LA GESTIONE DIAGNOSTICA e TERAPEUTICA DELL'ANEMIA PREOPERATORIA

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Udine, 15 novembre 2019

Alternatives to blood transfusion

Donat R Spahn, Lawrence T Goodnough

	Optimise erythropoiesis	Minimise blood loss	Manage anaemia
Preoperative	• Identify, assess, and treat anaemia • Consider preoperative autologous blood donation • Consider erythropoiesis-stimulating agents if nutritional anaemia is ruled out or treated • Refer for further assessment if necessary • Unmanaged anaemia (haemoglobin in women <120 g/L, haemoglobin in men <130 g/L) is a contraindication for elective surgery	• Identify and manage bleeding risk (past and family history) • Review medications (antiplatelet, anticoagulation treatment) • Minimise iatrogenic blood loss • Procedure planning and rehearsal	• Compare estimated blood loss with patient-specific tolerable blood loss • Assess and optimise patient's physiological reserve (eg, pulmonary and cardiac function) • Formulate patient-specific management plan with appropriate blood conservation modalities to manage anaemia
Intraoperative	• Time surgery with optimisation of red blood cell mass	• Meticulous haemostasis and surgical techniques • Blood-sparing surgical techniques • Anaesthetic blood-conservation strategies • Acute normovolaemic haemodilution • Cell salvage and reinfusion • Pharmacological and haemostatic agents • Avoid coagulopathy	• Optimise cardiac output • Optimise ventilation and oxygenation • Evidence-based transfusion strategies
Postoperative	• Manage nutritional or correctable anaemia (eg, avoid folate deficiency, iron-restricted erythropoiesis) • Treatment with erythropoiesis-stimulating agents if appropriate • Be aware of drug interactions that can cause anaemia (eg, ACE inhibitor)	• Monitor and manage bleeding • Maintain normothermia (unless hypothermia indicated) • Autologous blood salvage • Minimise iatrogenic blood loss • Management of haemostasis and anticoagulation • Awareness of adverse effects of medications (eg, acquired vitamin K deficiency)	• Maximise oxygen delivery • Minimise oxygen consumption • Avoid and treat infections promptly • Evidence-based transfusion strategies

Figure 1: **Patient blood management**

These recommendations apply in the perisurgical period enable treating physicians to have the time and methods to provide patient-centred and evidence-based patient blood management to minimise allogeneic blood transfusions. Modified from Goodnough and Shander,[1] by permission of the American Society of Anesthesiologists.

Lancet 2013; 381: 1855–65

ANEMIA PREOPERATORIA

- PERCHE' OTTIMIZZARE L'EP
- CHI TRATTARE
- COME TRATTARE

?

PERCHE' OTTIMIZZARE L'ERITROPOIESI PREOPERATORIA

- per ritardare il più possibile il ricorso alla trasfusione eritrocitaria

- più il paziente è lontano dalla soglia di Hb al di sotto della quale si determina un iniziale scompenso ossiforetico,tanto più ci saranno tempi adeguati e strumenti terapeutici per ripristinare livelli emoglobinici di sicurezza,compatibili con un approccio non trasfusionale

- l' effetto di una terapia farmacologica dell' anemia perdura per diverse settimane,mentre la terapia trasfusionale ha un effetto transitorio

- Il trattamento dell' anemia con terapie alternative alla trasfusione non deprime con feedback negativo l' increzione endogena di eritropoietina

Pre-operative haemoglobin levels and iron status in a large multicentre cohort of patients undergoing major elective surgery*

M. Muñoz,[1] M. J. Laso-Morales,[2] S. Gómez-Ramírez,[3] M. Cadellas,[4] M. J. Núñez-Matas[5] and J. A. García-Erce[6]

Summary

Pre-operative anaemia in patients undergoing major surgical procedures has been linked to poor outcomes. Therefore, early detection and treatment of pre-operative anaemia is recommended. However, to effectively implement a pre-operative anaemia management protocol, an estimation of its prevalence and main causes is needed. We analysed data from 3342 patients (44.5% female) scheduled for either: elective orthopaedic surgery (n = 1286); cardiac surgery (n = 691); colorectal cancer resection (n = 735); radical prostatectomy (n = 362); gynaecological surgery (n = 203) or resection of liver metastases (n = 122). For both sexes, anaemia was defined by a haemoglobin level < 130 $g.l^{-1}$; absolute iron deficiency by ferritin < 30 $ng.ml^{-1}$ (< 100 $ng.ml^{-1}$, if transferrin saturation < 20% or C-reactive protein > 5 $mg.l^{-1}$); iron sequestration by transferrin saturation < 20% and ferritin > 100 $ng.ml^{-1}$; and low iron stores by transferrin saturation > 20% and ferritin 30–100 $ng.ml^{-1}$. The overall prevalence of anaemia was 36%, with differences according to the type of surgery. Laboratory parameters allowing classification of iron status were available for 2884 patients. Among those with anaemia (n = 986), 677 (69%) were women, 608 (62%) presented with absolute iron deficiency, 101 (10%) with iron sequestration; and 150 (5%) with low iron stores. Iron status alterations were similar in women with haemoglobin < 130 $g.l^{-1}$ or < 120 $g.l^{-1}$. For those who were not anaemic (n = 1898), corresponding figures were 656 (35%), 621 (33%), 165 (9%) and 518 (27%), respectively. Anaemia was present in one-third of patients undergoing major elective procedures. Over two-thirds of anaemic patients presented with absolute iron deficiency or iron sequestration. Over half of non-anaemic patients presented with absolute iron deficiency or low iron stores. We consider these data useful for planning pre-operative management of patients scheduled for major elective surgery.

Anaesthesia 2017, 72, 826–834

Pre-operative haemoglobin levels and iron status in a large multicentre cohort of patients undergoing major elective surgery*

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PREVALENZA ANEMIA PREOPERATORIA

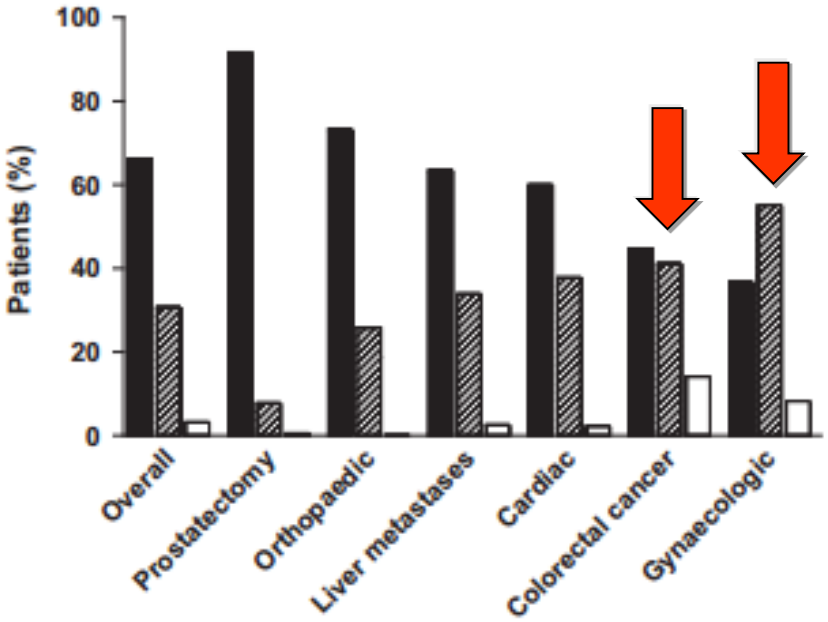
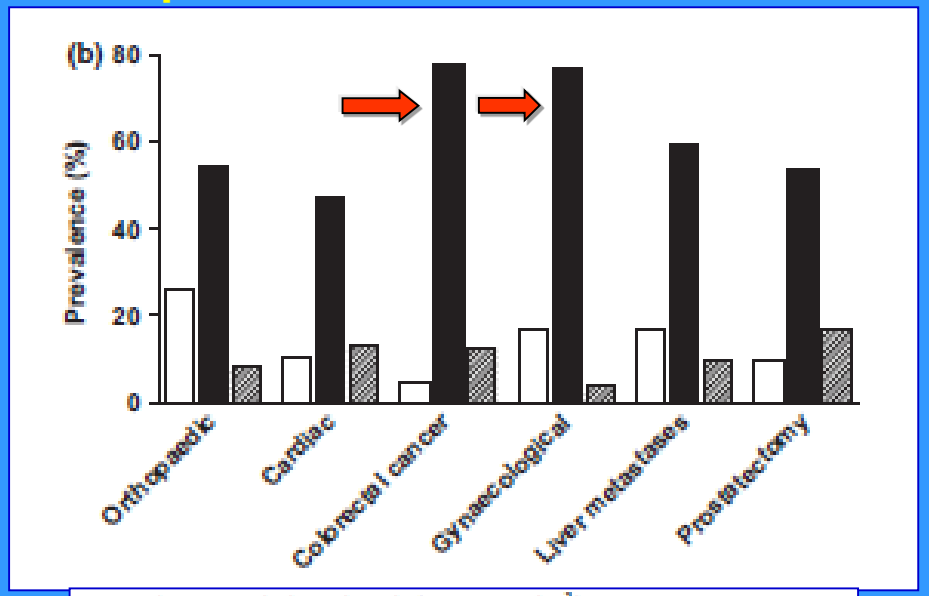


Figure 1 Distribution of pre-operative haemoglobin levels according to type of surgery. ■ Haemoglobin ≥ 130 g.l^{-1}; ▨ Haemoglobin 100–129 g.l^{-1}; □ Haemoglobin < 100 g.l^{-1}; p = 0.001 between groups.

