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PERIOPERATIVE ANEMIA: PREVALENCE, CONSEQUENCES AND PATHOPHYSIOLOGY

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Abstract

In major elective surgery, patient may be exposed to the effects of pre-operative anemia, blood loss and red cell transfusion, all of which may adversely influence post-operative rates of morbidity, mortality and readmission, and length of hospital stay. Preoperative anemia is prevalent among patients scheduled for major surgery (30-40%), while postoperative anemia is even more frequent (up to 80-90%). However, preoperative anemia is usually regarded as no more than a surrogated marker of patient's physical status, and it is not always adequately addressed before surgery, whereas red blood cell transfusion is the usual default treatment for postoperative anemia. Absolute iron deficiency and iron sequestration are the leading causes of preoperative anemia, whereas surgery-associated blood loss and inflammation may induce and/or maintain postoperative anemia. Hematinic deficiencies without anemia may hamper pre-operative hemoglobin optimization and/or recovery from postoperative anemia. As modifiable risk factors, preoperative anemia and hematinic deficiencies should be detected, classified and treated prior to any major surgery. For elective non-cancer procedures, this may entail to postpone surgery until anemia improvement or resolution.

Introduction

From a clinical point of view, anemia should be considered as a decrease blood erythrocyte mass that compromises tissue oxygenation, forcing compensatory mechanisms to be activated. This clinical concept of anemia can be very useful for the management of the surgical patient, especially in the postoperative period, where the speed of anemia onset, gender, age and previous health status (preoperative hemoglobin [Hb], physiological reserve) have a decisive impact on the clinical expression of the anemic syndrome and on the need and intensity of treatment.

However, in everyday clinical practice, anemia is defined in term of Hb concentrations. The World Health Organization (WHO) has established different Hb thresholds for the definition of anemia and its severity (mild, moderate or severe) according to age and gender, which are widely accepted and used in most clinical and epidemiological studies (1). In the case of iron-deficiency anemia (IDA), the WHO noted that “mild” is a misnomer, as iron deficiency (ID) is already advanced by the time anemia is detected, and has health consequences even when anemia is not clinically apparent (1). Additionally, adjustments of anemia Hb thresholds for altitude (to account for a reduction in oxygen saturation of blood) and cigarette smoking are necessary (1)

According to global estimates using WHO criteria, anemia is a public health problem that affected approximately 1.6 billion people worldwide in 2005. Its prevalence was highest among pre-school children (47%) and pregnant women (42%); followed by non-pregnant women (30%), school children (25%) and older persons (24%). The lowest prevalence was in men (12.7%). However, substantial differences in the prevalence of anemia are observed among geographical areas and between industrialized and non-industrialized countries (2).

More recently, data from 187 countries revealed a significant reduction in the prevalence of global anemia from 40.2% in 1990 to 32.9% in 2010, though the total number of anemic persons was around 2 billion (3). The lower prevalence of mild and moderate anemia accounted for most of the reduction, while the prevalence of severe anemia remained largely unchanged (3). IDA remains the most common type of anemia worldwide, accounting for about one-half of total anemia burden (3).

Prevalence also varies among Western countries. In USA, it has been reported an average prevalence of 6–8% in individuals up to age 74y (4). In those older than 75y, the prevalence of anemia increased progressively with age, up to 23% in those more than 85y (4). In contrast, an epidemiological study showed that anemia was more prevalent in Portugal (20%), though with marked regional asymmetries, and largely undiagnosed (5).

It is clear that anemia prevalence is higher among older persons (6), but differences between community living individuals and hospitalized patients have been also observed. In a meta-analysis (n>85,000), anemia prevalence in community living older adults was 12%, but >40% among those hospitalized or living in nursing homes (7). In a cross-sectional study (n= 2234), the prevalence of anemia among patients of any age hospitalized in the departments of digestive diseases, internal medicine, cardiology or respiratory diseases over was 50% (8).

