Screening e terapia della siderocarenza e dell'anemia siderocarenziale nel pre-operatorio

Dr. Ivo Beverina

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Centro Immunotrasfusionale

Ospedale di Legnano

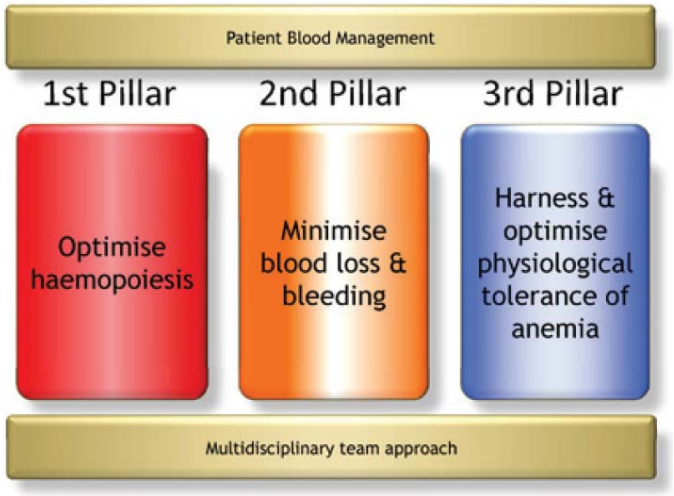
PBM: organizzazione, clinica e scenari futuri

Cesena- 28-29 Marzo 2019

PATIENT BLOOD MANAGEMENT
ASST OVEST MILANESE

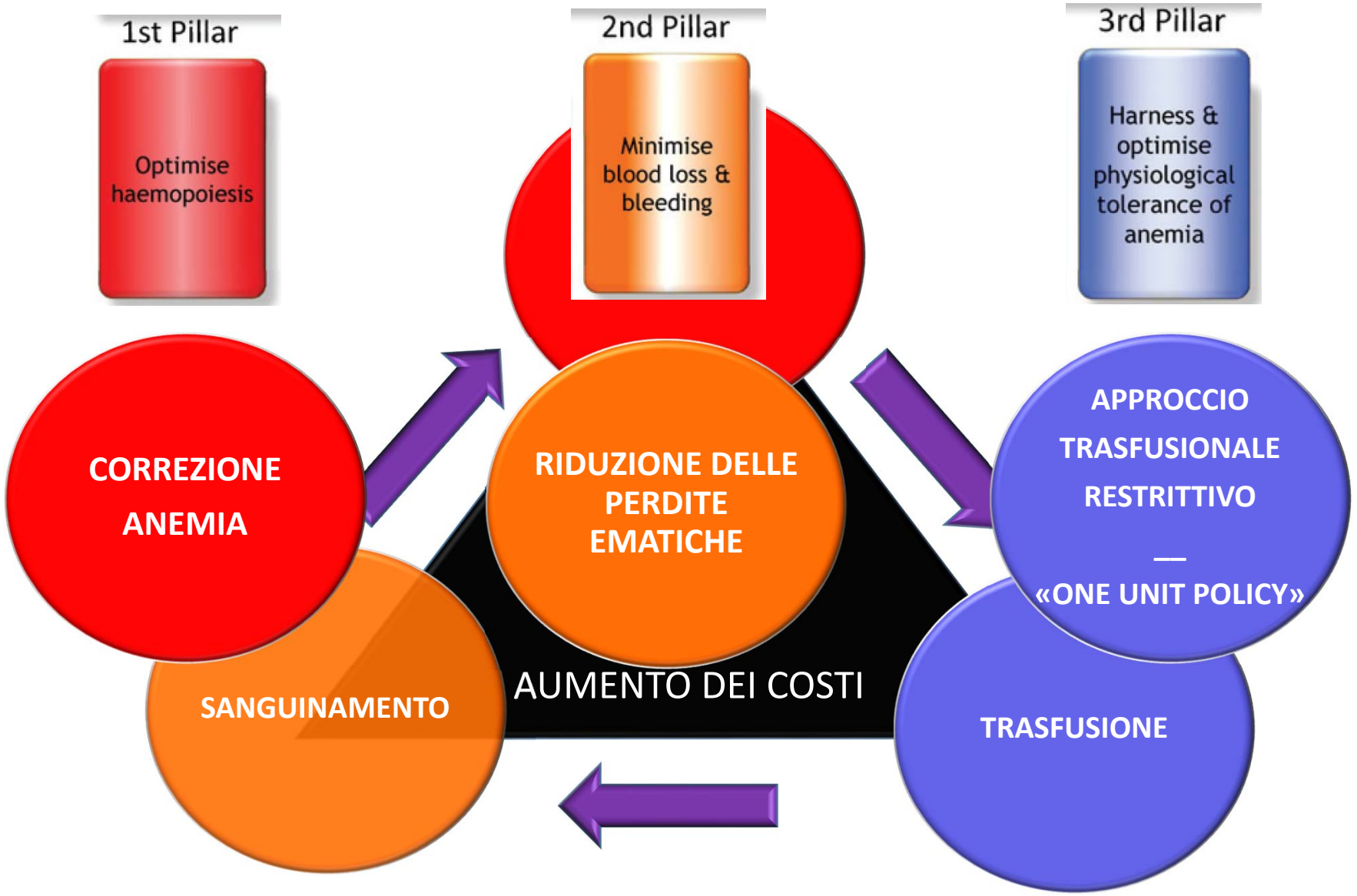
Sistema Socio Sanitario
Regione Lombardia
ASST Ovest Milanese

PROBLEMA



SOLUZIONE

BENEFICI



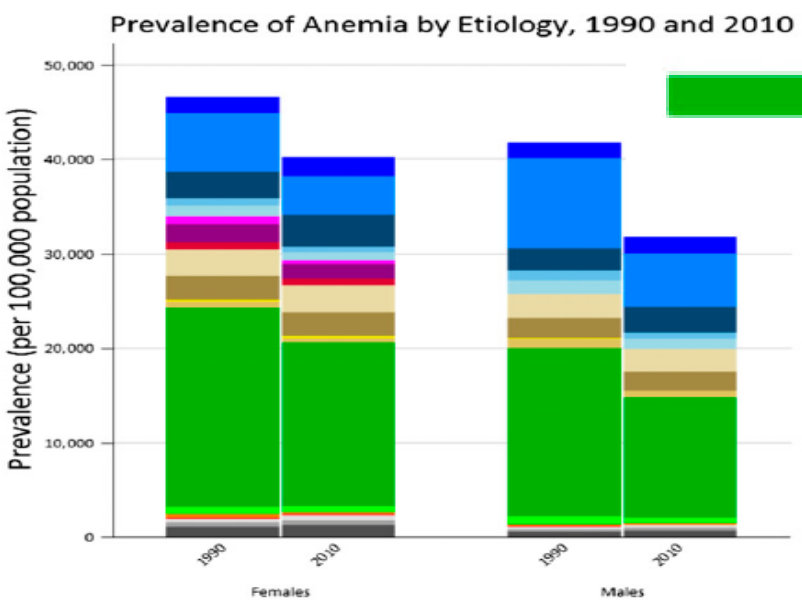
Modificato da: FarmerSL, Best Pract Res Clin Anesthesiol 2013

Plenary Paper

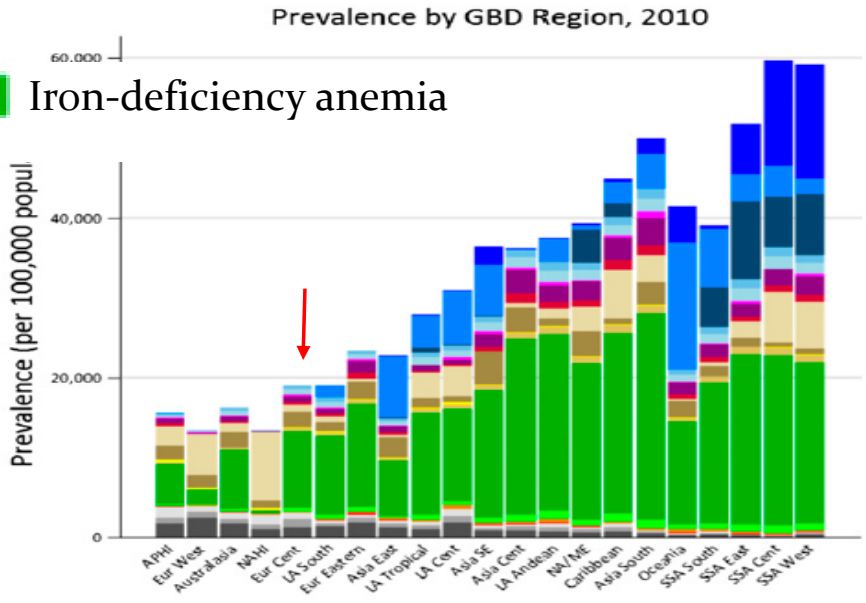
RED CELLS, IRON, AND ERYTHROPOIESIS

A systematic analysis of global anemia burden from 1990 to 2010

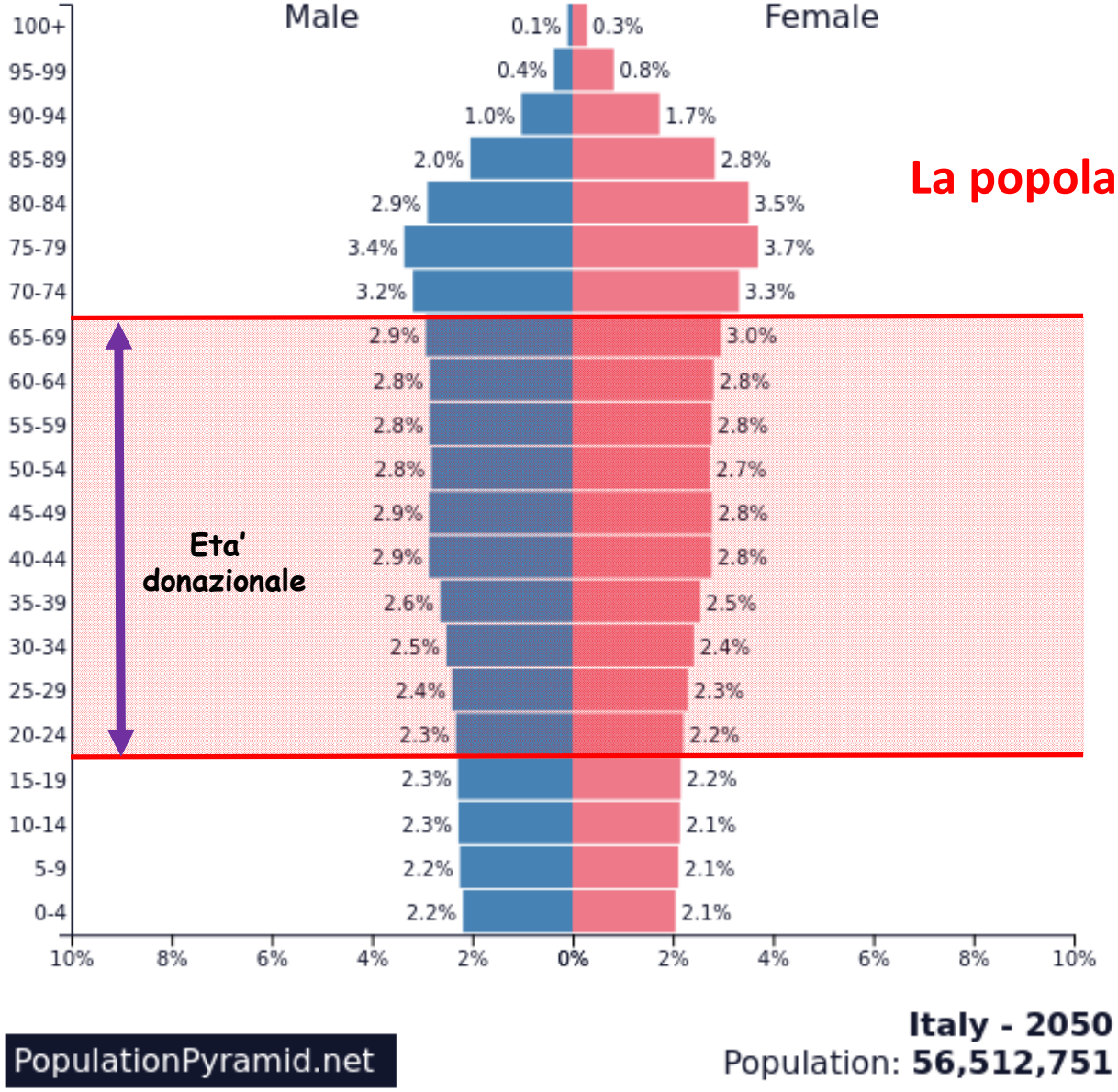
Nicholas J. Kassebaum,[1,2] Rashmi Jasrasaria,[3] Mohsen Naghavi,[1] Sarah K. Wulf,[1] Nicole Johns,[4] Rafael Lozano,[5] Mathilda Regan,[6] David Weatherall,[7] David P. Chou,[8] Thomas P. Eisele,[9] Seth R. Flaxman,[10] Rachel L. Pullan,[11] Simon J. Brooker,[11] and Christopher J. L. Murray[1]