ALTERAZIONI BILANCIO MARZIALE per TIPO DI INTERVENTO



Low haemoglobin level (< 130 g.l^{-1}). □ Low iron stores (p = 0.001 between surgical procedures, for both haemoglobin groups); ■ Absolute iron deficiency (p = 0.001 between surgical procedures, for both haemoglobin groups); ▨ Iron sequestration (p = 0.273 between surgical procedures, for haemoglobin ≥ 130 g.l^{-1}; p = 0.033 between surgical procedures, for haemoglobin < 130 g.l^{-1}).

Anaesthesia 2017, 72, 826–834

Dunne JR, et al J Surg Res 2002;102:237-44
Shander A. Am J Med 2004;116(7A) 58S-69S
Beattie WS,et al Anesthesiology 2009;110(3) 574-81
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Mussallam KM, et al Lancet 2011;378:1396-407
Baron DM, et al British Journal of Anaesthesia 2014;113:416-23
Fowler AJ, et al British Journal of Surgery 2015;102:1314-24
Klein AA, et al Anaesthesia 2016;71:627-35

ANEMIA

Fattore di rischio indipendente per

- **> MORTALITA'**
- **> MORBIDITA'**
- **> DURATA DI DEGENZA**

Anemia preoperatoria = controindicazione a chirurgia maggiore

Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study

Lancet 2011; 378: 1396–407

Khaled M Musallam, Hani M Tamim, Toby Richards, Donat R Spahn, Frits R Rosendaal, Aida Habbal, Mohammad Khreiss, Fadi S Dahdaleh, Kaivan Khavandi , Pierre M Sfeir, Assaad Soweid, Jamal J Hoballah, Ali T Taher, Faek R Jamali

Summary

Background Preoperative anaemia is associated with adverse outcomes after cardiac surgery but outcomes after non-cardiac surgery are not well established. We aimed to assess the effect of preoperative anaemia on 30-day postoperative morbidity and mortality in patients undergoing major non-cardiac surgery.

Methods We analysed data for patients undergoing major non-cardiac surgery in 2008 from The American College of Surgeons' National Surgical Quality Improvement Program database (a prospective validated outcomes registry from 211 hospitals worldwide in 2008). We obtained anonymised data for 30-day mortality and morbidity (cardiac, respiratory, CNS, urinary tract, wound, sepsis, and venous thromboembolism outcomes), demographics, and preoperative and perioperative risk factors. We used multivariate logistic regression to assess the adjusted and modified (nine predefined risk factor subgroups) effect of anaemia, which was defined as mild (haematocrit concentration >29–<39% in men and >29–<36% in women) or moderate-to-severe (≤29% in men and women) on postoperative outcomes.

Findings We obtained data for 227 425 patients, of whom 69 229 (30·44%) had preoperative anaemia. After adjustment, postoperative mortality at 30 days was higher in patients with anaemia than in those without anaemia (odds ratio [OR] 1·42, 95% CI 1·31–1·54); this difference was consistent in mild anaemia (1·41, 1·30–1·53) and moderate-to-severe anaemia (1·44, 1·29–1·60). Composite postoperative morbidity at 30 days was also higher in patients with anaemia than in those without anaemia (adjusted OR 1·35, 1·30–1·40), again consistent in patients with mild anaemia (1·31, 1·26–1·36) and moderate-to-severe anaemia (1·56, 1·47–1·66). When compared with patients without anaemia or a defined risk factor, patients with anaemia and most risk factors had a higher adjusted OR for 30-day mortality and morbidity than did patients with either anaemia or the risk factor alone.

Interpretation Preoperative anaemia, even to a mild degree, is independently associated with an increased risk of 30-day morbidity and mortality in patients undergoing major non-cardiac surgery.

British Journal of Anaesthesia **113** (3): 416–23 (2014)
Advance Access publication 14 May 2014 · doi:10.1093/bja/aeu098

BJA

Preoperative anaemia is associated with poor clinical outcome in non-cardiac surgery patients

D. M. Baron[1], H. Hochrieser[2], M. Posch[2], B. Metnitz[3], A. Rhodes[4*], R. P. Moreno[5], R. M. Pearse[6] and P. Metnitz[1*], for the European Surgical Outcomes Study (EuSOS) group for the Trials Groups of the European Society of Intensive Care Medicine and the European Society of Anaesthesiology

- Ferraris VA et al Archives of Surgery 2012;147:49-55
- Fowler AJ, et al British Journal of Surgery 2015;102:1314-24
- Klein AA, et al Anaesthesia 2016;71:627-35

HCV,HIV,HBV,CMV,WNV, Febbre,TRALI,GVHD, Anafilassi,…

TRASFUSIONE

ARDS,SIRS.MOF,Stroke, IMA,Arresto Cardiaco, Insufficienza renale, Immunomodulazione, Recidiva neoplastica, Risanguinamento, Prolungata Ventilazione Meccanica

Fattori di rischio indipendenti per

- > **mortalità**
- > **morbidità**
- > **durata degenza**

ANEMIA

SANGUINAMENTO

SCREENING PREOPERATORIO per ANEMIA
TERAPIA dell' ANEMIA PREOPERATORIA

AUMENTO Hb PREOPERATORIA
RIDUZIONE DELLE TRASFUSIONI
RIDUZIONE della DURATA di DEGENZA ❖

Cuenca J,et al International Journal of Surgery 2007;5:89-94
Gomez-Ramirez JR,et al;Transfusion Medicine 2009;19:35-42
Bisbe E,et al BJA 2011;107:477-8
Kotzè A,et al BJA 2012;108:943-52 ❖
Cadellas M,et al American Journal of Cardiology 2012;110:1021-6 ❖
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Froessler B,et al Annals of Surgery 2016;264:41-6 ❖
Wilson MJ,et al Transfusion 2018;58:795-803
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BJA
British Journal of Anaesthesia

Volume 115, Number 1, May 2015

British Journal of Anaesthesia **115** (1): 1–3 (2015)
Advance Access publication 15 April 2015 · doi:10.1093/bja/aev099

EDITORIALS

Non-treatment of preoperative anaemia is substandard clinical practice

D. R. Spahn[1,*] and K. Zacharowski[2]

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Non trattare l'anemia pre-operatoria equivale a fornire un' assistenza sanitaria subottimale poiché espone al rischio di trasfusioni potenzialmente evitabili

NICE National Institute for Health and Care Excellence

NICE quality standard

Blood transfusion

Quality standard
Published: 15 December 2016
www.nice.org.uk/guidance/qs138

Quality statement 1: Iron supplementation

Quality statement

People with iron-deficiency anaemia who are having surgery are offered iron supplementation before and after surgery.

Rationale

Preoperative anaemia is associated with increased postoperative morbidity and mortality, and with increased transfusion needs. Treating iron deficiency with iron supplements can reduce the need for blood transfusion. This avoids serious risks associated with blood transfusion, for example infection, fluid overload and incorrect blood transfusions being given. It may also reduce the length of hospital stays and the cost to the NHS. Depending on the circumstances, the cause of the iron deficiency should be investigated before or after surgery.

