

## Review Article

# An international consensus statement on the management of postoperative anaemia after major surgical procedures

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## Summary

Despite numerous guidelines on the management of anaemia in surgical patients, there is no pragmatic guidance for the diagnosis and management of anaemia and iron deficiency in the postoperative period. A number of experienced researchers and clinicians took part in a two-day expert workshop and developed the following consensus statement. After presentation of our own research data and local policies and procedures, appropriate relevant literature was reviewed and discussed. We developed a series of best-practice and evidence-based statements to advise on patient care with respect to anaemia and iron deficiency in the postoperative period. These statements include: a diagnostic approach to iron deficiency and anaemia in surgical patients; identification of patients appropriate for treatment; and advice on practical management and follow-up that is easy to implement. Available data allow the fulfilment of the requirements of Pillar 1 of Patient Blood Management. We urge national and international research funding bodies to take note of these recommendations, particularly in terms of funding large-scale prospective, randomised clinical trials that can most effectively address the important clinical questions and this clearly unmet medical need.

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## Recommendations for best clinical practice

- All patients who have undergone major surgery (defined as blood loss > 500 ml or lasting > 2 h) and who had pre-operative anaemia or moderate-to-severe blood loss during surgery must be screened for anaemia after surgery.
- During recovery from uncomplicated major surgery, haemoglobin concentrations should be monitored, either by standard laboratory or point-of-care testing, on a regular daily basis, at least until the third postoperative day, to detect anaemia (haemoglobin < 130 g.l<sup>-1</sup> for men, < 120 g.l<sup>-1</sup> for women).
- Postoperatively, iron deficiency should be defined by ferritin concentration < 100 µg.l<sup>-1</sup>, ferritin < 100–300 µg.l<sup>-1</sup> and transferrin saturation < 20%, or reticulocyte haemoglobin content < 28 pg. High blood loss during surgery may also indicate the need for iron replacement in anaemic patients.
- In the postoperative period, when the administration of iron is necessary, early intravenous (i.v.) iron therapy is recommended, after considering contraindications. Where possible, it should be administered using a single high-dose preparation for the repletion of iron stores.
- For non-cancer patients with severe postoperative anaemia and inflammation-induced blunted erythropoiesis, or those declining blood transfusion, we suggest considering additional treatment with an erythropoiesis-stimulating agent.
- If patient blood management measures did not prevent the development of severe postoperative anaemia, the adoption of a restrictive transfusion threshold (haemoglobin level: 70–80 g.l<sup>-1</sup>, depending on patient comorbidities) is recommended in most adult, clinically stable hospitalised patients.
- We recommend establishing a patient blood management expert group in every hospital.

## Why was this consensus statement developed?

The concept 'patient blood management' (PBM) is defined as "the timely application of evidence-based

medical and surgical concepts designed to manage anaemia, optimise haemostasis and minimise blood loss in order to improve patient outcomes after surgery" [1]. Patient blood management has been shown to reduce transfusion, healthcare costs and morbidity and mortality [2]. Treatment of pre-operative anaemia and isolated iron deficiency are crucial measures for PBM [3, 4]. However, detection and early treatment of pre-operative anaemia and iron deficiency is an accepted logistical challenge and, as a consequence, some patients may undergo surgery without the chance to address their anaemia [3]. In addition, there has been increased emphasis on accelerated discharge after surgery and the use of restrictive transfusion thresholds in order to improve outcomes and reduce transfusion requirements, which may have led to overlooking potential opportunities to optimise anaemic patients and improve their functional recovery [5, 6]. Therefore, an additional focus on the early detection and treatment of postoperative iron deficiency and anaemia is a novel and complementary measure within the concept of PBM; this allows the attending physician to target patients who lost significant red cell mass during surgery and may require specific attention postoperatively or following discharge [7].

## How does this consensus statement differ from other available statements and/or guidelines?

There are a number of statements and guidelines from professional associations recommending a systematic approach to this problem for the management of pre-operative anaemia [1, 7–15]. Most of these guidelines also recommend the use of a restrictive transfusion threshold for treating acute postoperative anaemia, but recommendations for pharmacological management of anaemia are scarce, or even absent [1, 7–15]. We aimed to update and utilise these few current recommendations to provide a working practice document, based on scientific evidence and the clinical experience of an expert panel, on 'how to' feasibly introduce these postoperative anaemia guidelines into clinical practice. Our goal was to provide pragmatic, clear and easy-to-follow clinical

guidance for the diagnosis and treatment of postoperative anaemia and iron deficiency in order to improve patient recovery, reduce the need for blood transfusion and improve functional outcomes in a cost effective manner. Our recommendations are intended for non-actively bleeding adult patients in whom all the principles of PBM have been implemented pre- and intra-operatively for the prevention of postoperative iron deficiency and anaemia.