Iron-deficiency anemia



Malaria
Hookworm
Schistosomiasis
Other infectious diseases
Other NTD
Maternal hemorrhage
Fibroids
Other gynecological disorders
Sickle cell
Thalassemias
G6PD deficiency
Other hemog
Iron-deficiency anemia
Other endocrine
Gastritis & duodenitis
Peptic ulcer
Diabetic CKD
Hypertensive CKD
Other CKD



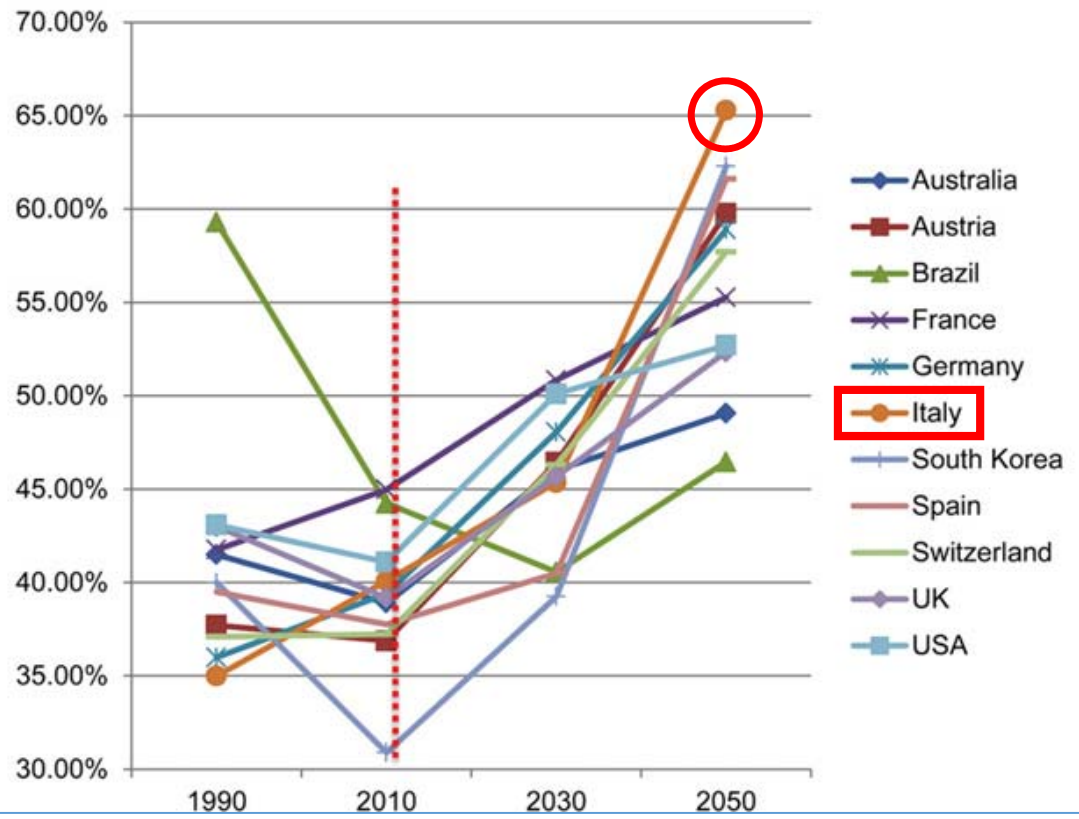
La popolazione invecchia….

$$TTDR = \frac{P_{ND}}{P_D} \times 100$$

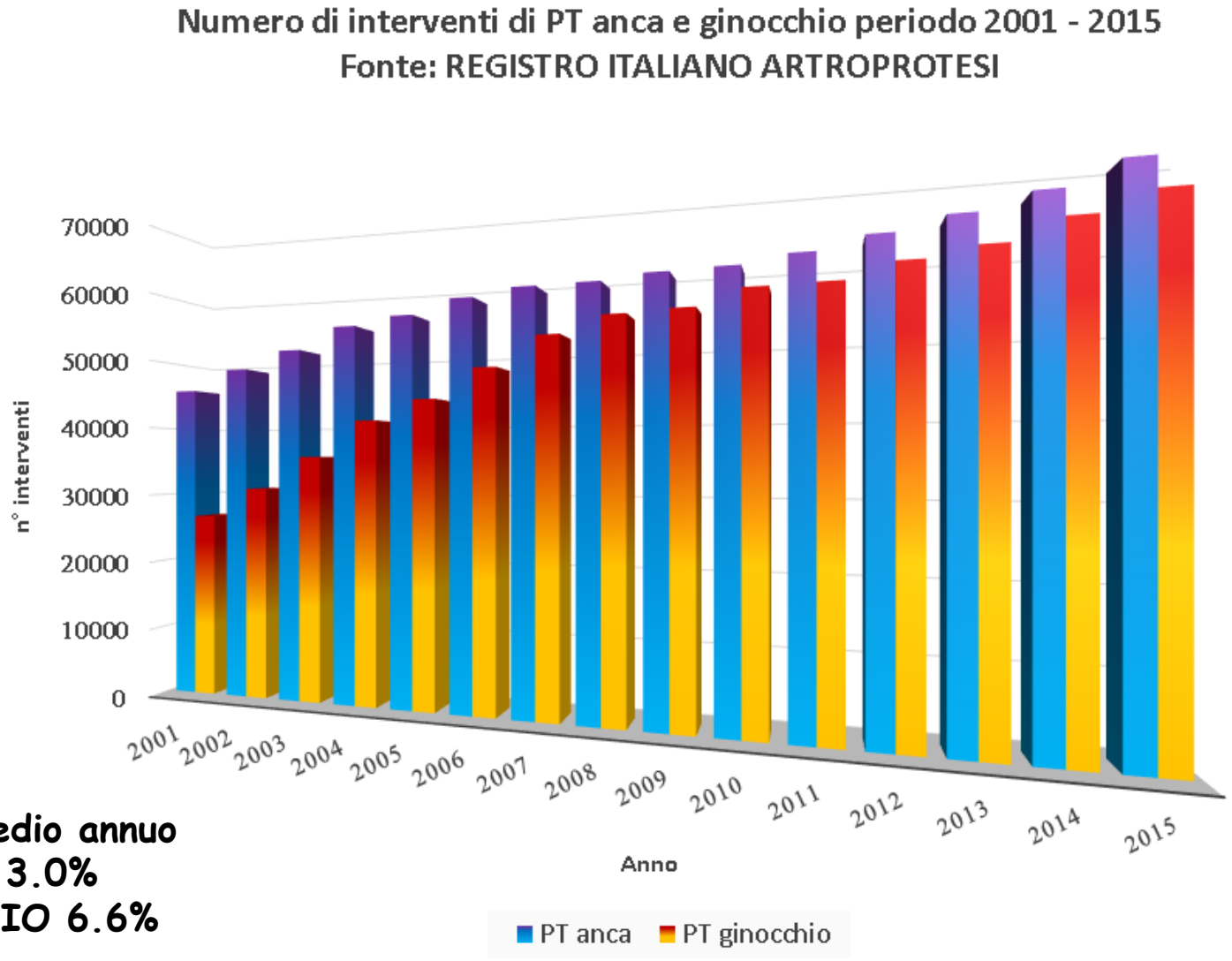
TTDR = Total transfusion dependency ratio

P_{ND} = Population non-donating

P_D = Population donating

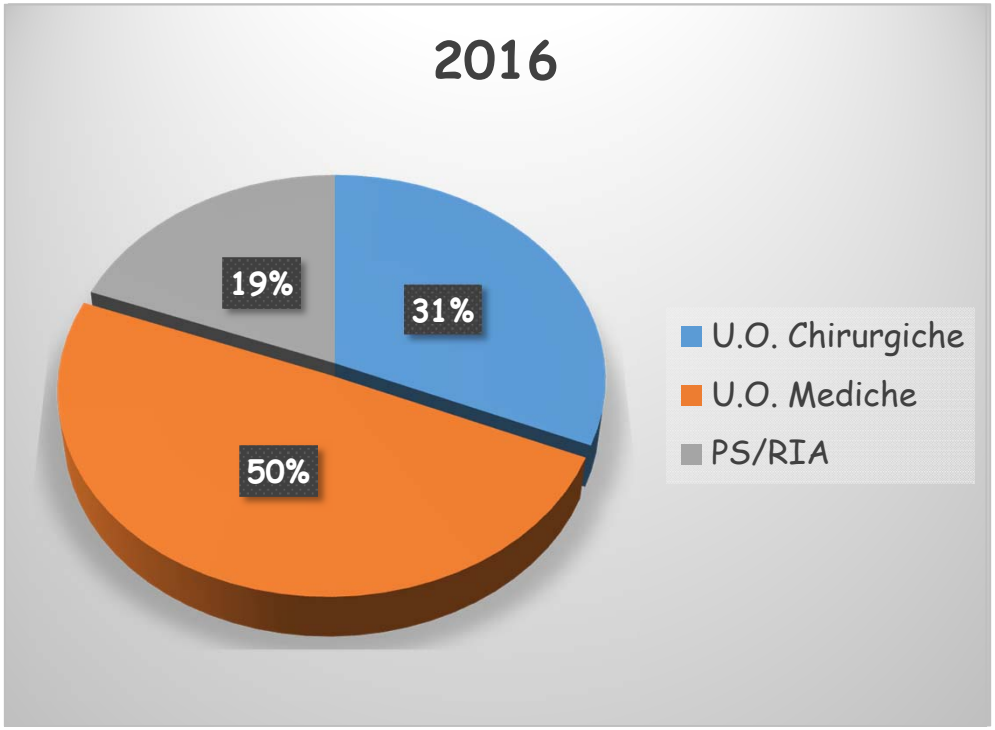


Farmer SL, Towler SC, Leahy MF, Hofmann A. Best Pract Res Clin Anaesthesiol. 2013

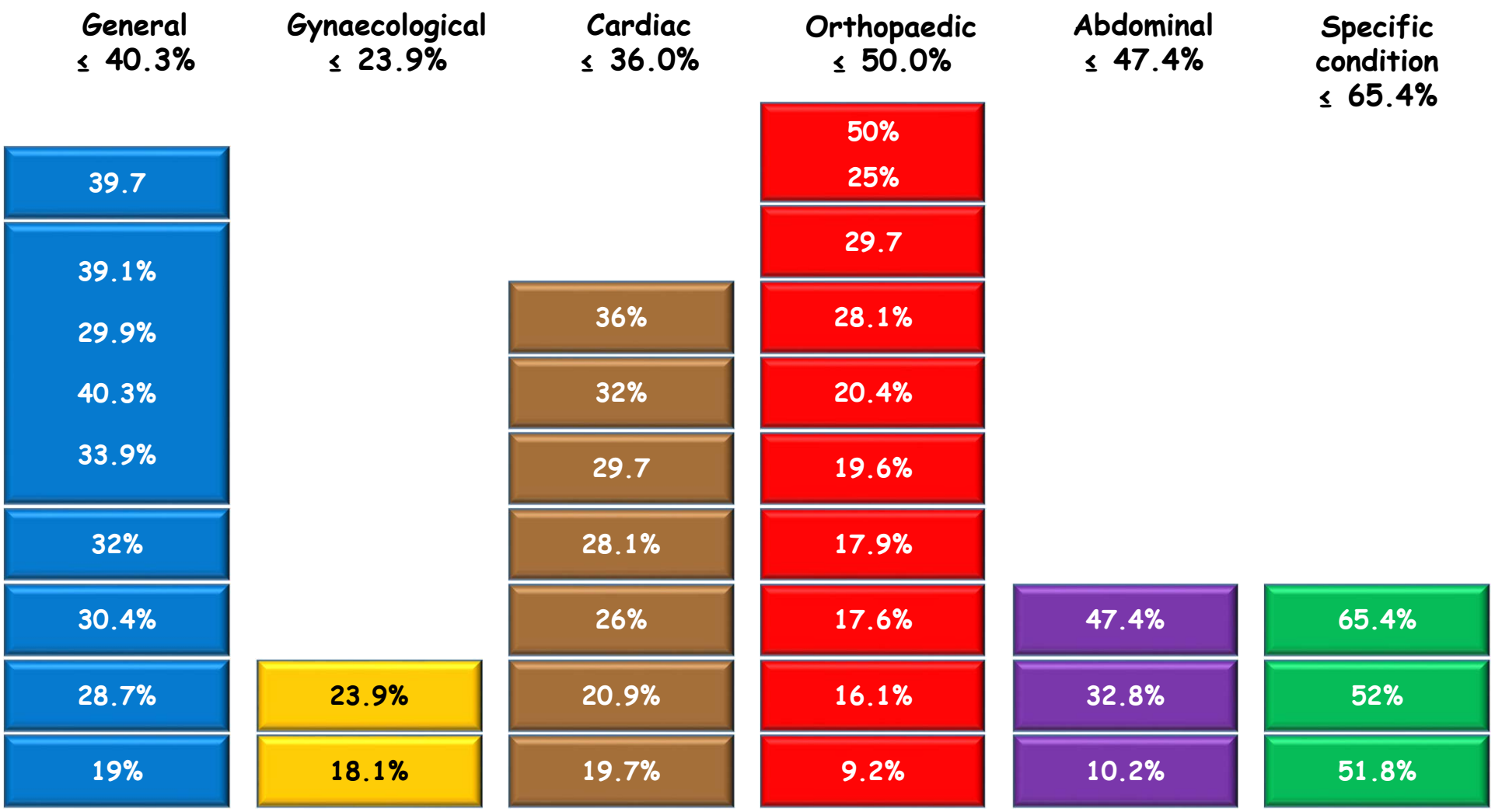


Incremento medio annuo
PT ANCA 3.0%
PT GINOCCHIO 6.6%

Ospedale di Legnano
Distribuzione delle unità di GRC trasfuse per tipologia di Reparto (2005 vs 2016)