Prevalence of anemia in surgical patients

Do these figures apply to surgical patients? Pre-operative anemia is a frequent condition among surgical patient, and its prevalence can reach up to 75%, depending on comorbidity, gender, age, and underlying pathology necessitating surgery, as well as the Hb cut-off used for its definition (9). Nevertheless, in developed countries, the prevalence of anemia among patients scheduled for major surgery is higher than among the general population.

According to WHO, anemia in adults is defined by an Hb <13 g/dL in men and <12 g/dL in women, at sea level (1). However, the WHO criteria for the definition of anemia 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 compared to males, but comparable amounts of blood loss when undergoing a particular procedure. This resulted in higher relative red cell mass loss and higher transfusion rates in females (10,11). More recently, a study of 1388 women who underwent cardiac surgery revealed that borderline anemia (Hb 12.0 – 12.9 g/dL) was associated with increased red cell transfusion and prolonged hospital stay compared to no anemia (Hb ≥13 g/dL)(12). Therefore, while waiting for more physiologically-sensible definitions, patients scheduled for a major surgical procedure and presenting with preoperative Hb <13 g/dL irrespective of gender should be considered anemic (13,14).

Using this latter cutoff, in a recent analysis of 3342 patients scheduled for major elective procedures, overall prevalence of anemia was 36%, but it was higher in women than in men (53% vs. 23%, respectively; p<0.001). There were also significant differences in preoperative anemia prevalence according to type of surgery:

gynecologic surgery (64%), colorectal cancer resection (58%), cardiac surgery (40%), liver metastases resection (37%), elective orthopedic surgery (26%), and radical prostatectomy (8%) (15). Up to 75% of patients undergoing hip fracture repair surgery (n=1004) presented with Hb <13 g/dL on admission (16).

Consequences of anemia

Patients undergoing major surgery may be exposed to the effects of anemia, blood loss and allogeneic red blood cell transfusion (RBCT), all of which may adversely influence postoperative outcomes, although there is not agreement on the relative contribution of each of them (17).

Preoperative anemia is usually regarded as no more than a surrogated marker of poor physical status (in many cases due to the underlying surgical pathology), which does not entail an increase in patient's risk, and therefore it is not always adequately treated before surgery (13). However, the association between preoperative anemia and poor outcome has long been described, and a recent meta-analysis including over 900,000 patients who underwent major elective surgery has confirmed that pre-operative anemia is an independent risk factor for poorer post-operative outcomes (18).

Recently, an International Consensus Conference on Patient Blood Management (ICC-PBM) was held at Frankfurt. Based on the analysis of data from 35 observational studies, the ICC-PBM multidisciplinary expert panel recognized that perioperative anemia is an important risk factor for peri-operative morbidity (acute myocardial infarction, ischemic stroke or kidney injury) and hospital and 30-day mortality, and therefore recommended to detect and classify anemia early before major elective

surgery (strong recommendation based on low certainty in the evidence of effects). The ICC-PBM panel noticed that the thresholds for definition of anemia are heterogeneous in the literature; therefore exact thresholds need to be addressed in future studies (https://europeanba.sharepoint.com/sites/ebase/workinggroups/ICC-PBM/Preoperative%20anemia/25-4_Plenary_Pre_Op_with_polling.pdf).

A sub-optimal hemoglobin level (<13 g/dL for both genders), is an independent predictive factor of the need for peri-operative RBCT (13,14,17). In major elective surgery, peri-operative blood loss may lead to acute severe anemia, especially in those with low pre-operative Hb. To avoid its deleterious effects, RBCT is usually prescribed, as it produces a quick, albeit transient, increase of Hb levels. However, RBCT carries its own risks, and there exists a great inter-center variability in the percentage of patients receiving peri-operative RBCT when undergoing a particular major surgical procedure (11,19). Introduction of best practice alerts within the electronic transfusion request system has been proved to reduce the number of transfused RBC units (with substantial saving in blood product acquisition costs), hospital length of stay and mortality (20). However, even using a restrictive threshold, transfused patients have poorer clinical outcomes when compared to non-transfused ones (21).