Ministero della Salute Istituto Superiore di Sanità Centro Nazionale Sangue	**LINEE GUIDA PER IL PROGRAMMA DI PATIENT BLOOD MANAGEMENT**	LG CNS 05 Rev. 0 27.10.2016

Visto il Decreto del Ministro della Salute 2 novembre 2015, recante "Disposizioni relative ai requisiti di qualità e sicurezza del sangue e degli emocomponenti", ed in particolare l'articolo 25, comma 5, che prevede che *"al fine della prevenzione della trasfusione evitabile, sono definiti e implementati, sul territorio nazionale, specifici programmi (Patient Blood Management), con particolare riferimento alla preparazione del paziente a trattamenti chirurgici programmati, sulla base di linee guida da emanare a cura del Centro nazionale sangue entro sei mesi dall'entrata in vigore del presente decreto";*

Raccomandazioni da adottare nel periodo pre-operatorio

10	Il valore *target* dell'emoglobina (Hb) prima degli interventi di chirurgia maggiore in elezione rientra nel *range* di normalità secondo i criteri dell'Organizzazione Mondiale della Sanità (OMS).
11	L'anemia è definita secondo i valori soglia di (Hb) indicati dall'OMS.
12	Qualora mediante la valutazione pre-operatoria sia rilevata una condizione di anemia, i successivi test diagnostici di laboratorio sono orientati all'identificazione di carenze marziali o altre carenze nutrizionali (acido folico e/o vitamina B_{12}), insufficienza renale cronica e/o patologie infiammatorie croniche.
13	Poiché il valore di Hb pre-operatorio è il principale fattore di rischio indipendente per ricevere supporto trasfusionale con concentrati eritrocitari, tutte le carenze di ferro, vitamina B_{12} e folati, una volta rilevate, sono trattate con ematinici.
14	Successivamente alla diagnosi di carenza marziale, quando la somministrazione di ferro per via orale non sia efficace o scarsamente tollerata oppure l'intervento di chirurgia maggiore elettiva sia programmato meno di quattro settimane dopo la predetta diagnosi, si suggerisce la somministrazione di ferro per via endovenosa.

CHI TRATTARE

ALGORITMO DI GESTIONE PREOPERATORIA

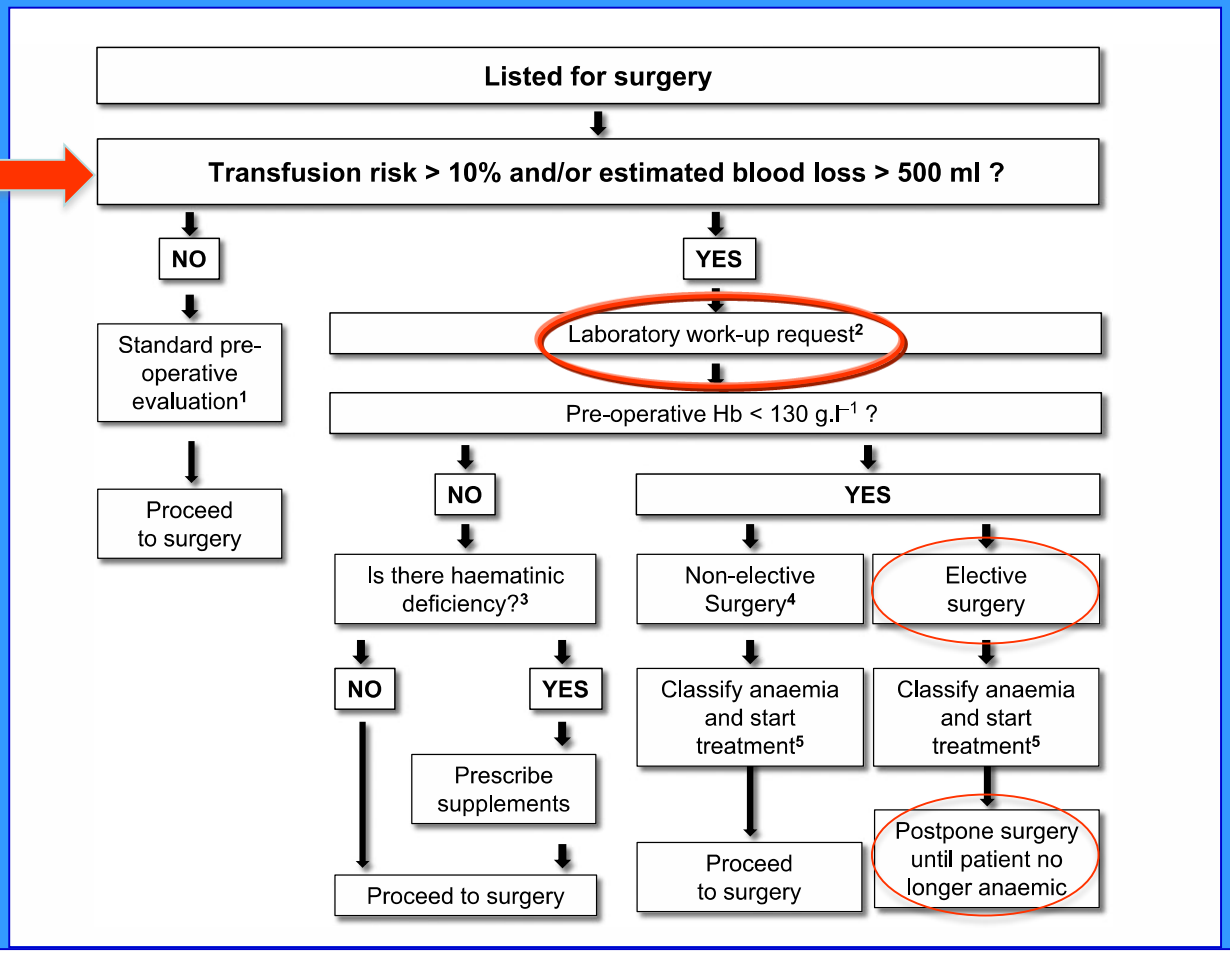


Figure 3 Algorithm for the management of a surgical patients. 1, According to centre protocol for each surgical procedure; 2, It should initially include at least full blood counts, serum ferritin, transferrin saturation, a marker of inflammation (e.g. serum C-reactive protein) and a marker of renal function (e.g. serum creatinine); 3, Haematinic deficiencies are defined by ferritin < 100 µg·l^{-1}, vitamin B_{12} < 270 pg·ml^{-1} and/or folate < 3 pg·ml^{-1}; 4, Including patients presenting late before surgery and non-deferrable surgery (e.g. cancer surgery); 5, According to algorithm depicted in Fig. 2.

ANEMIA

- Hb <13g/dl nel maschio
- Hb <12g/dl nella femmina

(WHO, 2008)

Ottimizzazione dell'eritropoiesi
Periodo pre-operatorio
Rilevazione dell'anemia
Si raccomanda di non effettuare interventi di chirurgia maggiore elettiva in pazienti nei quali venga rilevata una condizione di anemia, prima che la stessa venga correttamente inquadrata e trattata **[1B]**.
Si raccomanda che la valutazione pre-operatoria del paziente, finalizzata a rilevare un'eventuale anemia e a ottimizzare l'eritropoiesi, sia eseguita almeno 30 giorni prima della data programmata dell'intervento, in modo da consentire un approfondimento diagnostico e/o la pianificazione di adeguate misure terapeutiche **[1C]**.
Si raccomanda che, qualora sia rilevata una condizione di anemia, i successivi test diagnostici di laboratorio siano orientati all'identificazione di carenze marziali o altre carenze nutrizionali (acido folico e/o vitamina B_{12}), insufficienza renale cronica e/o patologie infiammatorie croniche **[1C]**.
Si raccomanda che la rilevazione e il trattamento dell'anemia, e gli ulteriori eventuali approfondimenti clinico-diagnostici correlati, siano inseriti nell'ambito di una strategia globale di PBM e divengano un **livello standard di assistenza** erogato a tutti i pazienti candidati a interventi di chirurgia elettiva, specialmente se il rischio di sanguinamento peri-operatorio è consistente **[1C]**.
Stimolazione dell'eritropoiesi
Poiché il valore di Hb pre-operatorio è il principale fattore di rischio indipendente per ricevere supporto trasfusionale con concentrati eritrocitari, **si raccomanda** che tutte le carenze nutrizionali (ferro, vitamina B_{12}, folati), una volta rilevate, vengano trattate con ematinici **[1C]**.
Si suggerisce che il valore *target* dell'emoglobina prima degli interventi di chirurgia ortopedica maggiore in elezione rientri almeno nel *range* di normalità secondo i criteri OMS precedentemente riportati **[2C]**.
Terapia marziale per via orale
Si suggerisce il ricorso alla terapia marziale per via orale per il trattamento dell'anemia sideropenica pre-operatoria e per il contenimento del fabbisogno trasfusionale nei pazienti adulti candidati a chirurgia ortopedica maggiore elettiva **[2B]**.
Terapia marziale per via endovenosa
Si suggerisce il ricorso alla terapia marziale per via endovenosa per il trattamento dell'anemia sideropenica pre-operatoria e per il contenimento del fabbisogno trasfusionale nei pazienti adulti candidati a chirurgia ortopedica maggiore elettiva **[2A]**.