## Definition, prevalence and pathophysiology of postoperative anaemia

Postoperative anaemia may be present in up to 80–90% of patients undergoing major surgery, although this prevalence varies widely according to different definitions [16, 17]. Anaemia is defined by the World Health Organization (WHO) as a haemoglobin concentration  $< 130 \text{ g.l}^{-1}$  for men,  $< 120 \text{ g.l}^{-1}$  for non-pregnant women and  $< 110 \text{ g.l}^{-1}$  for pregnant women [18]. Although debated [19], and since these definitions are widely accepted, they may be applied to postoperative patients. However, we previously pointed out that the WHO criteria for the definition of anaemia may not be reliable for the classification of non-pregnant women undergoing surgical procedures with expected moderate-to-high blood loss. Women have lower circulating blood volumes and reduced red cell mass when compared with men, but the same procedures performed in either sex often result in comparable volumes of blood loss, resulting in higher transfusion rates in women [4]. Therefore, pre-operative anaemia in non-pregnant women should be defined, as for men, as a haemoglobin concentration  $< 130 \text{ g.l}^{-1}$ .

According to the WHO, postoperative anaemia could be classified as mild (haemoglobin  $110\text{--}119 \text{ g.l}^{-1}$  in women and  $110\text{--}129 \text{ g.l}^{-1}$  in men, respectively ( $110\text{--}119/129 \text{ g.l}^{-1}$ )), moderate (haemoglobin  $80\text{--}109 \text{ g.l}^{-1}$ ) or severe (haemoglobin  $< 80 \text{ g.l}^{-1}$ ) [18].

Although multifactorial in origin, pre-operative anaemia, peri-operative blood loss (surgical bleeding, coagulopathy, phlebotomies, etc) and postoperative blunted erythropoiesis are the main contributing factors to postoperative anaemia after major surgery. Haemodilution due to excessive fluid administration, which may cause 'dilutional' anaemia or aggravate pre-existing anaemia, and other nutritional deficiencies (e.g. vitamin B<sub>12</sub>, folic acid) and pharmacological interactions are also contributing factors [20].

Low pre-operative haemoglobin, female sex and smaller body surface area have been identified as risk factors for the development of postoperative anaemia and increased transfusion needs [21]. Additionally, in the general population, the prevalence of anaemia increases with age; older persons are more likely to undergo major surgery and to present with comorbidities, thus increasing the risk of postoperative anaemia, and reducing its tolerability [22, 23].

The end of the surgical procedure does not always signify the end of blood loss. Ongoing postoperative blood loss can continue through drains or into traumatised tissue, or due to repeated phlebotomy during prolonged postoperative hospitalisation. As such, peri-operative blood loss may result in acute or late postoperative anaemia, especially in patients with the above-mentioned risks factors. To avoid the detrimental effects of

**Table 1** Dosing characteristics for intravenous iron formulations available in Europe.

	Iron gluconate <sup>a</sup>	Iron Sucrose <sup>b</sup>	LMWID <sup>c</sup>	Ferric carboxymaltose <sup>d</sup>	Iron isomaltoside <sup>e</sup>
Brand name	Ferrlecit <sup>®</sup>	Venofer <sup>®</sup>	Cosmofer <sup>®</sup>	Ferinject <sup>®</sup>	Monofer <sup>®</sup> Monoferro <sup>®</sup>
Maximal single dose (mg)	125	200 (max 600 mg/week)	20 mg/kg	20 mg/kg (max 1000 mg)	20 mg/kg
Suggested postoperative dosage:					
Dose (mg)/frequency (days)	125/2	200/1–2	500–1000/7 <sup>f</sup>	500–1000/7	500–1500/7
Infusion time (min)	60	30	≥ 60	≥ 10–15	≥ 15–30
Maximal total dose (mg)	2000	2000	2000	2000	2000

<sup>a</sup>Ferrlecit summary of product characteristics. <http://www.products.sanofi-aventis.us/ferrlecit/ferrlecit.pdf> (accessed 18/02/2018).

<sup>b</sup>Venofer summary of product characteristics. <http://www.luitpold.com/documents/22.pdf> (accessed: 18/02/2018).

<sup>c</sup>LMWID, low molecular weight iron dextran; Cosmofer summary of product characteristics. <http://www.cosmofer.com/product/cosmofer-spc/cosmofer-spc.aspx>. (accessed: 18/02/2018).

