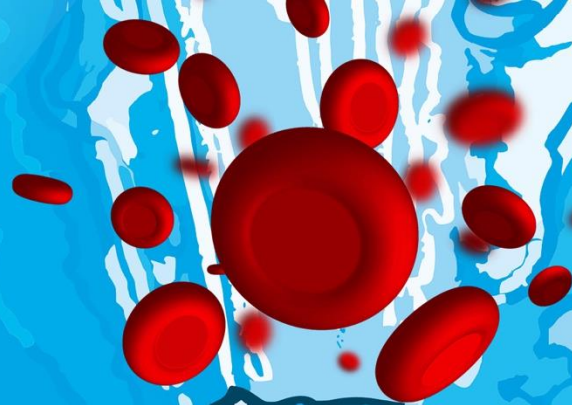




Meeting del CLUB DEL

Anemie da carenza: nuove prospettive diagnostiche

Irene Motta

Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
Università degli Studi di Milano

Globulo Rosso 2026

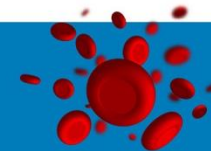
NAPOLI

28-29 SETTEMBRE 2026

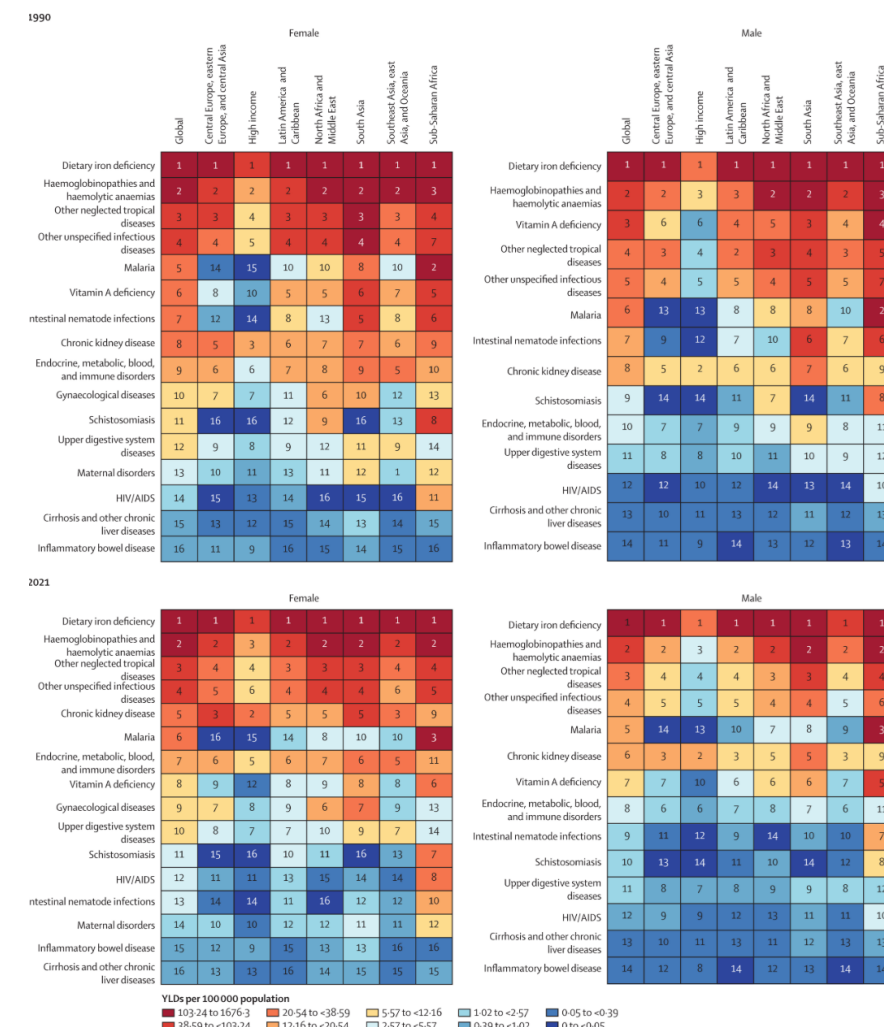
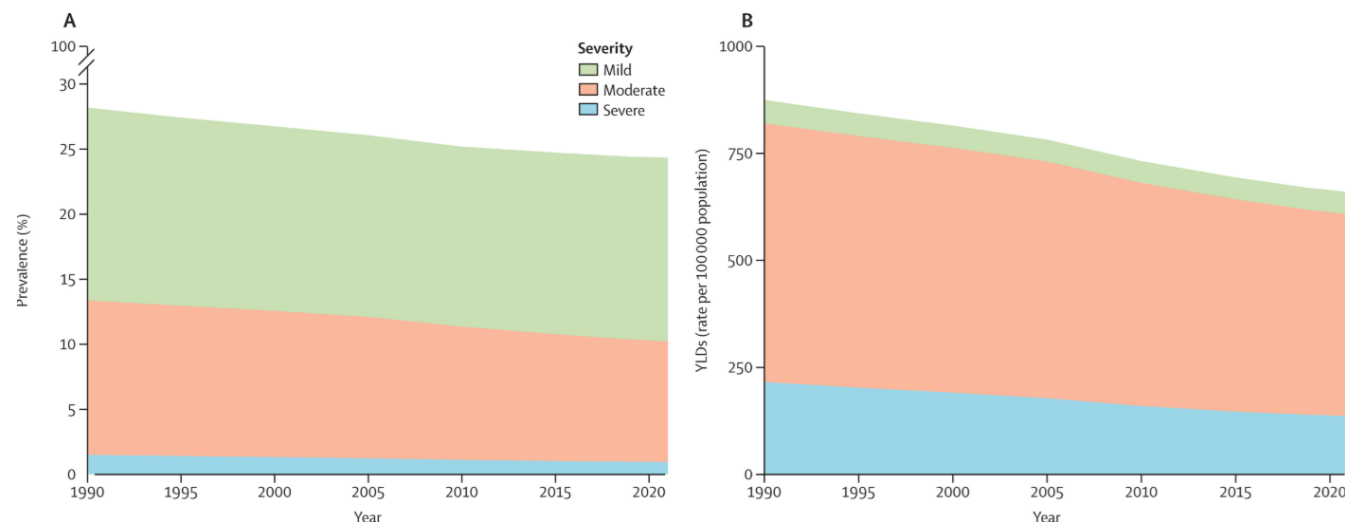
Complesso dei SS. Marcellino e Festo

Disclosures – Irene Motta

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Agios			x				
Avanzanite			x		x	X	
BMS			x		x	X	
Chiesi							
Sanofi	x		x		x	X	
Vertex			x		x	X	



Anemia: un problema di salute globale



- 24% della popolazione mondiale è anemica: **1.9 miliardi**
- **1 caso su 2** è dovuto a **sideropenia**
- Anemia sideropenica: tra le **prime 5 cause di YLD (WHO)**



GBD 2021 Anaemia Collaborators, Lancet Haematol 2023

MEETING DEL CLUB DEL GLOBULO ROSSO 2026

NAPOLI, 28-29 SETTEMBRE 2026

Carenza di ferro: una risoluzione lenta e incompleta

- **13084 pazienti** (2010-2020) con carenza di ferro (ferritina ≤ 25 ng/mL)
- **58.1%** senza risoluzione (ferritina ≥ 50 ng/mL) entro 3 anni dalla diagnosi
- Solo **6.8%** (882) con risoluzione a 1 anno
- Tempo mediano alla risoluzione: **1.9 anni** (IQR 0.8-3.9)

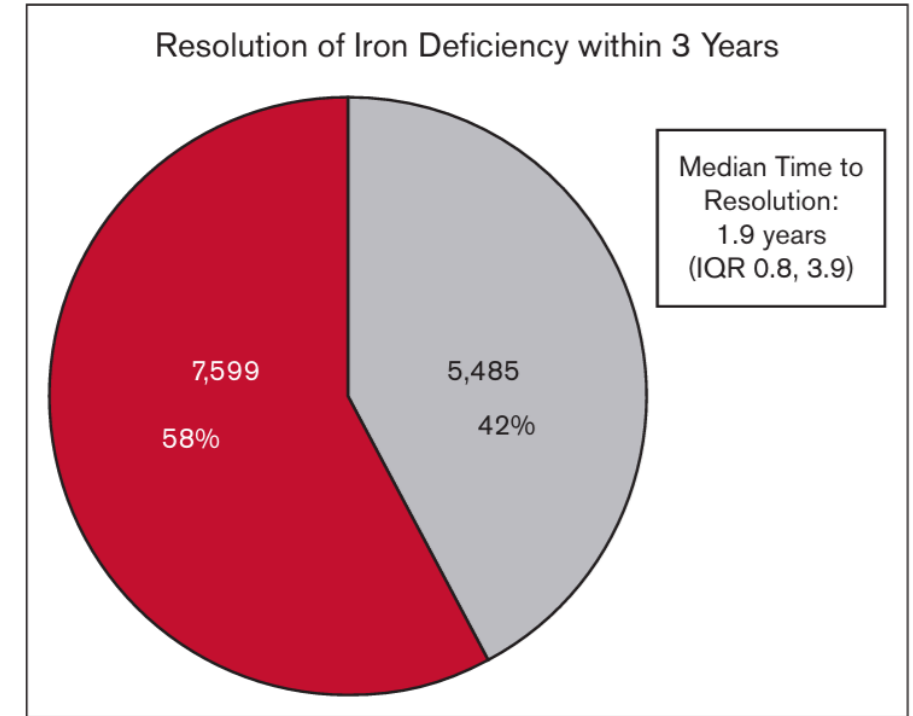


Figure 2. Rate of resolution of ID and time to resolution. Of 13 084 patients in the final study cohort, 5485 (42%) had documented ID resolution within 3 years of their initial diagnostic ferritin level. The median time to resolution among these patients was 1.9 years (IQR, 0.8-3.9). There were 7599 patients (58%) who did not have documented resolution within 3 years (eg, at least 1 additional ferritin level of <50 ng/mL).

Cogan CJ, Blood Advances 2024



Chi risolve la carenza di ferro?