Prevalenza di anemia preoperatoria in vari settings chirurgici

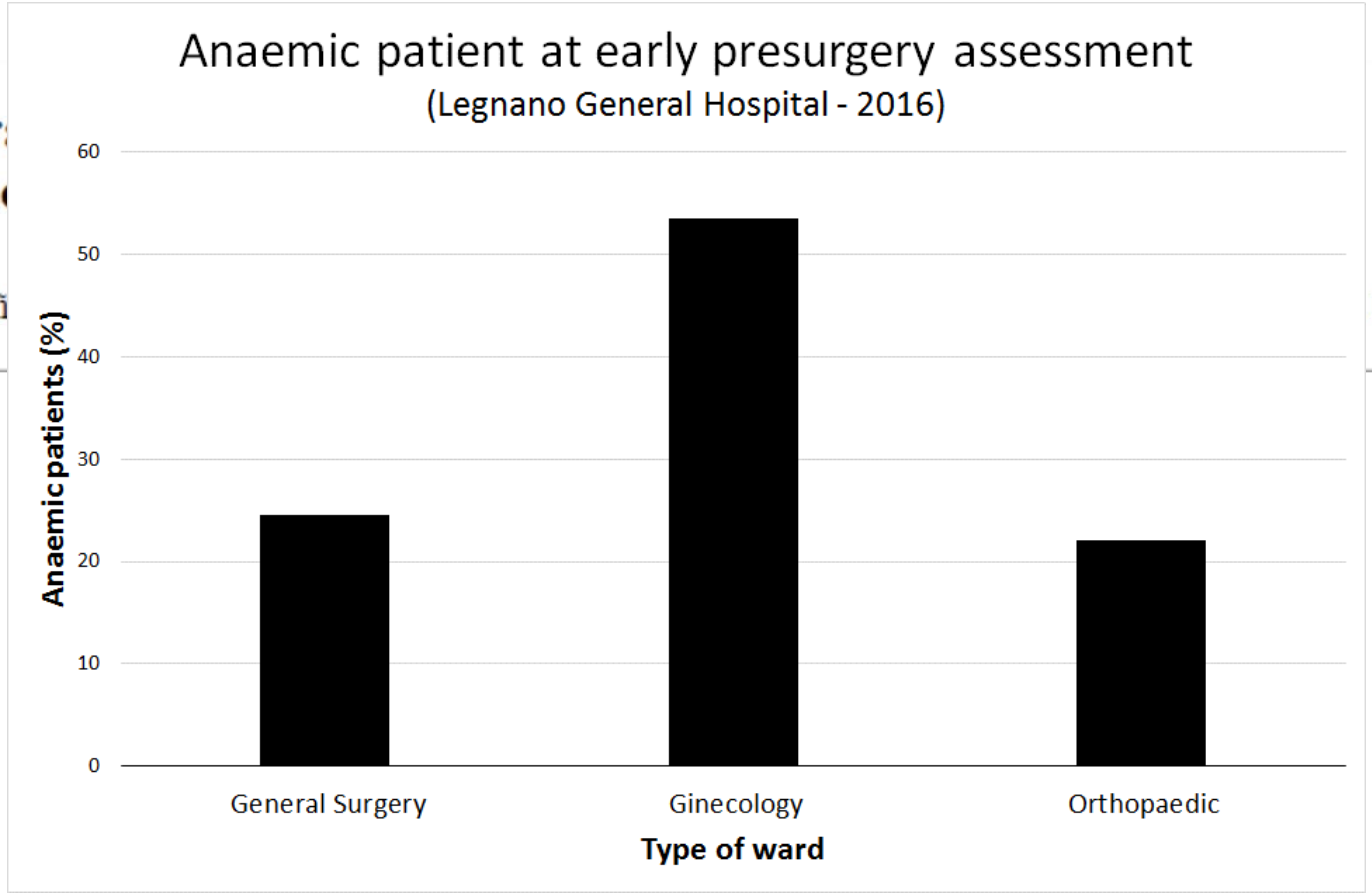


Anemia pre-operatoria: prevalenza generale

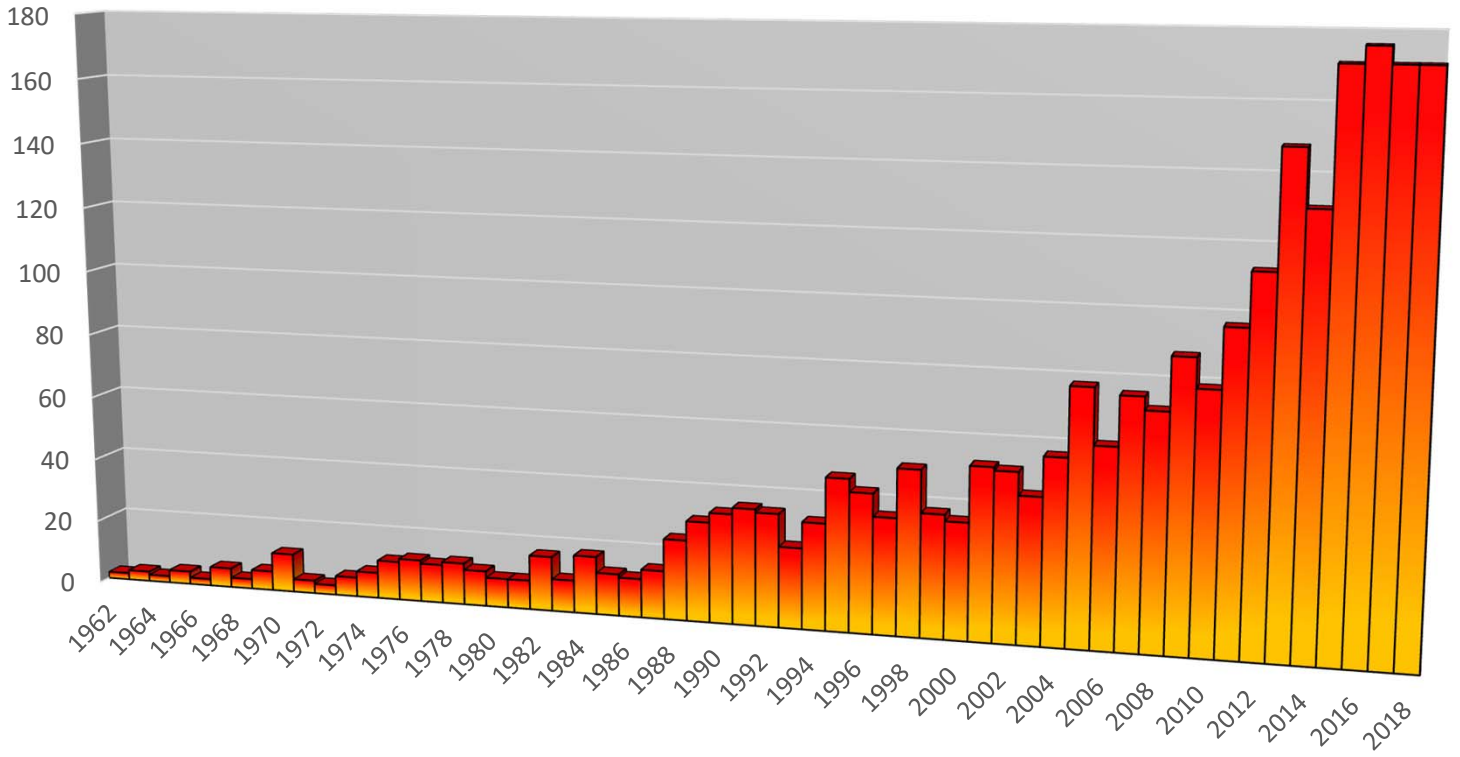
Pre-oper
prevalen

Manuel Muñ

Liumbruno[4]



Numero di articoli in PubMed / Anno per parola chiave «Preoperative anemia»



Anemia preoperatoria e outcome

Systematic review

Meta-analysis of the association between preoperative anaemia and mortality after surgery

A. J. Fowler[1], T. Ahmad[1], M. K. Phull[2], S. Allard[3], M. A. Gillies[4] and R. M. Pearse[1]

- **39% sono anemici (definizione WHO)**
- **Anemia associata a:**
  - ⇨ Mortalità perioperatoria ⬆ - OR 2.90 (2.30 – 3.68, p< 0.001)
  - ⇨ Danno renale acuto ⬆ - OR 3.75 (2.95 – 4.76, p< 0.001)
  - ⇨ Infezioni ⬆ - OR 1.93 (1.06 – 1.55, p< 0.01)
  - ⇨ Stroke in cardiochirurgia ⬆ - OR 1.28 (1.17 – 3.18, p< 0.01)
  - ⇨ Trasfusione di EC ⬆ - OR 5.04 (4.12 – 6.17, p< 0.001)

Fowler AJ, *Br J Surg* 2015

Open Access Research

BMJ Open

Association between preoperative anaemia with length of hospital stay among patients undergoing primary total knee arthroplasty in Singapore: a single-centre retrospective study

Hairil Rizal Abdullah,[1] Yilin Eileen Sim,[1] Ying Hao,[2] Geng Yu Lin,[3] Geoffrey Haw Chieh Liew,[1] Ecosse L Lamoureux,[4] Mann Hong Tan[5]

BMJ Abdullah HR, *et al. BMJ Open* 2017;**7**:e016403. doi:10.1136/bmjopen-2017-016403

Rischio di degenza superiore al 75% percentile della media

Anemia moderata → adjusted Odds Ratio 1.71

Anemia severa → adjusted Odds Ratio 2.29

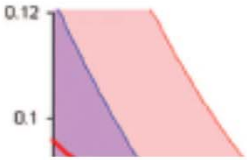
Anemia preoperatoria ed outcome

Anesthesiology 2009; 110:574–81

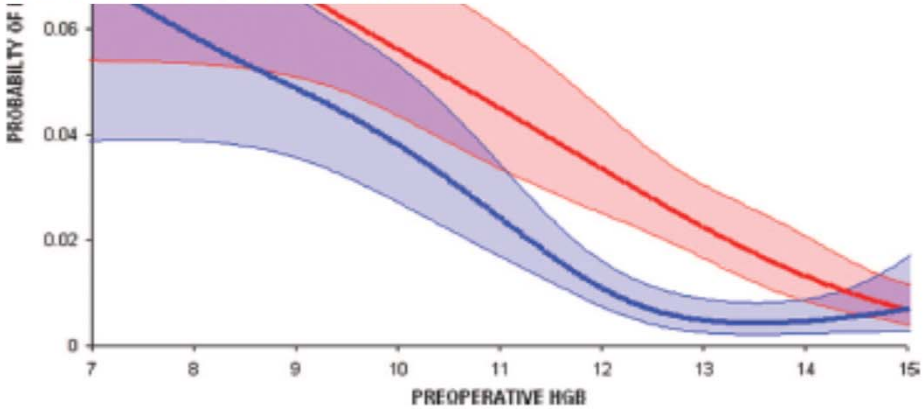
Risk Associated with Preoperative Anemia in Noncardiac Surgery