In cardiac surgical patients (n>16,000), preoperative anemia has also been shown to potentiate the negative effects of major blood loss and RBCT on mortality risk (22). In a large series of patients undergoing colorectal cancer resection, severity of preoperative anemia was associated with progressive prolongation of hospital length of stay (23).

In non-surgical patients, a single-center audit (n=320) found a high prevalence of anemia (53%) at the Internal Medicine ward. Anemia was moderate-to-severe in 53% of cases and seemed to be linked to longer hospital stay and increased in-hospital mortality, but it was largely underdiagnosed and undertreated (24).

As for postoperative anemia, the concerns relate to its potential impact on recovery, rehabilitation, hospital re-admission or re-operation, and patients' wellbeing. There are limited data on the consequences of postoperative anemia in the recovery phase from surgery, but some studies after cardiac and hip and knee surgery strongly suggest the association between postoperative anemia and adverse outcomes, including prolonged recovery, early postoperative myocardial infarction, and increased likelihood of re-admission and mortality (25-27).

Despite the lack of level-one evidence for improved outcomes, it is still recommended to treat perioperative anemia in all surgical patients as good clinical practice, but with a particular emphasis on those undergoing major surgery. Correction of perioperative anemia, a fundamental pillar of Patient Blood Management, could improve patient outcomes, but confirmatory studies are urgently needed (13,14).

Hematinic deficiency without anemia

A normal Hb level does not exclude hematinic deficiencies, especially ID. In surgical patients, hematinic deficiencies may hamper pre-operative Hb optimization and/or recovery from postoperative anemia. Therefore, non-anemic hematinic deficiencies should deserve pre-operative detection and treatment (13-15).

Non-anemic patients with reduced or absent iron stores (NAID) may have symptoms such as fatigue, restless leg syndrome, concentration impairment, depression or reduced exercise tolerance (iron is required for optimal mitochondrial function essential for respiration and energy production) (28).

In patients with cancer or inflammatory bowel disease, NAID may induce secondary thrombocytosis (platelet count ≥350,000/mL), which has been identified as an independent risk factor for thromboembolic events (29,30). In congestive heart failure, NAID was independently associated with compromised physical performance and quality of life, and an increase of all-cause and cardiovascular mortality; treatment of NAID with IV iron may improve functional status within four weeks, and these improvements are maintained after 24 weeks and 52 weeks (31).

Both preoperative anemia and NAID increased the rate of postoperative nosocomial infection. Following abdominal surgery, infections were significantly more likely with low preoperative serum ferritin compared with normal levels. The data were especially poignant in that confounders including Hb level were taken into account in the analysis (32). In abdominal surgical procedures, low plasma retinol (a marker of low vitamin A intake) and high erythrocyte protoporphyrin (an early marker of ID) were found to be surrogates of increased wound complications (33). Further evaluation of the benefits of preoperative NAID correction, as a standard of care, appears warranted.

Pathophysiology of anemia in surgical patients

Although all possible pathophysiological mechanisms may be involved, preoperative anemia can be mostly attributed to chronic or acute hemorrhage, adjuvant

chemotherapy or radiotherapy, nutritional deficiencies due to poor nutrition or malabsorption (iron, vitamin B_{12}, folic acid), and some drug interactions (e.g., inhibitors of angiotensin-converting enzyme, metformin, proton pump inhibitors)(17) (Figure 1). Other frequents causes are the activation of the immune system by underlying processes as well as certain immune and inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and interleukins (IL)-1, 6, 8 and 10 (34-36) (Figure 1).

However, the proportion of cases of preoperative anemia resulting from specific causes among surgical patients has not been extensively investigated. In 1142 consecutive admissions for orthopedic surgery, 224 (19.6%) patients presented with anemia (37). In 135 (64%), anemia was normochromic, suggesting anemia of chronic inflammation (ACI); in 49 (23%) was hypochromic, suggesting iron deficiency anemia (IDA); and in 26 (13%) was attributed to other causes (37).