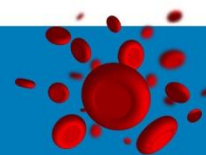
Table 2. Association of patient characteristics and resolution of ID

Characteristic	aHR	95% CI	P
Age, y			
40-59 vs 18-39	1.26	(1.18-1.35)	<.001
≥60 vs 18-39	1.56	(1.44-1.69)	<.001
Sex			
Male vs female	1.58	(1.48-1.70)	<.001
Race			
Asian vs White	0.89	(0.78-1.02)	.1
Black vs White	0.73	(0.66-0.80)	<.001
Multiracial vs White	0.97	(0.79-1.18)	1.0
Insurance			
Medicaid/other public vs private	1.03	(0.95-1.12)	.4
Medicare vs private	1.13	(1.05-1.21)	.001
Uninsured vs private	0.97	(0.86-1.10)	1.0
Medication type			
IV only vs oral only	2.96	(2.66-3.30)	<.001
Both vs oral only	1.93	(1.81-2.06)	<.001
Neither vs oral only	0.86	(0.79-0.93)	<.001

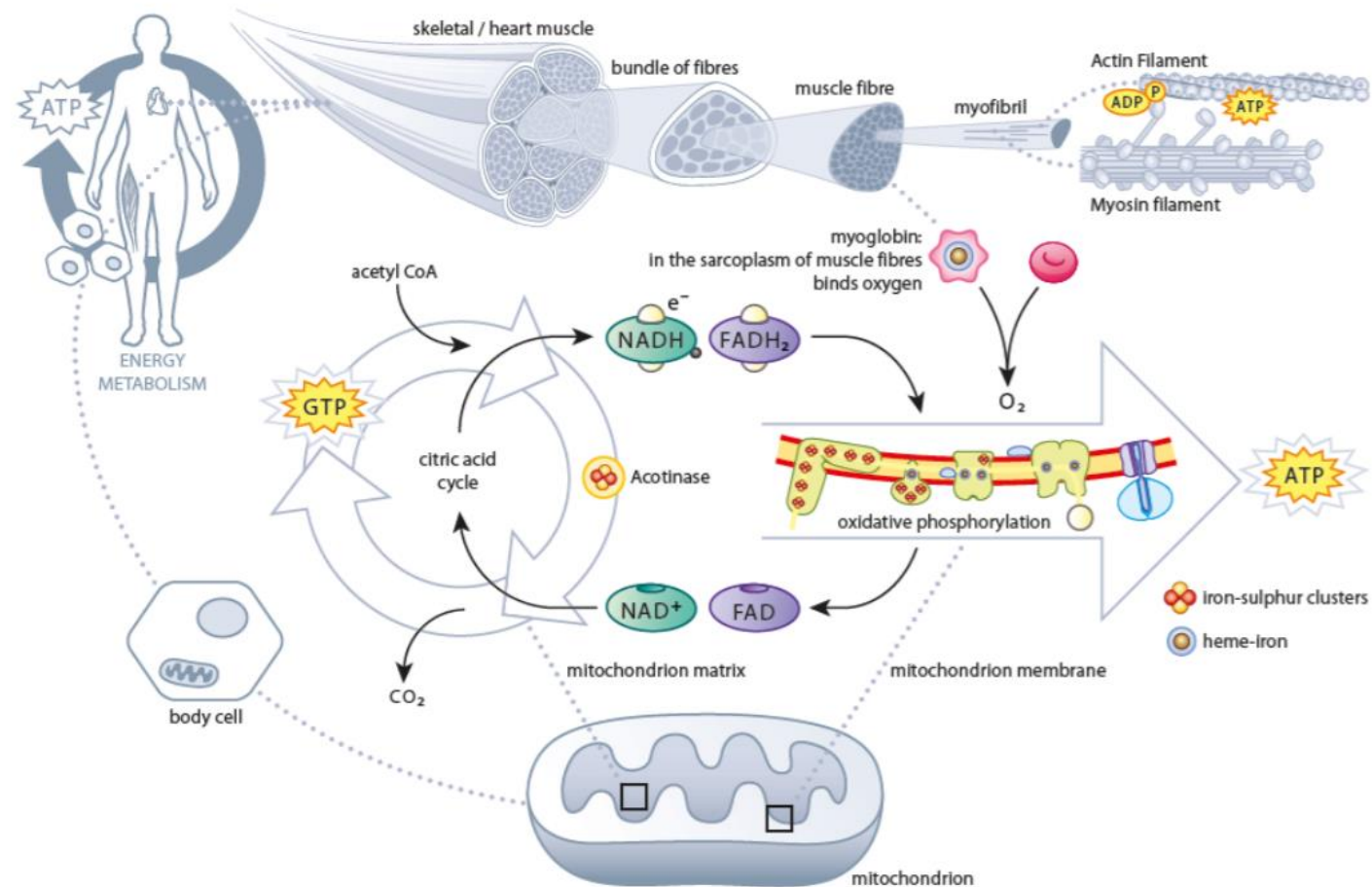
- **Età ≥60 anni:** maggior probabilità di risoluzione (aHR 1.56)
- **Donne e afroamericani:** minore probabilità di risoluzione
- **Ferro EV:** probabilità di risoluzione quasi tripla (aHR 2.96)



Cogan CJ, Blood Advances 2024



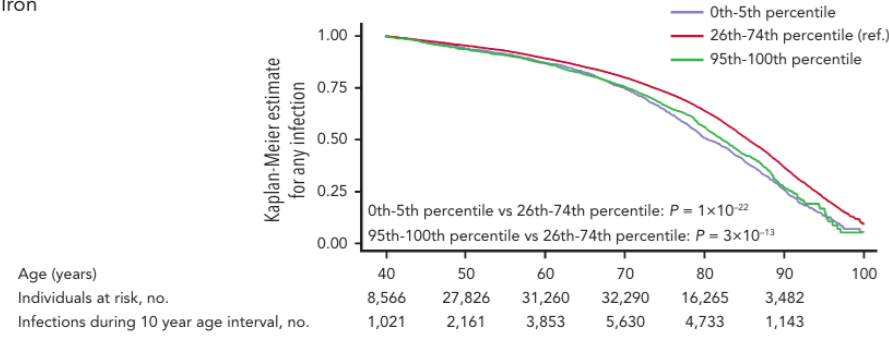
Il ferro è essenziale per l'organismo



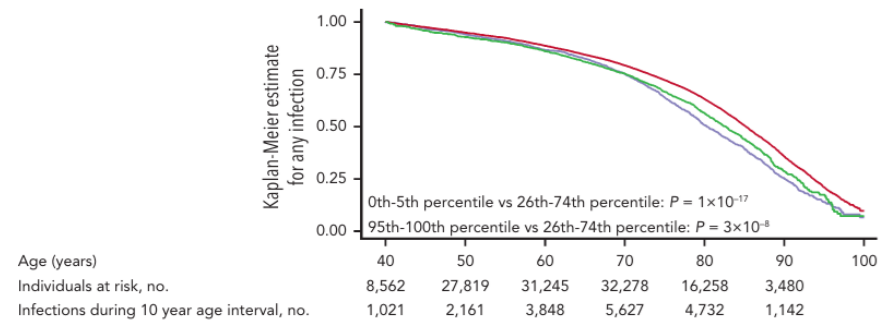
Musallam KM, Curr Med Res Opin 2017

Carenza e sovraccarico di ferro: un rischio infettivo a U

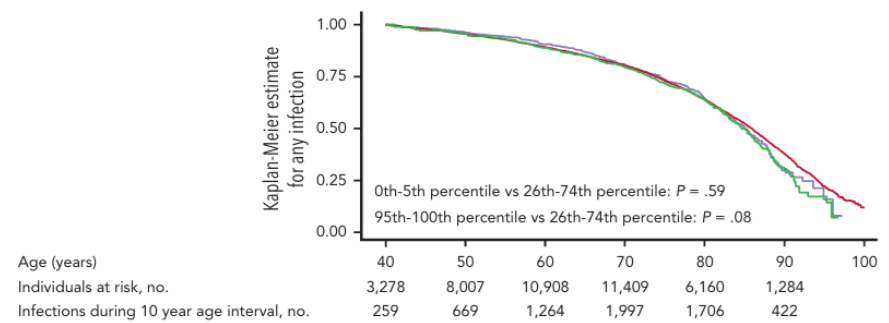
Iron



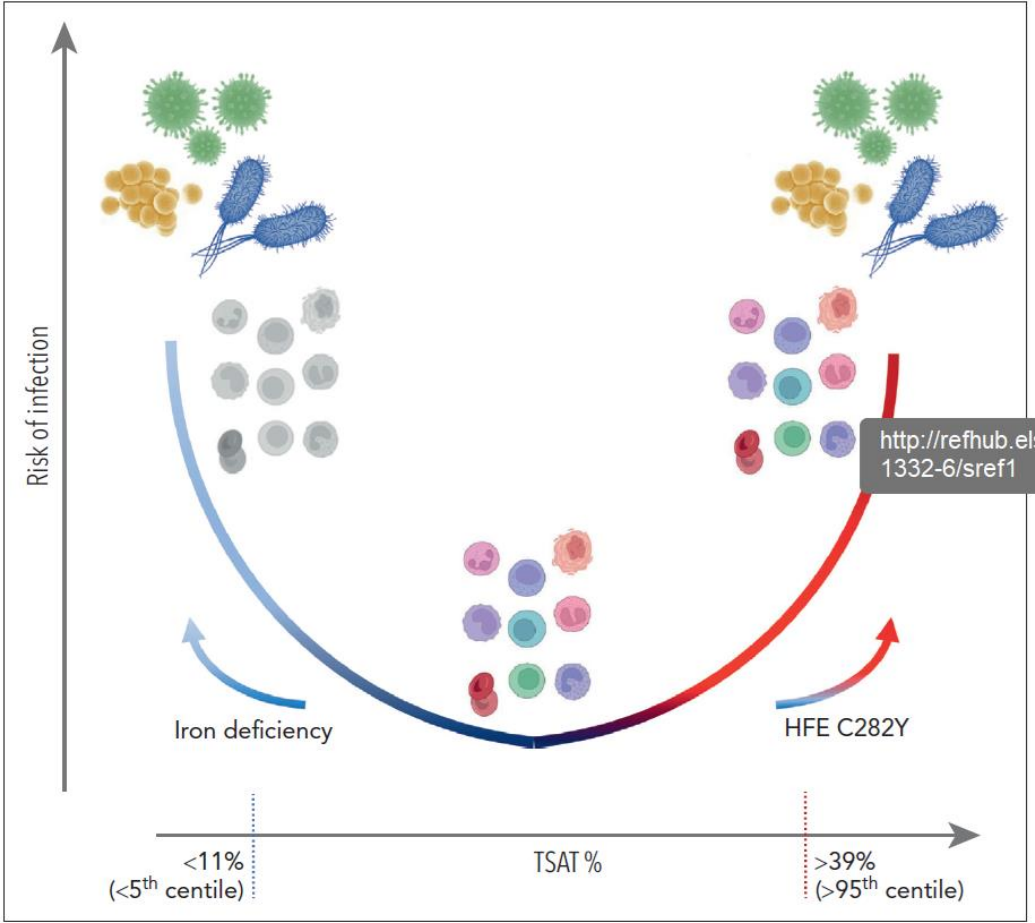
Transferrin saturation



Ferritin



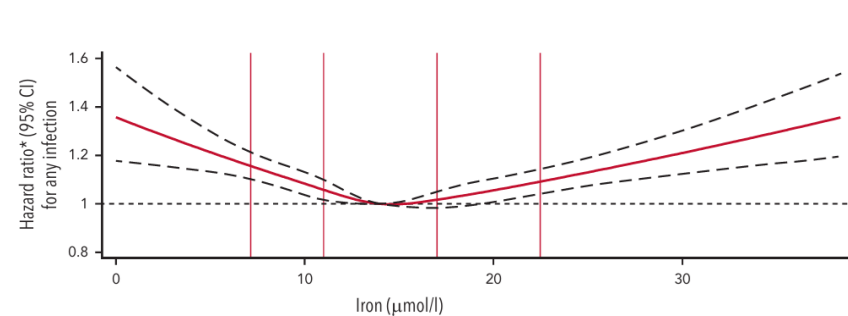
142.188 pazienti seguiti longitudinalmente, FU mediano 8 anni (0-38)



Mottelson M, Blood 2024



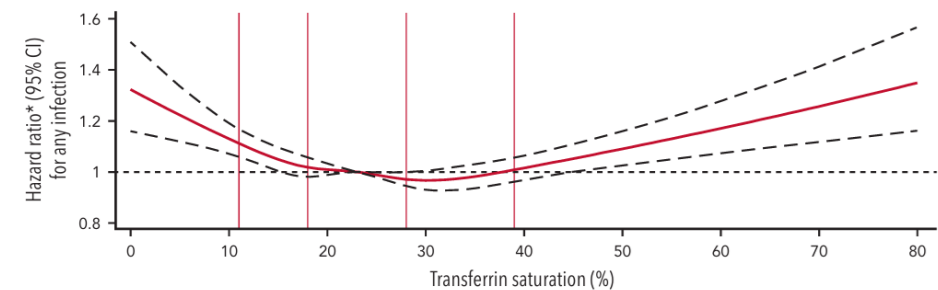
Stato marziale e rischio di infezioni



Percentiles	0th-5th	6th-25th	26th-74th	75th-94th	95th-100th
Iron (μmol/l)	0-7.1	7.2-11.0	11.1-17.0	17.1-22.4	22.5-130.2
Individuals, no.	7,234	29,815	63,570	28,859	7,178
Infections, no.	1,111	4,338	8,409	4,015	1,037
Hazard ratio* (95% CI)	1.20 (1.12-1.28)	1.08 (1.04-1.12)	(ref.)	1.04 (1.00-1.08)	1.14 (1.07-1.22)
P	4×10 ⁻⁸	.0001	(ref.)	.07	9×10 ⁻⁵