A Single-center Cohort Study

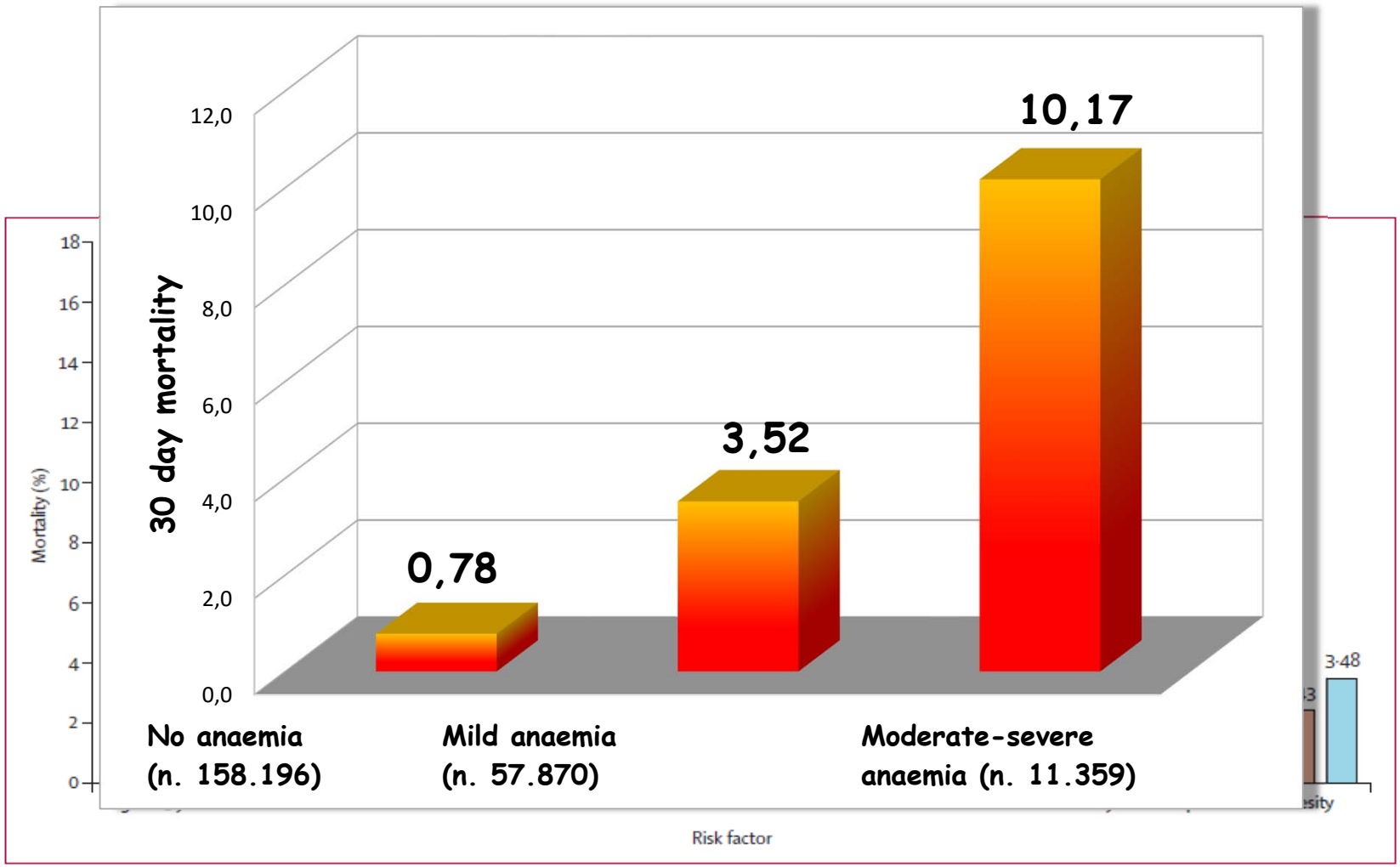
W. Scott Beattie, M.D., Ph.D., F.R.C.P.C., Keyvan Karkouti, M.D., M.Sc., F.R.C.P.C.,† Duminda N. Wijeysundera, M.D., F.R.C.P.C.,‡ Gordon Tait, Ph.D.§*



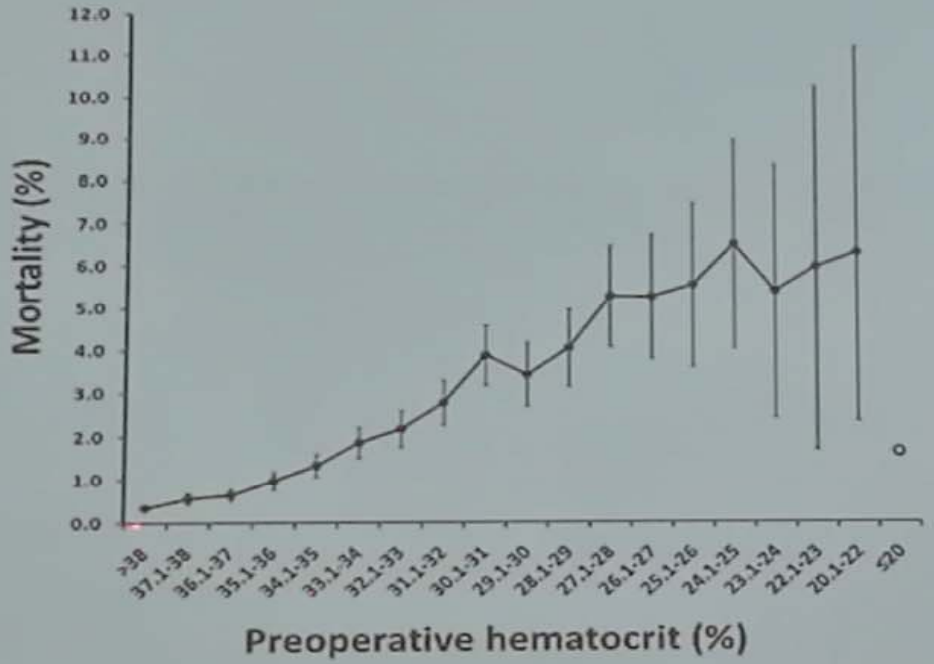
In a propensity-matched cohort of patients, anemia was associated with increased mortality (odds ratio, 2.29; 95% confidence interval, 1.45–3.63).

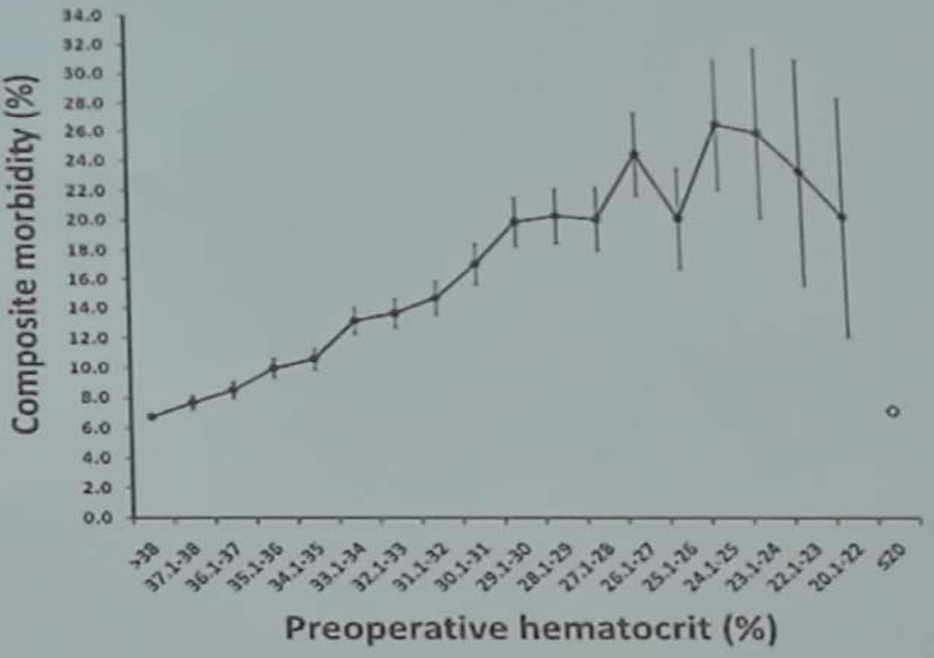


Anemia preoperatoria ed outcome



Effect of Anemia on Mortality and Composite Morbidity





Musallam, K.M., et al., Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. Lancet, 2011.

British Committee for Standards in Haematology Guidelines on the Identification and Management of Pre-Operative Anaemia

Alwyn Kotzé,[1] Andrea Harris,[2] Charles Baker,[3] Tariq Iqbal,[4] Nick Lavies,[5] Toby Richards,[6] Kate Ryan,[7] Craig Taylor[8] and Dafydd Thomas[9]

British Journal of Haematology, 2015, **171**, 322–331

Recommendation

- To avoid causing unnecessary delay to patients, anaemia screening should take place when referral for surgery is first made, in order to allow investigation and correction if appropriate (Grade 1C).
- Where surgery is urgent, whatever time is available before operation should still be used for anaemia investigation and treatment initiation (Grade 1C).

Iron therapy is indicated in anaemic patients with absolute or functional iron deficiency (Grade 1B).

Iron therapy is indicated for non-anaemic patients with low iron stores (ferritin <100 µg/l and transferrin saturation <20%) scheduled to undergo surgery with predicted total peri-operative erythrocyte loss >30 g/l (>1200 ml in a 70 kg adult), to protect against post-operative iron deficiency anaemia (Grade 1C).

The agent chosen should take account of the surgical pathway and local circumstances. Where the time to surgery is short and/or when it is more practicable, agents that allow for single-dose treatment are appropriate. (Grade 2C).

Oral iron is indicated in iron deficient anaemic patients whose surgery is not urgent (Grade 1B).

Treatment with intravenous iron is indicated when patients are intolerant of, or unresponsive to, oral iron. (Grade 1B)

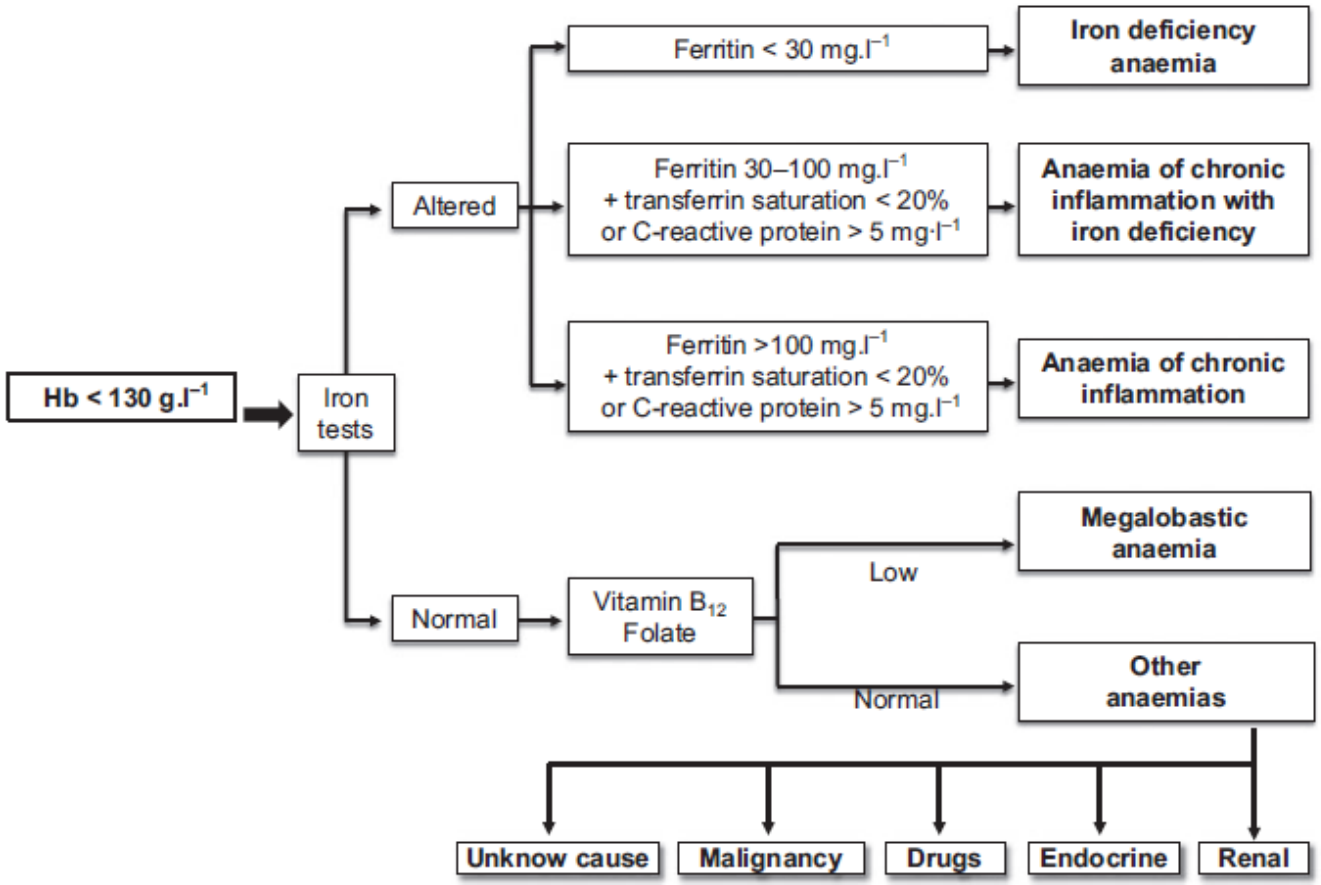
Intravenous iron is indicated in functional iron deficiency or where the interval between detection of anaemia and surgery is predicted to be short. (Grade 2B).