In another cohort of Spanish patients scheduled for elective major orthopedic surgery (n=715) the prevalence of anemia (WHO criteria) was 10.5% and increased with age, without gender-related differences (38). Interestingly, 19.4% of patients presented with preoperative Hb levels below <13 g/dL. Among anemic patients, 30.8% had hematinic-deficiency anemia (with a 20% prevalence of IDA), 30.8% had ACI, with or without chronic kidney disease, and 38.4% had anemia of mixed or unexplained origin.

In colon cancer resection, a study of 571 patients scheduled for potentially curative surgery found that 322 (56%) presented with preoperative IDA (39). In 576 patients undergoing cardiac surgery, logistic regression analysis showed that age, chronic kidney disease and treatment with loop diuretics and proton pump inhibitors or

histamine H_2 receptor antagonists were independent risk factors for the presence of preoperative anemia (40).

More recently, in the above mentioned multicenter study of patients scheduled for different types of elective surgery (n=3342), over two-thirds of anemic patients presented with absolute iron deficiency (ferritin <30 ng/mL or ferritin 30-100 ng/mL plus transferrin saturation <20%) or iron sequestration (ferritin >100 ng/mL plus transferrin saturation <20%); interestingly, over one-half of non-anemic presented with absolute iron deficiency or low iron stores (ferritin <100 ng/mL). Again, procedure-related differences were observed (15). Similar data were published for 882 unselected elective fast-track lower limb arthroplasty patients (41).

With respect to postoperative anemia after major surgery, pre-operative low Hb level, peri-operative blood loss (surgical bleeding, coagulopathy, phlebotomies, etc.) and postoperative blunted erythropoiesis (due to surgery-associated inflammation) are the main contributing factors. Hemodilution due to excessive fluid administration, which may cause 'dilutional' anemia or aggravate pre-existing anemia, nutritional deficiencies (e.g., vitamin B_{12}, folic acid) and pharmacological interactions are also contributing factors. In addition, widespread implementation of restrictive transfusion protocols have led to patients being discharged with lower Hb levels than before (42).

Altogether, these data indicate that IDA and ACI, with or without ID, are the leading causes of perioperative anemia in surgical patients. When anemia cannot be explained by acute blood loss, IDA, ACI or ACI+ID, it is important to consider other causes that would demand specific treatment. In these cases, further testing should include B_{12} (especially for those older than 60 year), lactate dehydrogenase, and serum creatinine

in order to exclude other nutritional deficiencies, hemolysis or renal disease (17). If malabsorption or severe malnutrition, a red cell folate may also be useful. Especially in the elderly and depending on available laboratory diagnostics tools, the origin of anemia may not be determined in a variable proportion of cases (anemia of unknown cause) (6).

Pathophysiology of iron deficiency anemia

Total body iron is about 3500 mg (50 mg/kg body weight), of which 65% is distributed in red blood cell Hb (2300 mg). Absorption of dietary iron (1-2 mg/day) is tightly regulated, and just balanced against iron loss. Thus, internal turnover of iron is essential to meet the requirements of erythropoiesis (20-30 mg/day). Macrophages and liver are the main iron-storage sites (ferritin), but transferrin-bound iron (3-4 mg) is the most important functional iron pool (35).

Transferrin-bound iron is the primary iron source for erythropoiesis, entering the erythroblast by a process involving transferrin receptor-mediated endocytosis. This iron may be obtained by absorption of dietary iron and/or mobilization of iron stores at macrophages and liver. Dietary non-hem iron primarily exists in an oxidized (Fe^{3+}) form which is reduced to the Fe^{2+} form by a ferrireductase enzyme, before being transported across the intestinal epithelium by a carrier protein called divalent metal transporter 1. Dietary hem iron enters the enterocyte by hem carrier protein and is metabolized by hem oxygenase to release Fe^{2+}, which enters a common pathway with dietary non-hem iron before being exported by ferroportin-1 across the basolateral membrane of the enterocyte (absorbed iron). Iron export from the stores at macrophages and hepatocytes is also accomplished primarily by ferroportin-1. Iron

released into the circulation is oxidized by ceruloplasmin, bound to transferrin and transported to sites of use (35). The amount of iron required for daily renewal of red blood cells is provided mostly by recycling the iron from senescent erythrocyte at macrophages (35).

