GB 9000/mmc, PLTs 151000/mmc, creatinina 1.3 mg/dL, Na 130 mEq/L, K 3.1 mEq/L.

A matter of debate…

Anemia of elderly → **Hb < 12 g/dL in both sexes** (Andrès E, *Geriatr Gerontol Int* 2013) **instead of classic WHO criteria**

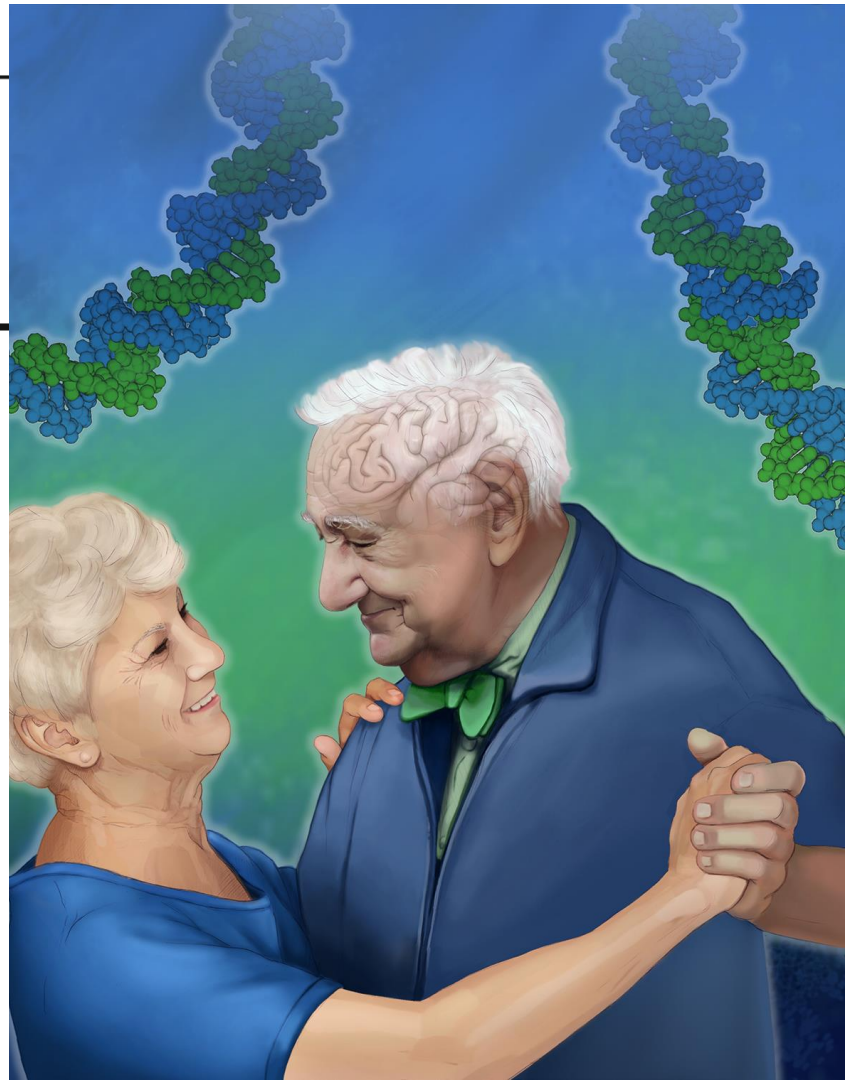
or…

Anemia in elderly? → ***Suggested*** **optimal Hb values to avoid hospitalization and mortality: 14-17 g/dL in males, 13-15 g/dL in females** (Zakai NA, *Arch Intern Med* 2005; Culleton BF, *Blood* 2006)

"Wellderly" subjects are not anemic

Table 3 Haematochemical parameters of the GEHA Italian 90+ siblings

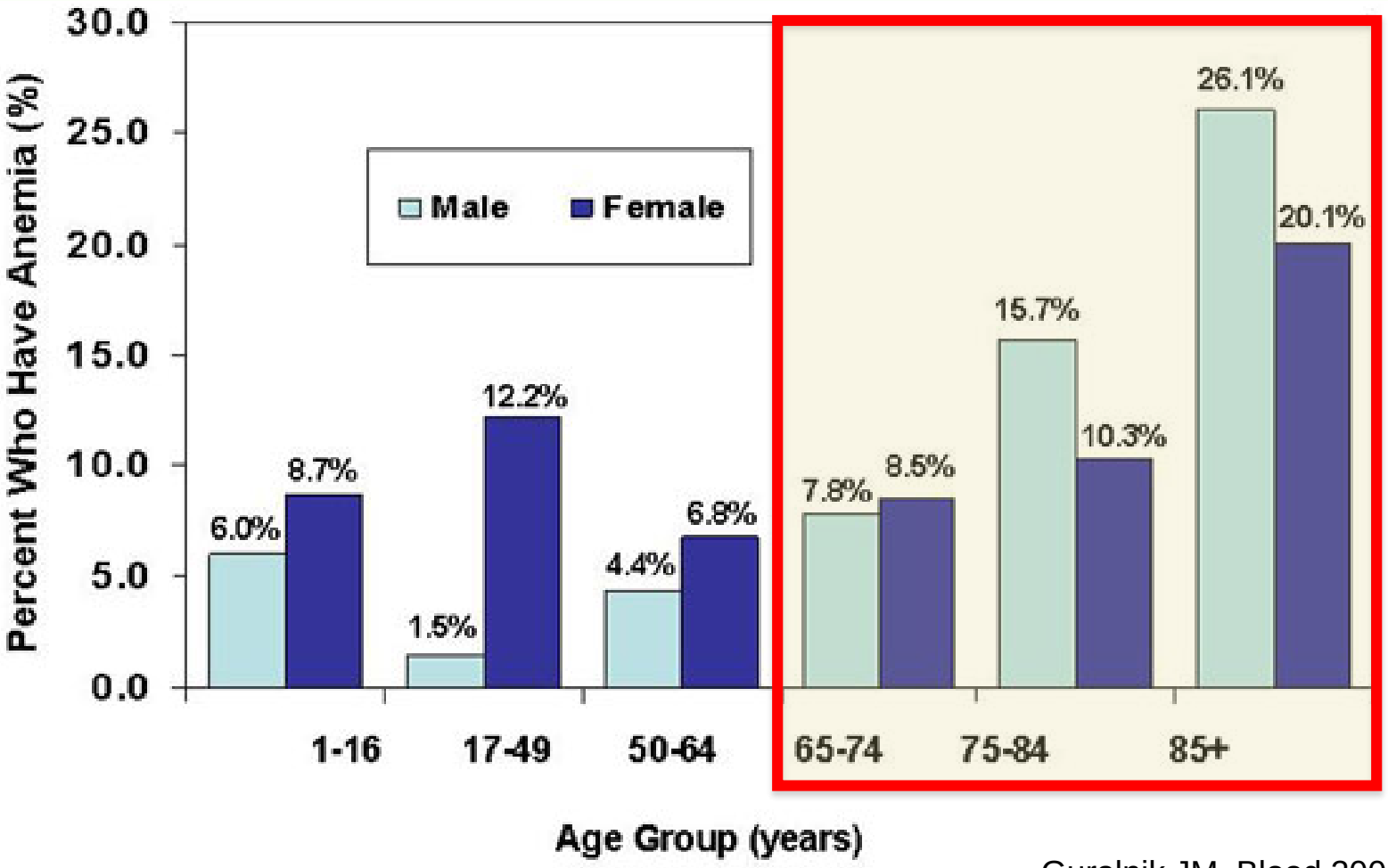
	Recruitment centre	Bologna	
	90+ Siblings	n=440	
Haemocytometric results	Reference values	Mean	SD
Males—red cells count (10^6/ml)	M: 4.50–6.10	4.5	0.5
Females—red cells count (10^6/ml)	F: 4.20–5.40	4.4	0.5
Males—haemoglobin (g/dl)	M: 13.0–16.5	13.6	1.6
Females—haemoglobin (g/dl)	F: 12.0–15.0	12.8	1.5
Males—haematocrit (%)	M: 42.0–52.0	40.8	4.8
Females—haematocrit (%)	F: 37.0–47.0	39.0	4.3
MCV (fl)	80.0–96.0	89.4	5.7
Leukocytes (10^3/ml)	4.20–9.0	6.5	2.8
Lymphocytes (%)	19.0–48.0	27.3	9.1
Monocytes (%)	3.0–9.0	5.9	1.6
Neutrophils (%)	40.0–74.0	61.2	10
Eosinophils (%)	0.0–6.0	3.1	2.1
Basophiles (%)	0.0–1.5	0.5	0.3
Platelets (10^3/ml)	150–380	243.3	77.4



Cevenini E, Age 2014

Anemia is common in the elderly

Third US National Health and Nutrition Examination Survey (NHANES)



Guralnik JM, Blood 2004

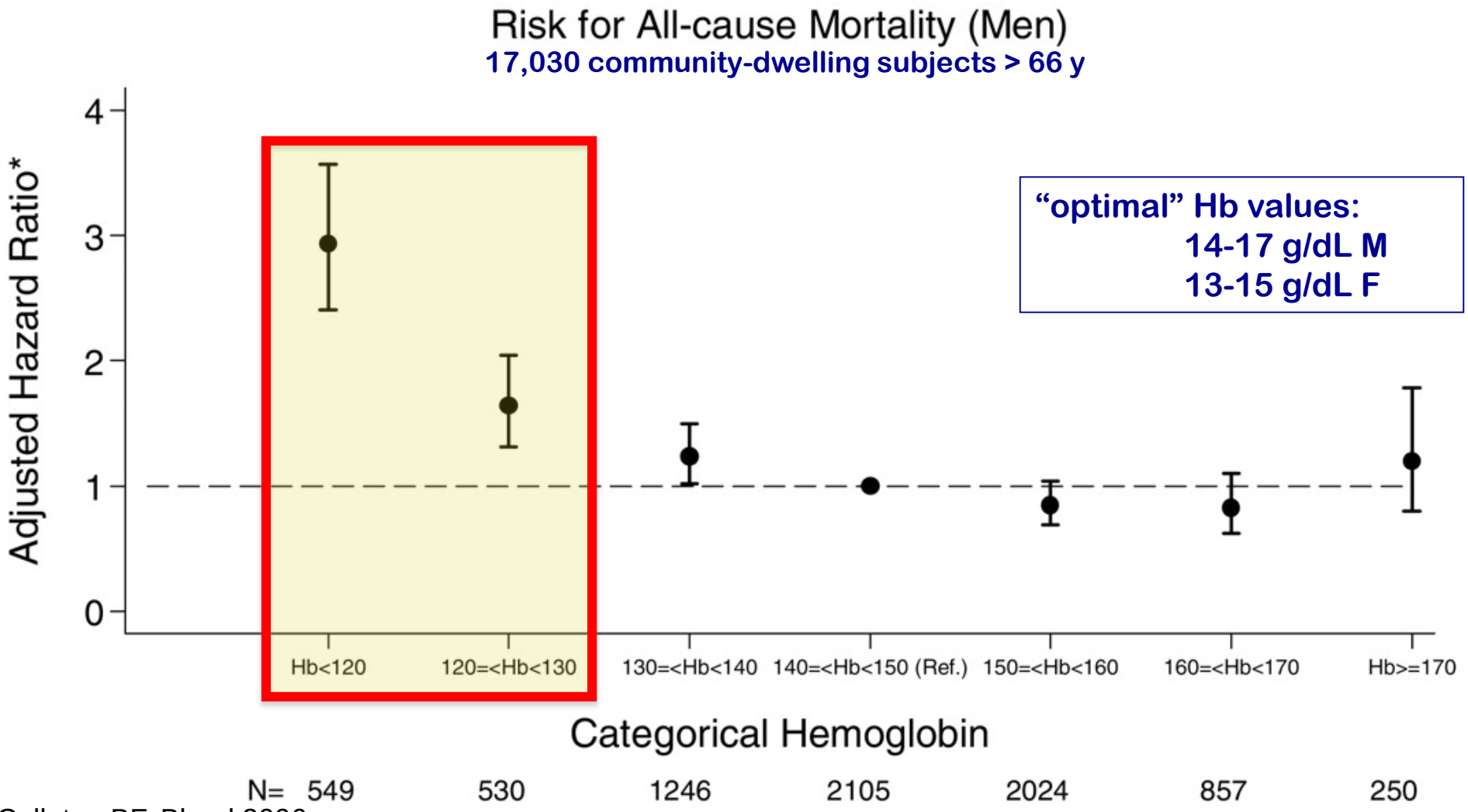
Impact of anemia in the frail elderly

Independent association with:

- ✓ **decreased physical performance**
  Pennix BW, Am J Med 2003
- ✓ **increased number of falls**
  Pennix BW, J Am Geriatr Soc 2002
- ✓ **increased dementia**
  Culleton BF, Blood 2006
- ✓ **increased hospitalization**
  Culleton BF, Blood 2006
- ✓ **increased mortality**
  Kikuchi M, J Am Geriatr Soc 2001 Zakai NA, Arch Intern Med 2005

Torpy JM, JAMA 2006

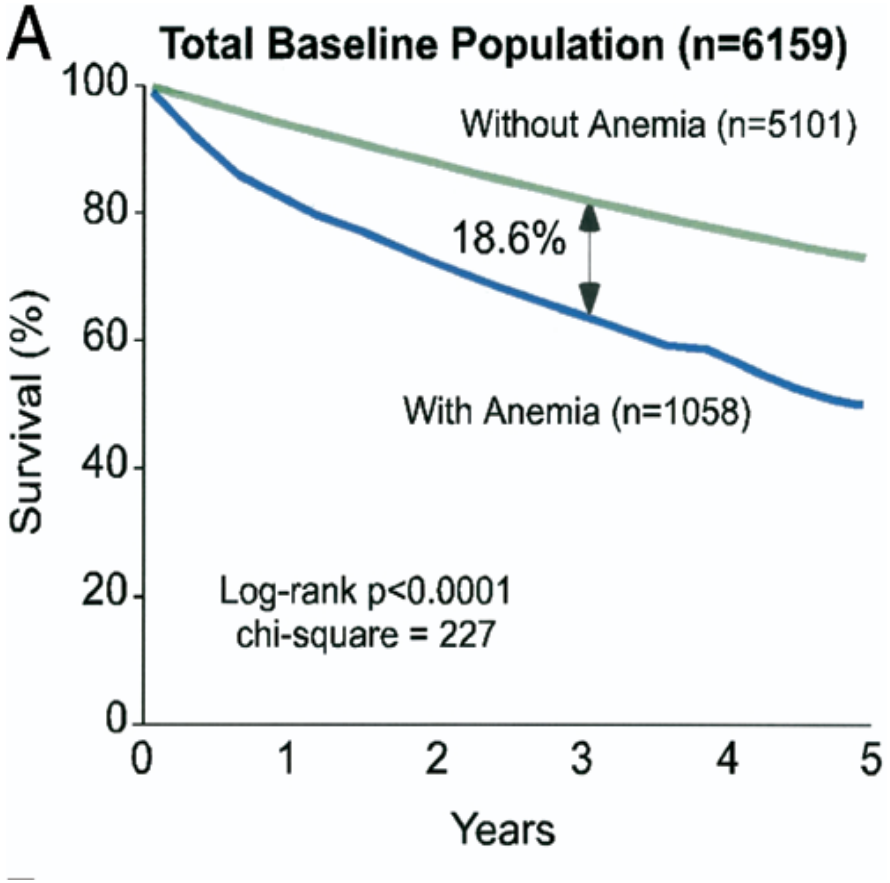
Impact of anemia on hospitalization and mortality in older adults