Consensus Statement

International consensus statement on the peri-operative management of anaemia and iron deficiency

M. Muñoz,[1] A. G. Acheson,[2] M. Auerbach,[3] M. Besser,[4] O. Habler,[5] H. Kehlet,[6] G. M. Liumbruno,[7] S. Lasocki,[8] P. Meybohm,[9] R. Rao Baikady,[10] T. Richards,[11] A. Shander,[12] C. So-Osman,[13] D. R. Spahn[14] and A. A. Klein[15]

Anaesthesia 2017, 72, 233–247



Esami indispensabili per la diagnosi di anemia sideropenica «classica»

Emocromo
GRC ↓
Hb ↓
MCV ↓ microcitosi
MCH ↓
MCHC ↓
Piastrine =/↑
Reticolociti =/↑

Bilancio marziale
Sideremia ↓
Transferrina ↑
Sat.Transferrina ↓
Ferritina ↓

Altro
Soluble transferrin receptor (sTfR) ↑
Reticulocyte hemoglobin content(CHr) ↓
Low Hemoglobin Density (LHD) ↑

Quanti [illegible] ferro e.v.?
Ripeto la domanda

Rossi

RBC	2.84	10^6/µL	
Hgb	8.8	g/dL	
Hct	26.2	%	
MCV	92.5	fL	
MCH	30.9	pg	
MCHC	33.4	g/dL	
RDW	13.3	%	
MAF	8.1		
LHD	4.5	%	

Piastrine — Blocca Plt

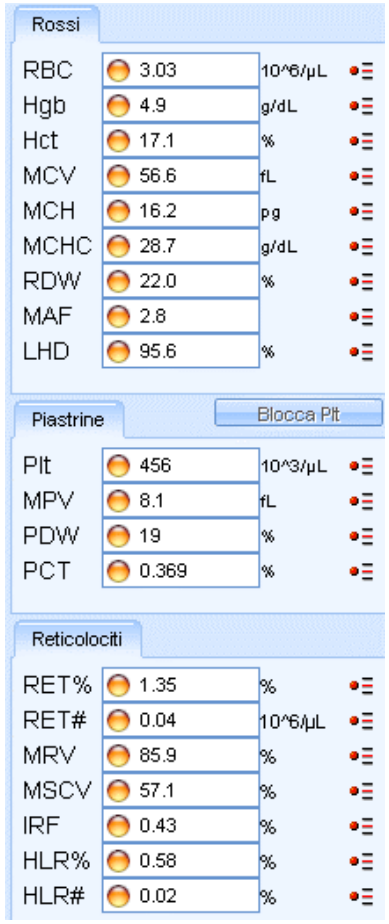
Plt	274	10^3/µL	
MPV	7.6	fL	
PDW	16.8	%	
PCT	0.208	%	

Reticolociti

RET%	1.06	%	
RET#	0.03	10^6/µL	
MRV	108.3	%	
MSCV	84	%	
IRF	0.45	%	
HLR%	0.47	%	
HLR#	0.01	%	

S--FERRO	**45**	µg/dL	37 - 145
S--FERRITINA	**43**	ng/mL	10 - 150
S--TRANSFERRINA			
Concentrazione	**347**	mg/dL	200 - 400
Saturazione	**9** <	%	30 - 40

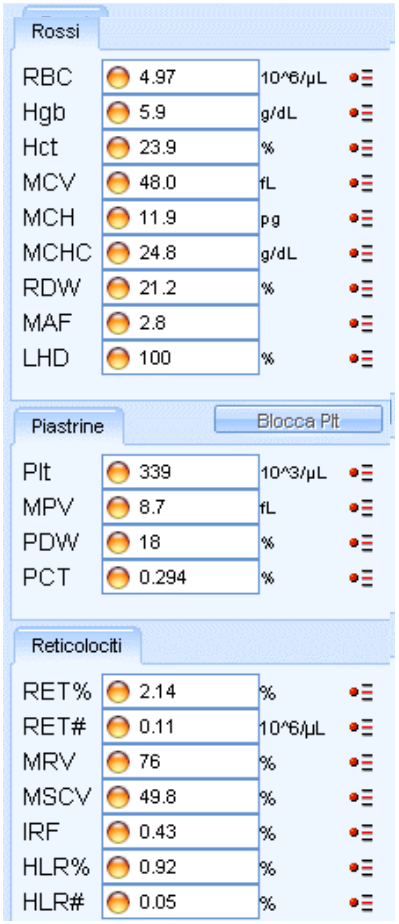
Presentazione classica



S--FERRO	**11**	<	µg/dL	37 - 145
S--TRANSFERRINA				
Concentrazione	**341**		mg/dL	200 - 400
Saturazione	**2**	<	%	30 - 40
S--FERRITINA	**2**	<	ng/mL	10 - 150

Ma un paziente con trait talassemico può sviluppare anemia sideropenica...

Microcitosi non è sempre sinonimo di sideropenia...



S--FERRO	**119**		µg/dL	37 - 145
S--FERRO	**12**	<	µg/dL	37 - 145
S--				
S--TRANSFERRINA				
Concentrazione	**364**		mg/dL	200 - 400
: S--FERRITINA	**3**	<	ng/mL	10 - 150

Non solo microcitosi…

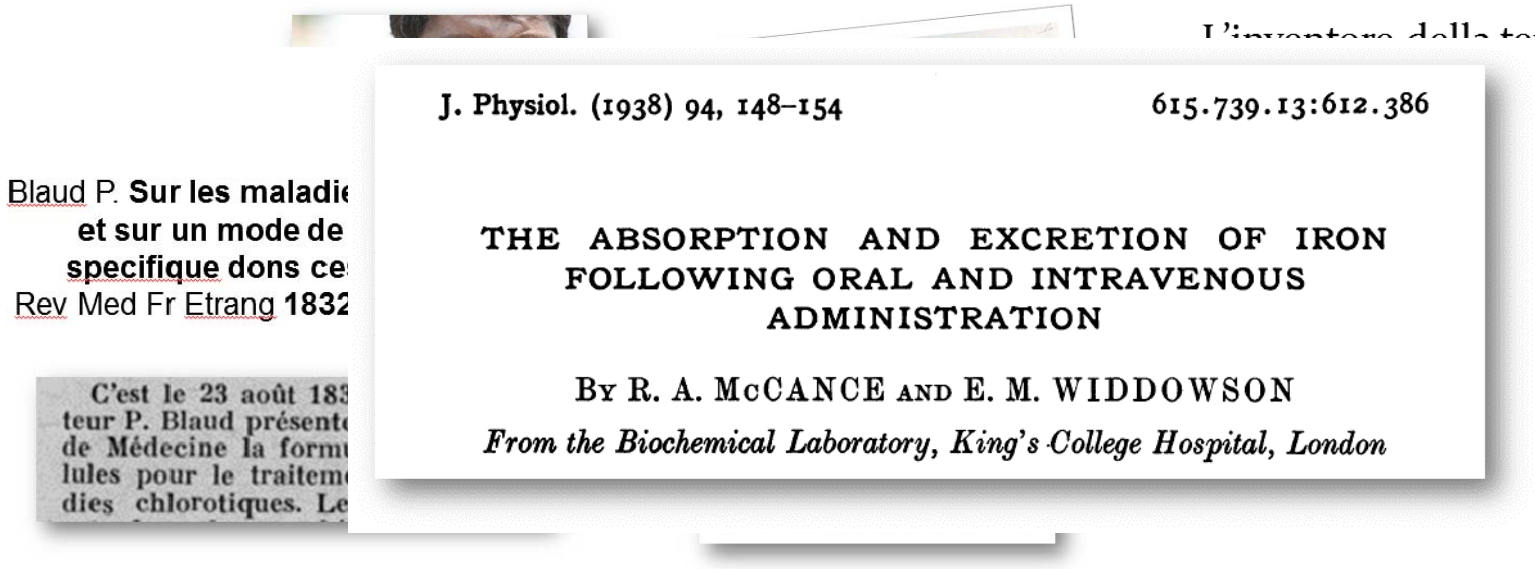
- Saturazione della transferrina → 7%
- B12 → 149 pg/mL (v.n. 191 – 663)
- Folati → 3.2 ng/mL (v.n. 4.6 – 18.7)

IRON THERAPY TIMELINE

AURO CORNELIO CELSO

PRIMO PRODOTTO PER TERAPIA

PRE



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TERAPIA MARZIALE
ORALE ANCESTRALE

PRIMO TENTATIVO DI TERAPIA
MARZIALE PER OS

INIZIA LO STUDIO
DEL METABOLISMO

IRON TIMELINE

1946

PRIMI TENTATIVI PROBLEMATICI
DI TERAPIA
ENDOVENA CON FERRO SACCARIDE

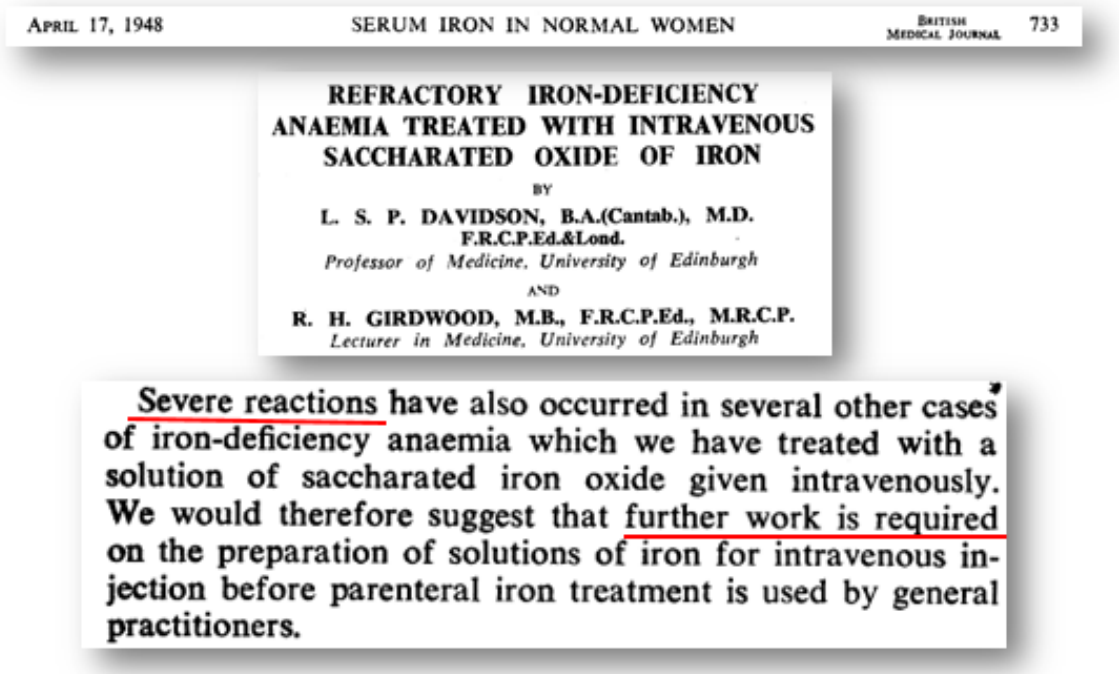
...MA LA TERAPIA
PROSEGUE

OBSERVATIONS ON
INTRAVENOUSLY

By ANNE TOMPK

«Non c'è dubbio che le re
ad alte dos
controindicare l'utili

FERRO DESTRANO LMWD



APRIL 17, 1948 SERUM IRON IN NORMAL WOMEN BRITISH MEDICAL JOURNAL 733

REFRACTORY IRON-DEFICIENCY ANAEMIA TREATED WITH INTRAVENOUS SACCHARATED OXIDE OF IRON

BY

L. S. P. DAVIDSON, B.A.(Cantab.), M.D. F.R.C.P.Ed.&Lond.
Professor of Medicine, University of Edinburgh

AND

R. H. GIRDWOOD, M.B., F.R.C.P.Ed., M.R.C.P.
Lecturer in Medicine, University of Edinburgh

Severe reactions have also occurred in several other cases of iron-deficiency anaemia which we have treated with a solution of saccharated iron oxide given intravenously. We would therefore suggest that further work is required on the preparation of solutions of iron for intravenous injection before parenteral iron treatment is used by general practitioners.

FERRO DESTRANO HMWD

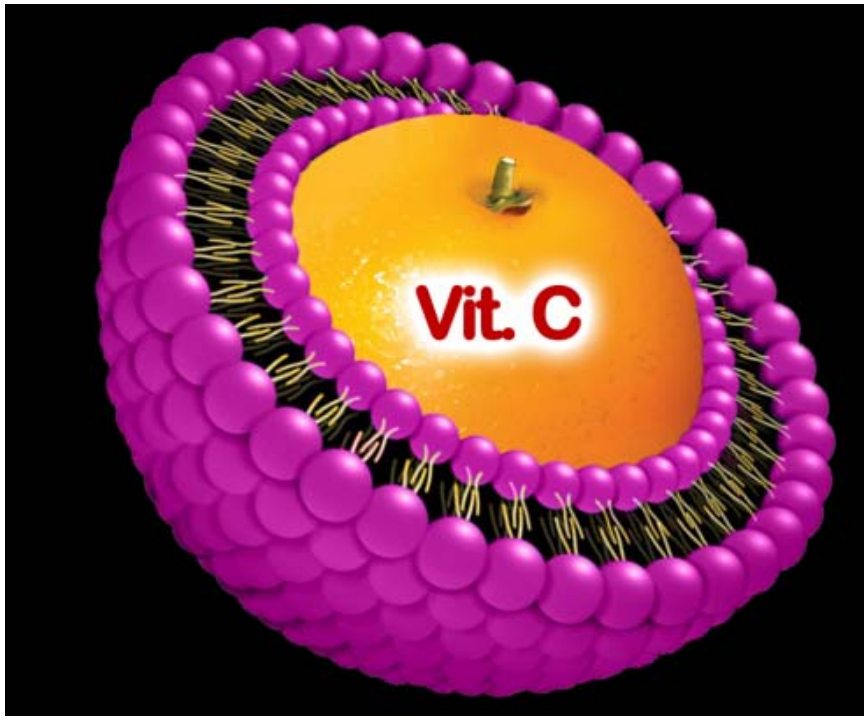
9 -

FEROMUXITOL
FERRO ISOMALTOSIDE
FERRO CARBOSSIMALTOSIO

Terapia marziale per os

- Poco costosa
- Assorbimento variabile (10% circa – fino a 30% se stato carenziale severo) ed influenzato da alcuni **alimenti** (es. Vitamina C ↑, the ↓) e **farmaci** (es. gastroprotettori)
- Ferro «Eme» (carne), assorbito meglio del ferro inorganico
- Durata della terapia per il ripristino dei depositi marziali: 3-6- mesi
- Effetti collaterali
  - Nausea, vomito
  - Senso di pesantezza gastrica, dispepsia
  - Stipsi, diarrea
  - Generalmente dose-correlati

Ferro orale: una novità nei prodotti!