<sup>d</sup>Ferinject summary of product characteristics. <http://www.ferinject.co.uk/smpc/> (accessed: 18/02/2018).

<sup>e</sup>Monofer summary of product characteristics. <http://www.monofer.com/spc.aspx>. (accessed: 18/02/2018).

<sup>f</sup>Although it is not an approved dosing by European Medicines Agency, Auerbach et al. (Am J Hematol 2011; 86: 860) have not observed any serious adverse events in over 5000 administrations of LMWID at doses of 1000 mg in 250 ml of normal saline over 1 h.

acute anaemia, packed red blood cells are usually transfused as a default measure [20]. However, the use of restrictive transfusion thresholds, as emphasised in the third pillar of PBM, also contributes to a higher prevalence of moderate-to-severe anaemia on discharge from hospital (haemoglobin concentration  $< 100 \text{ g.l}^{-1}$ ), unless proactive measures are implemented [20].

Anaemia in the postoperative period, as well as in critical illness, may be aggravated by reduced erythropoietin production and secretion due to inflammatory mediators; blunted bone marrow response to erythropoietin; and decreased iron availability due to down-regulation of intestinal absorption and impaired mobilisation of iron from body stores [24, 25]. Inflammatory cytokines stimulate the secretion of hepcidin, a hormone that targets ferroportin, the only known cellular exporter of iron. This induces the internalisation and degradation of ferroportin, thereby largely inhibiting intestinal iron absorption and greatly reducing iron release from body stores (iron sequestration) [26].

## What are the unmet medical needs of postoperative anaemia?

The concerns surrounding postoperative anaemia relate to its potential impact on recovery, rehabilitation, hospital re-admission or re-operation, and patient well-being. Reducing allogeneic blood transfusion improves long-term outcome and survival [27]. However, restrictive transfusion protocols have led to patients being discharged with lower haemoglobin levels than before. With the current paucity of data, it remains unclear whether a lower discharge haemoglobin level may allow optimal functional recovery and quality of life [28–34]. There has been limited research on the consequences of postoperative anaemia in the recovery phase from surgery, with only a small number of studies after cardiac and hip and knee surgery, which demonstrated the association between postoperative anaemia and adverse outcomes such as prolonged recovery, increased mortality and likelihood of re-admission [31–33]. Postoperative anaemia may also potentially be associated with early postoperative myocardial infarction [34]. Correction of postoperative anaemia, as suggested in this consensus statement, is intended to prevent such side-effects, but studies are urgently needed to prove this.

## Diagnosis of postoperative anaemia

### **When and how to measure haemoglobin concentration?**

Measurement of haemoglobin concentration is a routine procedure in postoperative care. Duration of testing for

postoperative anaemia depends on the peri-operative bleeding risk associated with the surgical intervention and patient-dependent factors. In most cases of uncomplicated recovery from surgery, a nadir in haemoglobin concentration can be observed within the first 3–4 days after surgery. In patients with major complications following major surgery, however, prolonged hospitalisation and exposure to low haemoglobin levels increase the duration of monitoring required.

Usually, blood gas analysis, capillary sampling (e.g. HemoCue, HemoCue AB, Ängelholm, Sweden) or near-infrared spectroscopy (e.g. Radical-67, Masimo Corporation, Irvine, CA, USA) are performed as a point-of-care assessment, whereas the full blood count is tested in the central laboratory. The use of non-invasive continuous haemoglobin monitoring devices instead of phlebotomy may reduce blood loss, pain and discomfort for the patient, but concerns about precision limit routine clinical use. Although the debate focuses on accuracy of a single check [35], the reliability of non-invasive haemoglobin monitoring devices for dynamic changes over time may permit detection of occult bleeding and response to therapy [36].

### **What are the confounding factors?**

In the setting of postoperative care, a number of confounding factors may impact on accurate haemoglobin measurement. Volume overload and haemodilution after major surgery are potential causes for low haemoglobin levels, despite normal and stable red cell mass. Therefore, the diagnosis of anaemia based on simple haemoglobin concentration may be misleading, and is confounded by plasma volume derangements, resulting in significant overdiagnosis [37]. Potential volume overload should be taken into account, and may improve after diuresis.

Similar conditions may be present in the peri-operative setting where prevention of intravascular volume deficit is a cornerstone of peri-operative management. Here, intravascular volume and fluid therapy are fundamental whenever fasting is indicated for medical reasons; in the event of high-fluid turnover rates during major surgery, or in cases of reduced enteral resorption due to sustained vomiting, severe diarrhoea or gastro-intestinal dysfunction following circulatory shock. The primary aim of intravenous fluid therapy (crystalloid and colloid solutions) is the restoration of plasma and blood volume to ensure appropriate cardiac output and tissue perfusion.