When additionally performing competing risk analysis with death as competing risk:

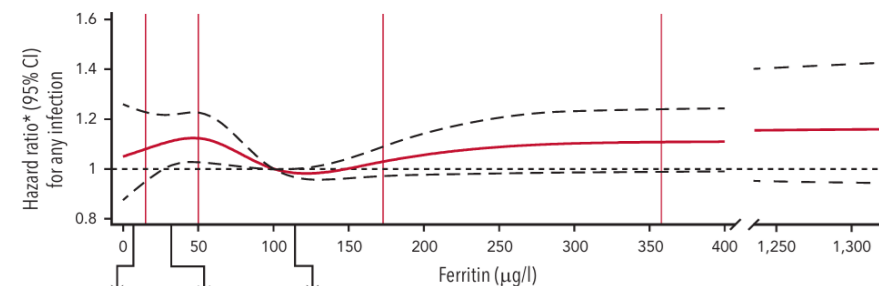
Subhazard ratio* (95% CI)	1.15 (1.08-1.23)	1.07 (1.03-1.11)	(ref.)	1.02 (0.98-1.06)	1.10 (1.03-1.17)
---------------------------	------------------	------------------	--------	------------------	------------------



Percentiles	0th-5th	6th-25th	26th-74th	75th-94th	95th-100th
Transferrin sat. (%)	0-11.0	11.1-18.0	18.1-27.9	28.0-38.9	39.0-195
Individuals, no.	7,401	31,749	58,997	32,176	6,276
Infections, no.	1,068	4,362	8,027	4,450	993
Hazard ratio* (95% CI)	1.18 (1.10-1.26)	1.03 (1.00-1.07)	(ref.)	0.98 (0.95-1.02)	1.10 (1.03-1.17)
P	9×10 ⁻⁷	.09	(ref.)	.33	.007

When additionally performing competing risk analysis with death as competing risk:

Subhazard ratio* (95% CI)	1.14 (1.07-1.22)	1.02 (0.98-1.06)	(ref.)	0.98 (0.95-1.02)	1.07 (1.00-1.14)
---------------------------	------------------	------------------	--------	------------------	------------------



Percentiles	0th-5th	6th-25th	26th-74th	75th-94th	95th-100th
Ferritin (μg/l)	0-15.0	15.1-50.0	50.1-172.9	173.0-357.9	358.0-17200
Individuals, no.	2,095	7,427	18,812	7,775	1,911
Infections, no.	278	1,161	3,297	1,371	318
Hazard ratio* (95% CI)	1.06 (0.93-1.21)	1.07 (1.00-1.15)	(ref.)	1.03 (0.96-1.09)	1.03 (0.91-1.16)
P	.36	.04	(ref.)	.44	.65

When additionally performing competing risk analysis with death as competing risk:

Subhazard ratio* (95% CI)	1.00 (0.88-1.13)	1.07 (1.00-1.15)	(ref.)	1.01 (0.95-1.08)	0.91 (0.81-1.02)
---------------------------	------------------	------------------	--------	------------------	------------------

- Ferro e TSAT bassi: **rischio infettivo aumentato**
- Rischio aumentato anche per **valori elevati**
- Ferritina: associazione debole



Mottelson M, Blood 2024

Cut-off per la diagnosi di carenza di ferro – nuove linee guida ASH 2026

Diagnostic thresholds for iron deficiency

ASH 2026 guidance • Diagnose irrespective of anemia



CHILDREN 9 MONTHS–4 YEARS

Ferritin ≤ 20 ng/mL

Without known or suspected inflammation



OLDER CHILDREN & ADOLESCENTS

>4 years to adolescence: **ferritin ≤ 20 ng/mL**

Non-menstruating adolescents:
ferritin < 30 ng/mL



ADULTS

Ferritin ≤ 30 ng/mL

With symptoms or ongoing risk factors: **≤ 50 ng/mL**
Excludes menstruating and pregnant individuals



MENSTRUATING INDIVIDUALS

Ferritin ≤ 30 ng/mL

HMB, AUB, symptoms, risk factors,
surgery or planning pregnancy:
 ≤ 50 ng/mL



PREGNANCY

Ferritin ≤ 30 ng/mL

With anemia: **≤ 50 ng/mL** may be
appropriate



ADULTS WITH ANEMIA OF INFLAMMATION

Measure ferritin + TSAT

Iron deficiency may be considered if:
TSAT $< 20\%$ OR ferritin < 100 ng/mL

Source: Powers JM et al. *Blood Advances*. 2026. doi:10.1182/bloodadvances.2025015950