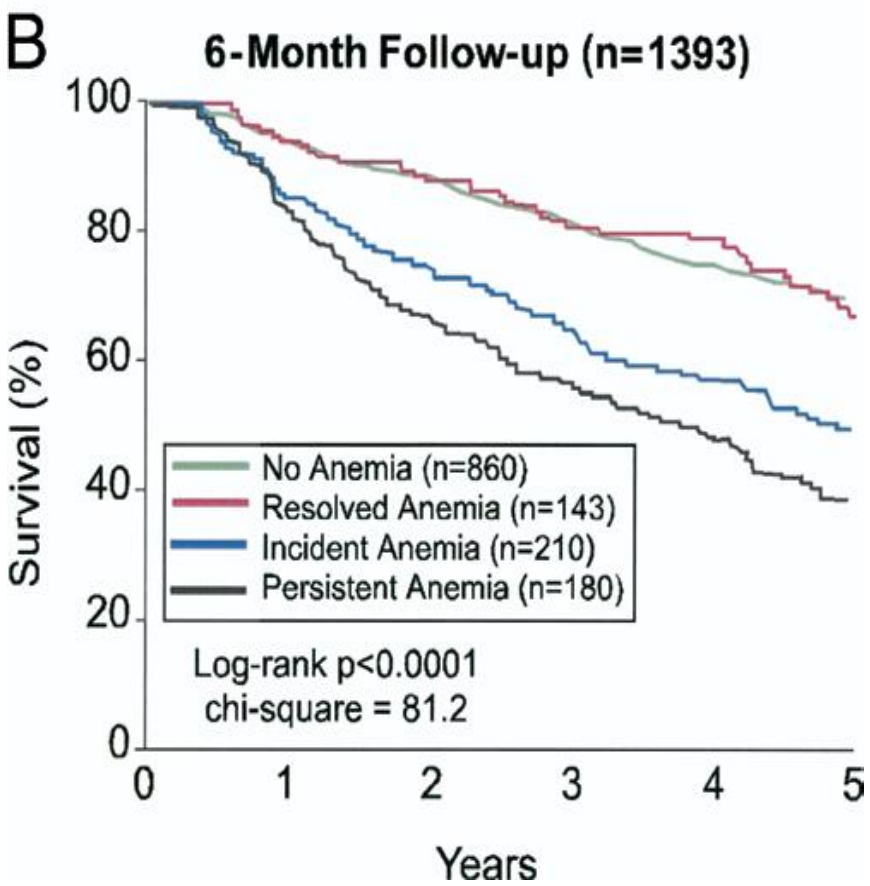


Culleton BF, Blood 2006

Anemia determines survival in Heart Failure pts.

Kaplan-Meyer survival curves in ambulatory HF patients according to anemia status

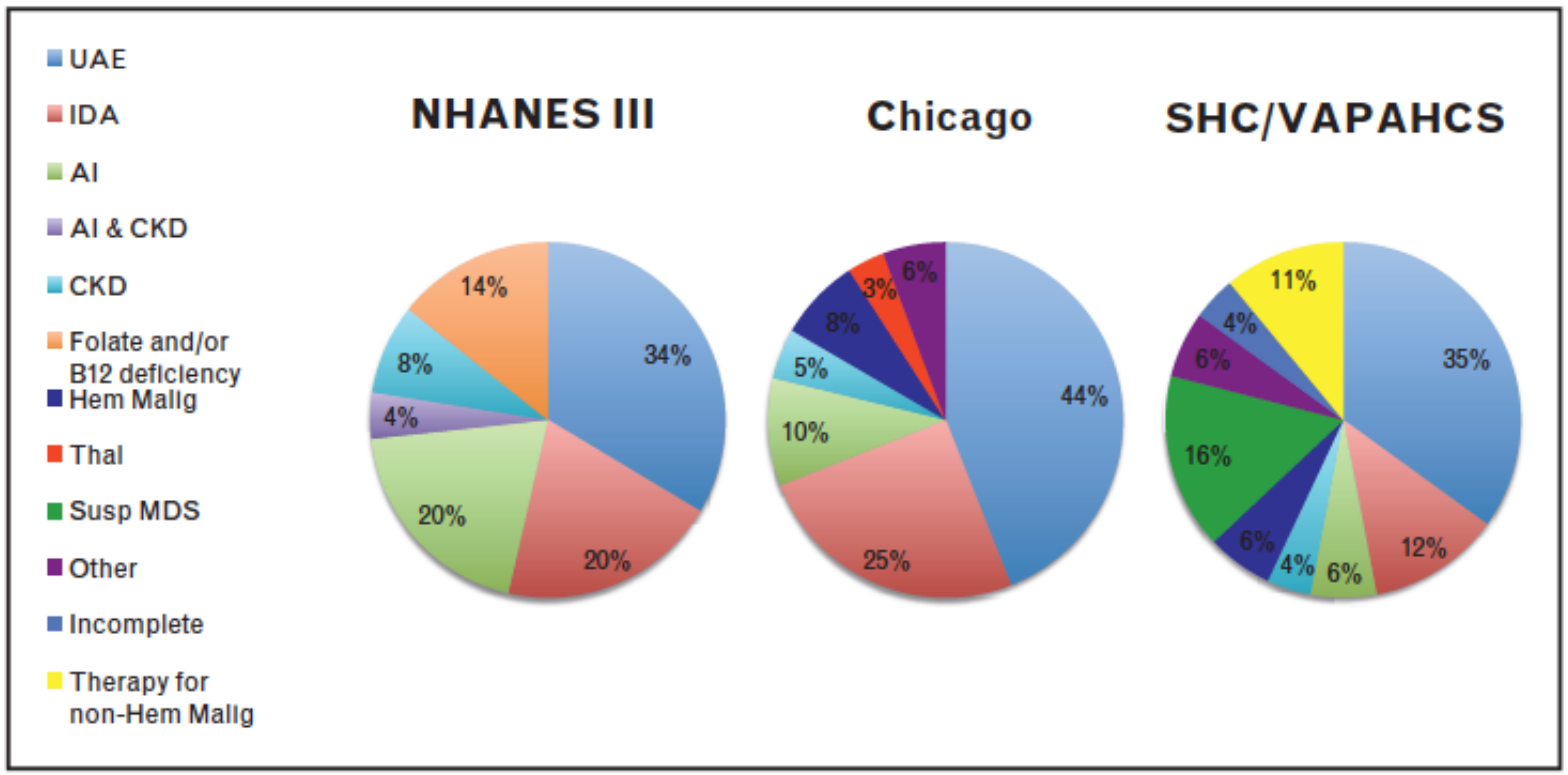




Persistent anemia significantly associated with mortality

Tang WH, J Am Coll Cardiol 2008

Causes of anemia in elderly in 3 different studies



Three broad categories (order of frequency):

1.Nutritional (iron / B12 / folate deficiency)

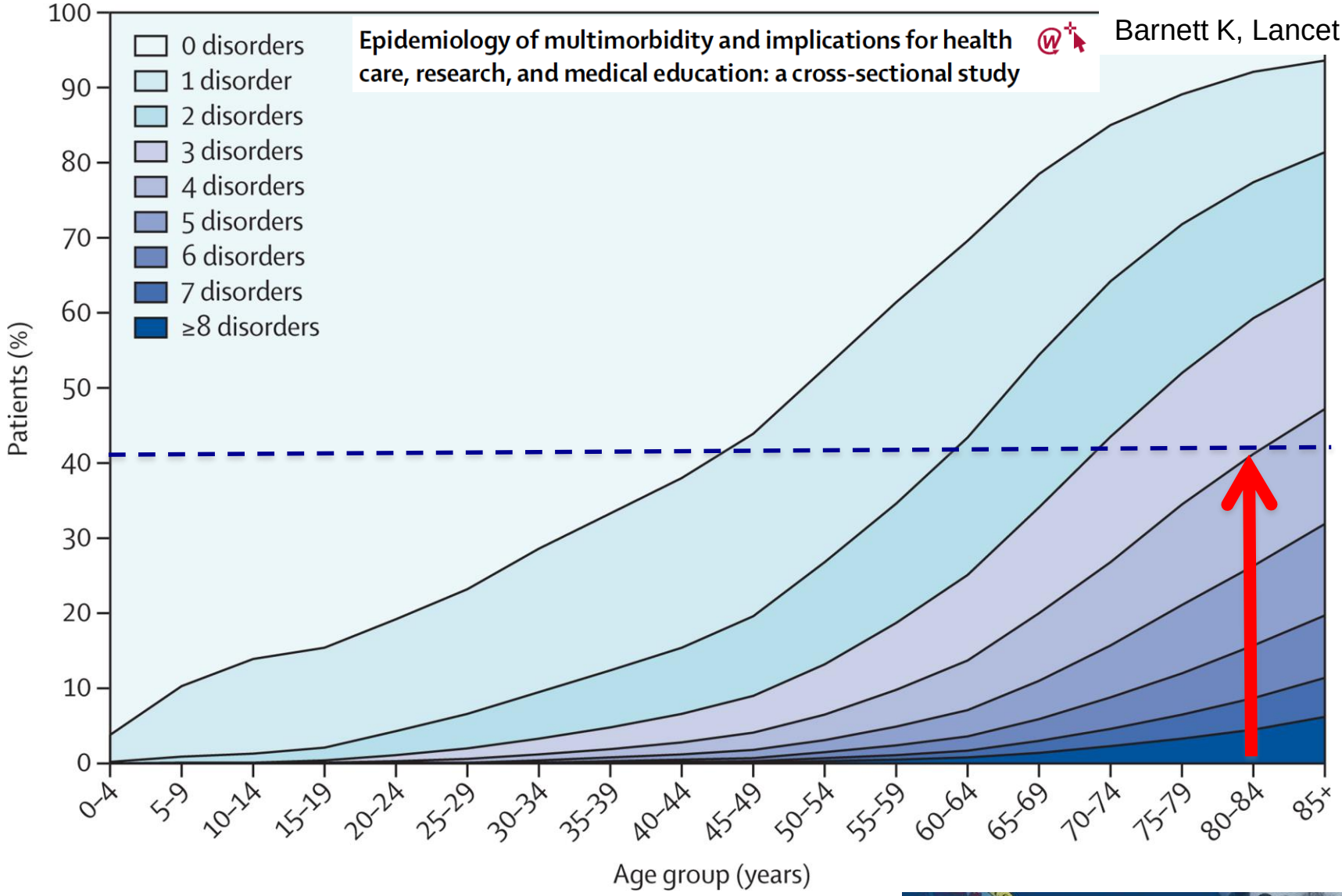
2.Anemia of chronic disease - ACD (including CKD)

1.“Unexplained” (including undiagnosed MDS)

→ **often mixed!**

Stauder R, Haematologica 2014

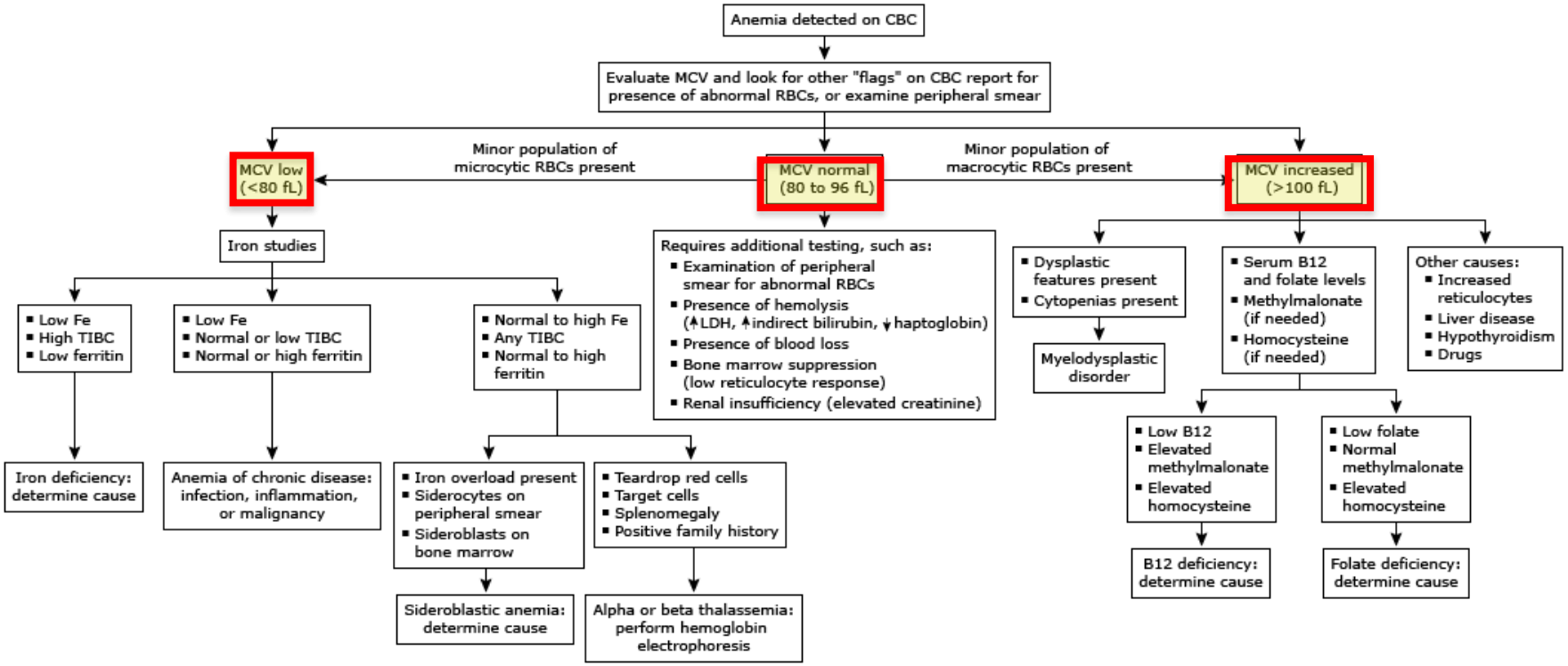
Multimorbidity in elderly



Barnett K, Lancet 2012

classical approach to anemia

Evaluation of anemia in the adult according to the mean corpuscular volume



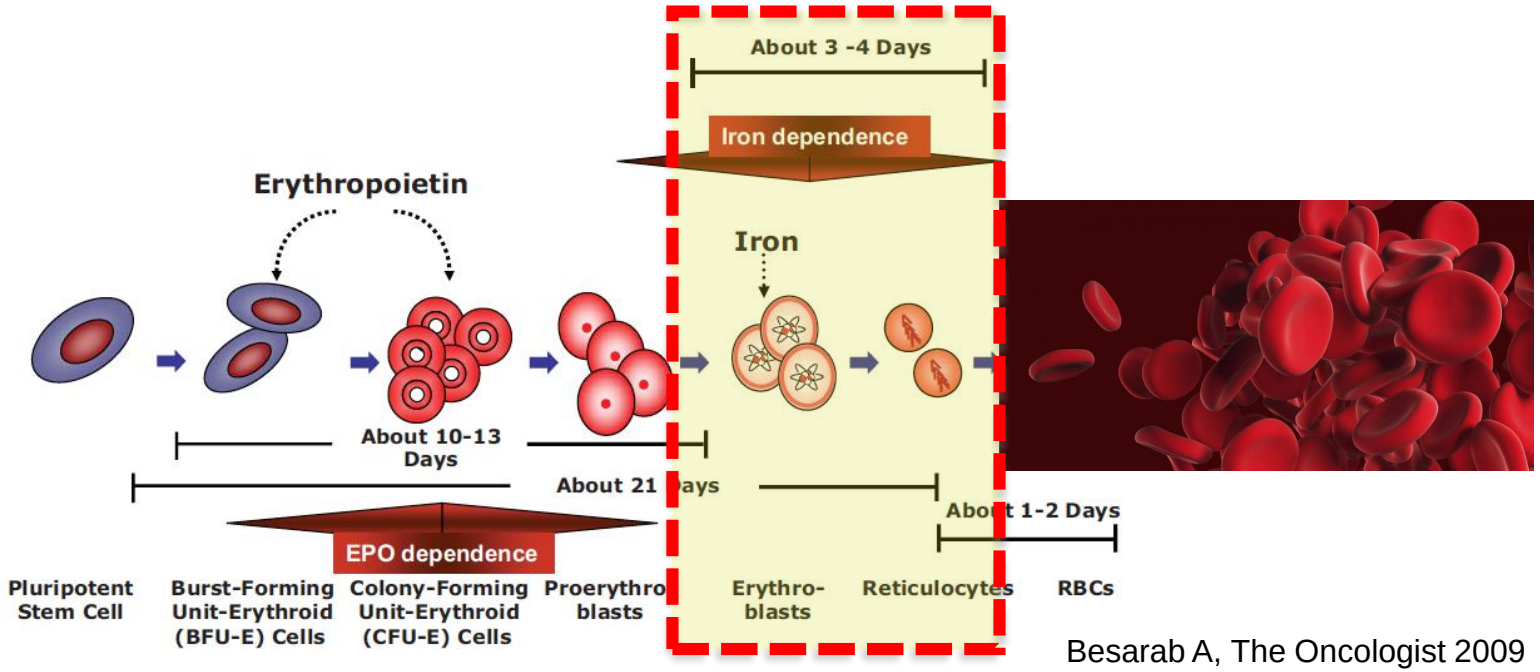
CBC: complete blood count; MCV: mean corpuscular volume; RBCs: red blood cells; Fe: iron; TIBC: total iron-binding capacity (transferrin); LDH: lactate dehydrogenase

UpToDate®

excellent in the young (single-cause anemias), doesn't work appropriately in multimorbidity (e.g. iron/B12 deficiency due to malnutrition)

IRON (and HEPCIDIN): central in common causes of anemia in elderly

Steady-state erythropoiesis: 200 billion new RBCs/day (2.4 million/sec), requiring 20 mg iron/day.