Dosaggio della terapia marziale
Ferro per via orale
Per il trattamento dell'anemia pre-operatoria **si raccomanda** una dose di 100 mg di ferro elementare/die per 2-6 settimane prima della procedura chirurgica **[1C]**.
Ferro per via endovenosa
Si suggerisce di calcolare la dose di ferro per via endovenosa necessaria per ricostituire le scorte marziali con la formula di Ganzoni: "fabbisogno totale di ferro (mg) = [Hb desiderata – Hb attuale (mg/dL)] x peso (kg) x 0,24 + 500 mg (deposito di ferro per scorte)" **[2C]**.
Si suggerisce di somministrare 200 mg di ferro elementare per via endovenosa per ogni 500 mL di perdita ematica **[2C]**.

COME TRATTARE

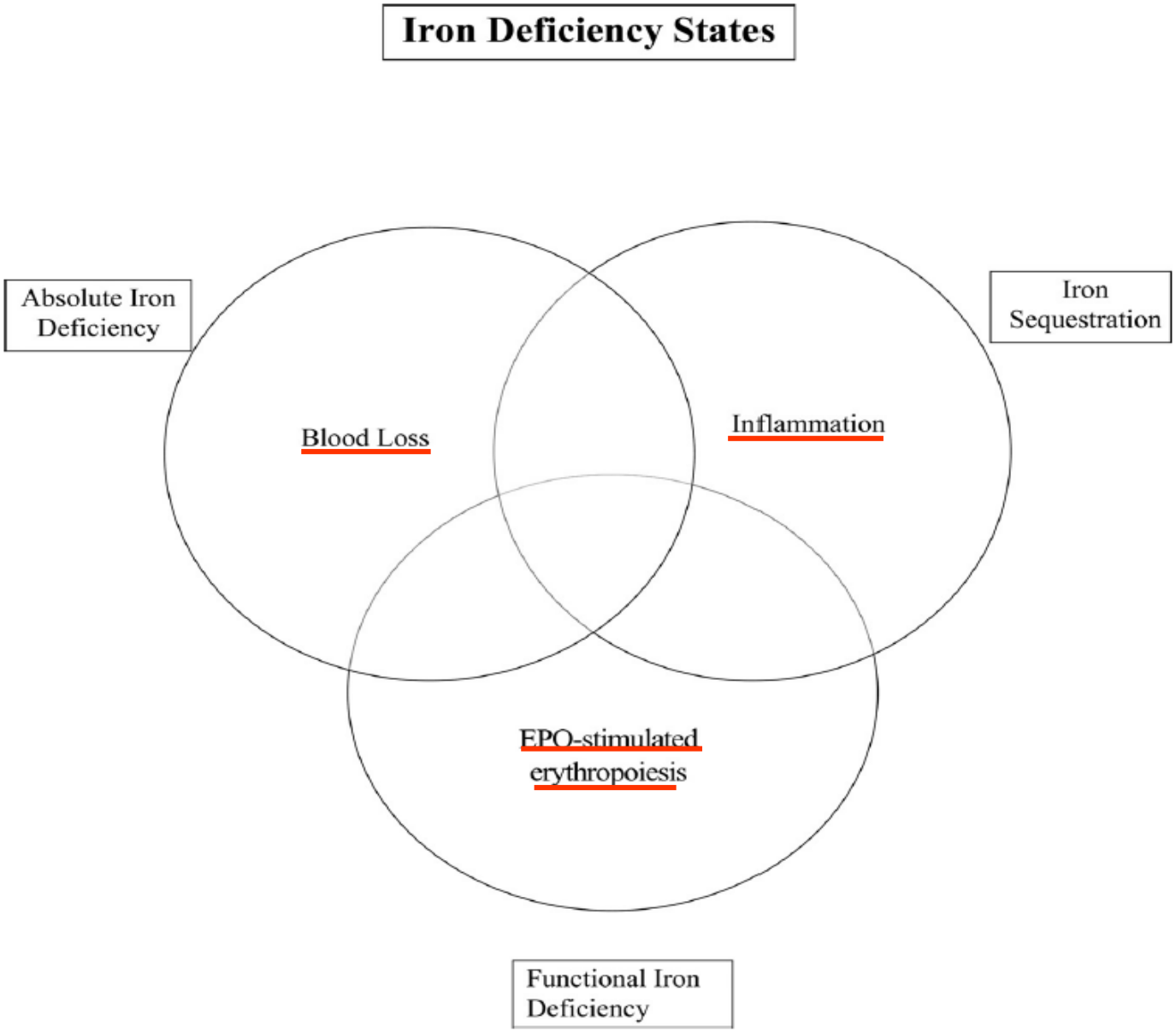


Fig. 5. Iron deficiency syndromes. The relationships between absolute iron deficiency, iron sequestration, and functional iron deficiency are illustrated. Patients can have one or more combinations that all result in iron-restricted erythropoiesis.

Epcidina e regolazione dell'omeostasi del Ferro

Kaitha S *et al*. Iron and inflammatory bowel disease

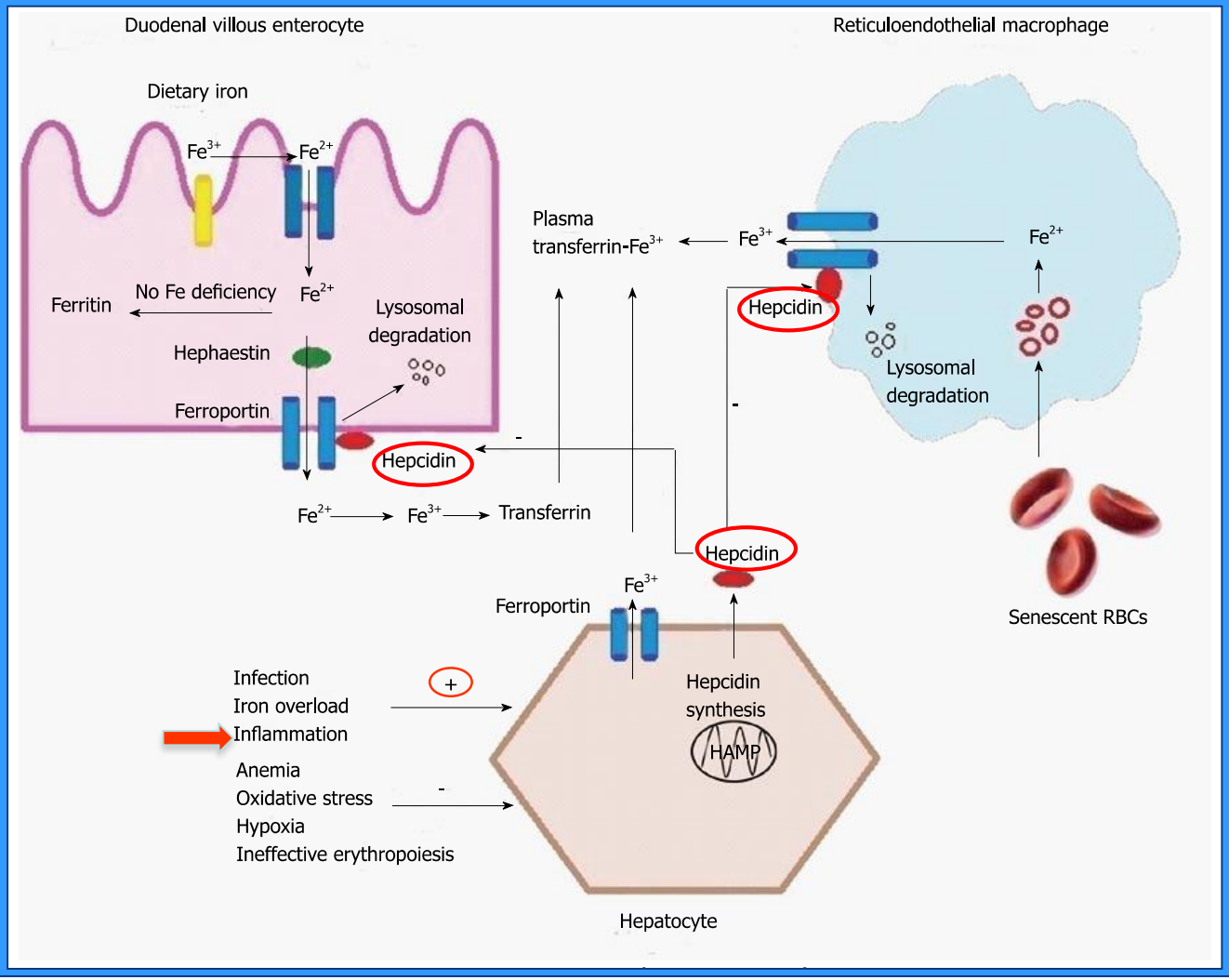


Figure 2 Role of hepcidin in the regulation of iron homeostasis. Fe^{3+} is reduced to Fe^{2+} by enterocyte brush border reductase Dcytb, transported across brush border membrane by DMT1. If iron demand is low, Fe^{2+} is stored as ferritin and sloughed with enterocytes. If iron demand is high, iron is oxidized by oxidase hephaestin and then exported into the plasma at the basolateral membrane by ferroportin[23]. Hepcidin binds to iron exporter, ferroportin 1, leading to its phosphorylation, internalization by binding to JAK 2 and lysosomal degradation, thus preventing iron release into the plasma[16]. DcytB: Duodenal ferric reductase; DMTI: Divalent metal transporter 1.