Unfortunately, appropriate assessment of volume status is complex. The diagnosis or quantification of moderate-to-severe volume deficit and volume responsiveness remains difficult, and may be attempted using

laboratory variables (e.g. lactate, base excess), positional manoeuvres (passive lifting of legs), new monitoring devices (measuring pulse variability and stroke volume indexes or other preload variables) or echocardiography. Recent guidelines highlight the importance of avoiding hypervolaemia [7]. During postoperative recovery, redistribution and excretion of fluids may lead to rapid recovery of haemodilution-induced low haemoglobin concentrations.

### **When and how to measure postoperative iron deficiency?**

Although underlying causes of postoperative anaemia are multifactorial, iron deficiency is often present. Although pre-operative iron deficiency can be diagnosed on the basis of low ferritin concentrations [4], diagnosis of postoperative iron deficiency is more difficult, as ferritin levels may be elevated as part of the acute phase inflammatory response after surgery [38]. Thus, patients undergoing major surgery with a high risk of developing moderate-to-severe postoperative anaemia should have their haemoglobin and iron status checked on the day of surgery, if it has not been already performed in the pre-operative assessment. This may also apply to patients with ongoing bleeding and anaemia (e.g. colorectal cancer) that have been treated in the pre-operative period. As ferritin levels will not be elevated by inflammation immediately after surgery, a postoperative ferritin concentration  $< 100 \mu\text{g.l}^{-1}$  within 24 h after surgery indicates insufficient iron stores to support erythropoiesis with the potential for significant falls in postoperative haemoglobin [8].

Further markers of postoperative iron deficiency are transferrin saturation  $< 20\%$  with ferritin concentrations  $100\text{--}300 \mu\text{g.l}^{-1}$ , or reticulocyte haemoglobin content  $< 28 \text{ pg}$ . These values and parameters may signal the need for intervention in anaemic patients [38–41].

### **When should postoperative anaemia be treated?**

There are limited supporting data regarding appropriate timing for management of anaemia after surgery, including red cell transfusion. Treatment choice depends on severity and type of anaemia, type of surgery, patient comorbidities and the presence of any surgical complications.

Iron supplementation should be considered in patients with iron deficiency or significant reduction in postoperative haemoglobin, starting early in the postoperative recovery phase where there are no major complications [39, 42–46]. It is important to note that there are no studies identifying the best time to start postoperative iron supplementation.

For non-cancer patients with severe postoperative anaemia and inflammation-induced blunted erythropoiesis or those declining blood transfusion, additional treatment with an erythropoiesis-stimulating agent (e.g. recombinant human erythropoietin [rHuEPO]) may be considered. However, we are aware that for patients without a previous indication this is an off-label use of rHuEPO, and recommendations vary across countries [10, 12, 15].

Red cell transfusion should be restricted to patients with severe anaemia (haemoglobin  $< 70\text{--}80 \text{ g.l}^{-1}$ ) and clinical signs and symptoms [7, 10–12, 47–49]. Red cell transfusion should be considered in patients with active bleeding and in those severely anaemic once bleeding has been stopped [7, 10–12, 47–49]. However, more research is required on specific transfusion thresholds in specific high-risk patients.

### **How should patients be treated postoperatively?**

Pharmacological optimisation of postoperative haemoglobin and erythropoiesis should allow correction of iron deficiency and rapid recovery from postoperative anaemia, which may lead to improved postoperative outcomes and improved quality of life. It may also result in a reduction of patient exposure to red cell transfusion and its related risk and complications, thus contributing further to improving surgical outcome and patient safety.

#### **Iron therapy: oral vs. i.v. iron?**

The National Institute for Health and Care Excellence in the UK (NICE) recommends offering oral iron after surgery to patients with iron deficiency anaemia [12]. However, in the postoperative period, oral iron is often not tolerated or absorbed and has several limitations including frequent gastro-intestinal side-effects and, as a consequence, poor treatment adherence. Additionally, the inflammatory response induced by surgery stimulates hepcidin synthesis and release, which in turn inhibits intestinal iron absorption, making oral iron therapy largely ineffective [10, 13, 50]. Various randomised placebo-controlled trials (RCT) in orthopaedic and cardiac surgery patients have demonstrated that oral iron therapy was not better than placebo in correcting postoperative anaemia and reducing transfusion requirements [51–57].