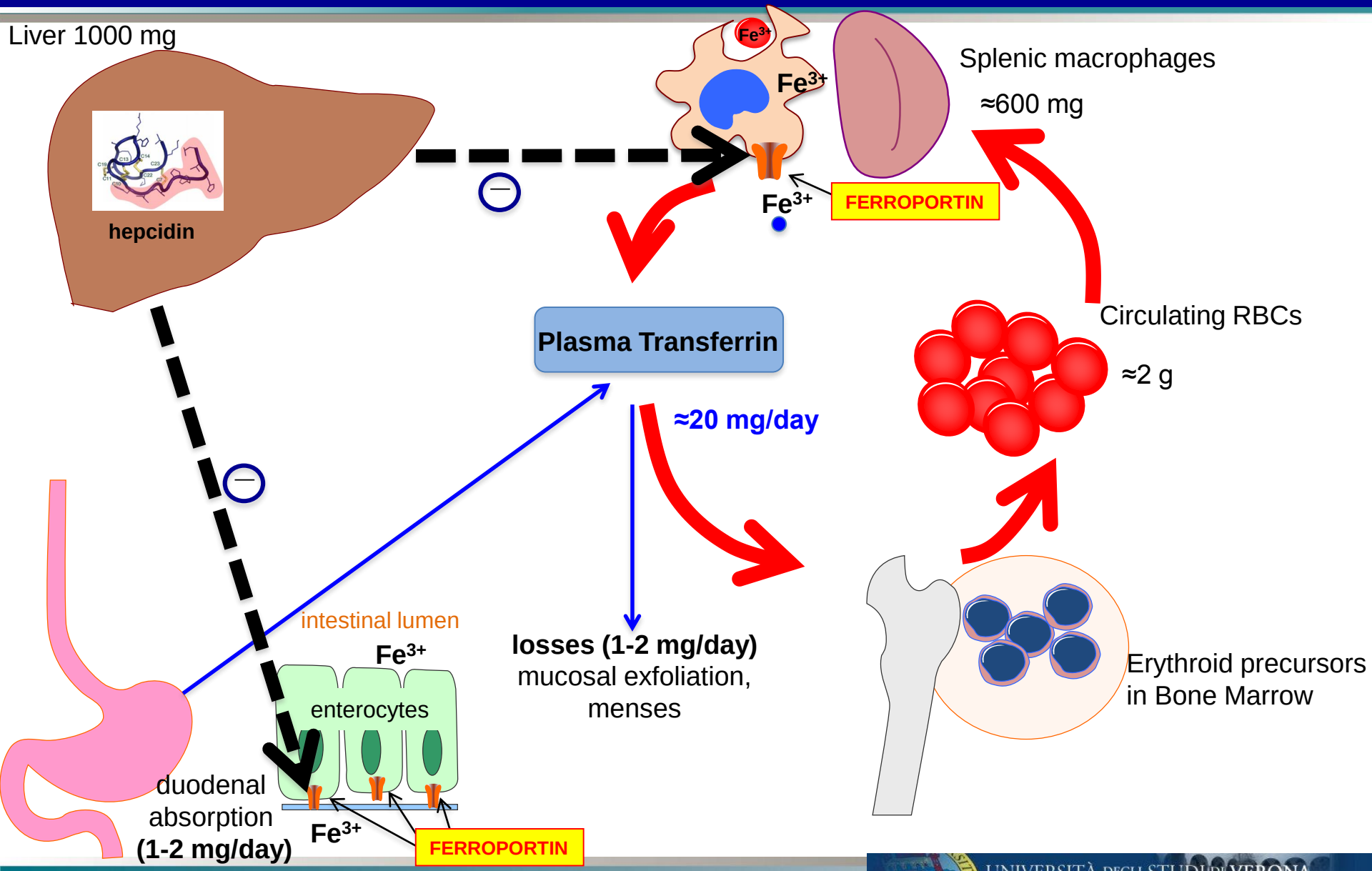


Besarab A, The Oncologist 2009

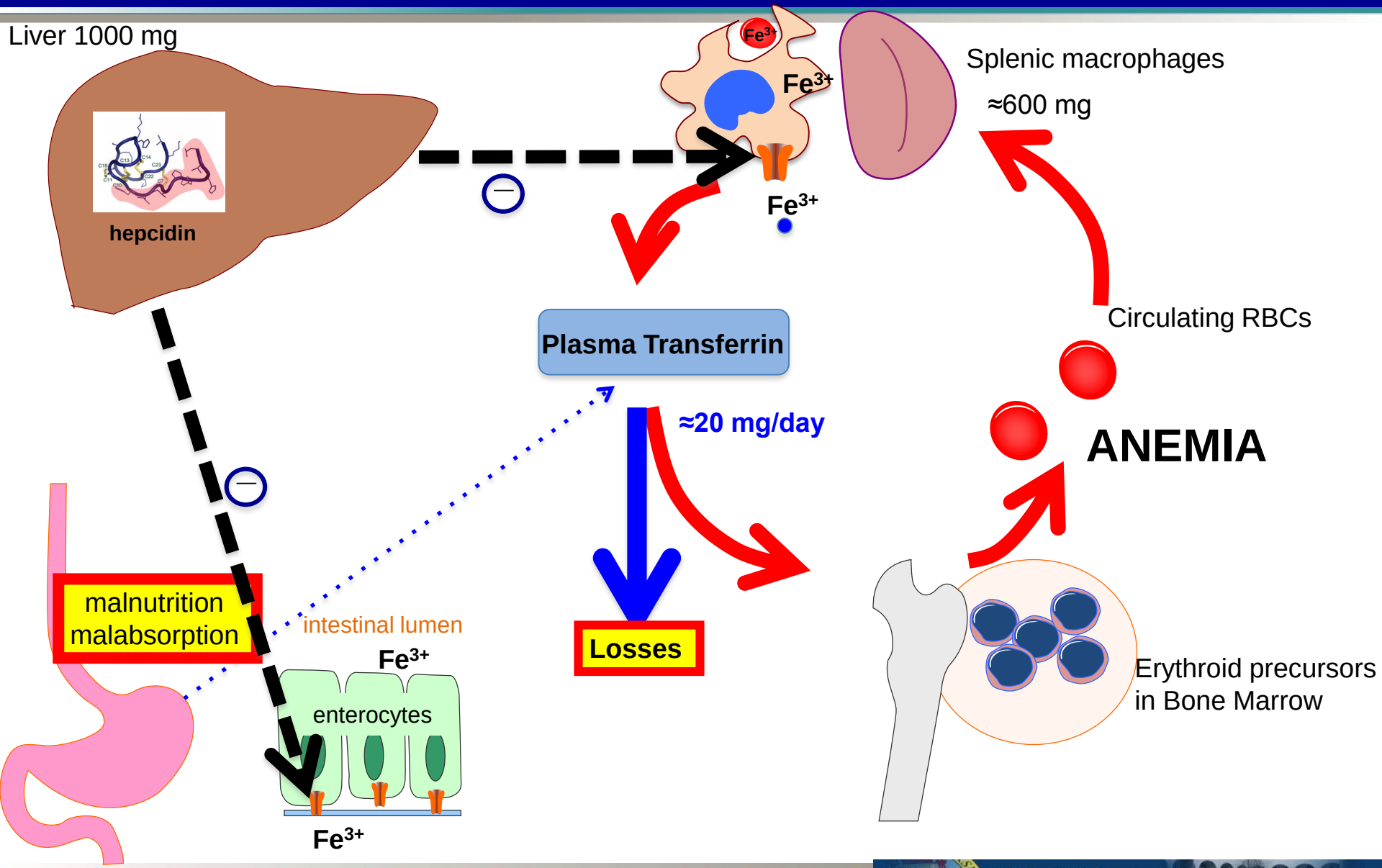
1. **Absolute iron deficiency**: iron deficiency anemia (**IDA**)

2. **Functional iron deficiency** → sequestration into macrophages→ iron-restricted erythropoiesis → anemia of chronic diseases (**ACD**).

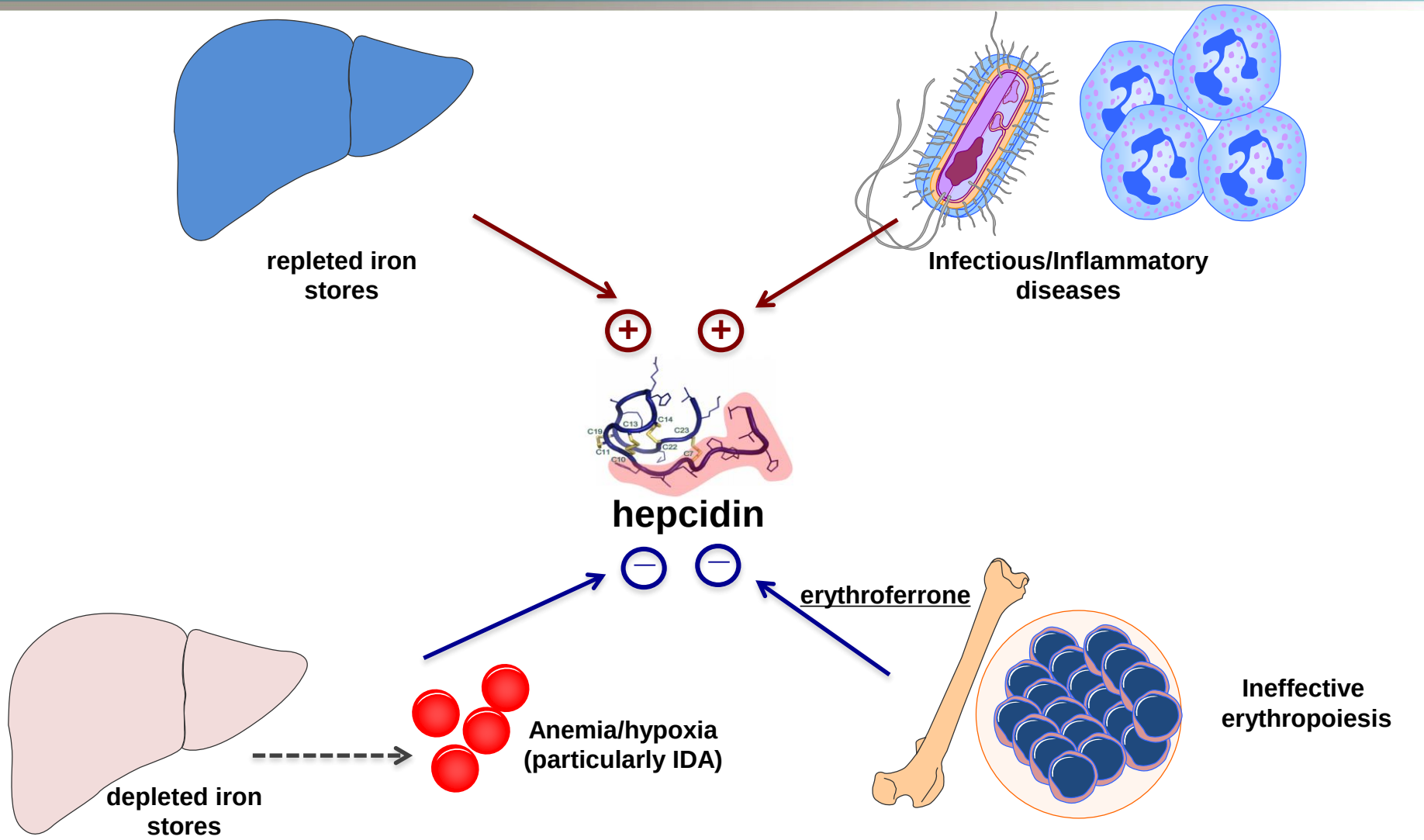
IRON "ECOLOGY"



ABSOLUTE IRON DEFICIENCY



Major “clinical” opposing stimuli regulating hepcidin

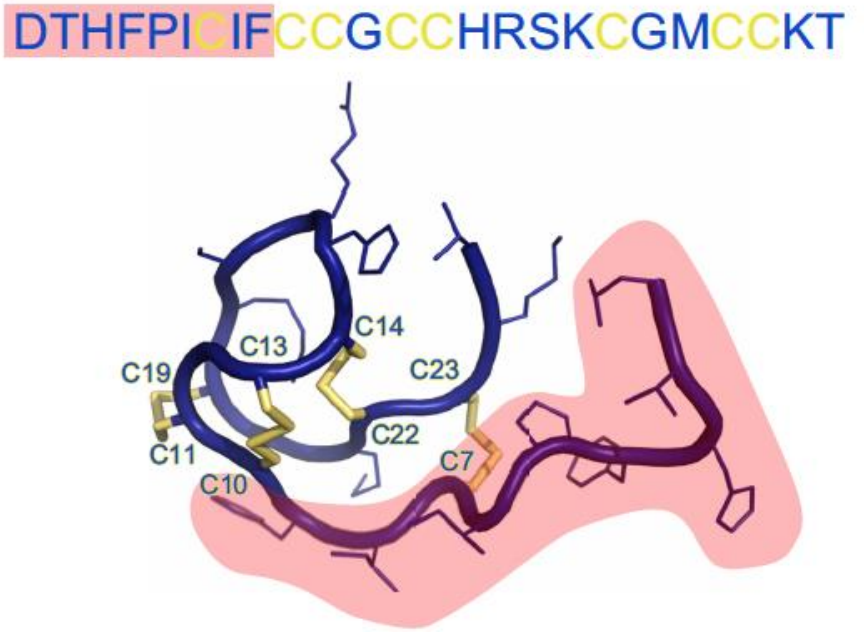


Girelli D, Blood 2016 (adapted)