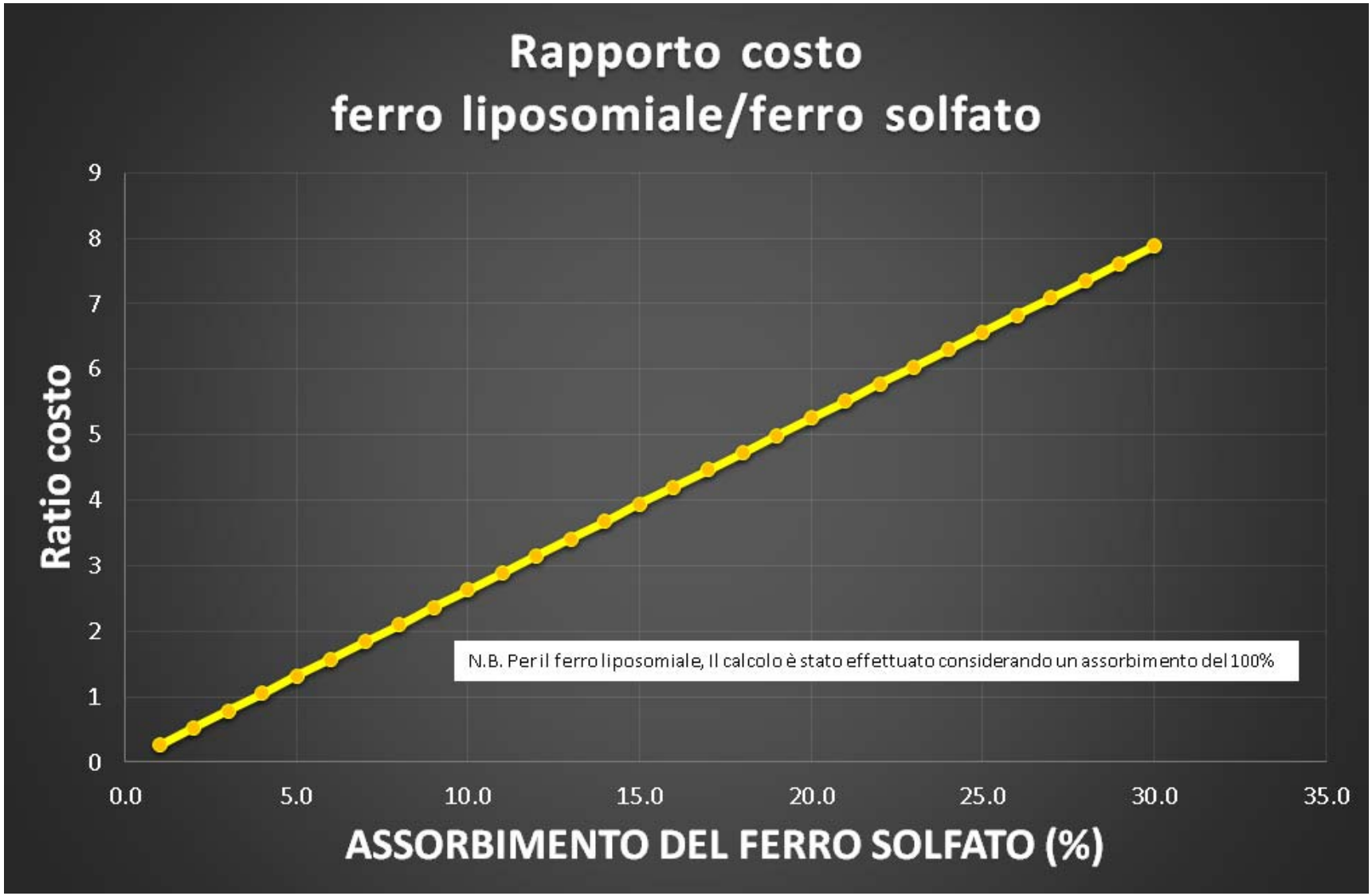
Ferro liposomiale

PRO

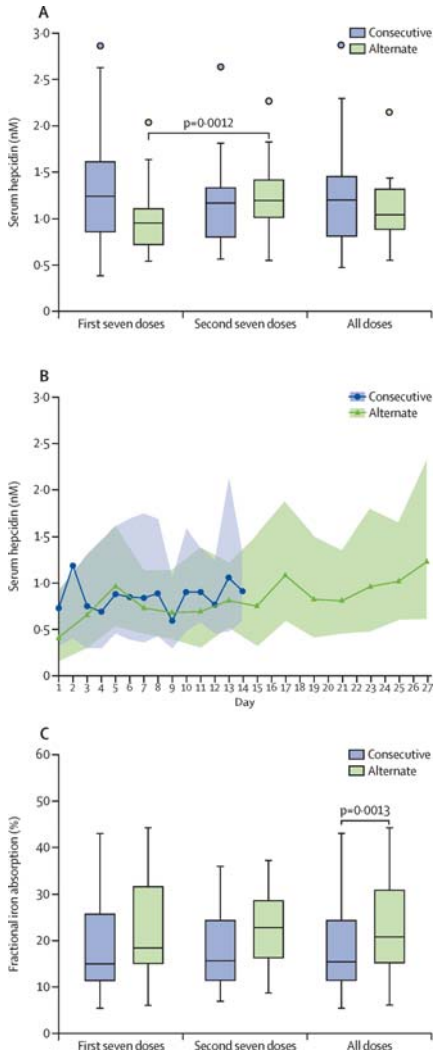
- Assorbimento teorico → 100%
- Effetti collaterali gastroenterici teorici → 0%

CONTRO

- Pochi studi
- Pochi pazienti arruolati
- Costi elevati


Rapporto costo
ferro liposomiale/ferro solfato
Ratio costo
9
8
7
6
5
4
3
2
1
0
0.0
5.0
10.0
15.0
20.0
25.0
30.0
35.0
N.B. Per il ferro liposomiale, Il calcolo è stato effettuato considerando un assorbimento del 100%
ASSORBIMENTO DEL FERRO SOLFATO (%)

Ferro orale: una novità nella posologia!



CLINICAL TRIALS AND OBSERVATIONS

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

Dieg
Alid

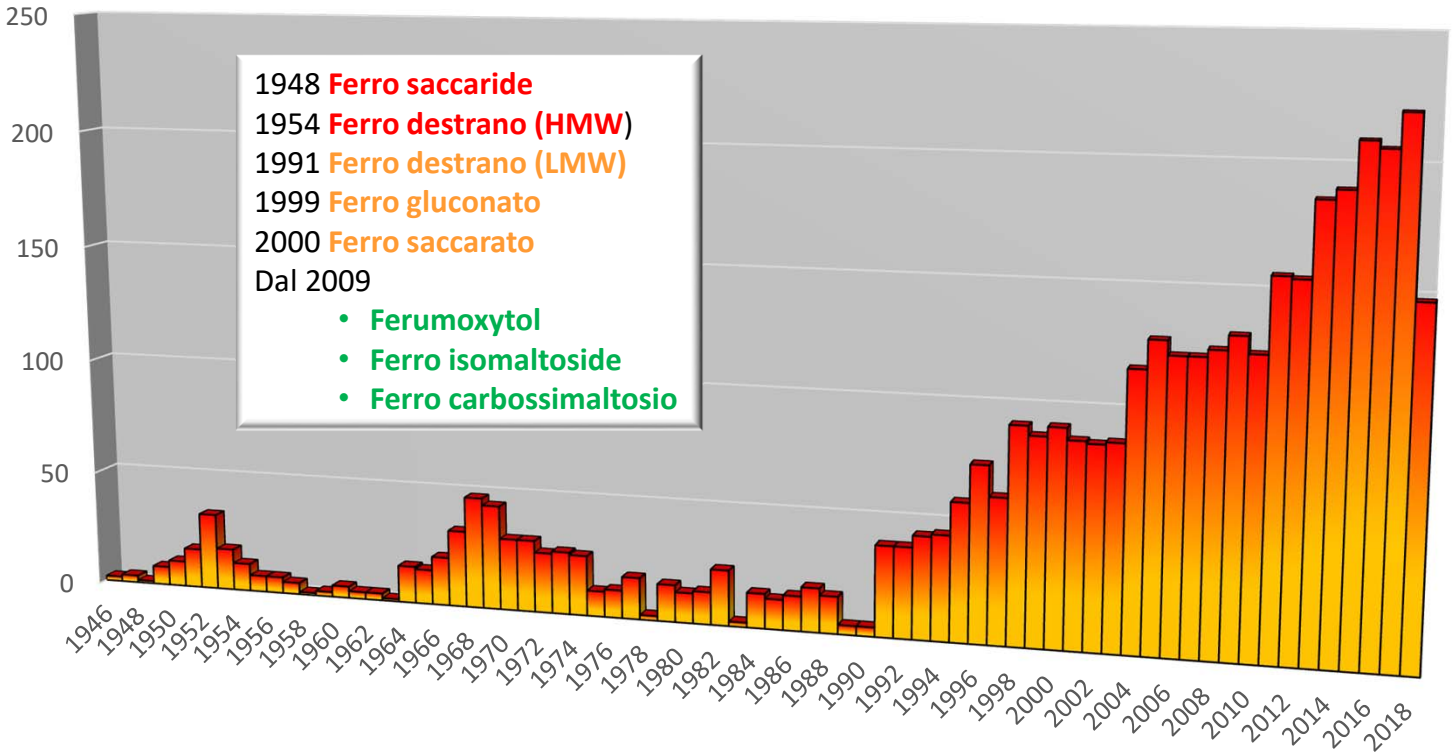
PER DOSI > 60 MG, LA SOMMINISTRAZIONE A GIORNI ALTERNI DETERMINA UN ASSORBIMENTO DI FERRO SUPERIORE RISPETTO ALLA SOMMINISTRAZIONE GIORALIERA

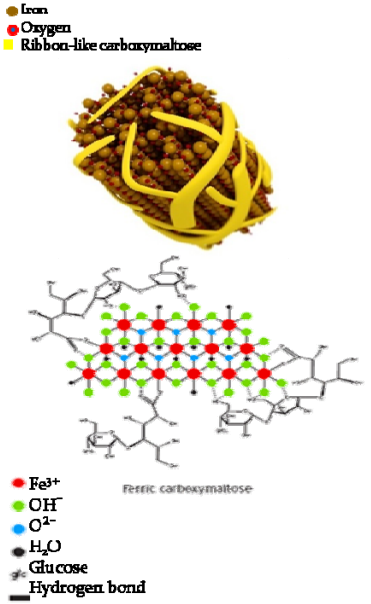
consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials

Nicole U Stoffel, MSc, Colin I Cercamondi, PhD, Prof Gary Brittenham, MD, Christophe Zeder, MSc, Anneke J Geurts-Moespot, BSc, Prof Dorine W Swinkels, PhD, Diego Moretti, PhD†, Prof Michael B Zimmermann, MD†