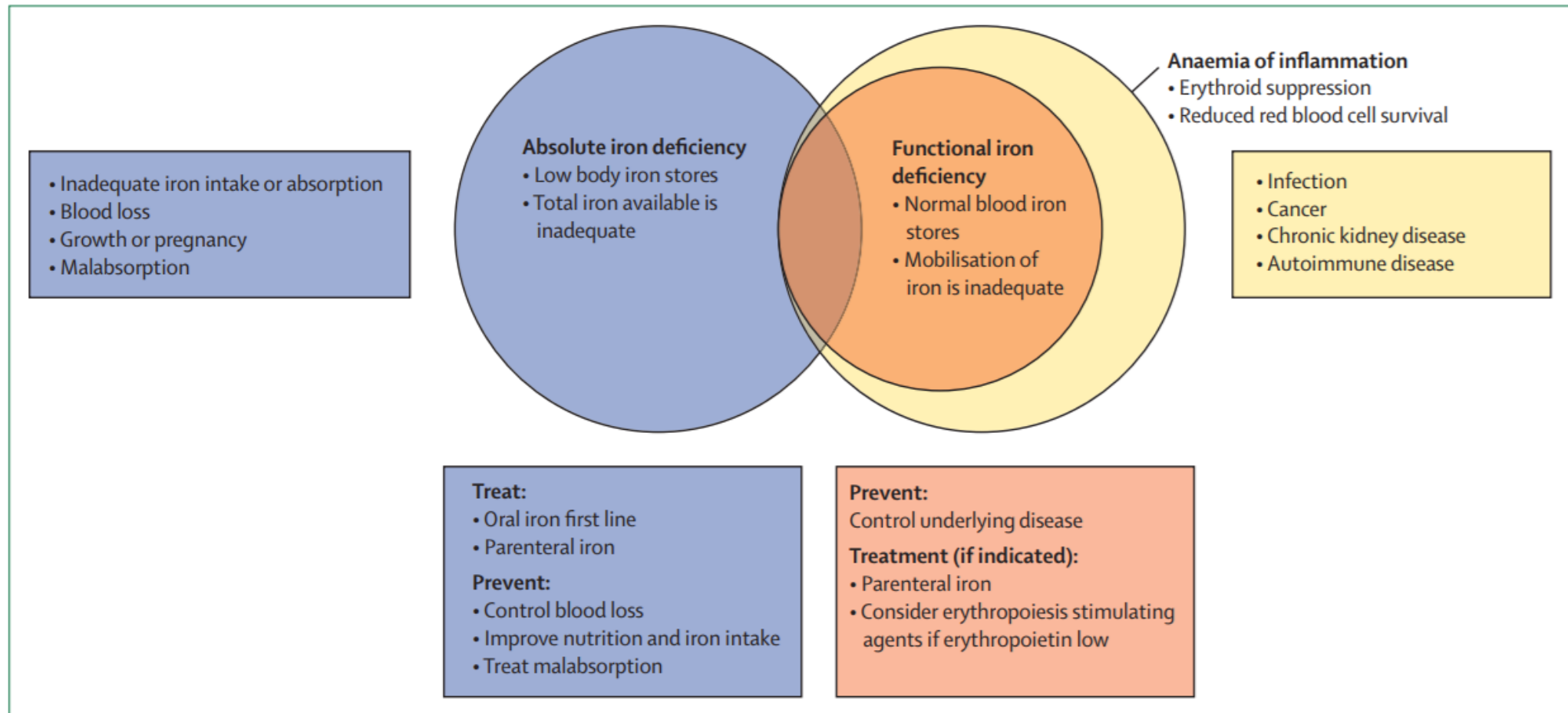


Powers JM, Blood Advances 2026

MEETING DEL CLUB DEL GLOBULO ROSSO 2026

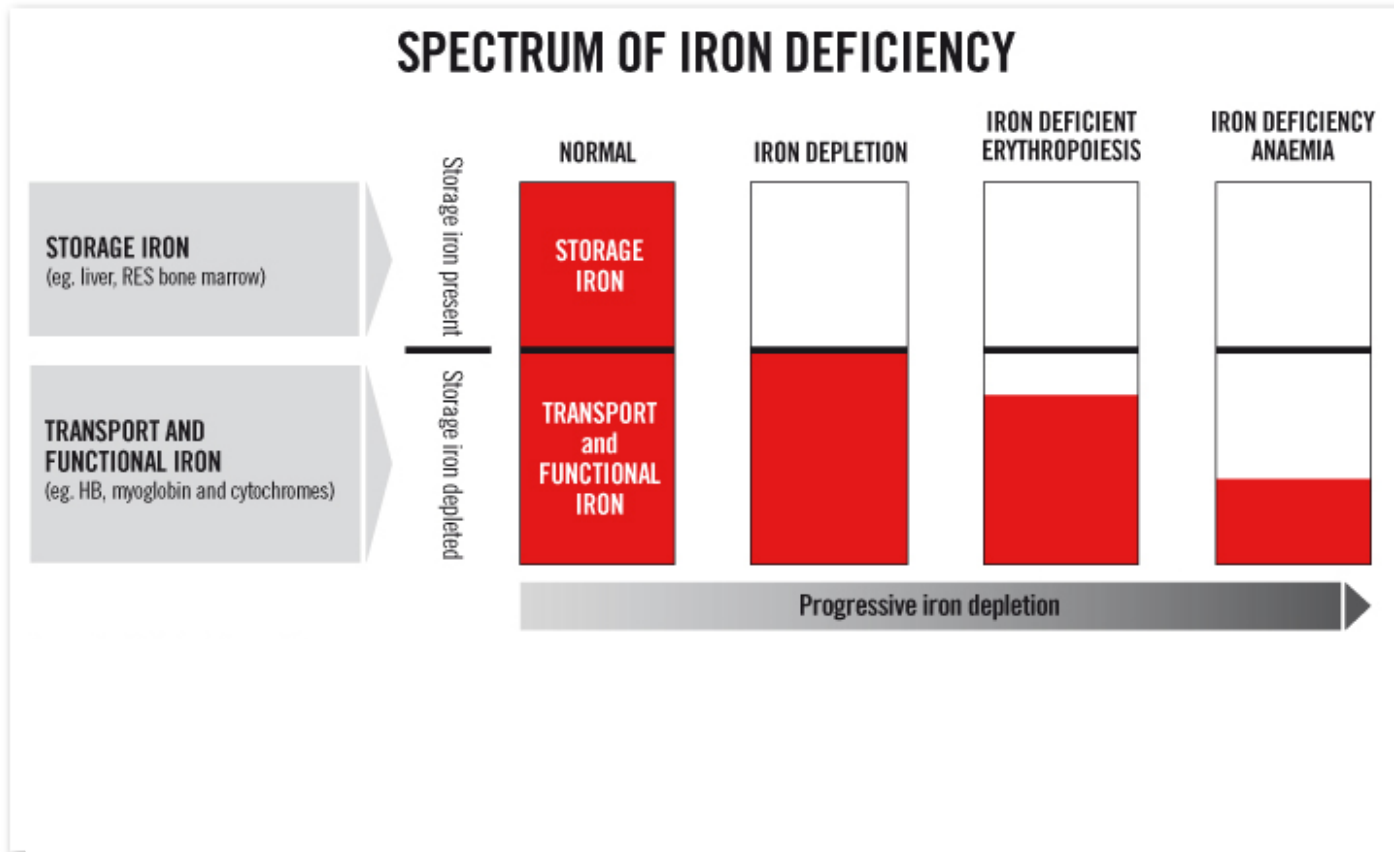
NAPOLI, 28-29 SETTEMBRE 2026

Carenza di ferro assoluta e funzionale



Pasricha SR, Lancet 2021

Dalla carenza di ferro all'anemia sideropenica



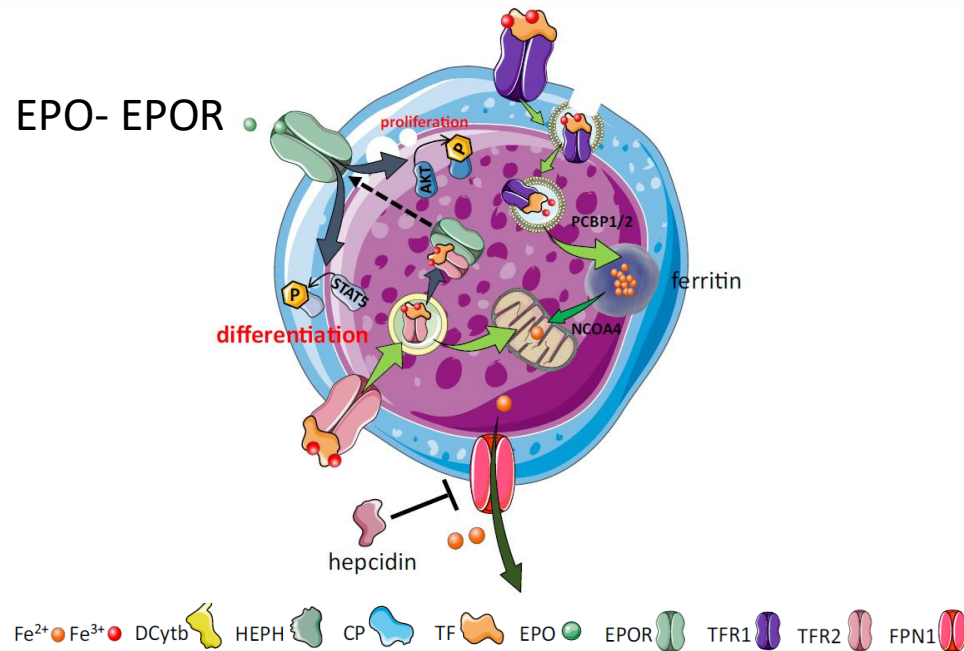
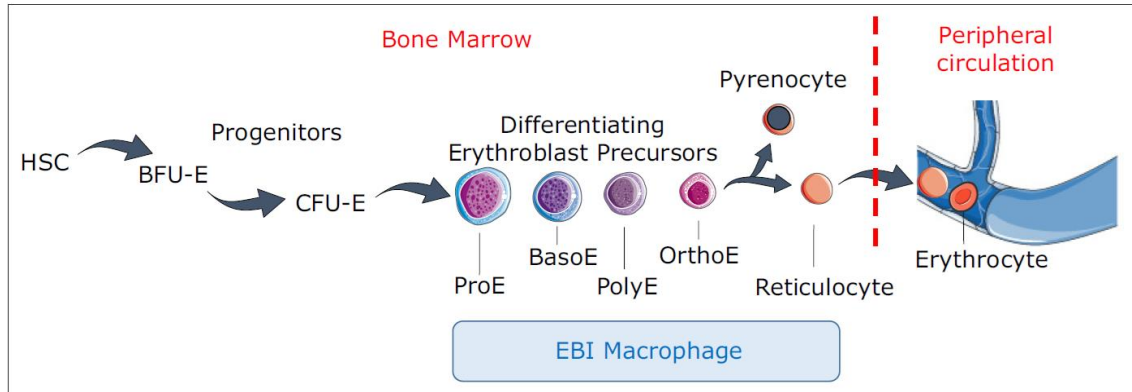
- Progressione graduale, spesso a lungo silente

Modified with permission from Sarah Cusick PhD, Centers for Disease Control and Prevention, 2008.

transfusion.com.au

 **Australian Red Cross**
BLOOD SERVICE

Eritropoiesi normale



EBI: erythroblastic island

Legame EPO-EPOR

- Induce la sopravvivenza dei precursori eritroidi, divisione cellulare e differenziazione (EPO/EPOR/JAK2/STAT5)

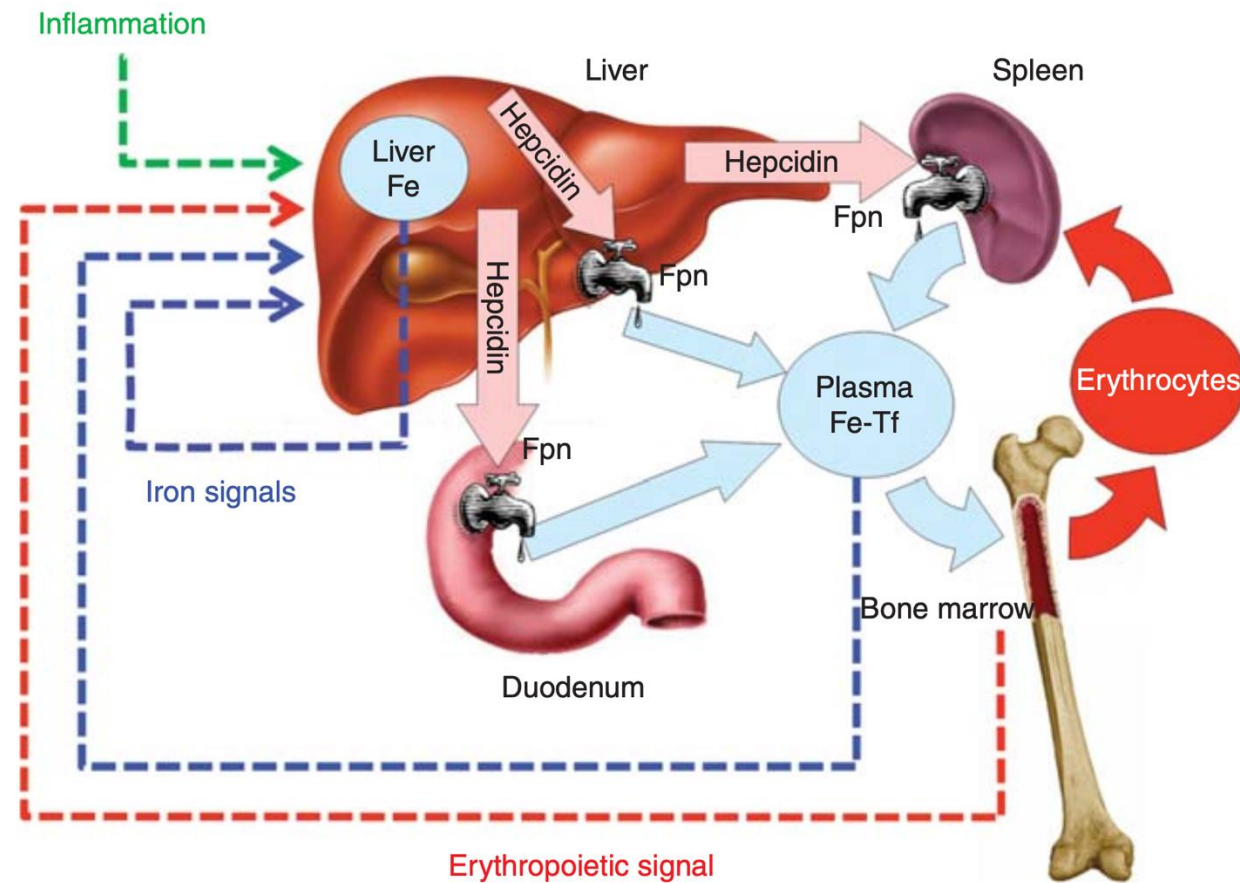


topi muoiono a livello embrionale se EPO o EPOR deleti

Ferro

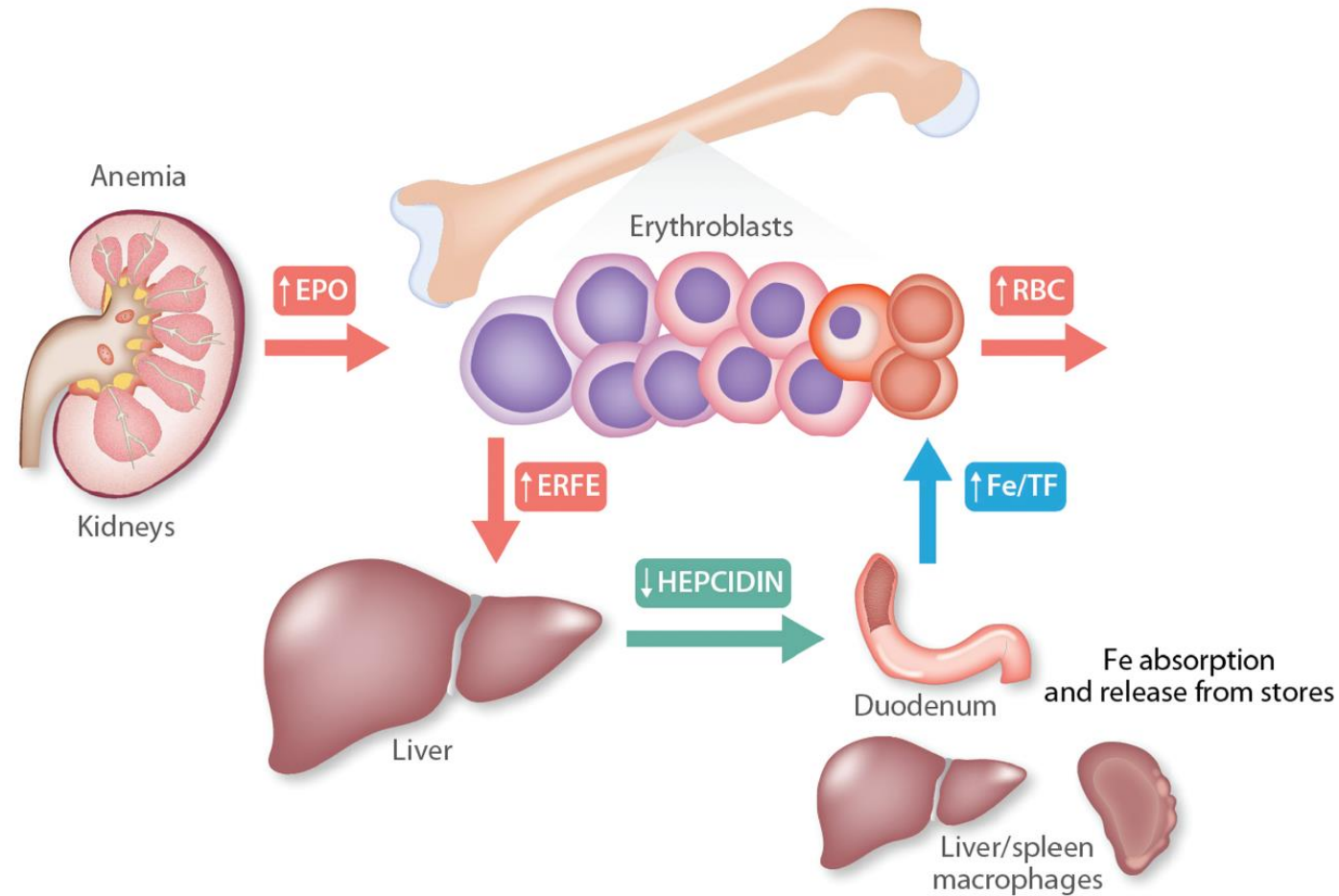
- Necessario per la sintesi di Hb (eme)
- Modula la risposta ad EPO
- È essenziale per la differenziazione da early a late-stage eritroblasti