HEP-(atic) CIDIN (antimicrobial)

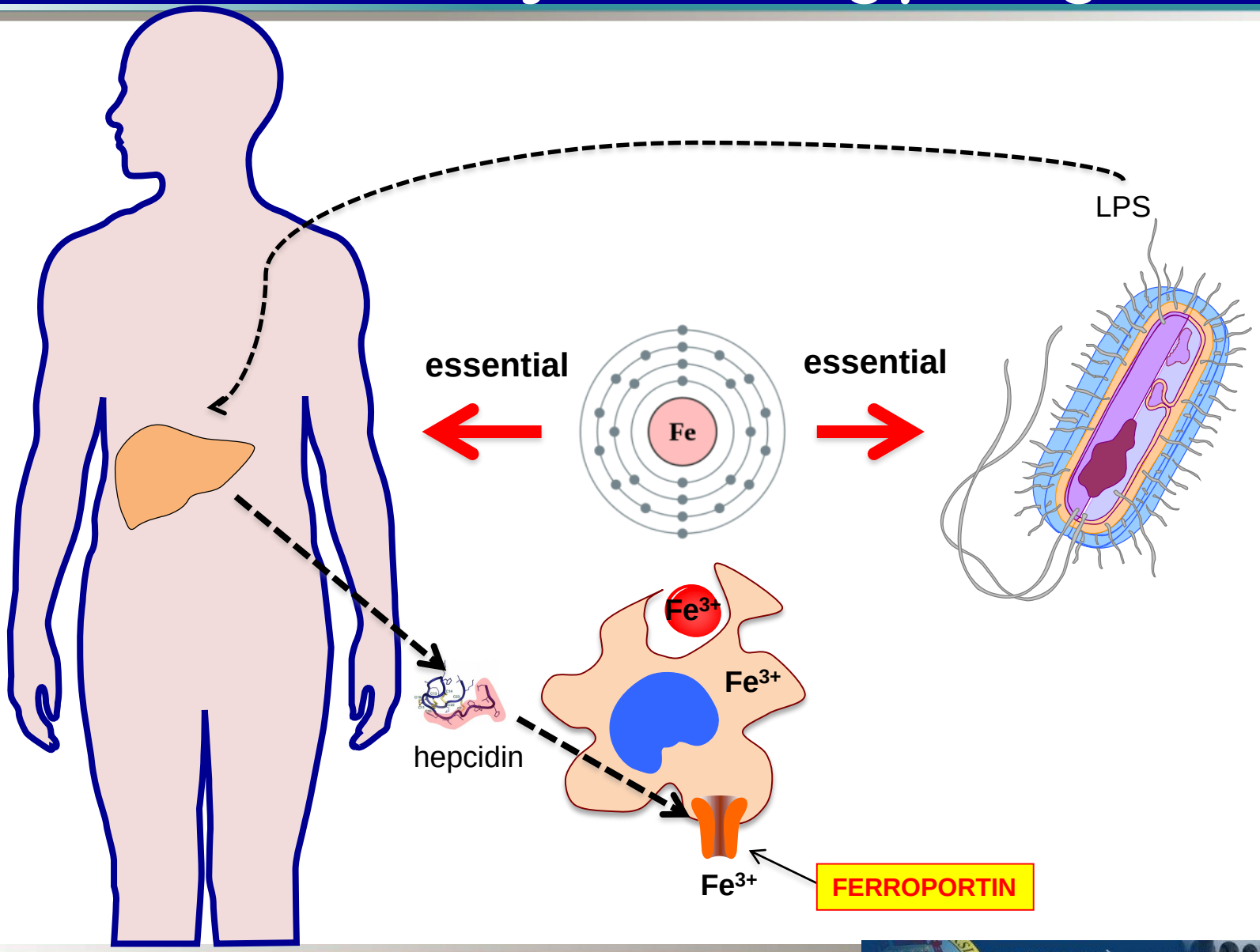
- **small (25 aa), cysteine-rich, cationic peptide**

- **defensin-like (innate immunity-related peptides with natural antimicrobial acitvity)**

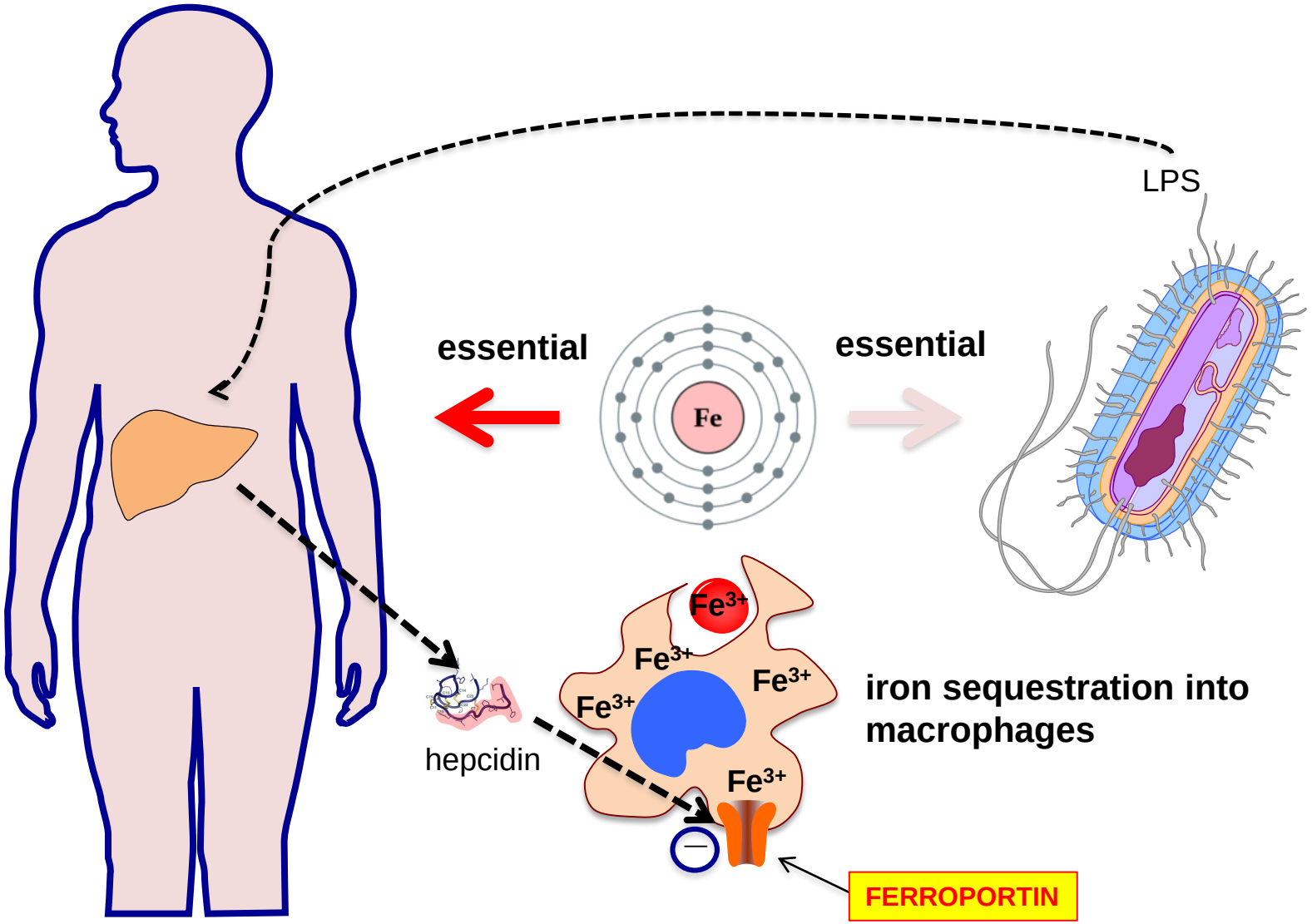


Ganz T, Physiol Rev 2013

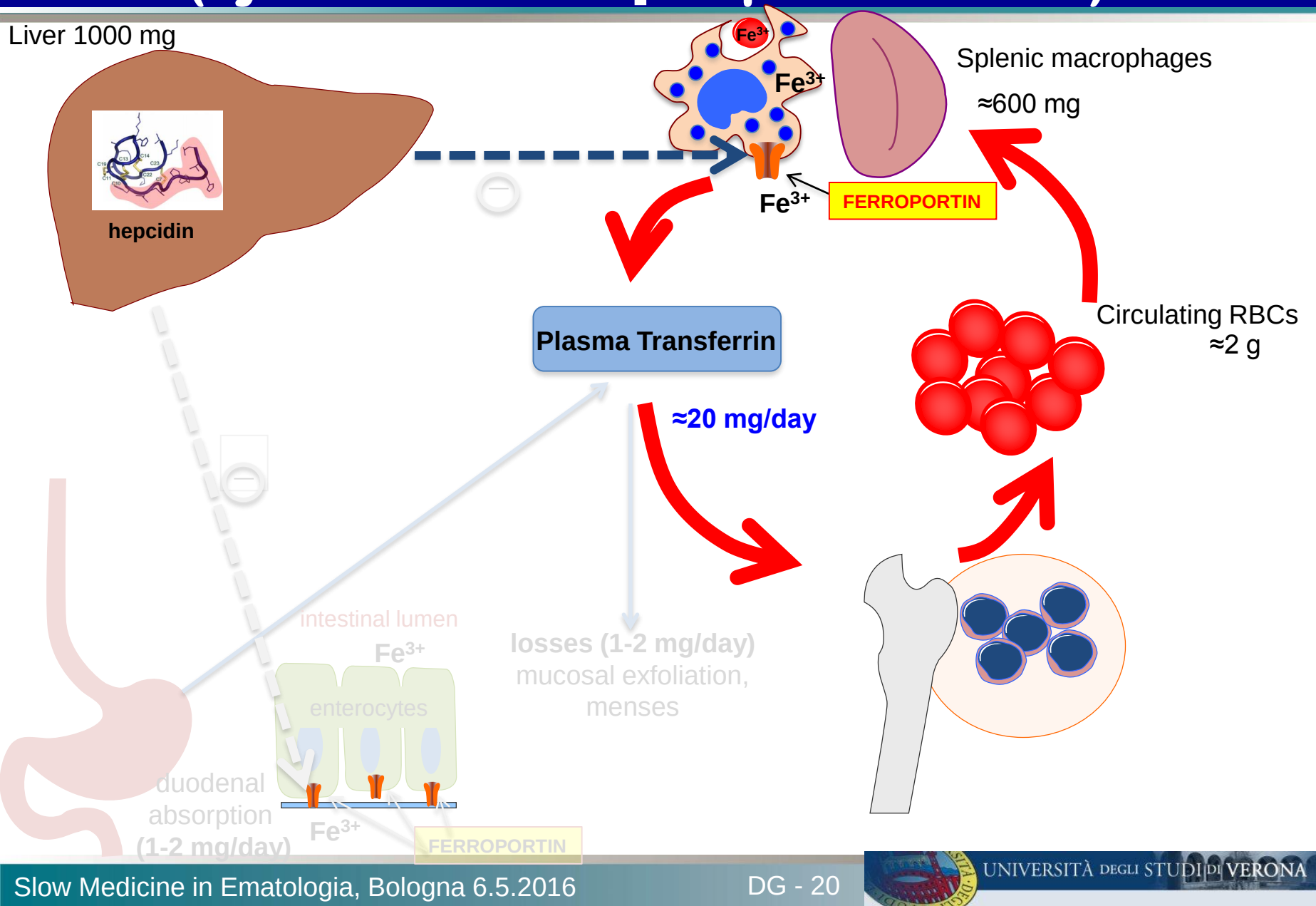
Hepcidin indirect antimicrobial activity by reducing iron availability to invading pathogens



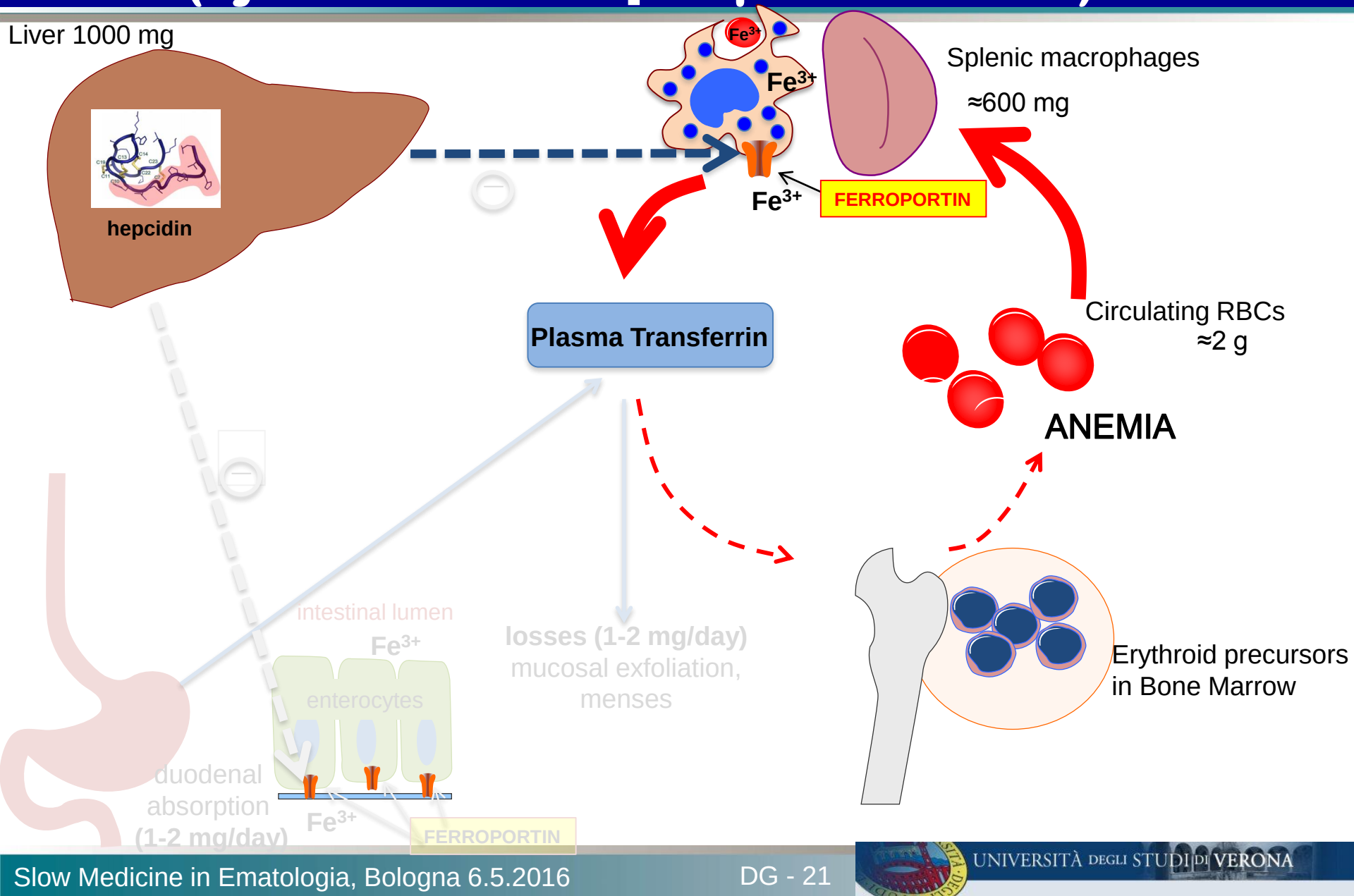
Hepcidin indirect antimicrobial activity by reducing iron availability to invading pathogens