On the other hand, NICE recommends considering i.v. iron after surgery for patients who have iron deficiency anaemia and cannot tolerate or absorb oral iron, or are unable to adhere to oral iron treatment, as well as for those who are diagnosed with functional iron



deficiency [12]. Thus, patients presenting with postoperative iron deficiency and/or moderate-to-severe postoperative anaemia (haemoglobin  $< 100 \text{ g.l}^{-1}$ ) may benefit from i.v. iron supplementation, which has proven to be more effective than oral iron in a number of surgical settings (Supporting Information online, Appendix S1) [39, 42–45, 58–63]. Most recent RCTs have shown improved outcomes following high-dose postoperative i.v. iron (e.g. 1000 mg) as demonstrated by increased haemoglobin and/or reduction in transfusion requirements, and no i.v. iron-related serious adverse events were reported (Supporting Information, Appendix S1) [39, 42, 44, 45]. Importantly, in orthopaedic surgical patients with postoperative haemoglobin  $< 100 \text{ g.l}^{-1}$  and/or uncorrected pre-operative iron deficiency (ferritin  $< 100 \mu\text{g.l}^{-1}$ ), a greater rise in haemoglobin and better scores for 'usual activities' were observed with high-dose i.v. iron compared with oral iron [42].

Similarly, compared with oral iron, the use of i.v. iron for treating postpartum anaemia has been shown to result in greater and faster haemoglobin increases, improved replenishment of iron stores, a lower incidence of adverse side-effects and greater improvement in quality of life [15, 46].

Therefore, should postoperative iron therapy be indicated, i.v. formulations are recommended. This is in line with recent management guidelines in surgical patients experiencing severe bleeding (GRADE 2C for i.v. iron preparations postoperatively) [7]. When calculating the total iron dose, it is important to take into account the pre-operative haemoglobin level and iron status, the magnitude of postoperative haemoglobin drop and whether patients have received postoperative red cell transfusion (Fig. 1). The use of i.v. iron formulations which allow rapid (15–60 min) infusion of high doses of iron (1000 mg or more) offers added convenience to both physicians and patients and should be preferred, despite their higher cost (Table 1) [40, 64].

### **What are the true risks and contraindications of i.v. iron?**

Many clinicians and health authorities still consider that i.v. iron is strongly associated with major side-effects such as anaphylaxis, infection or oxidative stress. However, these side-effects appear not to be significant with the newer i.v. iron preparations, such as ferric carboxymaltose, iron isomaltoside and low molecular weight iron dextran [64–66].

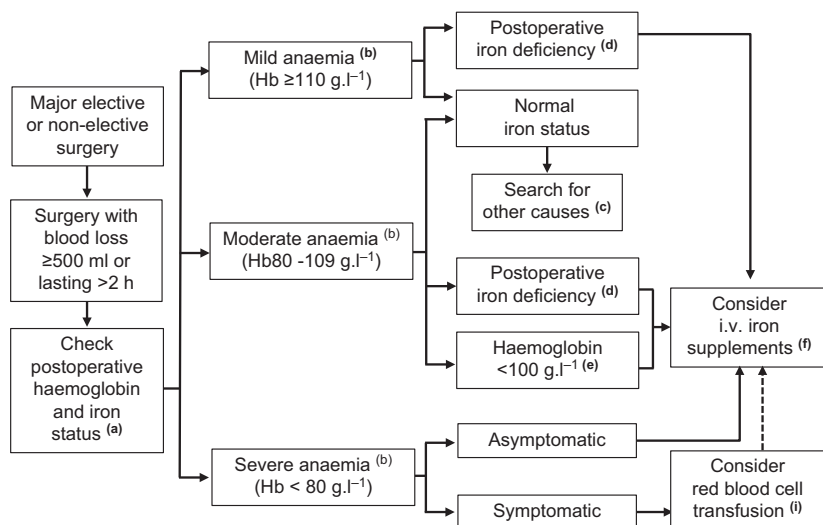
After an extensive review of the data, the European Medicines Agency's Committee for Medicinal Products

for Human Use (CHMP) concluded that "all i.v. iron medicines have a small risk of causing allergic reactions which can be life-threatening if not treated promptly" [67]. However, the reported incidence of potentially life-threatening hypersensitivity reactions ( $< 1:250,000$  administrations) is vastly overestimated; the pathophysiological mechanism is poorly understood, although a substantial proportion is thought to be mediated by complement activation, resulting in complement activation-related pseudo allergy (CARPA) [68, 69]. Minor infusion reactions due to 'labile' iron may occur, but are usually self-limiting without intervention and should not be misinterpreted as acute hypersensitivity events [65, 70].