Regolazione del ferro circolante



Ganz T, Cold Spring Harb Perspect Med 2012

Epcidina ed eritropoiesi



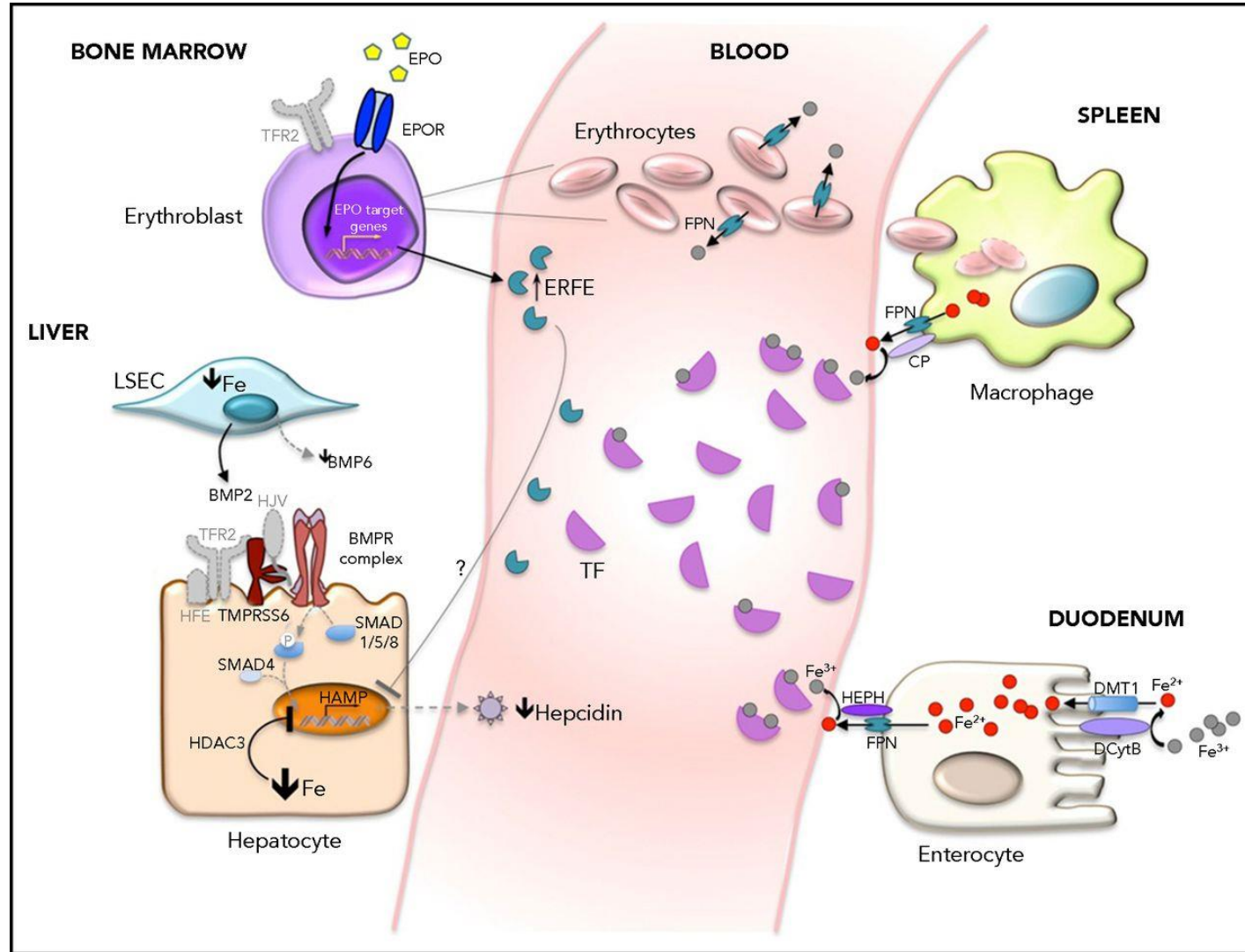
Coffey R, HemaSphere 2018

Anemia da carenza di ferro

↓ BMP-SMAD signaling

HJV è clivata dalla superficie da TMPRSS6

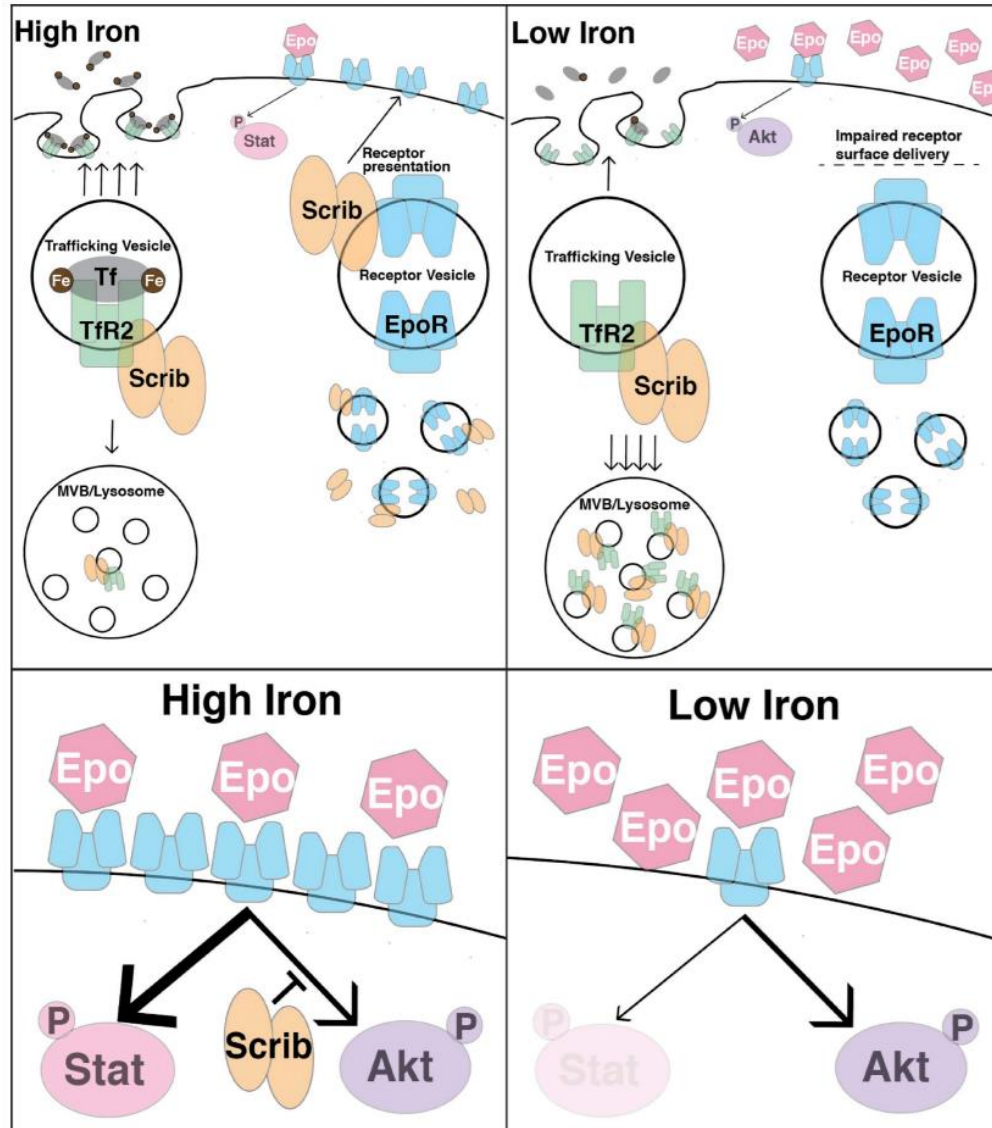
TFR2 non è stabilizzato sulla superficie cellulare



Camaschella C, Blood 2019

Iron-restricted erythropoiesis

Erythroid cell



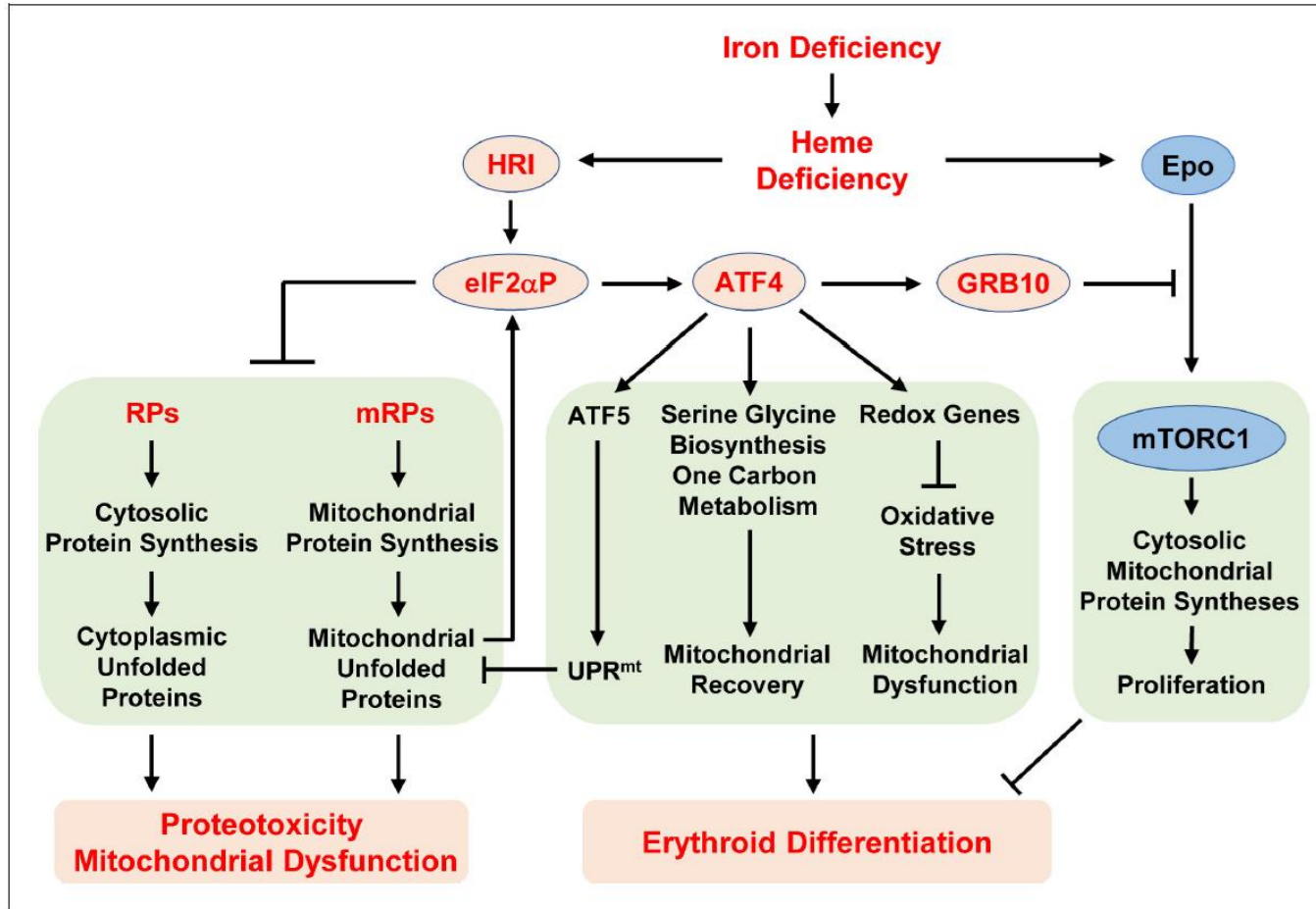
Iron Response Factors

- TFR2: Trafficking vescicole TfR2 principalmente verso lisosomi → accelerato catabolismo del complesso TfR2-Scribble
- Scribble down-regulation → compromissione del trasporto di EPOR sulla membrana