FUNCTIONAL IRON DEFICIENCY (cytokine-driven ↑ hepcidin in ACD) - 1



FUNCTIONAL IRON DEFICIENCY (cytokine-driven ↑ hepcidin in ACD) - 2

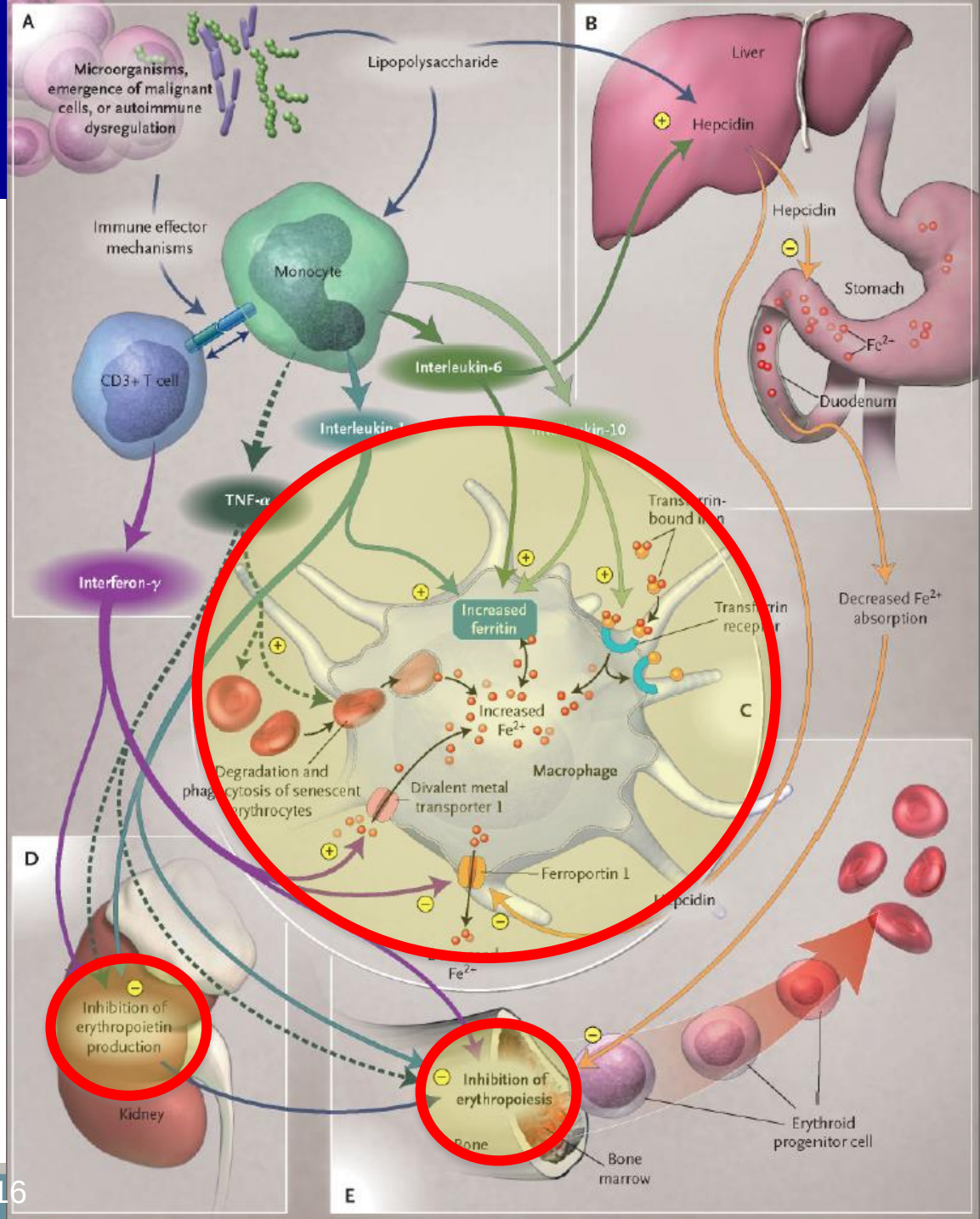


ACD pathogenesis

hepcidin-induced “macrophage block” → iron-restricted erythropoiesis → major contributing factor

(+ cytokine-driven ↓ EPO activity and ↓ proliferative capacity of RBC precursors)

Weiss G, N Engl J Med 2005
Weiss G, Semin Hematol 2015



IDA in the elderly: a challenging condition

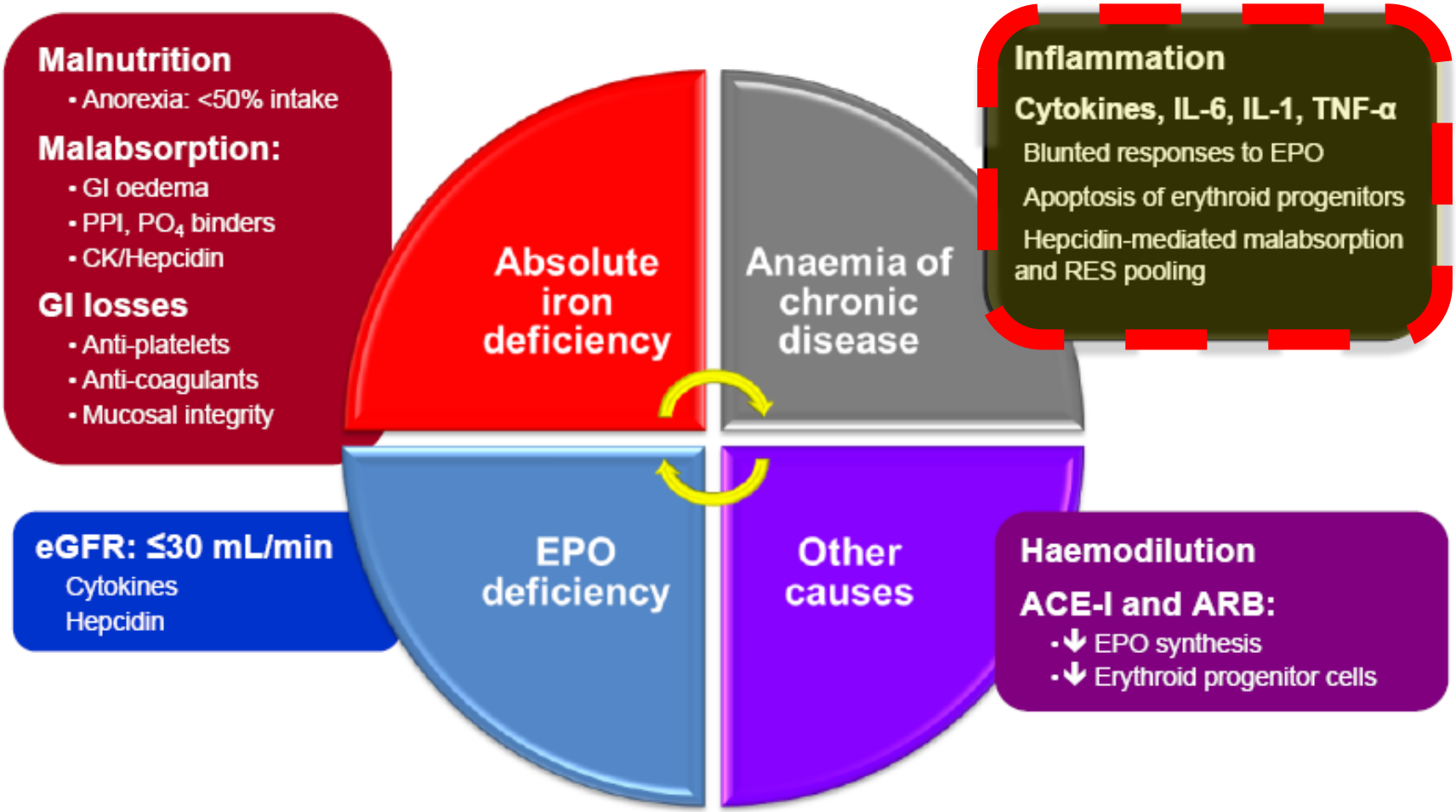
1) **often multifactorial, *e.g.* due to multiple concurring causes, including inadequate dietary intake or absorption, occult bleeding, medications.**

2) **due to the typical multimorbidity, other conditions leading to anemia (e.g. overt/subclinical inflammation) frequently coexist and make IDA diagnosis difficult.**

3) **treatment problematic: response to oral iron often slow, with a substantial fraction of pts. showing refractoriness and requiring cumbersome i.v. administration.**

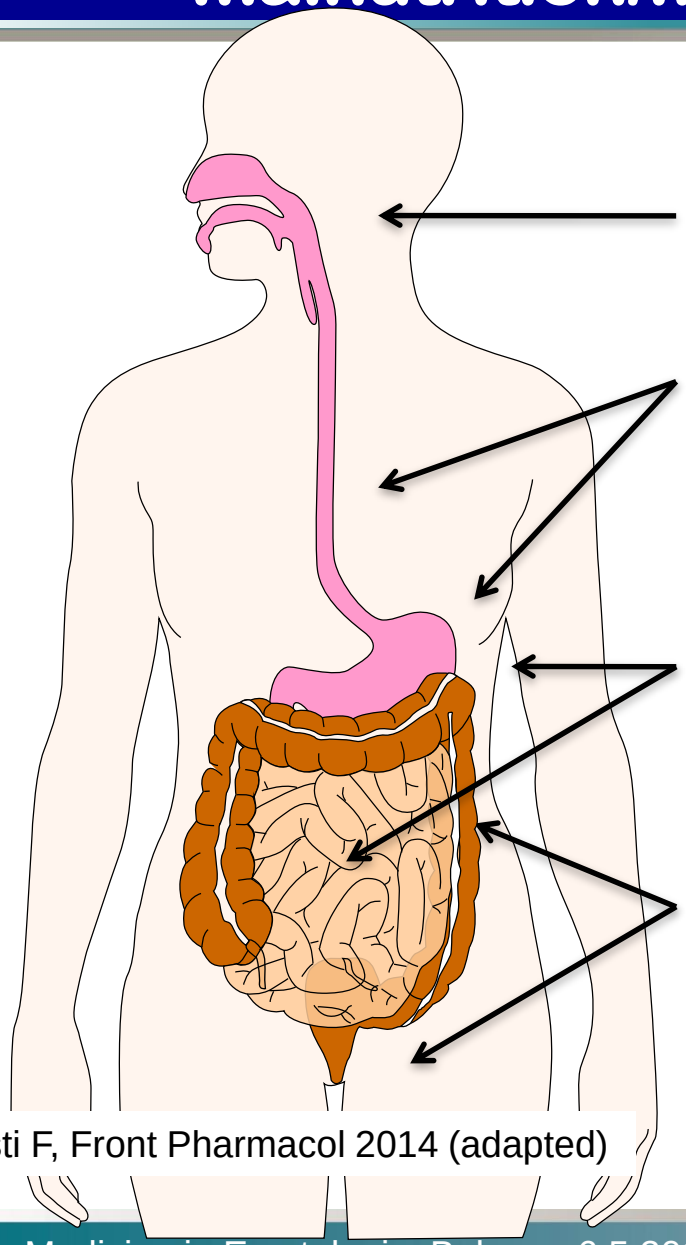
Busti F, Front Pharmacol 2014

Anemia in HF: a paradigm of multiple concurrent mechanisms (IDA-ACD-CKD)



Ble A, et al. Arch Int Med 2005;165:2222–7.

The bad triad leading to IDA in elderly: malnutrition/malabsorption/blood loss



Malnutrition

Anorexia
Inadequate dietary intake

Upper GI blood losses

Esophagitis
Gastritis
Cancer
angiodysplasia
Antithrombotic drugs

Malabsorption

Chronic gastritis
HP infection
CD
PPI

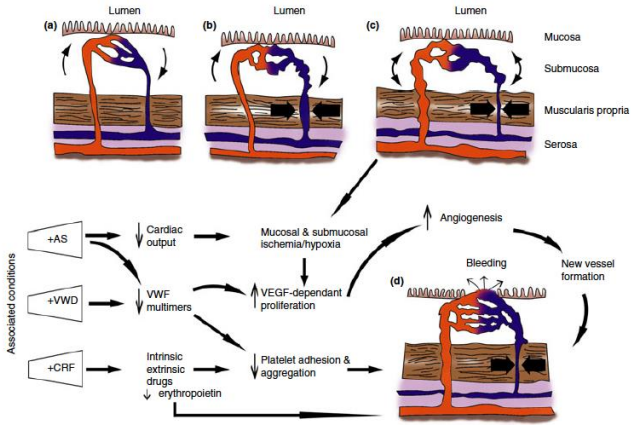
Lower GI blood losses

Pre-malignant lesions
Cancer
angiodysplasia
hemorroids
Antithrombotic drugs

Busti F, Front Pharmacol 2014 (adapted)

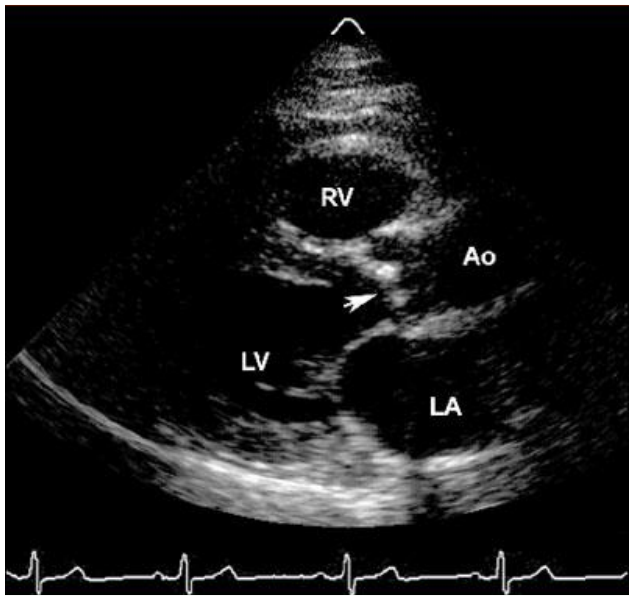
IDA in elderly: a paradigmatic case

- Female, aged 70 y
- “Unexplained” IDA since 2006
- Multiple exacerbations with Hb < 7 g/dl (transfused)
- Fecal Occult Blood intermittently +
- EGDS neg.
- Colon endoscopy neg. (badly tolerated)
- Virtual colonscopy (by CT) neg.