Under physiological conditions, there is a balance between iron absorption, iron transport and iron storage in the human body. Hepcidin, a 25-amino acid peptide produced mainly by hepatocytes in response to iron status and needs, plays a major role in regulation of systemic iron homeostasis (see below) (35). ID and IDA may result from the interplay of three distinct risk factors: increased iron requirements, limited external supply or absorption and increased blood loss (Table 1) (36). Molecular defects in iron transport, recycling and utilization, as well as high hepcidin levels (e.g., iron-refractory iron deficiency anemia, IRIDA), may also contribute to iron deficiency (Table 1).

Pathophysiology of anemia of chronic inflammation

These inflammatory mediators may cause anemia via a variety of pathophysiological mechanisms (Figure 1): a) decreased red cell half-life due to dyserythropoiesis with red cell damage and increased erythrophagocytosis; b) inadequate EPO response for the severity of anemia; c) impaired responsiveness of erythroid cells to EPO; d) inhibited proliferation and differentiation of erythroid cells; and e) pathological iron homeostasis (34,35, 43) (Figure 2).

As stated above, hepcidin is the main regulatory hormone of systemic iron homeostasis. Once synthesized, hepcidin is secreted into the bloodstream and interacts with ferroportin-1 (the only know iron exporting protein) at enterocyte

basolateral membrane, hepatocytes and macrophages. The binding of hepcidin to ferroportin-1 causes internalization and lysosomal degradation of the carrier protein. Thus, hepcidin regulates the rate of iron absorption by villous enterocytes and the rate of iron recirculation from macrophages and hepatocytes, resulting in hypoferremia (35,44).

Increased iron stores, oral or IV iron supplementation, blood transfusions, and infectious/inflammatory diseases enhance hepcidin expression, whereas reduced iron stores, anemia (particularly IDA), hypoxia, phlebotomy, treatment with erythropoiesis stimulating agents, estrogens and testosterone, alcohol abuse or chronic liver disease lower expression (Figure 3)(35,44).

Erythroferrone (ERFE), a recently discovered TNFα-like protein released by the bone marrow in condition of enhanced erythropoiesis due to phlebotomy or EPO injection, mediates the reduction of hepcidin expression through a still undefined mechanism (Figure 3)(45). However, though hypoxia down-regulates hepcidin expression to allow iron mobilization for sustaining erythropoietic expansion, it does not directly regulate ERFE. In fact, hypoxia-induced down-regulation of hepcidin is mediated by HIFα-stimulated platelet derived growth factor BB (PDGF-BB) expression (Figure 3)(46).

In contrast, during inflammation, increased IL-6 levels induced an over-expression of hepcidin resulting in surface ferroportin-1 down-regulation with inhibition of intestinal iron absorption and reduced iron mobilization from the stores. In addition, inflammatory mediators increased divalent metal transporter 1 (IFN-γ), transferrin receptor expression (IL-10) and ferritin synthesis (TNF-α, IL-1, IL-6, IL-10) in macrophages further increasing iron storage (35,36). Recently, it has been described

that inflammation may also cause a reduction of ferroprotin-1 expression by a hepcidin-independent pathway (47).

Reticuloendothelial iron sequestration results in decreased iron availability for the bone marrow, leading to iron restricted erythropoiesis and anemia of chronic inflammation (ACI). This is characterized by low serum iron and decreased transferrin saturation, in the face of adequate body iron stores defined by the presence of stainable iron in the bone marrow and/or a serum ferritin value within or above normal limits. Finally, when persisting decreased iron absorption and/or chronic blood loss are present, ACI may evolve to absolute iron deficiency (ACI+ID).