Carenza di ferro → impatto su differenziazione dei precursori eritroidi con ridotta risposta ad EPO da parte degli ERITROBLASTI

Khalil S, J Exp Med 2018
Nai A, Blood 2014

HRI e la risposta eritroide alla carenza di ferro



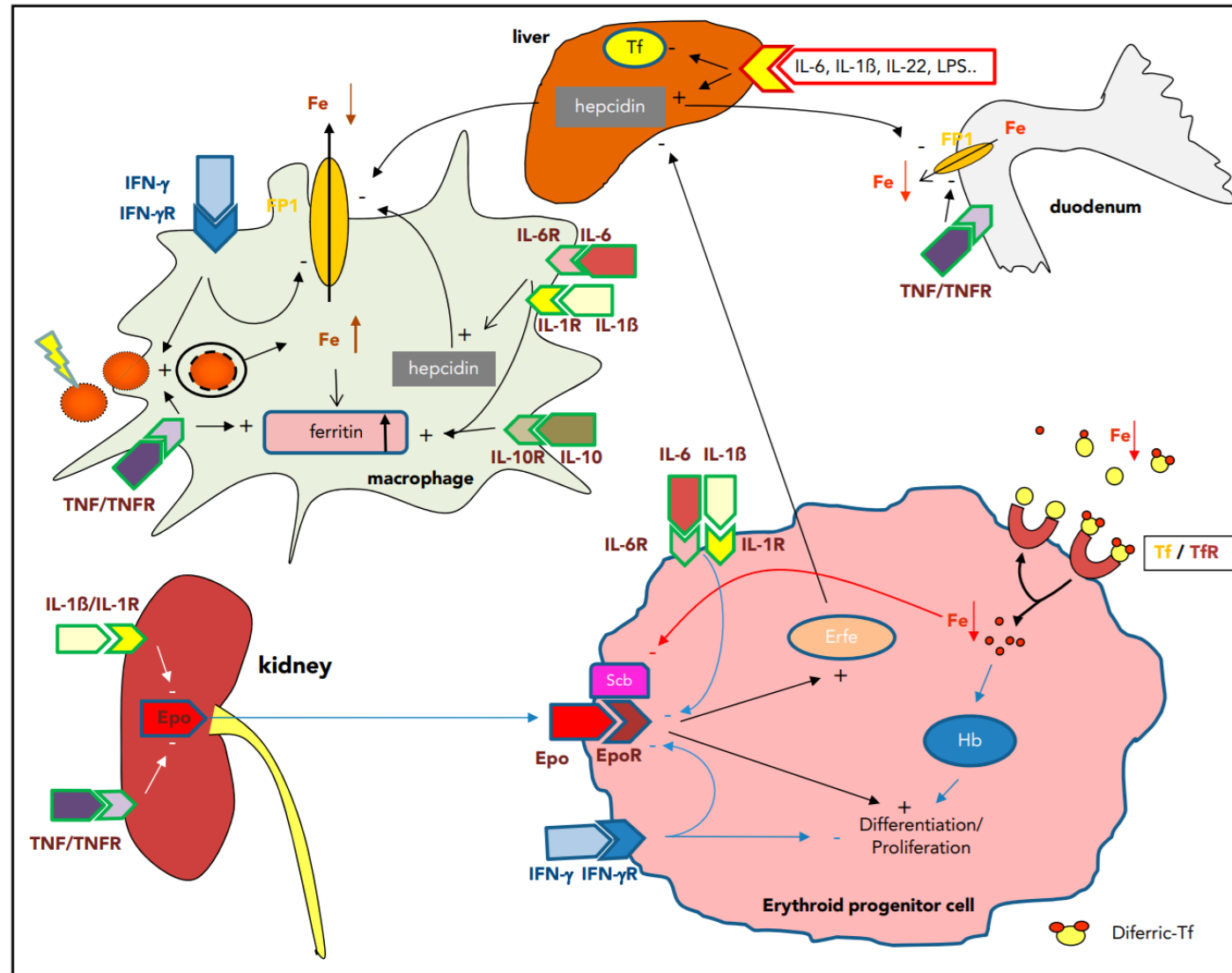
- Il deficit di ferro ed eme attiva la kinasi **HRI**
- HRI fosforila **eIF2α**: inibizione della sintesi proteica citosolica e mitocondriale → previene l'accumulo di proteine mal ripiegate (**proteotossicità**)
- **ATF4** attiva geni per il recovery mitocondriale e riduzione dello stress ossidativo
- ATF4 induce **GRB10**, che inibisce la via EPO–mTORC1 → ridotta proliferazione a favore della differenziazione nell'eritropoiesi da stress



HRI: heme-regulated inhibitor

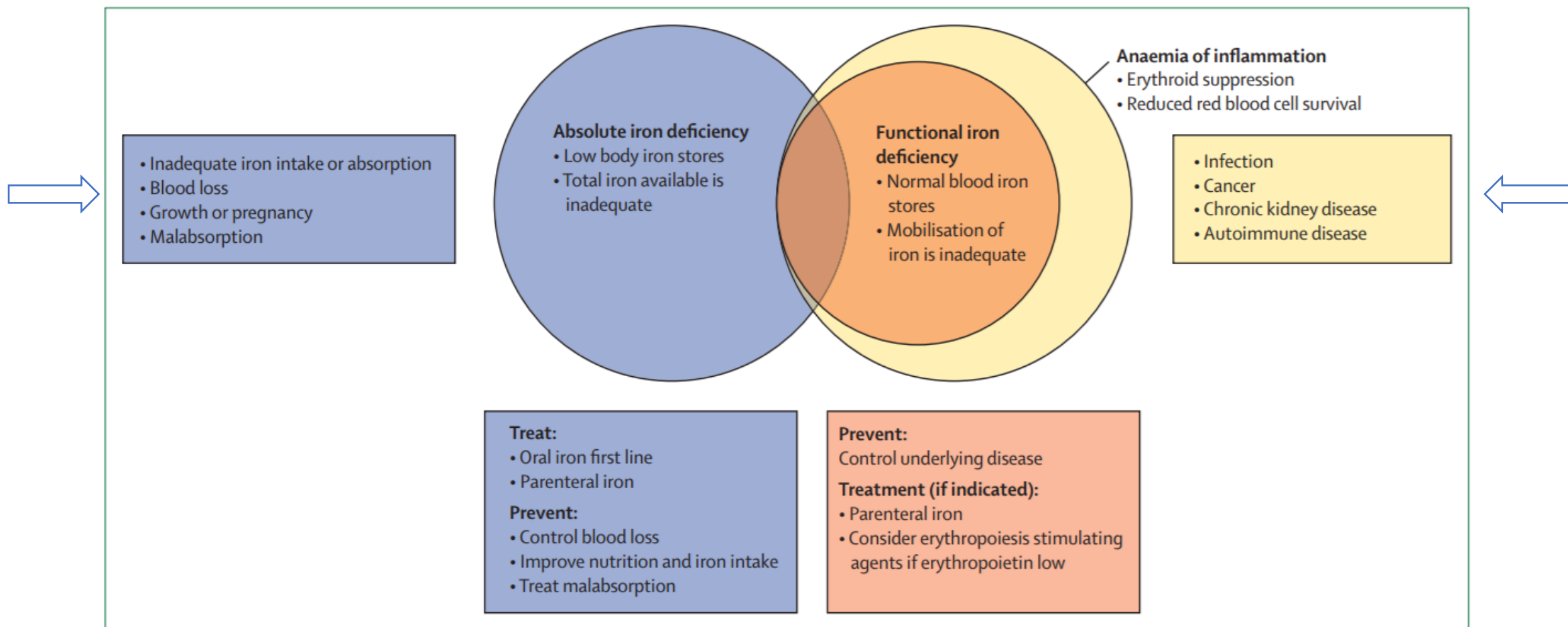
Zhang S, eLife 2019

Anemia dello stato infiammatorio



Weiss G, Blood 2019

Carenza di ferro assoluta e funzionale



Pasricha SR, Lancet 2021

Cause di carenza di ferro assoluta

Panel 1: Causes of absolute iron deficiency

Inadequate iron uptake

- Inadequate nutritional iron intake
 - Inadequate dietary iron content
 - Low haem iron content (eg, from a vegetarian or vegan diet)
 - ▶ • Food insecurity or low dietary diversity* (eg, resulting from poverty, especially in low-income countries)
 - ▶ • Low iron content complementary diet* (eg, prolonged breastfeeding, or milk preference)
- Inadequate nutritional iron absorption
 - Concomitant consumption of inhibitors of iron absorption (eg, calcium or tea)
 - Inadequate stomach acidification
 - Atrophic gastritis
 - ▶ • Use of antacids or proton pump inhibitors*
 - *Helicobacter pylori* infection
 - Procedures after gastric bypass
 - Intestinal mucosal dysfunction (eg, coeliac disease* or inflammatory bowel disease)
 - Obesity
 - Inappropriately increased hepcidin concentrations preventing iron absorption (eg, during chronic inflammation or iron-refractory iron deficiency anaemia caused by *TMPRSS6* mutations)

Increased iron requirements

- Growth (eg, during early childhood and adolescence)*
- Pregnancy*
- Physiological blood losses exceeding iron intake*
- Erythropoiesis stimulating agent therapy*

Blood loss

- Intestinal blood loss
 - Oesophageal
 - Varices
 - Carcinoma
 - Ulceration
 - Reflux oesophagitis
 - Gastric*
 - Gastric cancer and gastric polyps*
 - Gastric ulcers*
 - Use of aspirin and other non-steroidal anti-inflammatory drugs*
 - Angiodysplasia, telangiectasia, and gastric antral vascular ectasia (watermelon stomach)
 - Small bowel
 - Hookworm (*Ancylostoma duodenale* and *Necator americanus*)*
 - Inflammatory bowel disease*
 - Duodenal ulcers
 - Lymphoma, cancer, and polyps
 - Angiodysplasia, telangiectasia, and Meckel's diverticulum
 - Extreme exercise-induced gastrointestinal bleeding
 - Milk protein allergy (in infants younger than 12 months)
 - ▶ • Colon
 - Colon cancer*
 - Polyps*
 - Diverticular bleeding*
 - Angiodysplasia*
 - Inflammatory bowel disease*
 - Heyde's syndrome (severe aortic stenosis, acquired type 2 von Willebrand syndrome, angiodysplasia, and iron deficiency anaemia)
 - Hamartomatous polyps in Peutz-Jeghers syndrome
 - Anal
 - Haemorrhoids
 - Entire gastrointestinal tract
 - Hereditary haemorrhagic telangiectasia