The CHMP's review also concluded that "the benefits of these medicines are greater than their risks, provided that adequate measures are taken to minimise the risk of allergic reactions" [67]. To this end, i.v. iron preparations should only be given in an environment where resuscitation facilities are available, so that patients who develop an allergic reaction can be treated immediately, and patients should be closely observed for signs and symptoms of hypersensitivity reactions during and for at least 30 min following each injection of i.v. iron. Guidelines for the diagnosis and management of these reactions have been recently published [71]. In addition, the CHMP's report contraindicates the use of i.v. in patients with hypersensitivity to the active substance or excipients; with serious hypersensitivity to other parenteral iron products; or in the first trimester of pregnancy [67].

Elemental iron is an essential growth factor for bacteria, with many species expressing iron transport proteins that compete with transferrin, and it has long been suggested that patients with iron overload are at increased risk of infection [72]. However, data from meta-analyses and large observational studies showed that peri-operative i.v. iron did not increase postoperative infection or 30-day mortality rates in surgical patients [64, 66]. In contrast, red cell transfusion delivers haem and labile iron which readily supports bacterial growth [73]. Nevertheless, in the absence of definitive clinical data, it would seem logical to refrain from i.v. iron administration in the setting of acute infection [8].

The available evidence relating i.v. iron administration to oxidative stress leading to atherogenesis and vascular remodelling, is sparse and indirect. It is mostly derived from retrospective observational studies addressing long-term i.v. iron therapy [70], whereas in the postoperative period, very short-term i.v. iron courses are administered (one or two large doses) [64]. Thus, it does not seem to be of concern in the postoperative setting.



**Figure 1** Postoperative anaemia management. (a) Whenever possible, assess iron status within 24 h postoperatively, if it has not been already performed in the pre-operative assessment. Monitor haemoglobin for 3–4 days postoperatively. (b) According to WHO classification. (c) Appropriate treatment should be considered. (d) Postoperative ferritin  $< 100 \mu\text{g.l}^{-1}$ , ferritin  $< 300 \mu\text{g.l}^{-1}$  and transferrin saturation  $< 20\%$  or reticulocyte haemoglobin content  $< 28 \text{ pg}$ . (e) Due to pre-operative anaemia or heavy surgical bleeding, irrespective of iron status. (f) Total iron deficiency = (target haemoglobin – actual haemoglobin)  $\times$  weight (kg)  $\times 0.24$ . Add another  $10 \text{ mg.kg}^{-1}$  for replenishing iron stores, especially in patients with pre-operative iron deficiency. Consider adding recombinant human erythropoietin (40,000 IU) for patients with severe anaemia or declining transfusion. For i.v. iron dosing schedule, see Table 1. (i) Transfuse one red blood cell unit at the time, with post-transfusion re-assessment of further needs. Consider i.v. iron supplementation after transfusion, using post-transfusion haemoglobin as actual haemoglobin for total iron deficiency calculation.

## Should we treat iron deficiency without anaemia?

A normal haemoglobin level does not exclude iron deficiency. In fact, the WHO recognises that ‘mild’ anaemia (haemoglobin  $110\text{--}119/129 \text{ g.l}^{-1}$ ) is a misnomer, as iron deficiency is already advanced by the time anaemia is detected, and has consequences even when anaemia is not clinically apparent [18].

Non-anaemic patients with reduced or absent iron stores may have symptoms such as fatigue or reduced exercise tolerance, as iron is required for optimal mitochondrial function, and is essential for respiration and energy production [40, 74]. Current guidelines do not recommend routine iron screening in the absence of anaemia. However, the benefits of oral or i.v. iron replacement for non-anaemic iron deficiency-associated fatigue have been demonstrated in menstruating women, runners and blood donors [75–78].

In congestive heart failure, a frequent comorbidity among surgical patients, non-anaemic iron deficiency was independently associated with compromised physical performance and quality of life, and an increase in all-cause and cardiovascular mortality; treatment of non-anaemic iron deficiency with i.v. iron may improve

functional status within four weeks, and reduces hospitalisations for cardiovascular reasons and mortality [79, 80]. In addition, improvements are maintained after 24 and 52 weeks [79–81].

In observational studies of patients undergoing abdominal or cardiac surgery, pre-operative non-anaemic iron deficiency was associated with poor outcomes, including: increased rates of postoperative infection; transfusion; fatigue; and prolonged hospital stay [82–84]. Although it is presently unknown whether pre-operative correction of non-anaemic iron deficiency may offset the excess of risk of postoperative complications, some guidelines recommend peri-operative iron supplementation for patients with non-anaemic iron deficiency [14, 85].