Sami SS, Aliment Pharmacol Ther 2014

Angiodysplasia in the ascending colon (WCE)



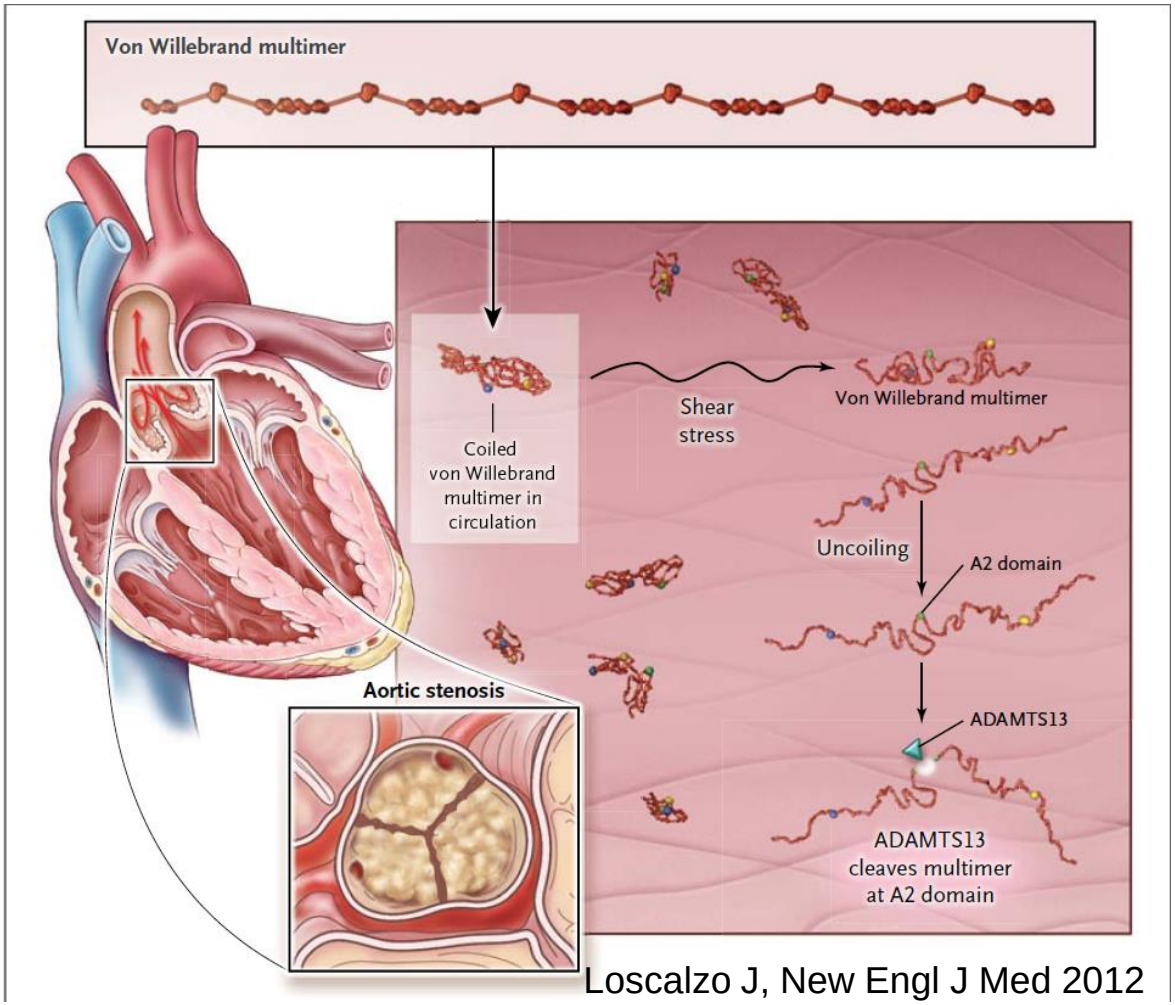
Heyde’s syndrome (1958)

Calcific aortic stenosis

Acquired von Willebrand's disease in Heyde's syndrome

CLINICAL IMPLICATIONS OF BASIC RESEARCH

From Clinical Observation to Mechanism — Heyde's Syndrome



Loscalzo J, New Engl J Med 2012

Shear stress through stenotic valve

↓

Consumption of vWf multimers

↓

Acquired coagulopathy

↓

IDA

↑

Bleeding source

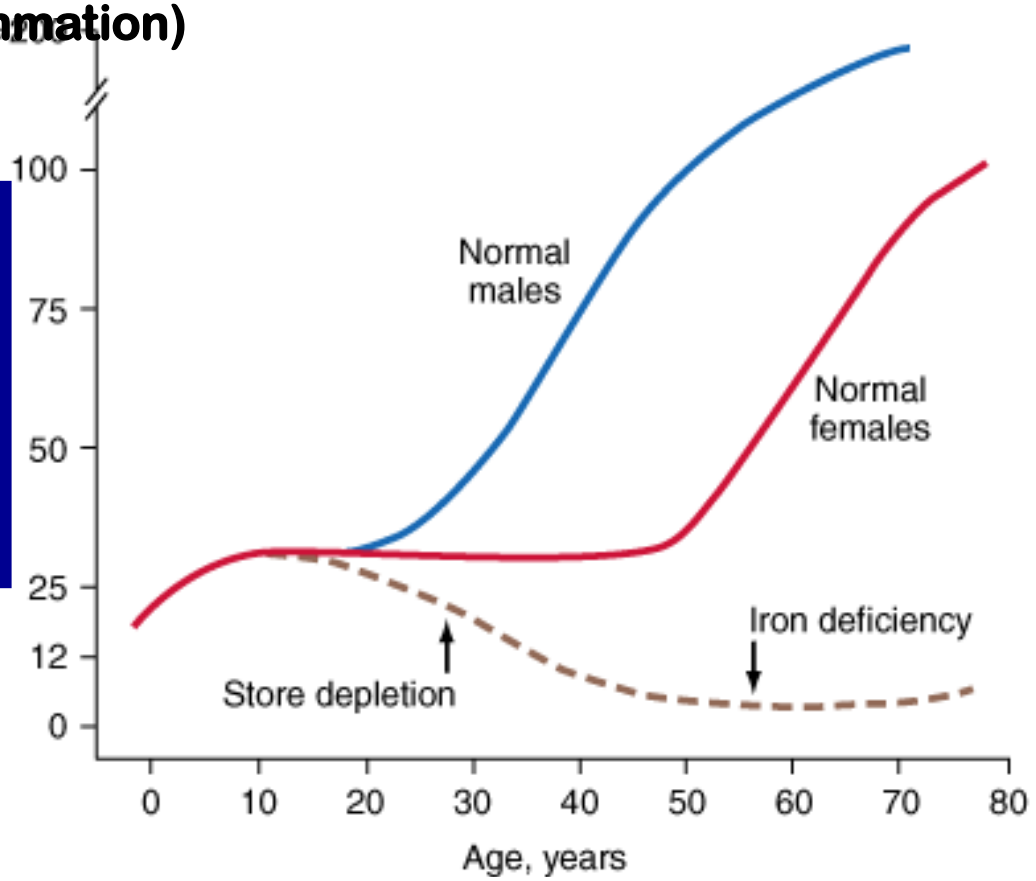
↑

angiodysplasia

IDA in elderly: caveats in lab diagnosis

s. ferritin ↑ with age (and confounded by inflammation)

	Normal	Negative iron balance	Iron-deficient erythropoiesis	Iron-deficiency anemia
Iron stores				
Erythron iron				
Marrow iron stores	1-3+	0-1+	0	0
Serum ferritin (µg/L)	50-200	<20	<15	<15

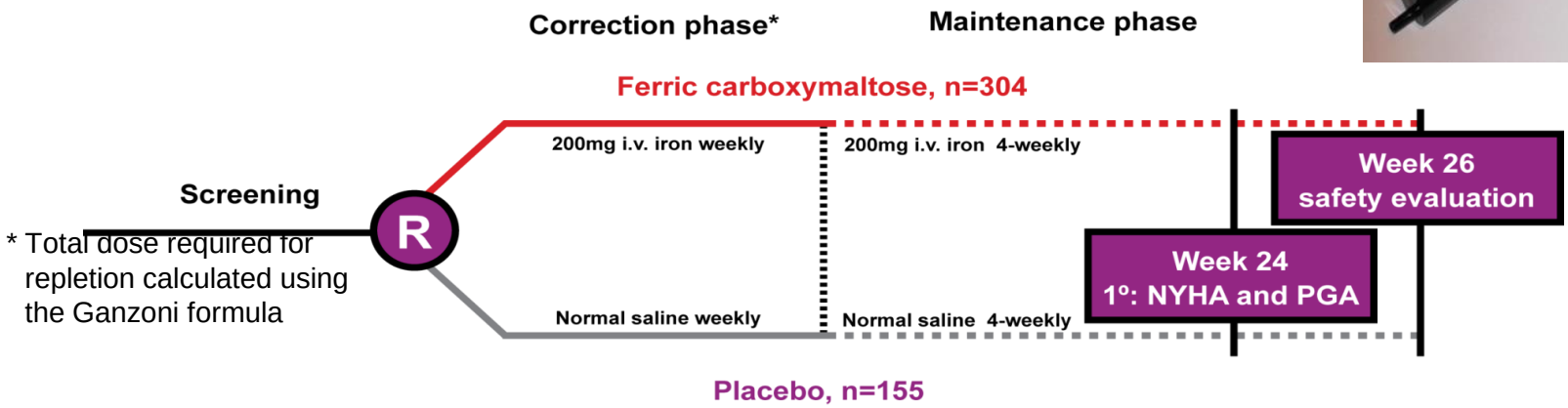


threshold values different and less well established than in younger pts.

FAIR-HF: study design

- **Main inclusion criteria**:
  - NYHA class II/III, LVEF ≤40% (NYHA II) or ≤45% (NYHA III)
  - Hb: 95–135 g/L
  - Iron deficiency: serum ferritin <100 µg/L or <300 µg/L, if TSAT ≤20%

- Blinding:
  - Clinical staff: unblinded and blinded personnel
  - Patients: usage of curtains and black syringes for injections



* Total dose required for repletion calculated using the Ganzoni formula

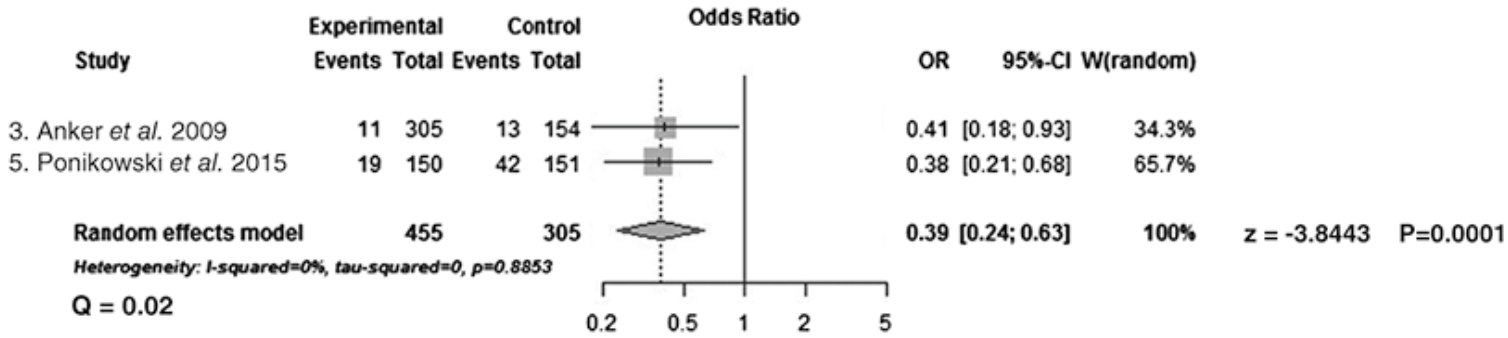
Hb, hemoglobin; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PGA, Patient Global Assessment; TSAT, transferrin saturation.

Anker SD, N Engl J Med 2009

European Journal of Heart Failure (2016)
doi:10.1002/ejhf.473

Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials

Cardiovascular death or hospitalization for worsening HF



Jankowska E, Eur J Heart Fail 2016

Iron therapy in the elderly: caveats

ORAL (1st choice)

- Response too slow (part. if anemia is severe)
- Prolonged administration required (2-3 months for store repletion) →
- suboptimal compliance (GI AEs, polytherapy, …)
- reduced absorption

I.V.

- Costly
- Only in H
- Multiple infusions needed (typical total therapeutic dose = 1 g)
- Multiple H accesses
- (severe) AEs

Busti F, Front Pharmacol 2014

Advances in I.V. iron formulations

1947: Fe-Saccharide

↓

1954: Fe-Dextran (HMW)

↓

1999: Fe-Gluconate

↓

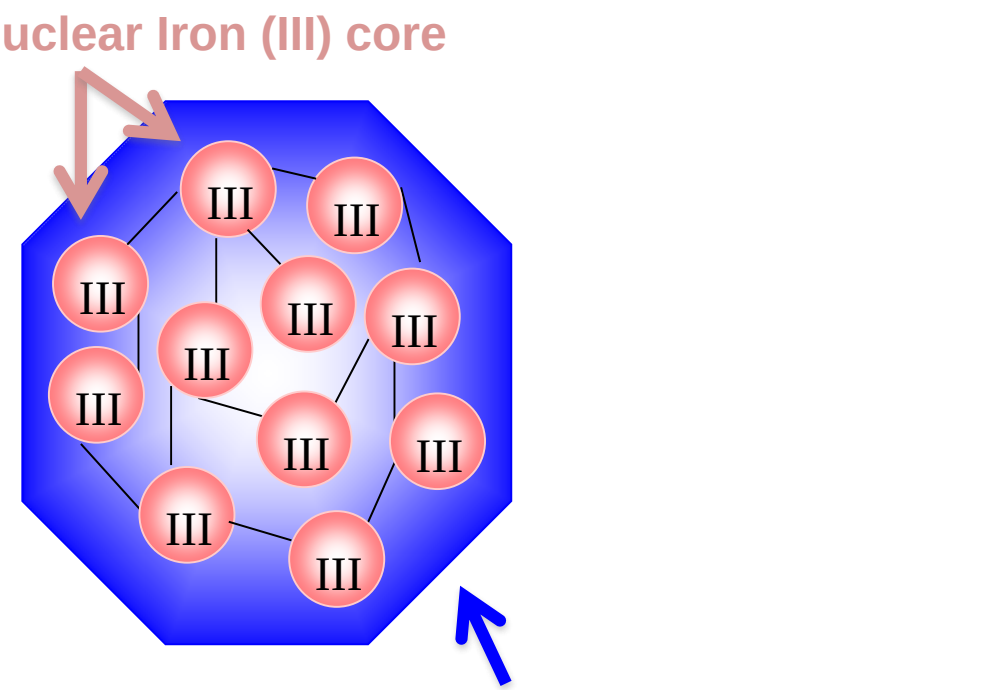
2000: Fe-Sucrose

↓

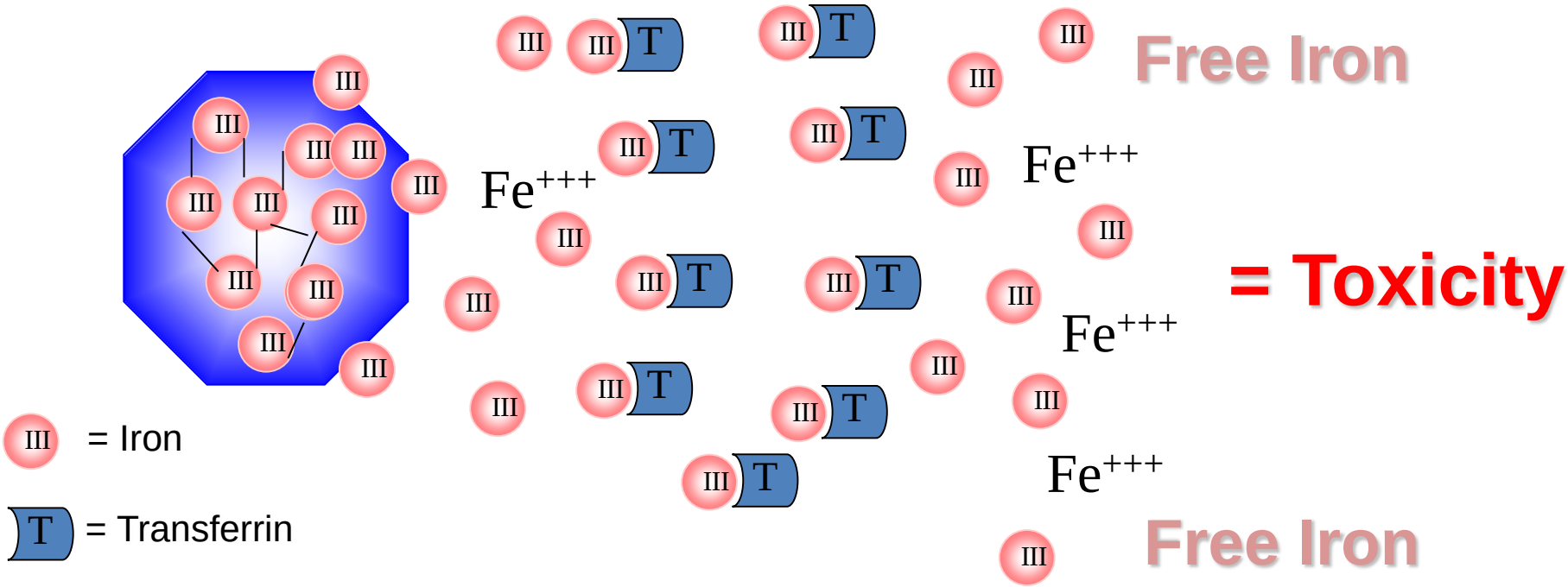
2009: Ferumoxytol

↓

2011: Fe-Carboymaltose



Stability of Iron complex: a major factor determining the maximal dose that can be given safely per single infusion.