- Gynaecological bleeding
 - Menstrual (eg, in premenopausal women and girls)*
 - Exacerbated by bleeding disorders (von Willebrand disease*, carrier for haemophilia A or B, and platelet dysfunction)
 - Use of an intrauterine device
 - Fibroids
 - Uterine or other reproductive tract cancers
- Urinary tract bleeding
 - Renal or bladder cancer
 - Urinary schistosomiasis (*Schistosoma haematobium*)
 - Intravascular haemolysis (eg, paroxysmal nocturnal haemoglobinuria)
 - Intravascular haemolysis (eg, valve haemolysis, march haemoglobinuria, and malaria)
- Respiratory bleeding
 - Severe haemoptysis (eg, lung cancer and infection)
- Blood donation (especially whole blood donation*)
- Excess iatrogenic blood losses (eg, excessive blood collection for diagnostic testing and iron losses during haemodialysis)
- Self-inflicted blood loss (Munchausen syndrome)

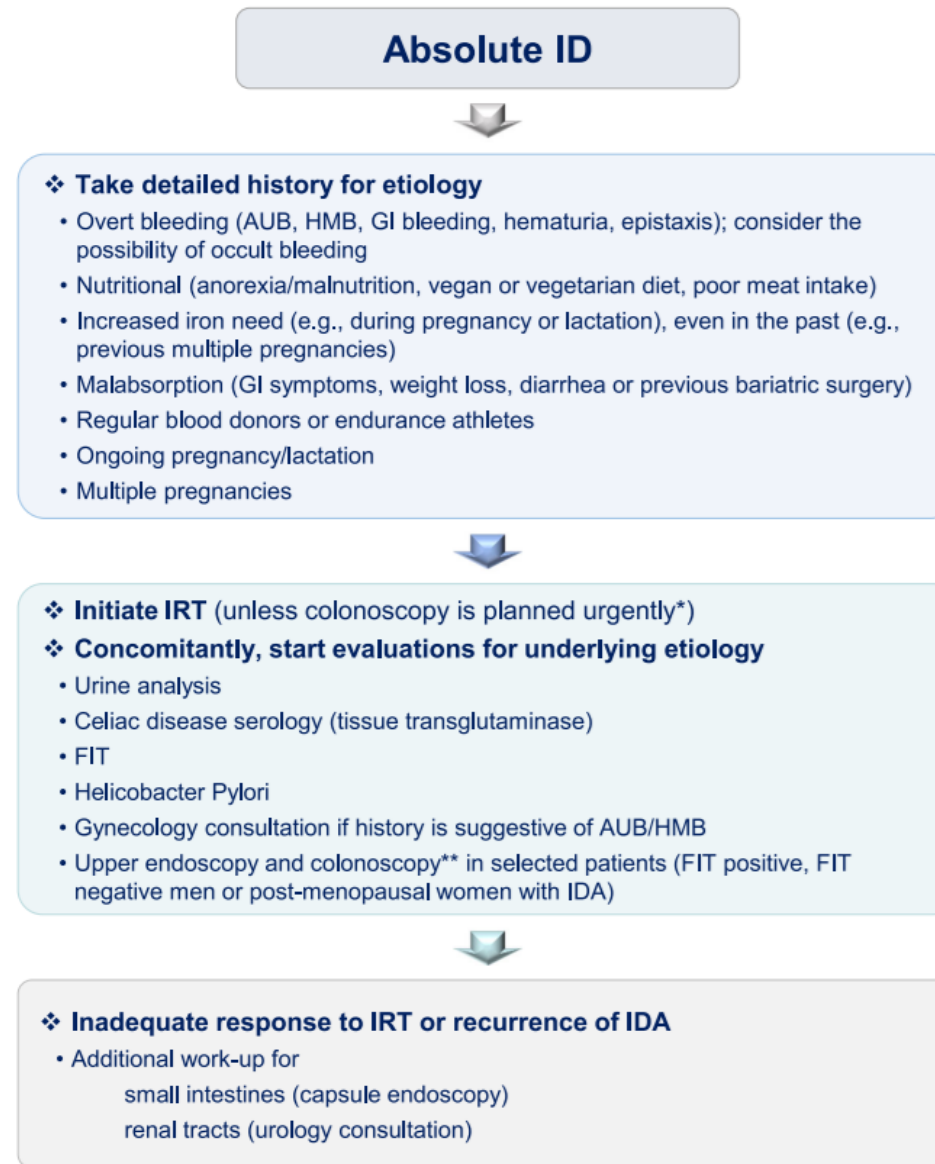
Exercise

- Multifactorial: reduced dietary iron intake, reduced iron absorption due to inflammation, increased losses in sweat, gastrointestinal bleeding, and haemolysis with haemoglobinuria

*Common important causes to consider in primary care.

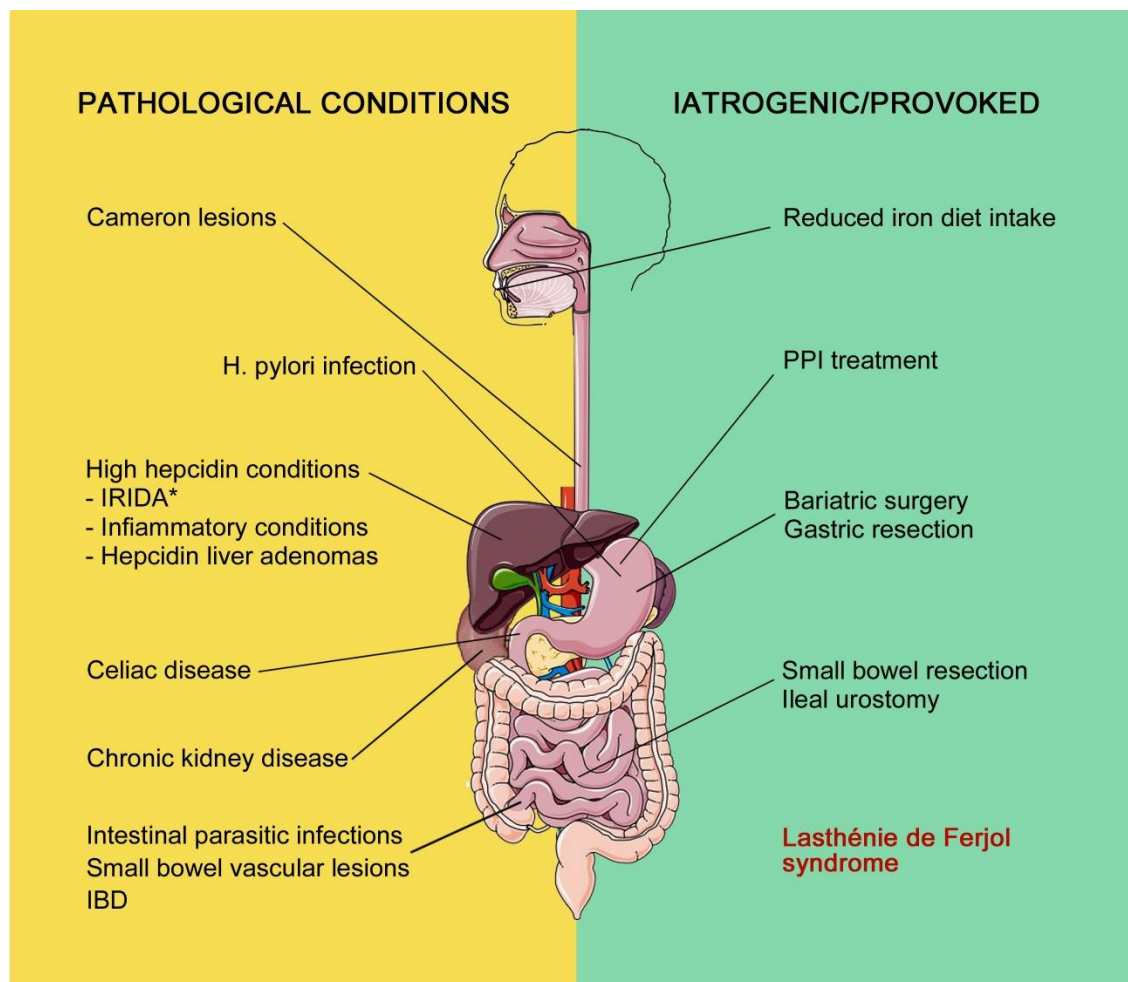
Pasricha SR, Lancet 2021

Approccio al paziente



Iolascon A, Hemasphere 2024

Refrattarietà alla terapia con ferro per os



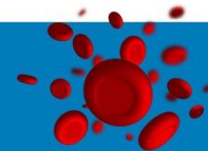
ID/IDA più frequente manifestazione extra-intestinale della celiachia

Prevalenza della celiachia in soggetti con IDA: 5.5% (95% CI, 4.1%–6.9%)



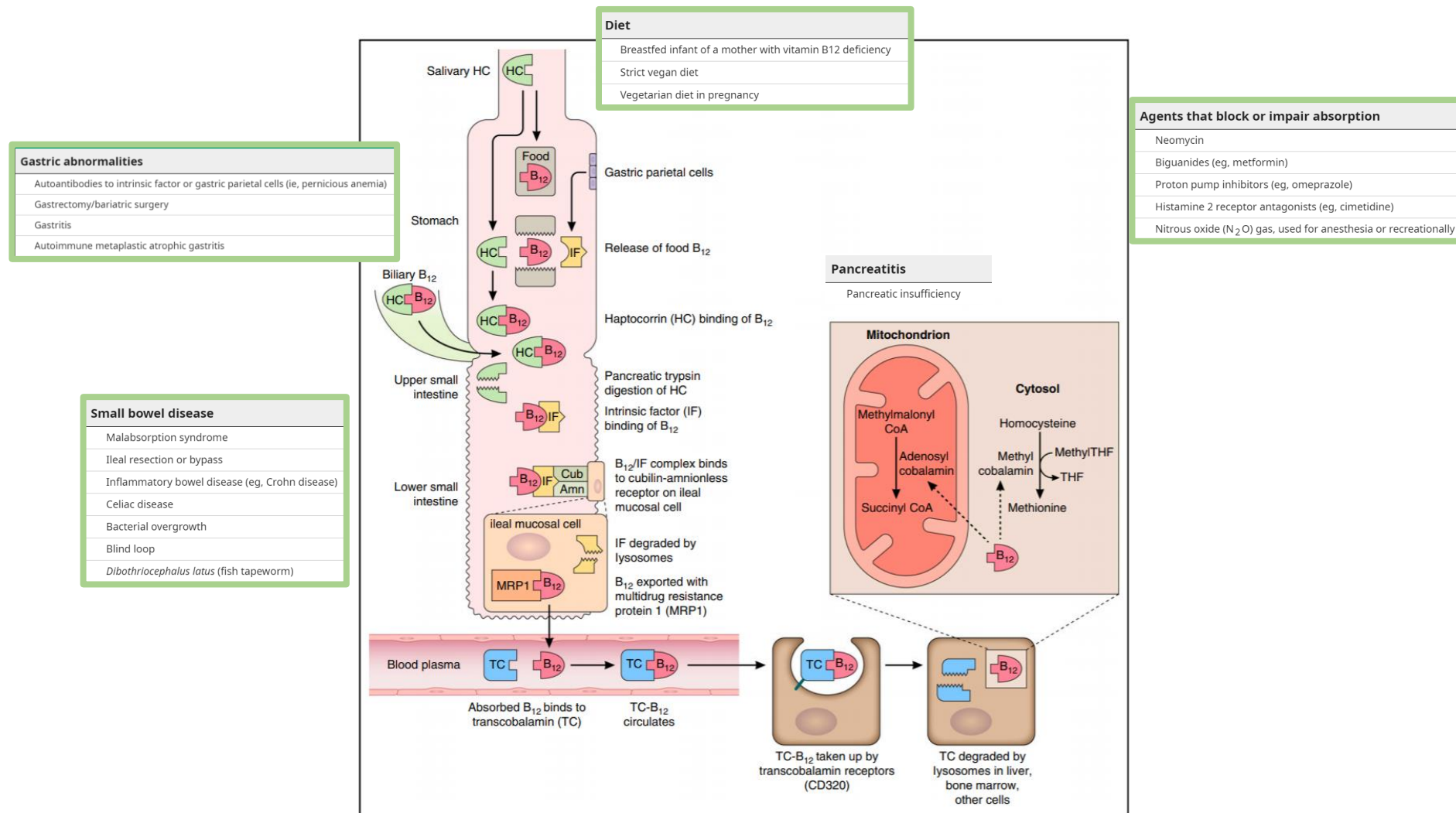
Migone De Amicis M, Mediterr J Hematol Infect Dis 2021