Secondary thrombocytosis can also be seen after major surgery, as platelets behave as an acute phase reactant. Iron deficiency has also been shown to induce secondary thrombocytosis in several clinical settings. Correction of iron deficiency usually lowers platelet count and platelet activation in patients with chronic kidney disease, cancer or inflammatory bowel disease-associated secondary thrombocytosis, and may contribute to reduced risk of thrombo embolic events [86–89].

## Is there a role for erythropoiesis-stimulating agents?

In patients without a previous indication, postoperative administration of rHuEPO is an off-label use of this medicinal product. The effects of postoperative rHuEPO have been evaluated in case series, mostly in Jehovah's Witnesses and in two RCTs, yielding inconclusive results due to selection bias [58] or premature interruption [59].

In women with moderate-to-severe postpartum anaemia, five RCTs evaluated the effects of iron sucrose (300–1600 mg) or iron sucrose plus rHuEPO (20,000–40,000 IU) on haemoglobin recovery and transfusion needs [15]. A trend to faster haemoglobin increment was observed with rHuEPO plus i.v. iron compared with i.v. iron alone, but no significant differences in transfusion rates which were very low, were observed. The benefits seemed to be greatest in the rHuEPO-treated sub-group with elevated C-reactive protein levels after Caesarean section [15].

Although it does not strictly refer to surgical patients, a recent meta-analysis also found a reduction in mortality rates (risk ratio (RR) 0.63, 95%CI 0.49–0.79,  $p < 0.0001$ ) in critically ill trauma patients who received rHuEPO (nine studies, 2607 patients), without increasing the risk of thromboembolic complications [90]. In cardiac surgery patients, rHuEPO seems to exert neurological and renal protective effect [91, 92]. The mechanisms underlying these non-erythropoietic effects of rHuEPO need to be elucidated before recommending its use in patients without an approved indication.

Short-term pre-operative (1–4 days before operation) administration of rHuEPO to anaemic patients, with or without i.v. iron, has been shown to reduce postoperative transfusion in elective orthopaedic and cardiac surgery [93, 94]. In hip fracture repair surgery, there are conflicting data. One RCT failed to show a reduction in red cell transfusion in patients receiving rHuEPO plus i.v. iron [95]. However, they included patients with haemoglobin  $< 100 \text{ g.l}^{-1}$  but did not study women with haemoglobin  $\geq 120 \text{ g.l}^{-1}$ , and transfused fixed amounts of red cells according to pre-defined transfusion thresholds (e.g. patients with haemoglobin  $\leq 70 \text{ g.l}^{-1}$  received three units of red cells, and those with haemoglobin 71–89  $\text{g.l}^{-1}$  and severe symptoms received two units). In contrast, in an observational study of 196 anaemic hip fracture patients managed with peri-operative i.v. iron and a restrictive transfusion protocol, administration of rHuEPO on admission was associated with reduced transfusion requirements and higher haemoglobin levels on discharge and at postoperative day 30

[96]. An analysis including 544 women with haemoglobin  $< 130 \text{ g.l}^{-1}$  undergoing hip fracture repair showed that the blood-sparing effect of this strategy was restricted to those presenting with haemoglobin concentrations between 120 and 130  $\text{g.l}^{-1}$  ( $n = 305$ ) [97].

Thus, in non-cancer patients with severe postoperative anaemia and blunted erythropoiesis due to infection and/or inflammation, as well as in those who refuse blood transfusion, we suggest considering treatment with rHuEPO. However, as stated above, some guidelines do not support the off-label use of this medicinal product [12].

## Red blood cell transfusion: transfusion thresholds for whom and when?

Allogeneic red cell transfusion is associated with a significant increase in peri-operative morbidity and mortality [2, 98–100]. In addition, there is a worldwide shortage of blood, with substantial associated costs to the manufacturer and health systems [101]. Moreover, red cell transfusion risks infectious, immunological, haemolytic, non-haemolytic adverse reactions, cardiac and pulmonary complications [2, 98]. Despite successful implementation of PBM programmes, red cell transfusion is still widely used as a default treatment for the majority of patients with acute postoperative anaemia [102].

Historically, the standard for red cell transfusion was a liberal transfusion threshold, namely haemoglobin level  $< 100 \text{ g.l}^{-1}$  (or haematocrit  $< 30\%$ ). This arbitrary transfusion threshold has been gradually lowered towards haemoglobin 70–80  $\text{g.l}^{-1}$ , according to data derived from a number of RCTs evaluating the effect on patient outcomes of restrictive vs. more liberal red cell transfusion strategies in a variety of clinical settings. When subjected to pooled analysis in several systematic reviews and meta-analyses (Supporting Information online, Appendix S2) [103–108], data from these RCTs show that, in terms of morbidity and mortality, a restrictive red cell transfusion strategy is equivalent to or more beneficial than a liberal strategy [101, 109].