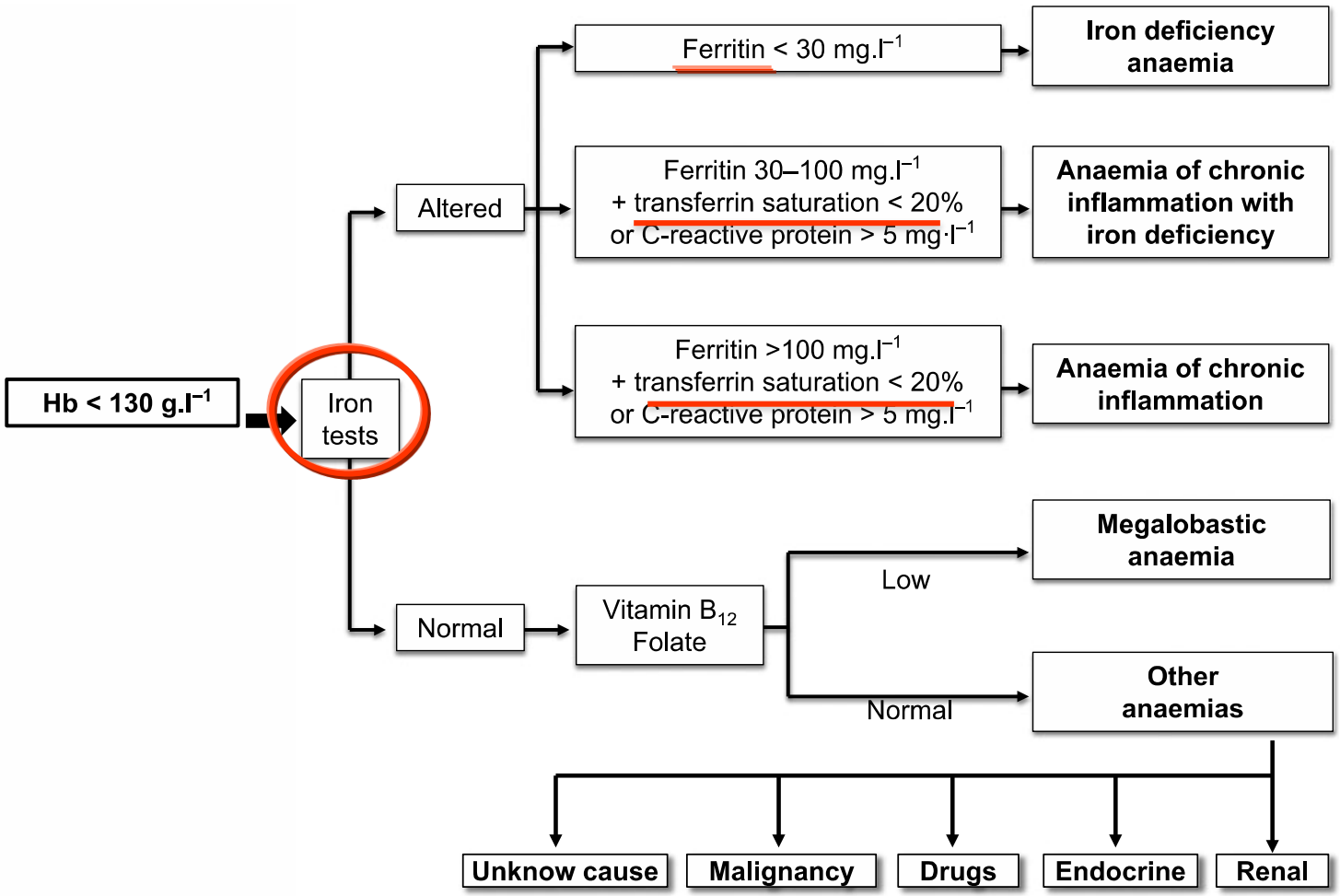
Impatto dei livelli di Epcidina sull'efficacia della terapia marziale orale

Hepcidin levels predict nonresponsiveness to oral iron therapy in patients with iron deficiency anemia

David B. Bregman,[1,2] David Morris,[3] Todd A. Koch,[1] Andy He,[1] and Lawrence T. Goodnough[4]

Levels of hepcidin, a major regulator of iron homeostasis, may identify patients with iron deficiency anemia (IDA) who will not respond to oral iron therapy. In this study, IDA patients underwent a 14-day trial (run-in) course of ferrous sulfate therapy. Nonresponders (Hgb increase <1 g/dL with 67% compliance rate) were randomized to IV ferric carboxymaltose (FCM; two injections of 750 mg) or further oral iron for 14 days. Screening hepcidin levels were 38.4 versus 11.3 ng/mL, $P = 0.0002$ in nonresponders versus responders to a trial of oral iron. Hepcidin of > 20 ng/mL, showed sensitivity of 41.3%, specificity of 84.4%, and positive predictive value of 81.6% for predicting nonresponsiveness to oral iron. PPVs for ferritin> 30 ng/mL or transferrin saturation (TSAT)>15% were 59.2 and 55%, respectively. Negative predictive values for hepcidin, ferritin, and TSAT were 46.3, 22.7, and 19.7, respectively. FCM versus oral iron showed Hgb increases of ≥1 gm/dL in 65.3% versus 20.8% ($P < 0.0001$) and Hgb increases of 1.7 ± 1.3 versus 0.6 ± 0.9 g/dL ($P = 0.0025$), respectively. We conclude that hepcidin predicts nonresponsiveness to oral iron in patients with IDA and is superior to TSAT or ferritin for this purpose. Nonresponse to oral iron therapy does not rule out IDA, since two-thirds of patients subsequently responded to intravenous iron. Am. J. Hematol. 88:97–101, 2013.