While hepcidin affects iron trafficking in ACI and ACI+ID, individuals suffering from ACI+ID have significantly lower hepcidin levels than those with ACI without ID, and can absorb some dietary iron from the gut and mobilize some iron from macrophages. Thus, hepcidin levels may be useful in differentiating between ACI and ACI+ID and in selecting appropriate therapy for these patients (48). This is supported by a recent presentation by Steensma et al. (49) who noted a 92% response rate to IV iron in chemotherapy induced anemia patients with low pretreatment hepcidin levels. Hepcidin levels have been also shown useful in predicting non-responsiveness to oral iron therapy in patients with IDA (50).

Pathophysiology of anemia of acute inflammation

The pathophysiology of acute inflammation-related anemia, as the one associated with trauma or surgery, is somewhat different to that of ACI. In this setting, acute inflammatory responses are mediated mainly by IL-6 and IL-8 with transient contribution from TNF-α and IL-1 in some visceral surgeries, such as gastrointestinal or

cardiac procedures, whereas plasma IFN-γ concentrations are undetectable or within the normal range (51-53).Therefore, in most of these conditions, perioperative or traumatic blood loss and blunted erythropoiesis due to decreased iron availability are the two major mechanisms leading to anemia. In contrast, EPO concentrations are normal or near normal (54), though its stimulatory effects on erythroid precursors may be reduced.

Pathophysiology of macrocytic anemia

Vitamin B_{12} and acid folic deficiencies are responsible for most macrocytic anemias (95%, megaloblastic anemia), but other causes are possible (6). Vitamin B_{12} is essential for normal production of red blood cells and normal nervous system functioning. Its deficiency does not only lead to anemia (with macrocytosis and ineffective erythropoiesis), but also to demyelination of the cervical and thoracic dorsal and lateral columns of the spinal cord, occasional demyelination of cranial and peripheral nerves, and demyelination of white matter in the brain (55). Should vitamin B_{12} replacement not be initiated early after the onset of symptoms, the involvement of the central nervous system may be irreversible (55). Other less common, but serious, condition is thrombosis which has been attributed to the marked hyperhomocysteinemia observed in severe cases of vitamin B_{12} deficiency (55).

Gastrointestinal absorption of vitamin B_{12} depends on the intrinsic factor, which is synthesized by gastric parietal cells, and is produced by the intervention of the mucosal cell receptors of cobalamin-intrinsic factor complexes at the distal ileum. Decrease the absorption of vitamin B_{12} is the main pathophysiological mechanism and may be due to different factors (55,57) (Table 1). The most frequent cause of severe

vitamin B_{12} deficiency is the intrinsic factor loss secondary to autoimmune atrophic gastritis, leading "pernicious anemia" or Adisson-Biermer anemia, although many patients have mainly neurologic manifestations. Autoimmune gastritis can cause malabsorption of iron, with clinical manifestations of iron deficiency, and subsequently affects vitamin B_{12} absorption. It should be noted that up to 20% of older adults may be affected by *Helicobacter pylori* infection or milder forms of atrophic gastritis, hypochlorhydria and inability to absorb vitamin B_{12} from the diet, leading to relatively low serum levels (<200 pmol/L). Other less common causes of vitamin B_{12} deficiency are shown in Table 1. Folate deficiency is less frequent among surgical patients, and it can also be caused by poor intake, problems of absorption or drug interactions (Table 1).

Regarding non-megaloblastic macrocytic anemias, one of the most common causes is alcohol abuse causing macrocytosis in the absence of anemia, even without detectable alteration of liver function. Liver disease, obstructive jaundice, hypothyroidism, chronic pulmonary disease and smoking also produce macrocytosis, while physiological macrocytosis can be seen during pregnancy and in the neonatal period (6).

Conclusion

- Preoperative anemia (Hb < 13 g/dL) is prevalent among patients scheduled for major surgery (30-40%), while postoperative anemia is even more frequent (up to 80-90%).
- Perioperative anemia is associated with increased risk of postoperative morbidity, mortality, prolonged hospital stay, delayed functional recovery and readmission.