In addition, evidence-based guidelines have translated the results of RCTs and meta-analyses into clinical practice [7, 10–12, 47–49]. One of the most recently published guidelines on red cell transfusion thresholds recommends a restrictive red cell transfusion threshold (haemoglobin  $< 70 \text{ g.l}^{-1}$ ) for hospitalised adult patients who are haemodynamically stable, including critically ill patients [49]. However, a transfusion threshold of at least 80  $\text{g.l}^{-1}$  is suggested for patients undergoing



orthopaedic surgery, cardiac or oncological surgery, and those with pre-existing cardiovascular disease [12, 49, 110, 111]. Nevertheless, transfusion of red cells for higher haemoglobin levels should be evaluated case by case, considering acute ongoing blood loss, comorbidities and signs of organ ischaemia or symptoms indicative of hypoxia. In any case, published guidelines agree that red cell transfusion is not beneficial when haemoglobin is  $> 100 \text{ g.l}^{-1}$  [7, 10–12, 47–49, 112]. Confounding factors on haemoglobin levels have to be considered, as discussed above.

### Cost assessment implications

There are very few studies on the cost implications of the management of postoperative anaemia. Most such studies have evaluated pre-operative interventions, and since the pre-operative haemoglobin value is strongly associated with the postoperative haemoglobin, interventions aimed to improve pre-operative anaemia also influence postoperative well-being and its related costs [113].

Costs of anaemia management and PBM may vary from institution to institution and depend on the extent to which different aspects of PBM have been implemented. The following costs per patient were recently calculated in a single German University Hospital: diagnosis of anaemia €49–124; treatment of anaemia (including iron deficiency anaemia and megaloblastic anaemia) €13–128 [114].

Similarly, data from  $> 600,000$  patients (2008–2014) who were enrolled in a PBM, peri-operative management programme targeting anaemia and iron deficiency, demonstrated a risk-adjusted reduction in postoperative red cell transfusion, infection and mortality rates, shortened length of hospital stay and an estimated US\$ 78–97 million in activity-based savings [2].

A recent RCT that investigated the use of i.v. iron vs. standard care in the management of postoperative anaemia did not include a formal cost analysis; however, transfusion rates, infections and length of hospital stay were decreased, suggesting cost effectiveness [39]. A retrospective, matched cohort reported on costs of postoperative i.v. iron therapy in total lower limb arthroplasty, and found that use of iron formulations was cost neutral (–25.5 to 62.1 €/patient for iron sucrose and –51.1 to 64.4 €/patient for ferric carboxymaltose) compared with red cell transfusion [43]. In contrast, although NICE guidelines still recommend oral iron in the pre-operative and postoperative settings [12], available evidence on the lack of efficacy of oral iron in the postoperative period

suggests that cost analysis of this intervention is not meaningful [51–57].

### Suggestions for further research

During the writing of this consensus statement, it became apparent that there are areas of postoperative anaemia management for which further research is required:

- **Monitoring.** It is really important to emphasise the need for detailed anaemia studies following discharge with periodic monitoring of haemoglobin and iron parameters in relation to functional recovery.
- **Interventions.** More data and clinical trials are required to firmly establish the impact of postoperative anaemia management strategies (i.v. iron vs. oral iron, rHuEPO, red cell transfusion and nutritional support) on functional recovery and quality of life; on end-points in addition to laboratory end-points, such as haemoglobin increase; and interventional end-points, such as reduction or avoidance of red cell transfusion. Further research is required to assess the effects of correction of iron deficiency, with or without anaemia, on platelet counts, platelet activation and thromboembolic events, especially in the elderly. Timing of interventions in the postoperative course needs to be addressed in future trials. Dosing of anti-anaemia treatment and combination of means of treatment must be systematically investigated.
- **Patients.** It is also necessary to define which patient groups are most likely to benefit from such treatments.
- **Mechanisms of action.** The mechanisms underlying non-erythropoietic effects of rHuEPO, such as neurological and renal protective effects, and iron need to be elucidated.
- **Cost.** The cost effectiveness of postoperative anaemia correction must be investigated at the different time-points for its administration, using formal cost evaluation. Until such data are available, the predominant signal from available publications and peer reviewed recommendation support the concept of postoperative anaemia screening, diagnosis and appropriate treatment.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Appendix S1.** Studies evaluating the effect of postoperative intravenous iron administration (11 studies, 1855 patients).

**Appendix S2.** Recent systematic reviews and meta-analyses comparing restrictive versus liberal packed red cell transfusion strategy.