ALGORITMO PER LA CLASSIFICAZIONE DELL'ANEMIA PREOPERATORIA

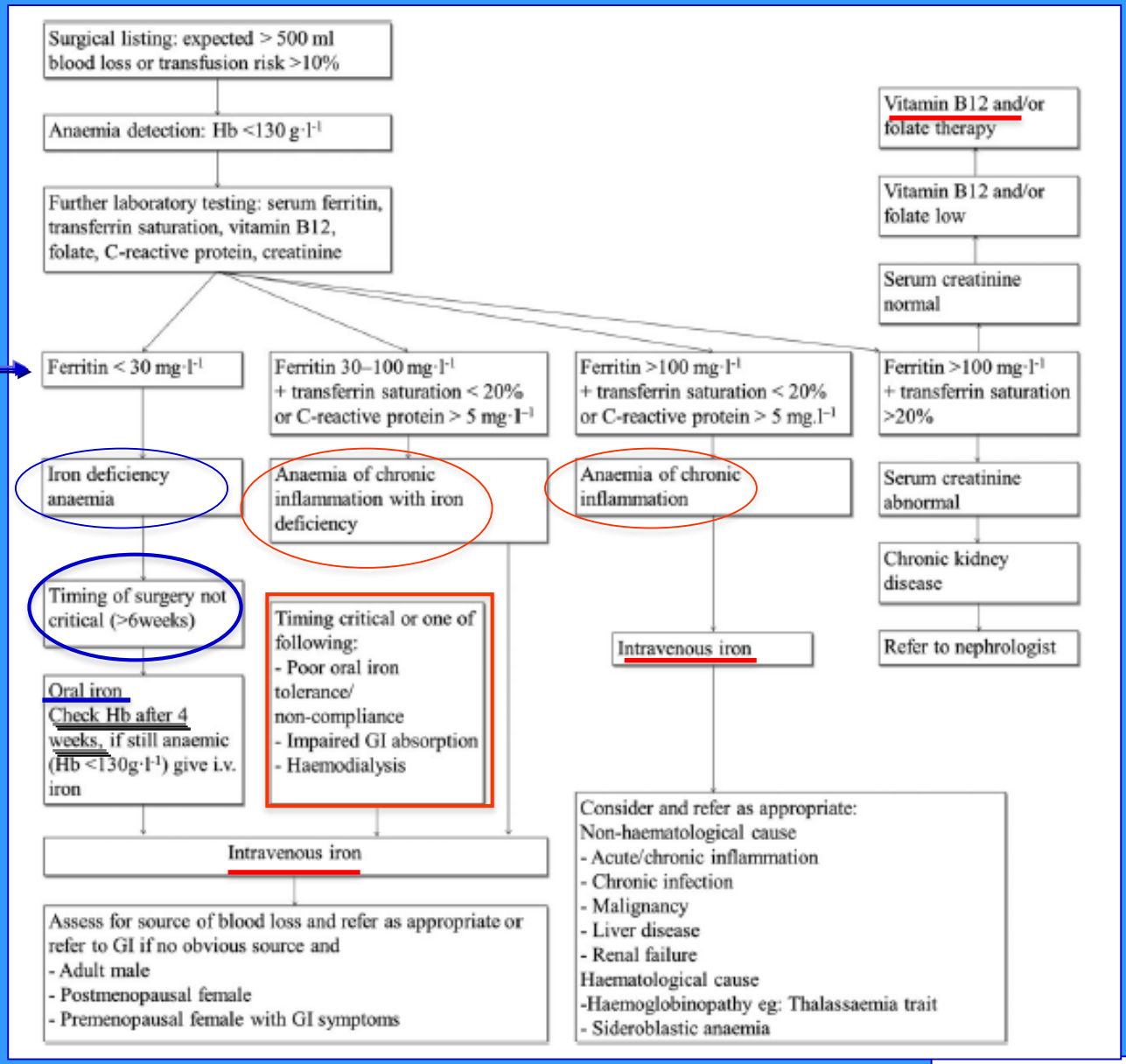


NON BASTA LA FERRITINA PER FARE DIAGNOSI DI CARENZA MARZIALE!

Anaesthesia 2017, 72, 233–247

ALGORITMO DI TRATTAMENTO DELL'ANEMIA PREOPERATORIA

LAB.



Anaesthesia 2019, 74 (Suppl. 1), 49-57

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

Iron status	Laboratory findings	Initial treatment	Adjuvant treatment
Normal	Ferritin 30–300 $\mu g.l^{-1}$ TSAT 20–50% CRP < 5 $mg.l^{-1}$	None	None
Low iron stores (for surgery with moderate-to-high blood losses)	Ferritin < 100 $\mu g.l^{-1}$	Low dose oral iron (40–60 mg iron per day or 80–100 mg alternate days, 6–8 weeks)	Intravenous iron, if intolerance, contraindication or no response to oral iron or short time to surgery
Iron deficiency	Ferritin < 30 $\mu g.l^{-1}$	Low dose oral iron (40–60 mg iron per day or 80–100 mg alternate days, 6–8 weeks)	Gastro-intestinal/urological investigations Intravenous iron, if intolerance, contraindication or no response to oral iron or short time to surgery
	*Ferritin 30–100 $\mu g.l^{-1}$ TSAT < 20% and/or CRP > 5 $mg.l^{-1}$	Intravenous iron (Calculated dose)†	Treat underlying chronic disease if possible Recombinant erythropoietin in the selected case if anaemia does not respond to i.v. iron alone
Functional iron deficiency*	Ferritin 100–500 $\mu g.l^{-1}$ TSAT < 20%	Intravenous iron (Calculated dose)†	Revise erythropoietin dose Check folic acid and vitamin B_{12}
Iron sequestration*	Ferritin > 100 $\mu g.l^{-1}$ TSAT < 20% and/or CRP > 5 $mg.l^{-1}$	Recombinant erythropoietin, if anaemia	Intravenous iron, if functional iron deficiency develops

LA TERAPIA MARZIALE ENDOVENA

TABLE 1. Characteristics of Different Intravenous Iron Preparations

Iron Preparation	Molecular Weight (kDa)	Carbohydrate Shell	Complex Stability	Maximum Approved Single Dose	Maximum total Dose
Iron dextran, low molecular weight	73	Dextran (branched polysaccharide)	High	200 mg (<30 min)	20 mg/kg
Iron sucrose	43	Sucrose (disaccharide)	Moderate	200 mg (≥30 min)	7 mg/kg (300 mg in some countries)
Iron gluconate	37	Gluconate (monosaccharide)	Low	62.5 mg (≥ 50 min)	62.5 mg (125 mg in some countries)
Ferric carboxymaltose	150	Carboxymaltose (branched polysaccharide)	High	1000 mg (≥15 min)	20 mg/kg
Iron isomaltoside 1000	150	Isomaltoside (linear oligosaccharide)	High	1000 mg (≥15 min)	20 mg/kg
Ferumoxytol*	721	Polyglucose sorbitol carboxymethylether	High	510 mg (≤1 min)	510 mg

* Not yet approved for IBD in Europe. The information given is from iron deficiency anemia in patients with chronic kidney disease.

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Carbossimaltosio Ferrico
POSOLOGIA

- *dose singola massima* : 1000 mg di ferro
- *dose settimanale massima*: 1000 mg di ferro
- *dose cumulativa massima:* determinata in base al peso corporeo e al livello di emoglobina del paziente

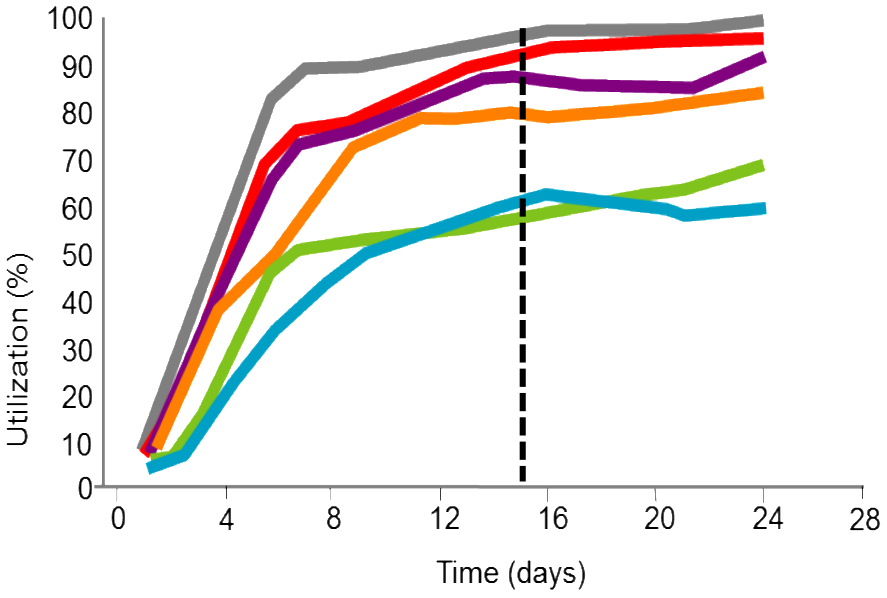
Hb (g/dL)	Patients with body weight 35 kg to <70 kg	Patients with body weight ≥70 kg
<10	1,500 mg	2,000 mg
≥10	1,000 mg	1,500 mg

CASI PARTICOLARI:

- Pazienti di peso corporeo < 35 Kg: non deve essere superata una dose di ferro cumulativa di 500 mg
- Pazienti in sovrappeso: si deve presumere un normale rapporto peso corporeo/volemia

Carbossimaltosio Ferrico
Proprietà farmacologiche

Proprietà farmacologiche di Ferinject®: elevato tasso percentuale di utilizzazione del Ferro nel globuli rossi in Pazienti con forme diverse di Anemia e/o carenza di Ferro valutato con PET (1)



L'impiego del ferro da parte dei globuli rossi dopo 24 giorni è risultato del 91%-99% nei pazienti con anemia da carenza di ferro e del 61%-84% nei pazienti con anemia da insufficienza renale (anemia da carenza di ferro funzionale)

A multicentre comparative study on the efficacy of intravenous ferric carboxymaltose and iron sucrose for correcting preoperative anaemia in patients undergoing major elective surgery

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Table 1 Patients' characteristics and preoperative i.v. iron supplementation. Values are expressed as mean (range), mean (SD) or incidence (%). *$P<0.05$; **$P<0.001$, IS *vs* FCM. †There were differences between groups with respect to patient distribution by surgical procedure ($P<0.001$, IS *vs* FCM). ‡Final Hb=last Hb assessment before surgery. ¶Hb increment=final Hb−baseline Hb. §Response=Hb increment ≥ 1.5 g dl^{-1} or final Hb ≥ 13 g dl^{-1}. ‖According to WHO definition: Hb ≥ 12 g dl^{-1} in women, and Hb ≥ 13 g dl^{-1} in men