Old formulations: less stable, high release of toxic Fe+++

new formulations: more stable, allowing high doses to be safely administered in a single and quick infusion.

Ferric Carboxymaltose

Iron preparations for I.V. use

Formulation	Dose per Infusion	
	Standard	Maximum per Single Infusion
Ferric gluconate (Ferlecit)	125 mg/10–60 min	250 mg/60 min
Iron sucrose (Venofer)	100–400 mg/2–90 min	300 mg/2 hr
Low-molecular-weight iron dextran (INFeD)†	100 mg/2 min	1000 mg/1–4 hr)
Ferumoxytol (Feraheme)†	510 mg/>1 min	510–1020 mg/15–60 min
Ferric carboxymaltose (Ferinject)†	750–1000 mg/15–30 min	750–1000 mg/15–30 min
Iron isomaltoside (Monofer)†‡	20 mg/kg of body weight/15 min	20 mg/kg of body weight/15 min

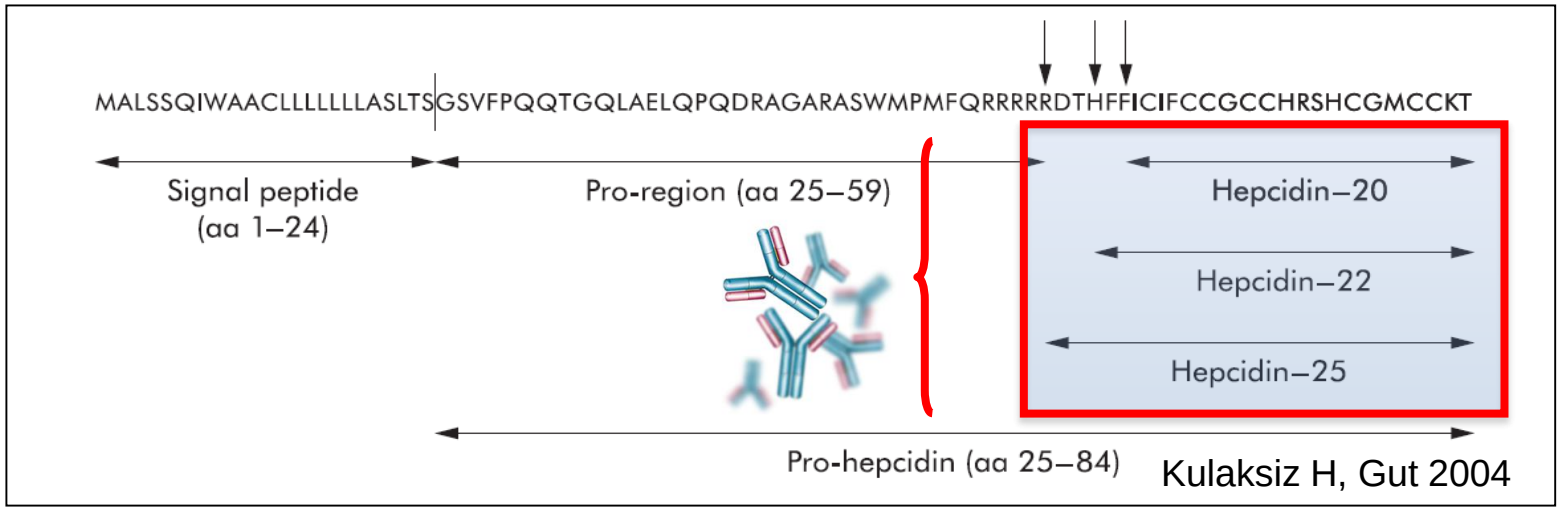
total therapeutic doses in few minutes

obvious advantage, part. in the elderly!

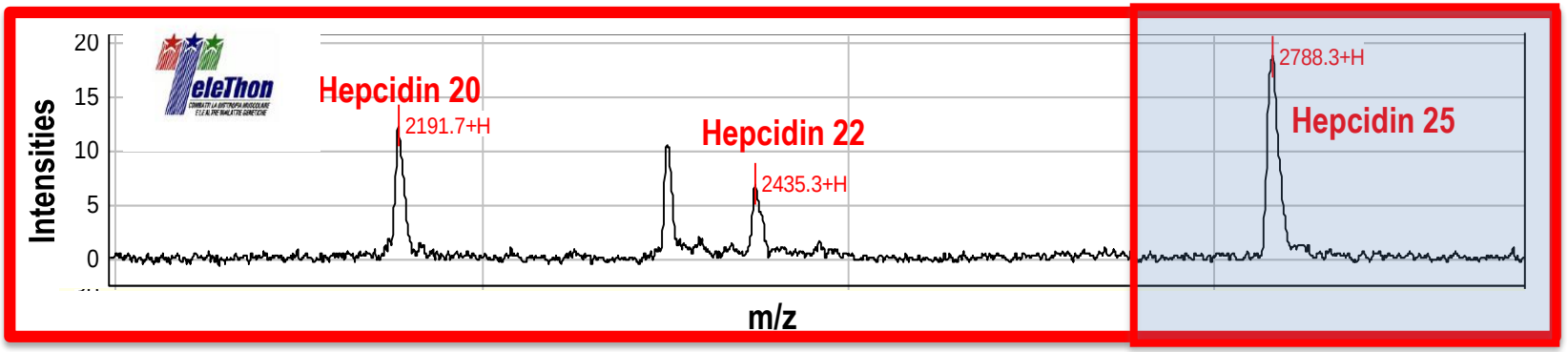
Camaschella C, NEJM 2015

How hepcidin discovery can help in approaching anemia in the elderly?

Hepcidin-25 (only iron-active isoform) assays



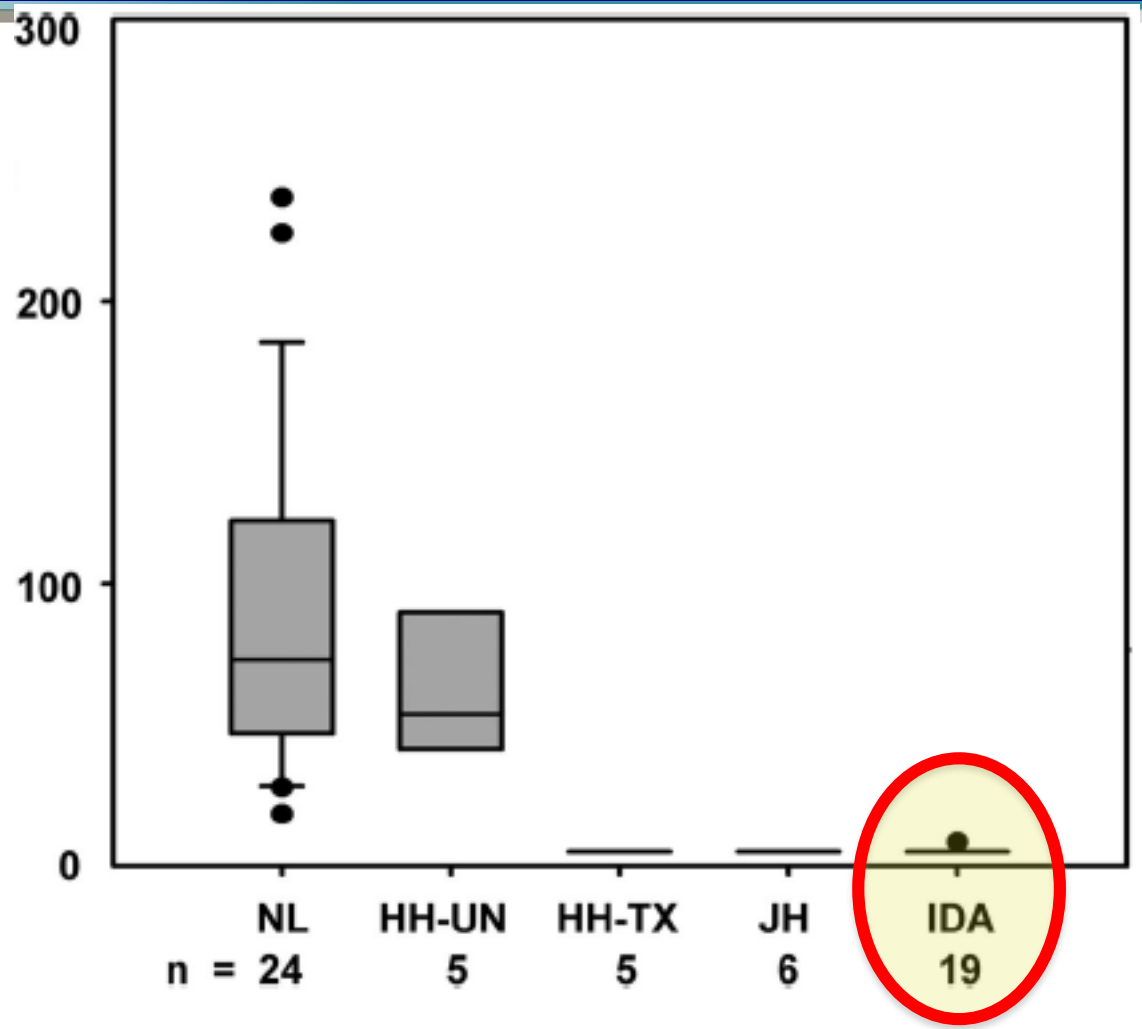
ELISA: Ab cross-reacting with smaller inactive isoforms (total hepcidin measured)



Mass-Spectrometry based assay: highly specific in distinguishing hepc-25

Castagna A, J Proteom 2010

Serum Hepcidin levels are suppressed in IDA

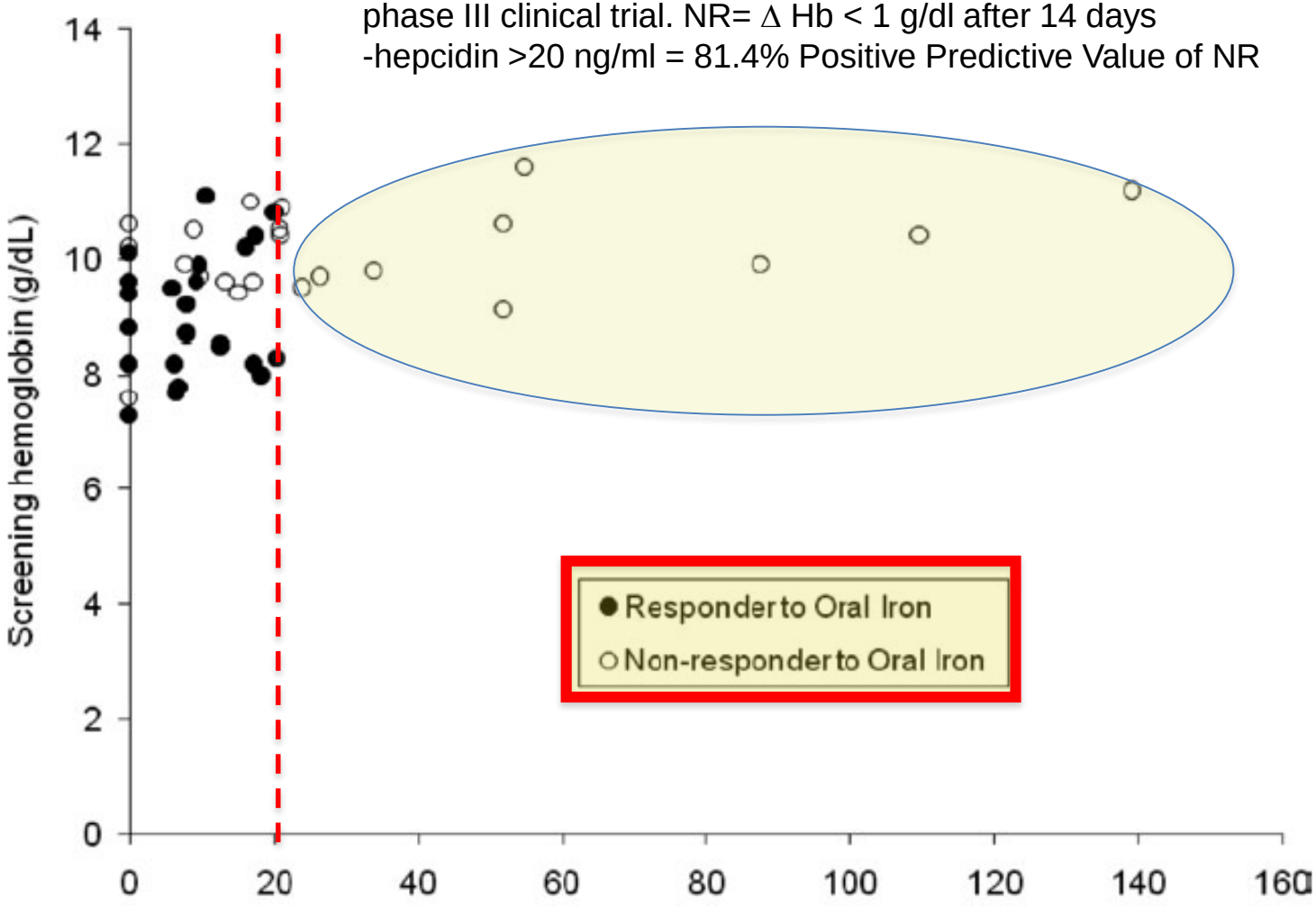


Less influenced by concurrent inflammation as compared to ferritin

Ganz T, Blood 2008

Promising application in the clinic: hepcidin levels predict nonresponsiveness to oral iron in IDA

phase III clinical trial. NR= Δ Hb < 1 g/dl after 14 days
-hepcidin >20 ng/ml = 81.4% Positive Predictive Value of NR