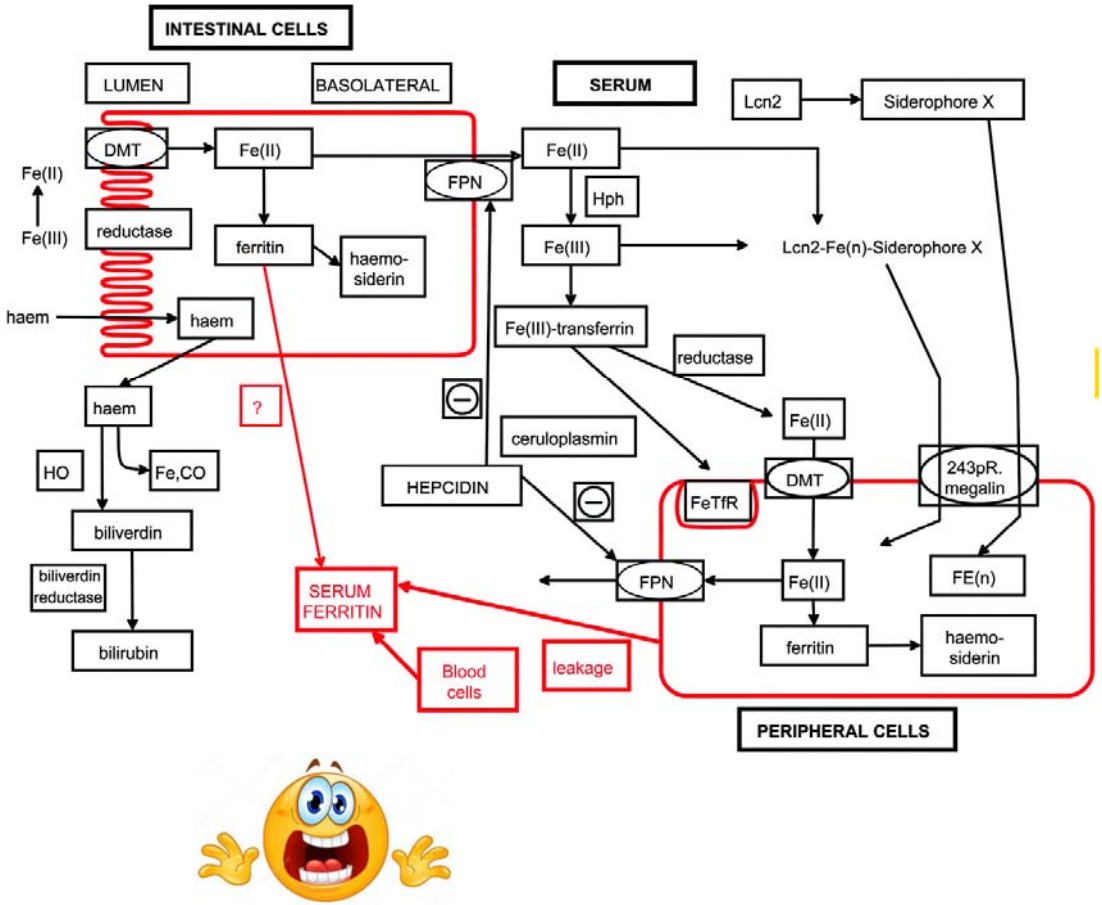
THE LANCET Haematology **November 2017**

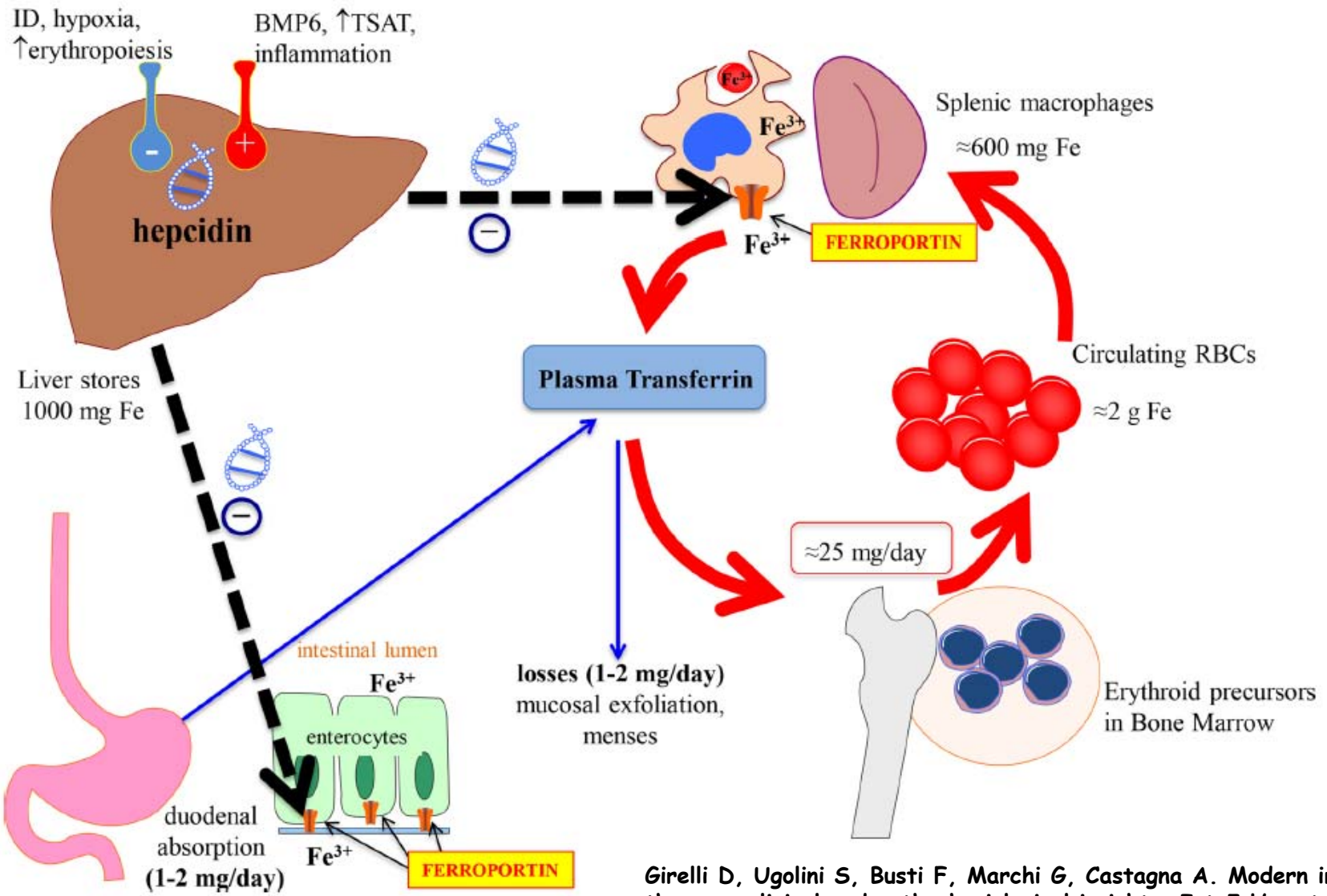
Numero di articoli in PubMed / Anno per parola chiave «Iron Intravenous Therapy»



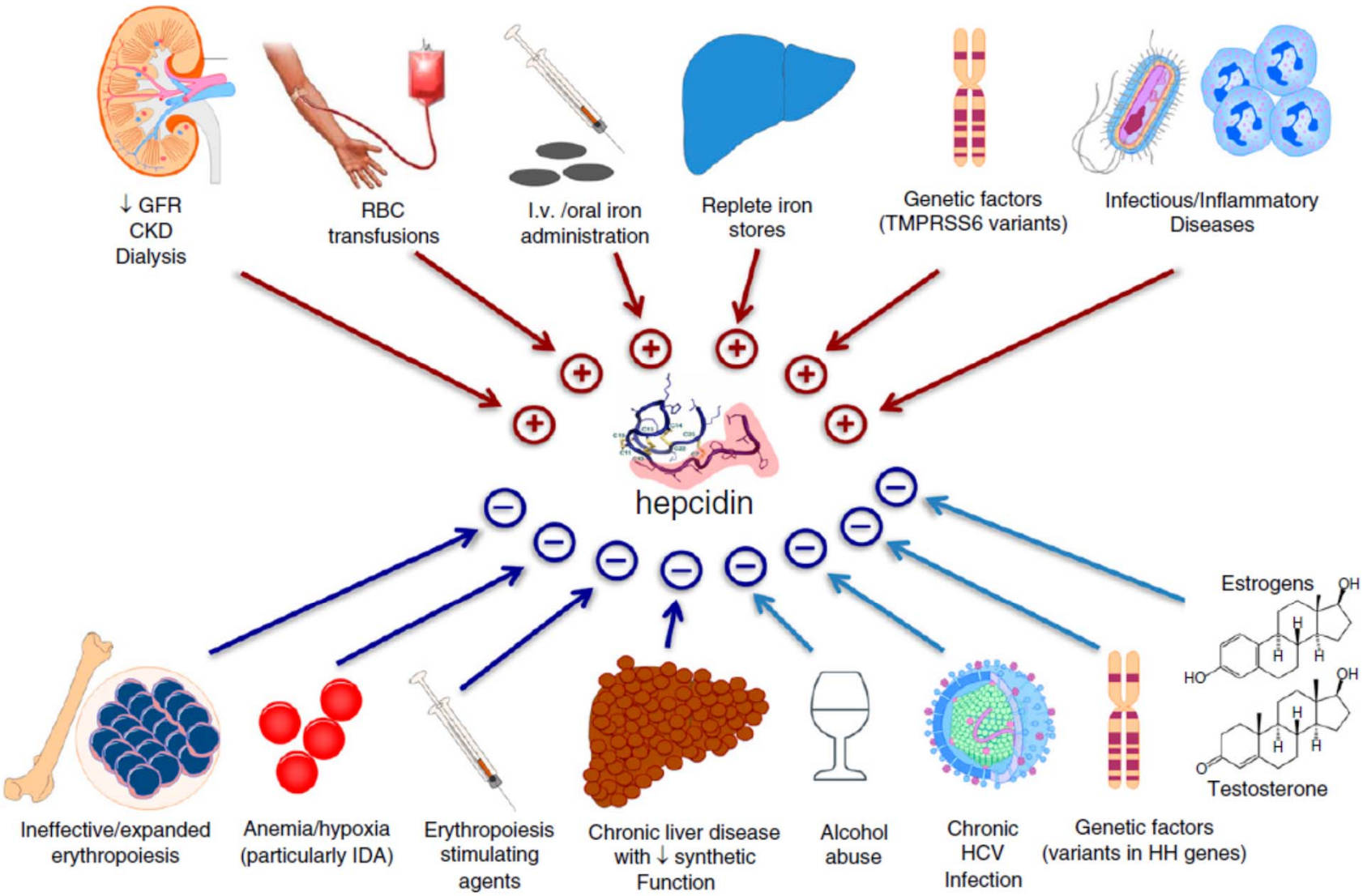


Dal metabolismo alla terapia…

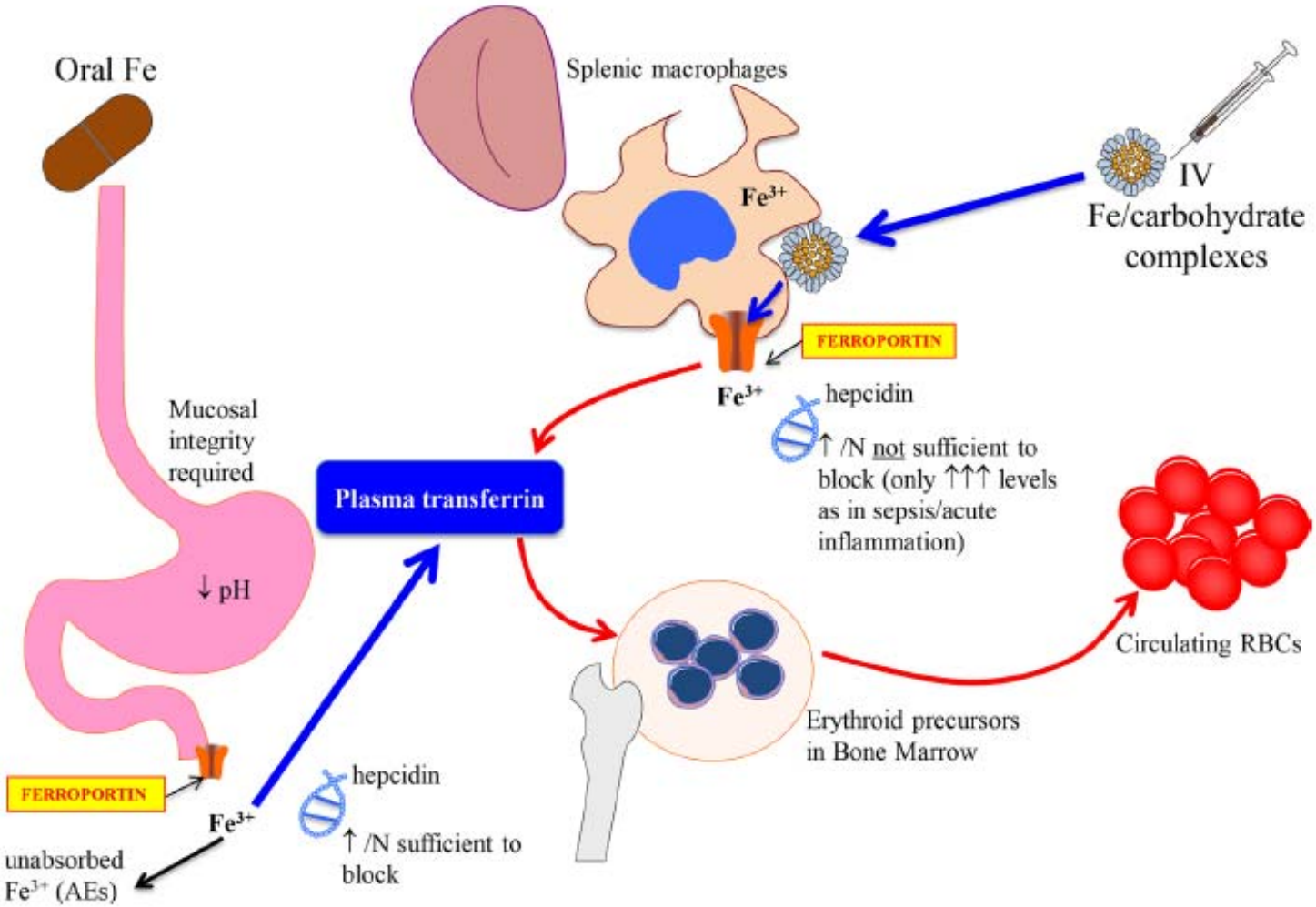




Girelli D, Ugolini S, Busti F, Marchi G, Castagna A. Modern iron replacement therapy: clinical and pathophysiological insights. Int J Hematol. 2018 Jan;107(1):16–30



Girelli D, Nemeth E, Swinkels DW. Hepcidin in the diagnosis of iron disorders. Blood. 2016 Jun 9;127(23):2809–13.