	Iron sucrose				Ferric carboxymaltose			
	All	Colon cancer resection	Abdominal hysterectomy	Lower limb arthroplasty	All	Colon cancer resection	Abdominal hysterectomy	Lower limb arthroplasty
Patients (*n*)†	84	30	33	21	76	15	19	42
Gender (female/male)	59/25	8/22	33/0	17/4	66/10	5/10	19/0	37/5
Age (yr)	60 (32–88)	67 (36–83)	45 (32–55)	72 (53–88)	62 (36–87)	65 (36–87)	48 (36–75)	68 (46–82)
Weigh (kg)	72 (12)	74 (9)	68 (16)	76 (7)	71 (14)	68 (14)	62 (10)	75 (14)
Ferritin (ng ml^{-1})	18 (20)	15 (10)	12 (14)	33 (31)	21 (21)	16 (19)	20 (19)	23 (22)
C-reactive protein (mg dl^{-1})	1.0 (1.3)	1.6 (1.2)	0.5 (0.6)	1.5 (1.6)	0.8 (1.4)	1.1 (1.4)	0.3 (0.3)	1.0 (1.7)
Total iron deficiency (mg)	1000 (220)	1025 (240)	1050 (210)	920 (190)	950 (310)	1125 (230)	935 (210)	900 (350)
Total i.v. iron dose (mg)	1010 (440)	1140 (570)	1000 (350)	830 (270)	1120 (530)	1550 (650)*	1030 (330)	1000 (490)
Sessions (n)	5 (2)	6 (3)	5 (2)	4 (4)	2 (1)**	3 (1)**	2 (1)**	2 (1)**
Baseline Hb (g dl^{-1})	10.1 (1.3)	10.1 (1.2)	9.7 (1.2)	10.7 (1.1)	10.4 (1.6)	9.2 (1.0)*	10.6 (1.3)	10.9 (1.7)
Final Hb (g dl^{-1})‡	12.1 (1.4)	11.0 (1.4)	12.7 (0.8)	12.6 (1.0)	12.5 (1.0)*	11.7 (0.8)**	12.4 (1.2)	12.8 (0.9)
Hb increment (g dl^{-1})¶	2.0 (1.6)	0.9 (1.5)	3.0 (1.2)	1.8 (1.1)	2.1 (1.4)	2.5 (1.3)*	2.3 (1.1)	1.8 (1.4)
Response rate [*n* (%)]§	56 (67)	10 (33)	32 (97)	14 (67)	53 (70)	11 (73)*	13 (68)*	29 (69)
Anaemia correction [*n* (%)]‖	50 (59)	6 (20)	29 (88)	15 (71)	55 (72)	5 (33)	13 (68)	37 (88)
Allogeneic transfusion [*n* (%)]	20 (24)	12 (40)	2 (6)	6 (29)	7 (9)*	1 (7)*	0 (0)	6 (14)
Adverse events [*n* (%)]	6 (7)	0 (0)	5 (15)	1 (5)	4 (5)	1 (7)	1 (5)	3 (7)
Iron treatment costs (€)								
Acquisition costs	117 (51)				224 (106)			
Administration costs	190 (83)				21 (10)			
Total costs	307 (133)				244 (134)			

Br J Anaesth 2011; 107: 477–478.

The Important Role for Intravenous Iron in Perioperative Patient Blood Management in Major Abdominal Surgery

A Randomized Controlled Trial

Bernd Froessler, MD, MClinSc,† Peter Palm, MD,* Ingo Weber, MD,* Nicolette A. Hodyl, PhD,‡ Rajvinder Singh, MBBS, MPhil,§¶ and Elizabeth M. Murphy, PhD||*

Objective: To determine if preoperative intravenous (IV) iron improves outcomes in abdominal surgery patients.

Summary Background Data: Preoperative iron deficiency anemia (IDA) occurs frequently; however if left untreated, increases the risk of blood transfusion allogeneic blood transfusion (ABT). Limited evidence supports IDA treatment with preoperative IV iron. This randomized controlled trial aimed to determine whether perioperative IV iron reduced the need for ABT.

Methods: Between August 2011 and November 2014, 72 patients with IDA were assigned to receive either IV iron or usual care. The primary endpoint was incidence of ABT. Secondary endpoints were various hemoglobin (Hb) levels, change in Hb between time points, length of stay, iron status, morbidity, mortality, and quality of life 4 weeks postsurgery.

Results: A 60% reduction in ABT was observed in the IV iron group compared with the usual care group (31.25% vs 12.5%). Hb values, although similar at randomization, improved by 0.8 g/dL with IV iron compared with 0.1 g/dL with usual care ($P = 0.01$) by the day of admission. The IV iron group had higher Hb 4 weeks after discharge compared with the usual care group (1.9 vs 0.9 g/dL, $P = 0.01$), and a shorter length of stay (7.0 vs 9.7 d, $P = 0.026$). There was no difference in discharge Hb levels, morbidity, mortality, or quality of life.

Conclusions: Administration of perioperative IV iron reduces the need for blood transfusion, and is associated with a shorter hospital stay, enhanced restoration of iron stores, and a higher mean Hb concentration 4 weeks after surgery.

Ferric carboxymaltose reduces transfusions and hospital stay in patients with colon cancer and anemia

José Luis Calleja[1] · Salvadora Delgado[2] · Adolfo del Val[3] · Antonio Hervás[4] · José Luis Larraona[5] · Álvaro Terán[6] · Mercedes Cucala[7] · Fermín Mearin[8] · on behalf of the Colon Cancer Study Group

Int J Colorectal Dis (2016) 31:543–551

Abstract

Purpose The purpose of the study was to evaluate the efficacy of preoperative intravenous (IV) ferric carboxymaltose (FCM) administration vs. no-IV iron in colon cancer (CC) anemic patients undergoing elective surgery with curative intention.

Methods This was a multicenter, observational study including two cohorts of consecutive CC anemic patients: the no-IV iron treatment group was obtained retrospectively while FCM-treated patients were recorded prospectively.

Results A total of 266 patients were included: 111 received FCM (median dose 1000 mg) and 155 were no-IV iron subjects. Both groups were similar in terms of demographic characteristics, tumor location, surgical approach, and intraoperative bleeding severity. The FCM group showed a significant lower need for red blood cell (RBC) transfusion during the study (9.9 vs. 38.7 %; OR: 5.9, $p<0.001$). In spite of lower hemoglobin levels at baseline diagnosis and lower transfusion rates in the FCM group, the proportion of responders was significantly higher with respect to the no-IV group both at hospital admission (48.1 vs. 20.0 %, $p<0.0001$) and at 30 days post-surgery (80.0 vs. 48.9 %, $p<0.0001$). The percentage of patients with normalized hemoglobin levels was also higher in the FCM group (40.0 vs. 26.7 % at 30 days, $p<0.05$). A lower number of reinterventions and post-surgery complications were seen in the FCM group (20.7 vs. 26.5 %; $p=0.311$). The FCM group presented a significant shorter hospital stay (8.4±6.8 vs. 10.9±12.4 days to discharge; $p<0.001$).

Conclusions Preoperative ferric carboxymaltose treatment in patients with CC and iron deficiency anemia significantly reduced RBC transfusion requirements and hospital length of stay, reaching higher response rates and percentages of normalized hemoglobin levels both at hospital admission and 30 days post-surgery.

	No-IV iron	FCM	*p*
Need for RBC transfusion (overall), %	38.7	9.9	<0.001
Need for RBC transfusions (peri-surgery period), %	31.8	8.3	<0.001
Need for RBC transfusion (post-surgery until day 30), %	16.7	5.0	0.005
Need for RBC transfusion (by surgery), %			
Open surgery, %	37.7	17.1	<0.05
Laparoscopic, %	25.4	0.0	<0.0001
Mean units of RBC transfused (overall)	0.8	0.2	<0.0001
Mean units of RBC transfused (peri-surgery)	0.5	0.1	<0.0001
Mean units of RBC transfused (post-surgery until day 30)	0.3	0.1	<0.05
Mean units of RBC transfused (by surgery)			
Open surgery	1.0	0.4	<0.01
Laparoscopic	0.6	0.0	<0.0001

FCM ferric carboxymaltose, *RBC* red blood cell

Assessing the costs and benefits of perioperative iron deficiency anemia management with ferric carboxymaltose in Germany

Bernd Froessler[1,2]
Alexandra M Rueger[3,4]
Mark P Connolly[5,6]

Risk Management and Healthcare Policy 2018:11

Background: Perioperative administration of ferric carboxymaltose (FCM) was previously shown to reduce both the need for transfusions and the hospital length of stay in patients with preoperative iron deficiency anemia (IDA). In this study, we estimated the economic consequences of perioperative administration using FCM vs usual care in patients with IDA from the perspective of a German hospital using decision-analytic modeling.

Materials and methods: The model was populated with clinical inputs (transfusion rates, blood units transfused, hospital length of stay) from a previously reported randomized trial comparing FCM vs usual care for managing IDA patients undergoing elective abdominal surgery. We applied a hospital perspective to all costs, excluding surgery-related costs in both treatment arms. One-way sensitivity analyses were undertaken to evaluate key drivers of cost analysis.