Deficit vitamina B12

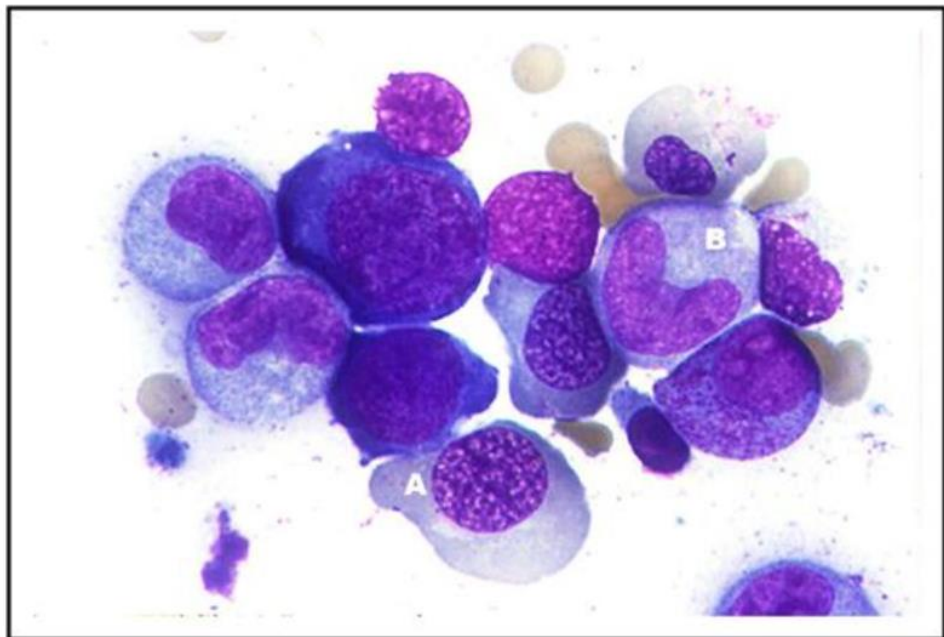


Vitamina B12: assorbimento, trasporto e cause di carenza

- Nell'adulto B₁₂ 3 - 5 mg
- Contenuta negli alimenti di origine animale



Vitamina B12 e alterazioni ematologiche



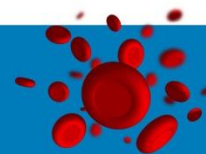
Alterata sintesi del DNA → prolungamento della fase S del ciclo cellulare → arresto della maturazione

Modifiche in senso megaloblastico nel midollo:

- precursori eritroidi più grandi, preponderanza di eritroblasti basofili rispetto a forme più mature contenenti emoglobina
- precursori granulocitari: metamielociti e forme a banda con nuclei voluminosi a ferro di cavallo
- Megacariociti megaloblastici con nuclei ingranditi e polilobati



Green R, Blood 2017



Approccio al paziente

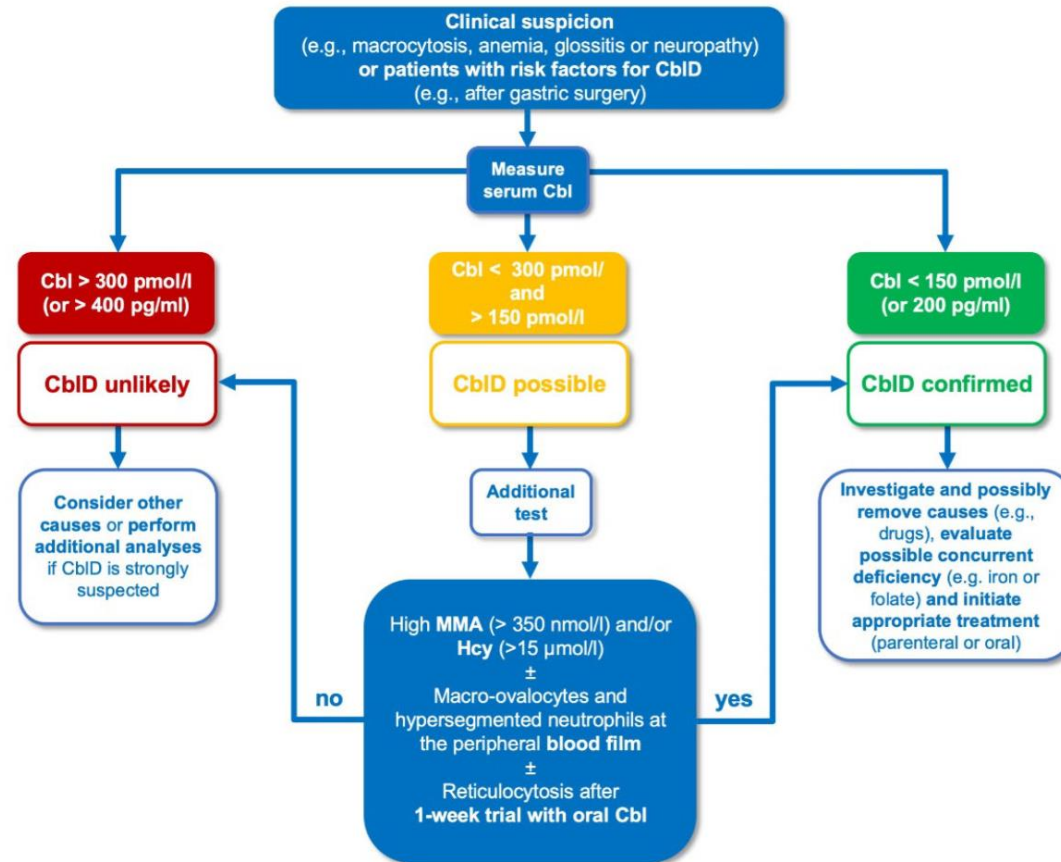
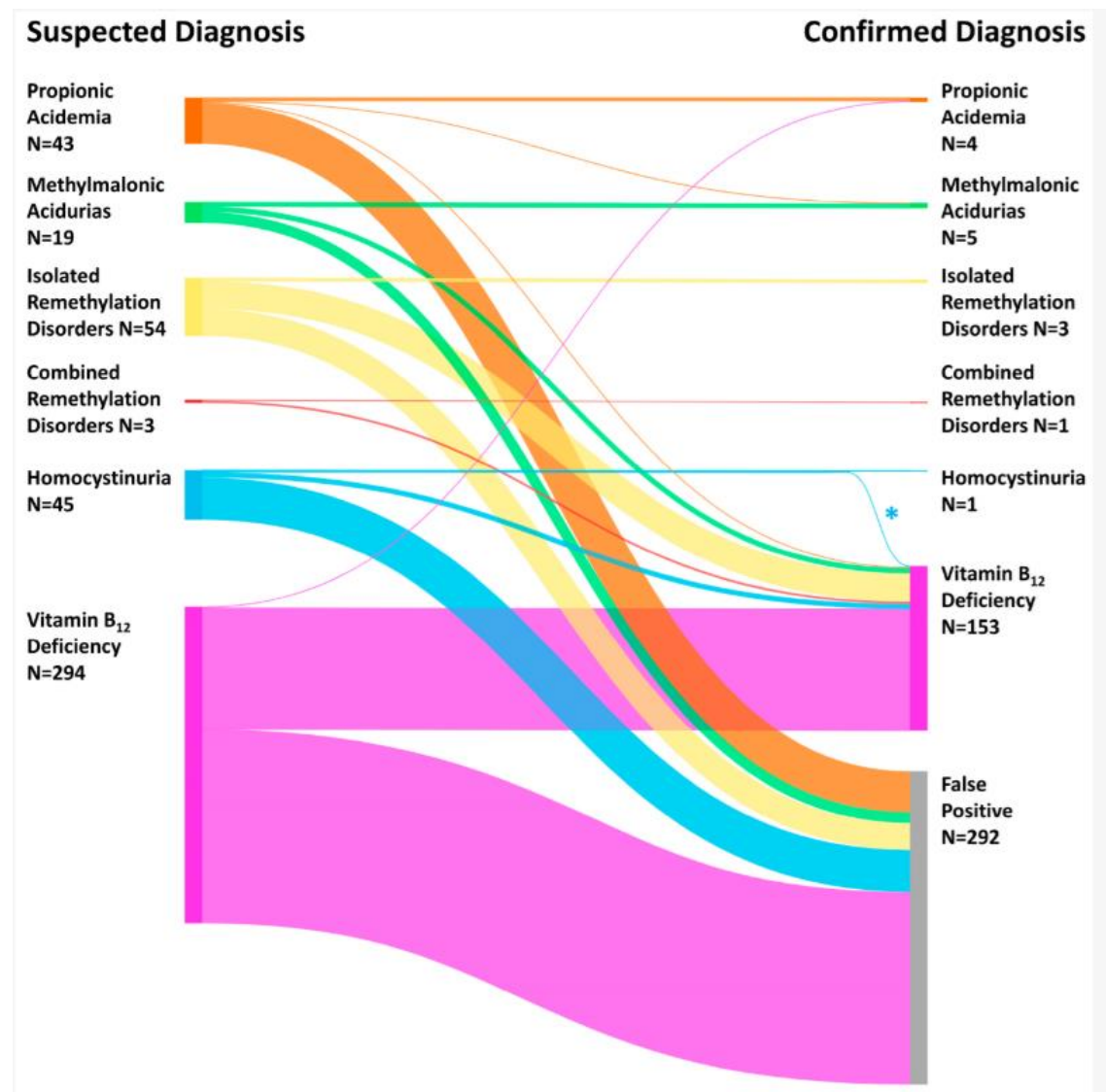


Figure 2. Possible algorithm for the diagnosis of CblD in the elderly. The diagnosis of CblD should be based on clinical signs and symptoms, and the combined use of biochemical and hematological indicators, including serum Cbl, MMA and Hcy levels, peripheral blood smear, and a trial with oral Cbl supplements.



MMA e screening neonatale

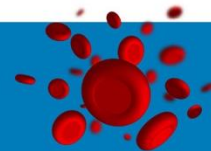


Reischl-Hajiabadi AT, Nutrients 2022



Take home messages

- L'anemia carenziale è un problema globale
- La carenza di ferro è poco riconosciuta e risolta nonostante il ferro abbia un ruolo cruciale per l'organismo
- Nuove linee guida ASH sottolineano l'importanza del problema
- Carenza di ferro assoluta e funzionale vanno riconosciute e necessitano di un inquadramento diagnostico
- Lo screening neonatale ci suggerisce che anche il deficit di vitamina B12 è poco riconosciuto e trattato





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