Bregman DB, Am J Hematol 2013

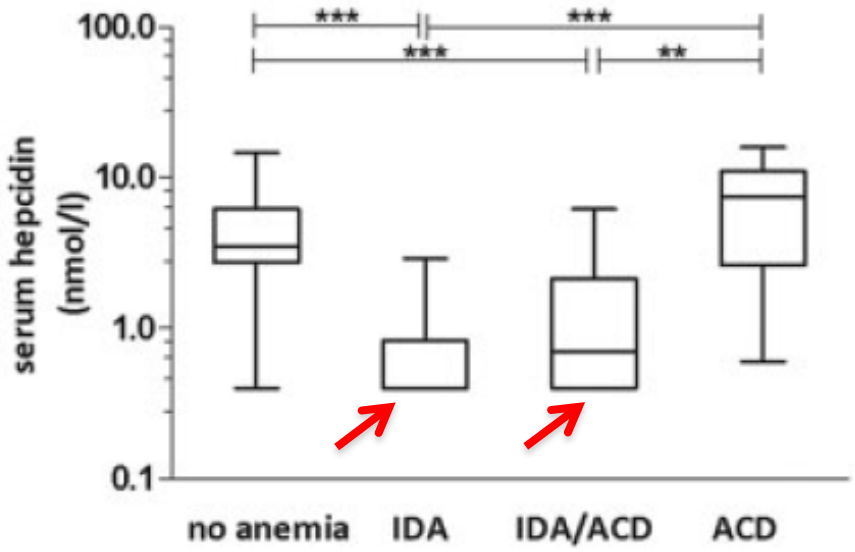
Hepcidin measurement in clinical practice. A Decalogue for the hematologists

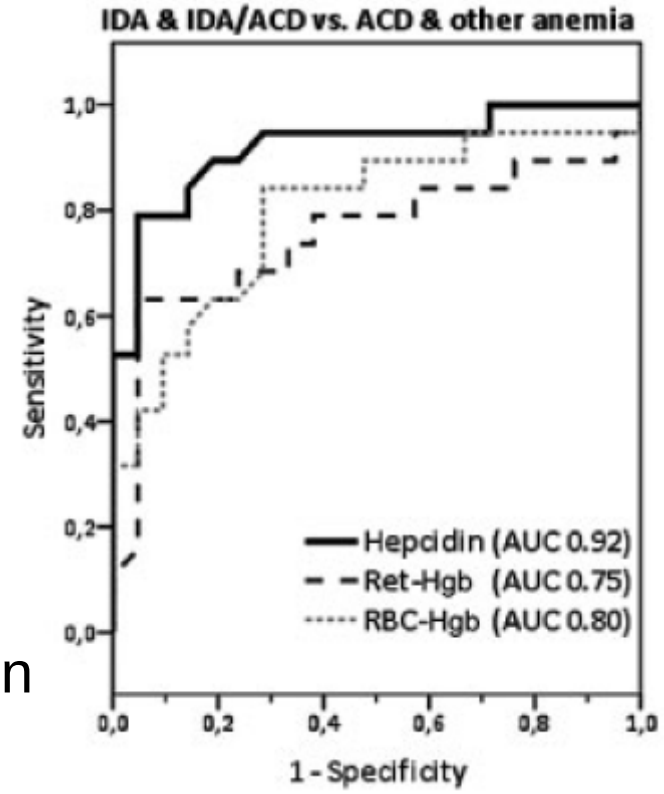
A) Checklist before ordering the assay			
		Comments	References
1.	Ensure local availability of a validated assay	See text and Supplementary Table 1	(19)
2.	Ensure control of pre-analytical conditions (including diurnal rhythm)	See text	(8, 25, 26)
3.	Refer to age- and sex-specific ranges	Significant differences between males and females, particularly during fertile period.	(22, 23)
4.	Interpret hepcidin value into a minimum laboratory context (CBC, ferritin, transferrin saturation, CRP, serum creatinine, liver function tests).	See Figure 1	-
5.	Be aware of many potential confounders/comorbidities in the individual patient	See Figure 1	

B) Most promising applications			
6.	Evaluation of suspected IRIDA	Virtually diagnostic in an appropriate clinical context	(41, 42)
7.	Evaluation of iron overload disorders	e.g.: ferroportin disease due to hepcidin resistant mutations (see text)	(34, 37, 45, 46, 48, 49)
8.	Diagnosis of concomitant iron deficiency in patients with anemia of chronic disease	Promising reports in rheumatoid arthritis, inflammatory bowel disease, and African children	(53, 62, 66, 67)
9.	Guide for iron therapy	e.g.: selection of patients for direct I.V. supplementation; oral administration in children from developing countries with high prevalence of infectious diseases (see text)	(6, 50, 52-54, 62)
10.	Monitoring of treatments targeting the hepcidin/ferroportin axis	To be confirmed by further studies	(69)

Girelli D, Blood 2016

Low hepcidin levels allow detection of concurrent iron deficiency in anemic patients with Rheumatoid Arthritis

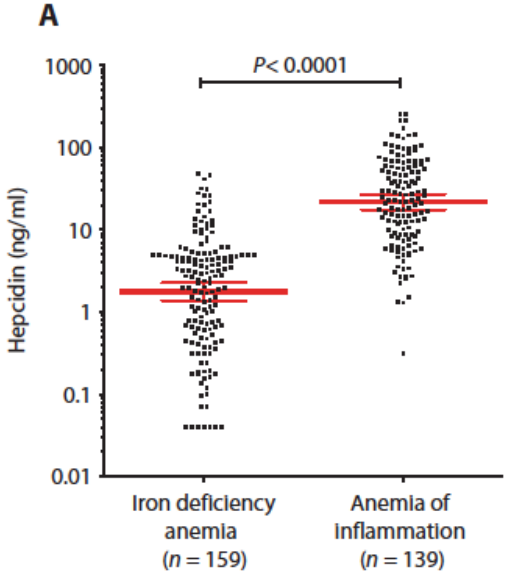


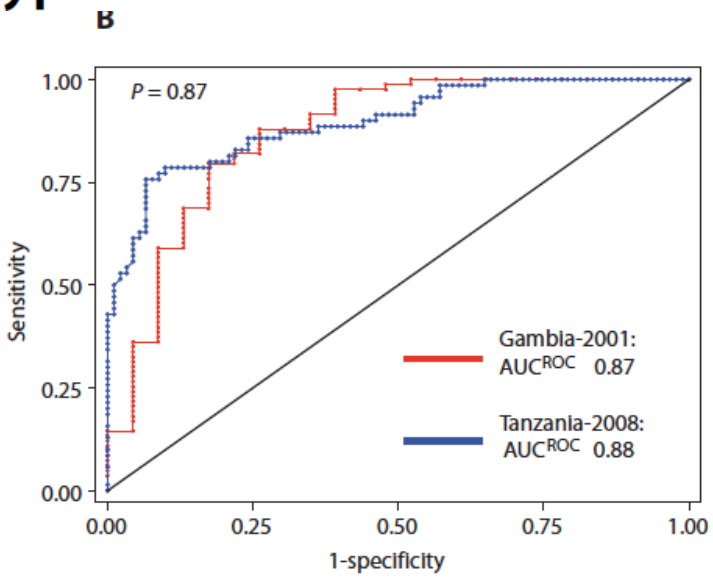


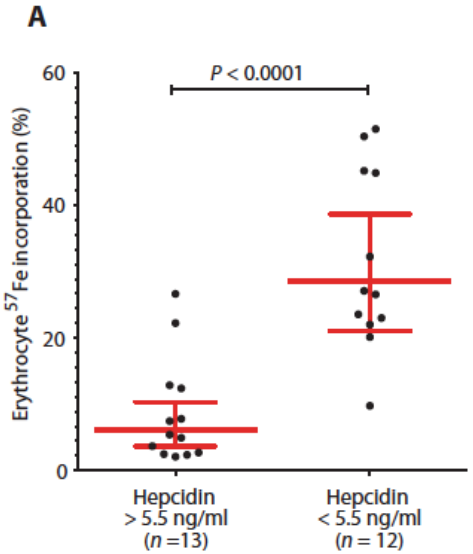
↓ hepcidin pts. may benefit from iron

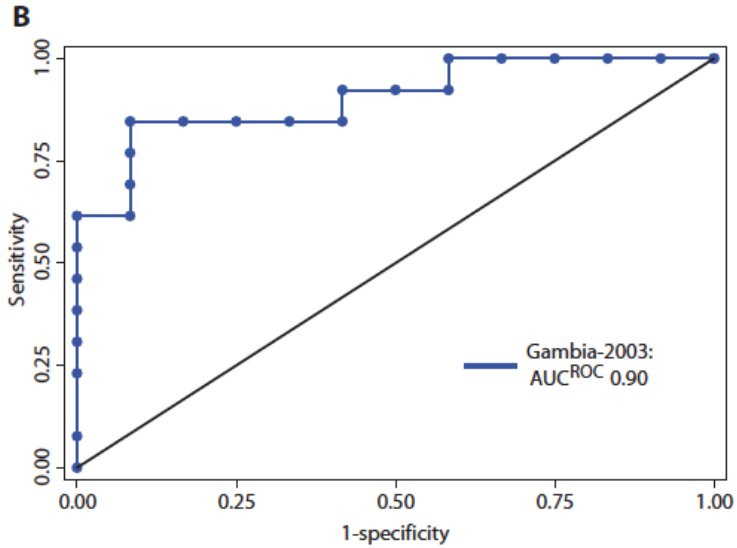
van Santen S, Arthritis & Rheumatism 2011

Expression of the Iron Hormone Hepcidin Distinguishes Different Types of Anemia in African Children



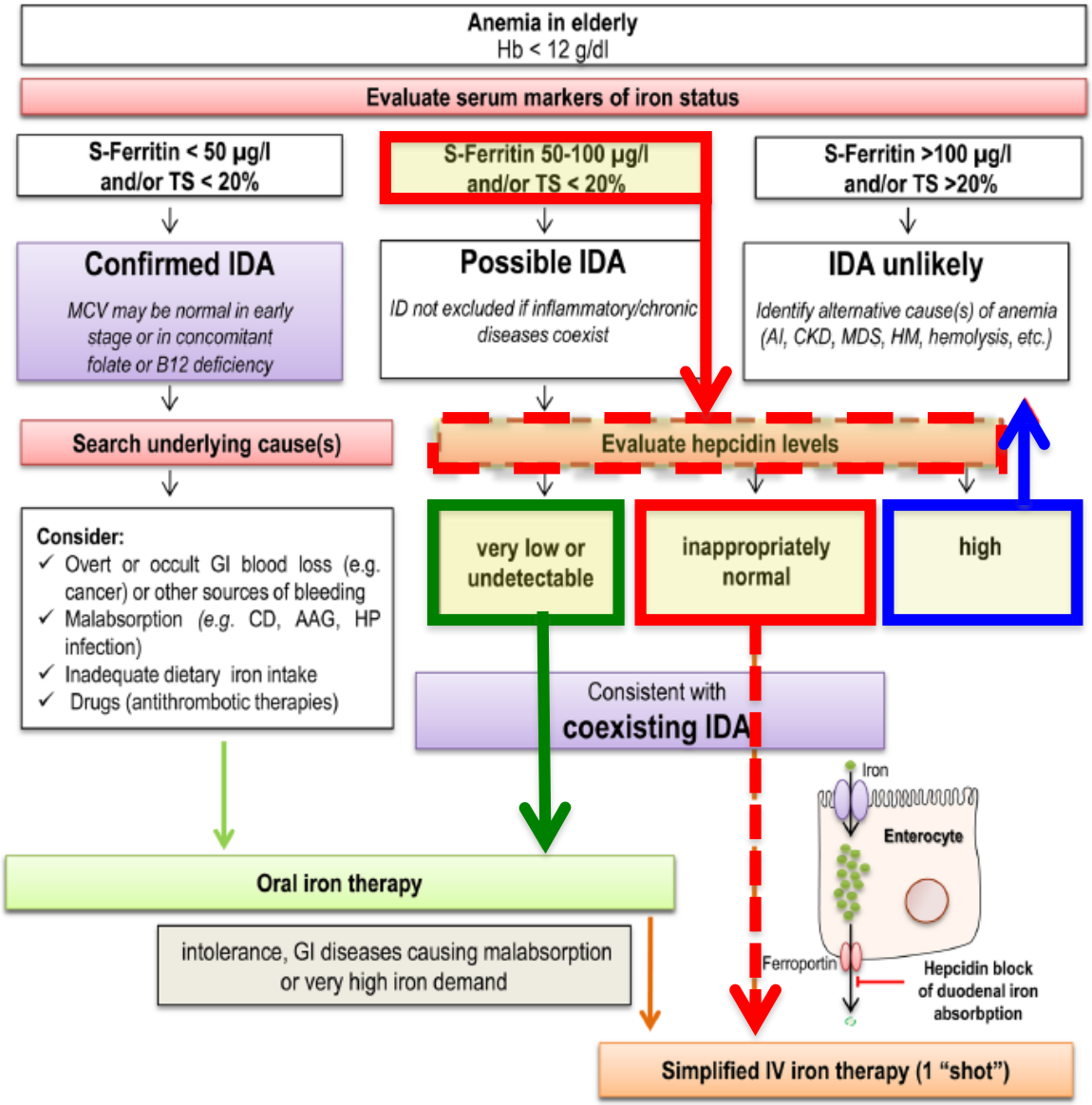






Pasricha SR, Sci Transl Med 2014

IDA in elderly: revisited in the hepcidin era



Busti F, Front Pharmacol 2014

Pharmacology of hepcidin

Review

Cell PRESS

The pathophysiology and pharmacology of hepcidin

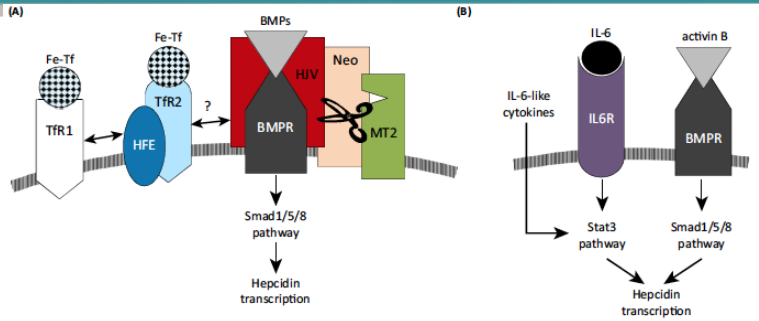


Table 1. Principles of hepcidin-targeting therapeutic approaches

Therapeutic approach	Targeted disease	Mode of action	Agents
Hepcidin agonists	Iron overload (hereditary hemochromatosis and iron-loading anemias)	Hepcidin mimics	Minihepcidins [47]
		Stimulators of hepcidin production	Gene silencing of TMPRSS6 [50,51]
			BMP pathway agonists [52]
Hepcidin antagonists	Iron-restricted anemias (anemia of inflammation, anemia of chronic kidney disease, anemia of cancer, IRIDA)	Suppressors of hepcidin production	BMP pathway inhibitors [54,56,74]
			Anti-inflammatory agents [60–62]
			Erythropoiesis-stimulating agents [65]
			Gene silencing of hepcidin and its regulators [66][a]
		Hepcidin peptide neutralizing binders	Anti-hepcidin antibodies [67][b]
			Anticalins [68]
			Spiegelmers [69]
		Agents interfering with hepcidin–ferroportin interaction	Anti-ferroportin antibodies [71]
			Thiol modifiers [72]

[a] http://ir.isispharm.com/phoenix.zhtml?c=222170&p=irol-newsArticle&ID=1828284&highlight=

[b] http://www.clinicaltrials.gov/ct2/show/NCT01340976

Ruchala P & Nemeth E, Trends Pharmacol Sci 2014

Anemia in elderly: TAKE-HOME MESSAGES

- ✓ **Anemia in elderly → major influence on QoL and mortality.**
- ✓ **Whenever possible, the cause(s) should be identified and treated (part. nutritional deficiencies).**
- ✓ **IDA and ACD (both involving iron/hepcidin) are the most frequent forms, which often coexists because of typical multimorbidity in elderly.**
- ✓ **The classical diagnostic criteria for single-cause anemia in the younger does not work adequately.**
- ✓ **Recent advances in iron metabolism may be of help in either diagnosis or in selecting the best treatment option, particularly since IV iron therapy is becoming simpler than ever.**

Busti F, Front Pharmacol 2014 (adapted)

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

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