Girelli D, Ugolini S, Busti F, Marchi G, Castagna A. Modern iron replacement therapy: clinical and pathophysiological insights. Int J Hematol. 2018 Jan;107(1):16–30

Terapia marziale parenterale

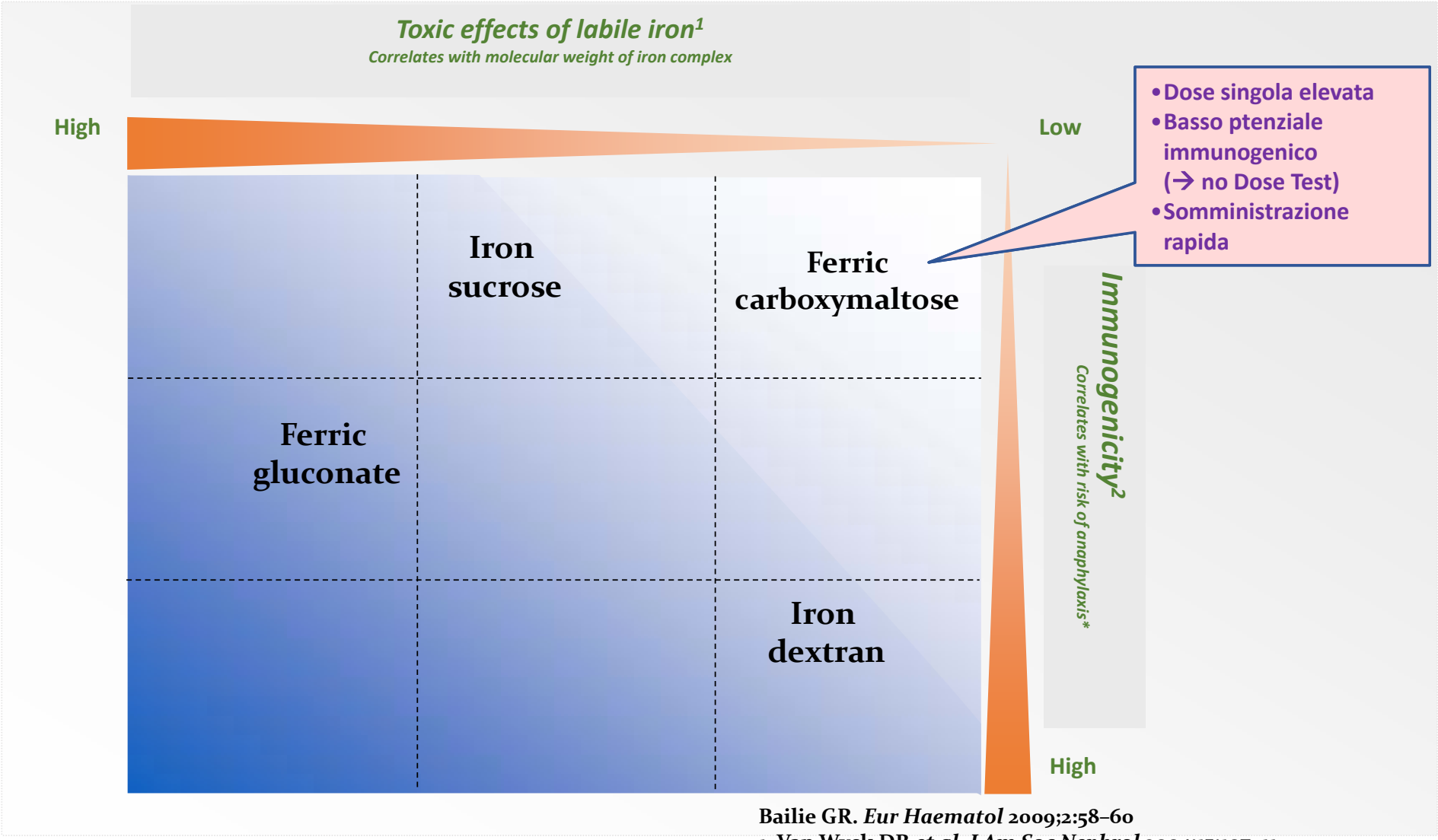
Quali prodotti abbiamo a disposizione?

Ferro gluconato vs Ferro Carbossimaltosio

Table 4. Iron Preparations for Intravenous Use.*

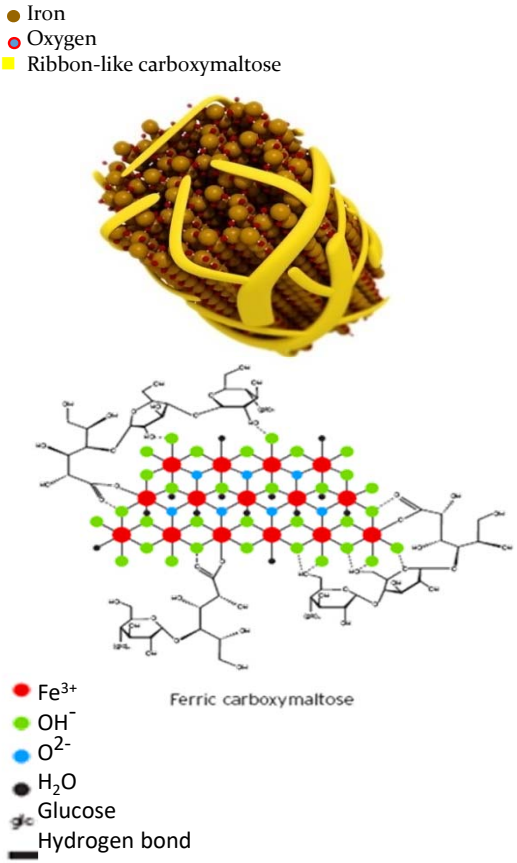
Formulation	Dose per Infusion	
	Standard	Maximum per Single Infusion
Ferric gluconate (Ferlecit)	125 mg/10–60 min	250 mg/60 min
Iron sucrose (Venofer)	100–400 mg/2–90 min	300 mg/2 hr
Low-molecular-weight iron dextran (INFeD)†	100 mg/2 min	1000 mg/1–4 hr)
Ferumoxytol (Feraheme)†	510 mg/>1 min	510–1020 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

Camasachella C. Iron-deficiency anemia. N Engl J Med 2015;372:1832-43



Bailie GR. *Eur Haematol* 2009;2:58–60
1. Van Wyck DB *et al. J Am Soc Nephrol* 2004;15:107–11
2. Hörl W *et al. Nephrol Dial Transplant* 2007;22(Suppl 3):iii2–6

Proprietà fisicochimiche del Ferro Carbossimaltosio (FCM)

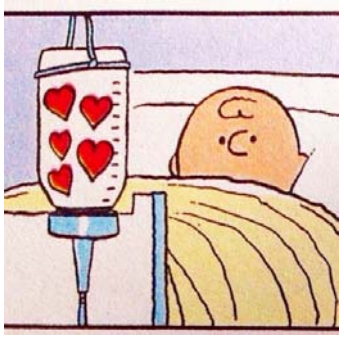


Carbossimaltosio Ferrico:

- Complesso Macromolecolare Polimerico
  - Polynuclear iron(III)-hydroxide core
  - Macromolecular carbohydrate shell
- Peso Molecolare approx. 150 kD
- Altissima stabilità del complesso Ferro Carboidrato

Geisser P. *Port J Nephrol Hypert* 2009;23:11–6
Ferric carboxymaltose, SmPCs, EU

Terapia marziale parenterale (1)



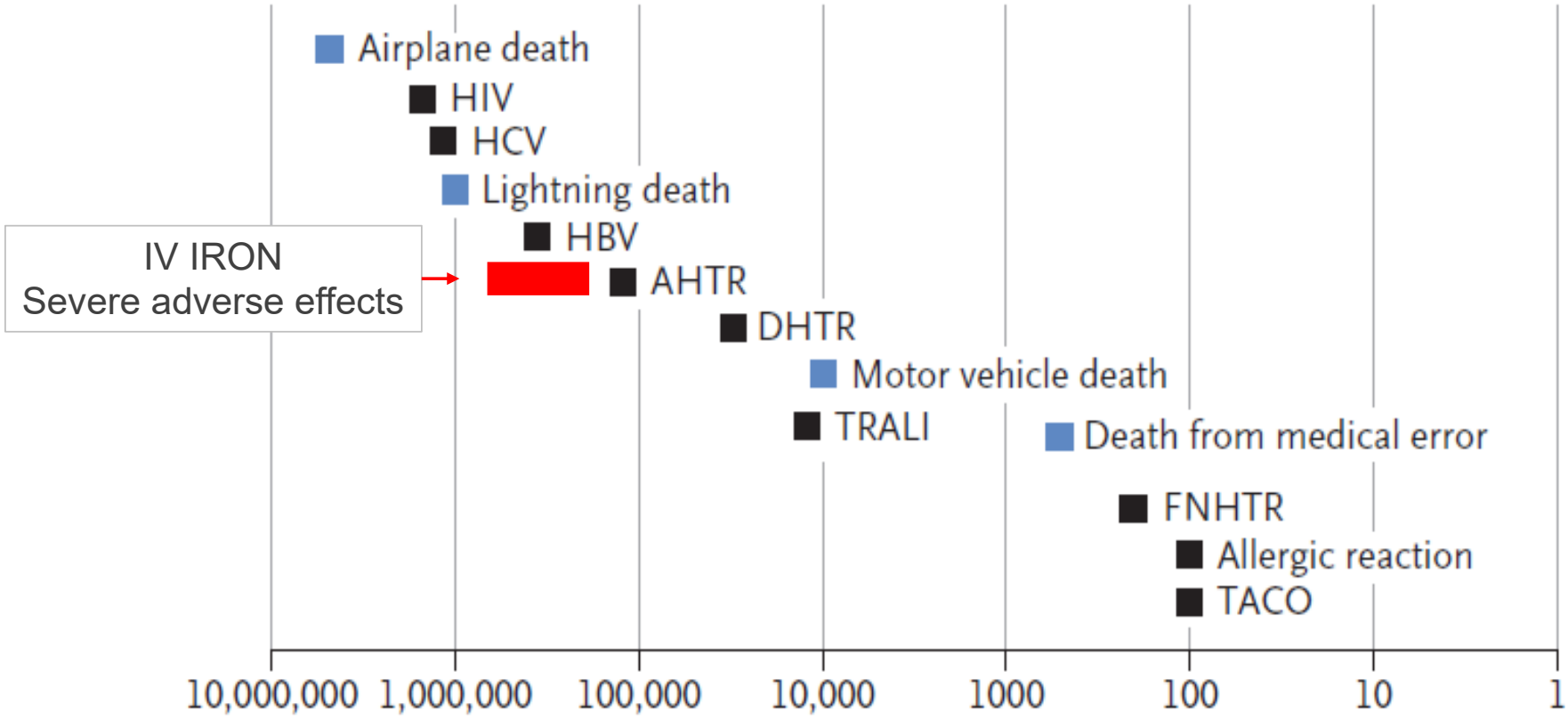
- Più costosa di quella orale
- Il 100% del ferro somministrato raggiunge il circolo sanguigno
- Indicazioni consolidate:
  - Inefficacia, anche su base genetica (IRIDA), della terapia orale
  - Intolleranza alla terapia orale
  - Necessità di rapido recupero dei valori di emoglobina
  - In sostituzione della trasfusione in soggetti che la rifiutano per motivi religiosi (se sideropenici…)
  - In pazienti con insufficienza renale cronica in associazione a terapia con agenti che stimolano l'eritropoiesi
- Durata della terapia per il ripristino dei depositi marziali: 1-2 mesi circa (ma a volte meno…)

Terapia marziale parenterale (2)

Effetti collaterali

- Nausea, vomito
- Prurito
- Orticaria
- Cefalea
- Arrossamento al volto, senso di calore (flushing), palpitazoni autolimitantesi
  - Non trattare con antistaminici
- Mialgia, artralgia, dolori in sede renale o al torace (risoluzione generalmente entro 48 ore)
- Shock anafilattico (< 1/250.000 infusioni, con gli attuali preparati)

Infectious and Noninfectious Adverse Effects of Red-Cell Transfusion as Compared with Other, Unrelated Risks



Carson JL, Triulzi DJ, Ness PM. N Engl J Med. 2017

Descrizione del

Progetto PBM ASST Ovest Milanese

PATIENT BLOOD MANAGEMENT

ASST OVEST MILANESE

Il percorso preoperatorio abituale …
Il percorso preoperatorio ideale!…

Fase pre-operatoria

Obbiettivo n° 1

TUTTO IN UN GIORNO

Fase pre-operatoria

Obbiettivo n° 2

CONDIVISIONE

FRA DIFFERENTI ED ETEROGENEI PROFESSIONISTI…

… E CON IL PAZIENTE

Fase pre-operatoria

Obbiettivo n° 3

STANDARDIZZAZIONE DEL PERCORSO