Results: The average costs per case treated using FCM compared to usual care were €2,461 and €3,246, respectively, for resource expenses paid by hospital per case. This would suggest potential savings achieved with preoperative intravenous iron treatment per patient of €786 per case. A sensitivity analysis varying the key input parameters indicated the cost analysis is most sensitive to changes in the length of stay and the cost of hospitalization per day.

Conclusion: Perioperative administration of FCM results in cost savings to hospitals based on reduced blood transfusions and length of stay following elective abdominal surgery.

Table 2 Results of the per patient economic model comparing FCM with usual care

Outcome	FCM	Usual care	Incremental
Cost of an iron therapy	€340.51[a]	€0.00	€341
Cost of RBC	€20.18	€96.22	–€76
Cost of length of stay (normal ward)	€2,100.00	€3,150.00	–€1,050
Total	€2,461	€3,246	–€786

Note: [a]Costs based on mean FCM dose of 1,200 mg.[18]
Abbreviations: FCM, ferric carboxymaltose; RBC, red blood cell.

Effect of ultra-short-term treatment of patients with iron deficiency or anaemia undergoing cardiac surgery: a prospective randomised trial

Donat R Spahn, Felix Schoenrath*, Gabriela H Spahn, Burkhardt Seifert, Philipp Stein, Oliver M Theusinger, Alexander Kaserer, Inga Hegemann, Axel Hofmann, Francesco Maisano, Volkmar Falk*

Lancet 2019; 393: 2201–12

Methods In this single-centre, randomised, double-blind, parallel-group controlled study, patients undergoing elective cardiac surgery with anaemia (n=253; haemoglobin concentration (Hb) <120 g/L in women and Hb <130 g/L in men) or isolated iron deficiency (n=252; ferritin <100 mcg/L, no anaemia) were enrolled. Participants were randomly assigned (1:1) with the use of a computer-generated range minimisation (allocation probability 0·8) to receive either placebo or combination treatment consisting of a slow infusion of 20 mg/kg ferric carboxymaltose, 40 000 U subcutaneous erythropoietin alpha, 1 mg subcutaneous vitamin B12, and 5 mg oral folic acid or placebo on the day before surgery. Primary outcome was the number of RBC transfusions during the first 7 days. This trial is registered with ClinicalTrials.gov, number NCT02031289.

Findings Between Jan 9, 2014, and July 19, 2017, 1006 patients were enrolled; 505 with anaemia or isolated iron deficiency and 501 in the registry. The combination treatment significantly reduced RBC transfusions from a median of one unit in the placebo group (IQR 0–3) to zero units in the treatment group (0–2, during the first 7 days (odds ratio 0·70 [95% CI 0·50 0·98] for each threshold of number of RBC transfusions, p=0·036) and until postoperative day 90 (p=0·018). Despite fewer RBC units transfused, patients in the treatment group had a higher haemoglobin concentration, higher reticulocyte count, and a higher reticulocyte haemoglobin content during the first 7 days (p≤0·001). Combined allogeneic transfusions were less in the treatment group (0 [IQR 0–2]) versus the placebo group (1 [0–3]) during the first 7 days (p=0·038) and until postoperative day 90 (p=0·019). 73 (30%) serious adverse events were reported in the treatment group group versus 79 (33%) in the placebo group.

Interpretation An ultra-short-term combination treatment with intravenous iron, subcutaneous erythropoietin alpha, vitamin B12, and oral folic acid reduced RBC and total allogeneic blood product transfusions in patients with preoperative anaemia or isolated iron deficiency undergoing elective cardiac surgery.

Implications of all the available evidence

Physicians should routinely measure haemoglobin and iron parameters in patients undergoing cardiac surgery and consider combination treatment of preoperative anaemia or iron deficiency even the day prior to surgery. This is of particular relevance since a growing percentage of elective cardiac surgery is done within a few days after an acute cardiac event.

Gestione dell' anemia preoperatoria in chirurgia maggiore elettiva

AZIENDA OSPEDALIERO UNIVERSITARIA Santa Maria della Misericordia di Udine

COMITATO AZIENDALE BUON USO DEL SANGUE | Versione n. del 08/09/2015

FLOW CHART PROCEDURA OPERATIVA

VISITA CHIRURGICA: indicazione chirurgica

VISITA ANESTESIOLOGICA PRE-OPERATORIA

ESAMI PREOPERATORI

-Tipo di intervento
-Rischio trasfusionale secondo MSBOS

Hb preoperatoria
Femmine < 12 g/dL
Maschi < 13 g/dL

Timing Chirurgico
15-28 gg.

Approfondimento laboratoristico se non già eseguito: saturazione transferrina, ferritina, B12, folati, creatinina (Cl Cr Cockcroft-Gault), SOF x 3

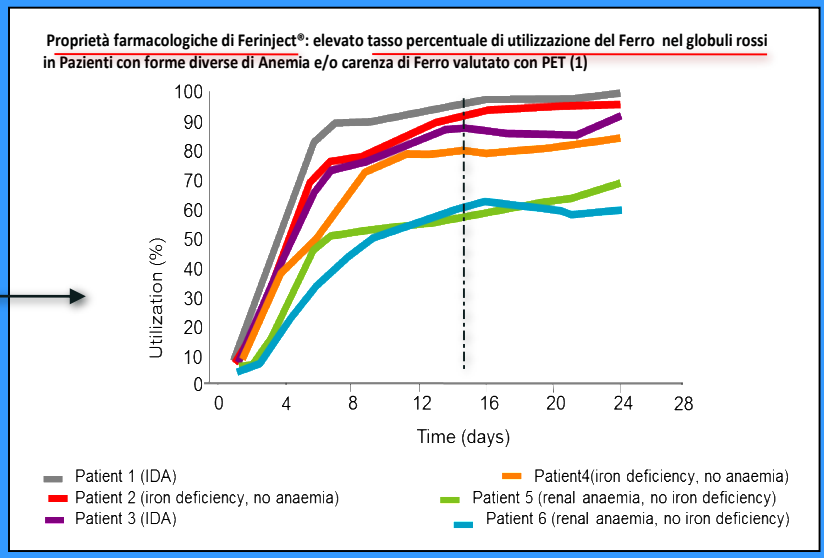
Consulenza su G2
"AMBULATORIO TRASFUSIONALE"

TERAPIA MARZIALE:
Carbossimaltosio Ferrico
max. 1000mg ev. (1 o 2 dosi) in monosomministrazione settimanale

Vit. B12 e/o acido folico

Controllo Emocromo preoperatorio

Intervento



Pazienti ASUIUD(n)	54 (32 chir.addominale;10 CCH; 7 ortopedia;5 altra chirurgia)
Età media (range)	68 aa.(32-91 aa.)
Sesso (F/M)	35/19
Ferritina basale media (range)	51 ng/mL(2-368 ng/mL) Mediana = 10 ng/mL
Dose totale CMF(mg)	500 - 1500
Sedute terapeutiche(n)	1-3
Timing chirurgico medio (range) Mediana	22.3 gg (4-52 gg) 21 gg
Hb basale media (range) Mediana	9.7 g/dL(6.6-12.6 g/dL) 9.85 g/dL
Hb finale media pre intervento (range)	11.3 g/dL(9.4-13.6 g/dL) Mediana = 11.4 g/dL
Incremento medio Hb (g/dL) (finale – basale)	1.6
Risposta terapeutica [n (%)] (aumento di Hb≥1.5 g/dL o Hb finale ≥ 13 g/dL)	30(55%)
Correzione dell'anemia [n (%)]	17(31%)
Hb media alla dimissione (range)	10.8 g/dL (9-14.7 g/dL) Mediana = 10.8 g/dL
Trasfusione allogenica [n (%)]	7(13%) di cui 5 CCH e 2 resez.colon
Eventi avversi severi[n (%)]	0

CONCLUSIONI

- L'anemia preoperatoria è una controindicazione alla chirurgia maggiore e pertanto deve essere identificata,valutata e trattata in modo appropriato.
- E' stato dimostrato che lo screening preoperatorio precoce dell'anemia e il trattamento della stessa riducono il ricorso alla trasfusione.
- La carenza marziale è la causa più comune di anemia nel paziente chirurgico.
- La terapia marziale deve essere preceduta da un' accurata valutazione del bilancio marziale (Ferritina e Saturazione della Transferrina).
- Il **Ferro orale** è indicato come terapia di prima linea nell'anemia lieve-moderata con deficit assoluto di ferro e timing chirurgico > 6 settimane, in assenza di cause note di refrattarietà.
- Il **Ferro endovena** è indicato in caso di anemia severa, deficit funzionale di ferro,intolleranza o refrattarietà alla terapia orale,timing chirurgico di almeno 2 settimane.