- In major surgery, a low preoperative Hb level (<13 g/dL) is one of the most important predictors of red blood cell transfusion, which in turn is another risk factor for poor outcome.
- Absolute iron deficiency and iron sequestration are the leading causes of preoperative anemia, whereas surgery-associated blood loss and inflammation may induce and/or maintain postoperative anemia.
- Preoperative anemia and hematinic deficiencies should be detected, classified and treated prior to major surgery. For elective non-cancer procedures, this may entail to postpone surgery until anemia improvement or resolution.

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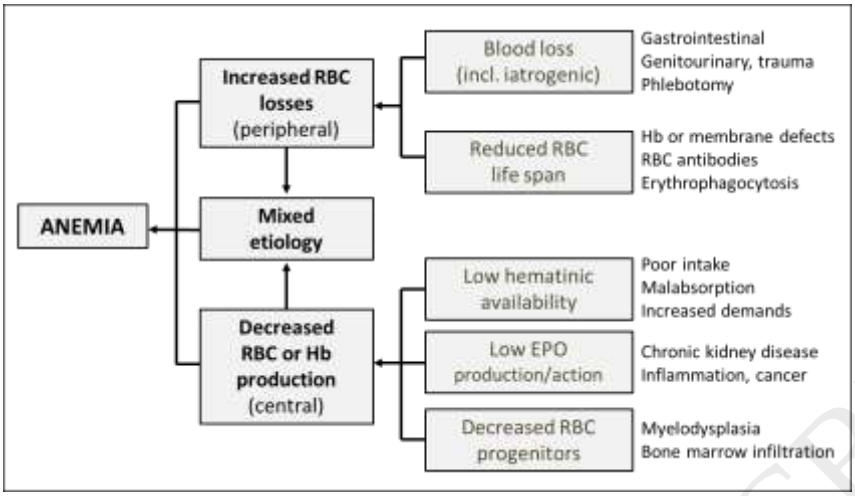
Table 1. Main causes of hematinic deficiency in surgical patients.

- **A. Iron deficiency**
  - ***Increased iron losses:***
    - Bleeding trauma
    - Gastrointestinal bleeding (peptic ulceration, neoplasia, inflammatory bowel disease, vascular malformations, medications [anti-inflammatory, anti-platelet or anticoagulant agents])
    - Genitourinary bleeding
    - Menses and multiparity
    - Multiple phlebotomies (medical "vampirism")
    - Blood donation
    - Dialysis (particularly hemodialysis)
  - ***Limited external supply or absorption***
    - Poor intake
    - Inappropriate diet with deficit in bioavailable iron and/or ascorbic acid (including excess of dietary fiber, phenolic compounds from tea or coffee, and soya products)
    - Malabsorption (gastric atrophy, gastric resection, bypass surgery, inflammatory bowel disease, celiac disease, *Helicobater pylori* infection)
    - Medication (AntiH_2, PPI, antacids, etc.)
    - Increased hepcidin levels (e.g., IRIDA or ACI)
    - Molecular defects in iron transport proteins (e.g., heme oxygenase or DMT1 deficiencies)
  - ***Increased demands:***
    - Recovery from blood loss
    - Pregnancy and lactation
    - Treatment with erythropoiesis stimulating agents
- **B. Vitamin B_{12} deficiency:**
    - Poor intake: veganism, alcoholism, malnutrition
    - Gastric pathology (autoimmune atrophic gastritis, gastrectomy, chronic atrophic gastritis*, Helicobacter pylori*)
    - Bowel diseases (malabsorption syndrome, ileac resection o *bypass*, Crohn disease, "blind loop" syndrome)
    - Pancreatic insufficiency
    - Medications (PPI and anti-H_2, metformin, colchicine, neomycin, cholestyramine)
- **C. Folate deficiency:**
    - Nutritional deficiency (alcohol and drug abuse, malnutrition, over-cooked meals)
    - Malabsorption (inflammatory bowel disease, celiac disease, "short intestine" syndrome)
    - Medications (methotrexate, trimethoprim, sulfasalazine, phenytoin)
    - Increased demands (hemolysis, exfoliative dermatitis)

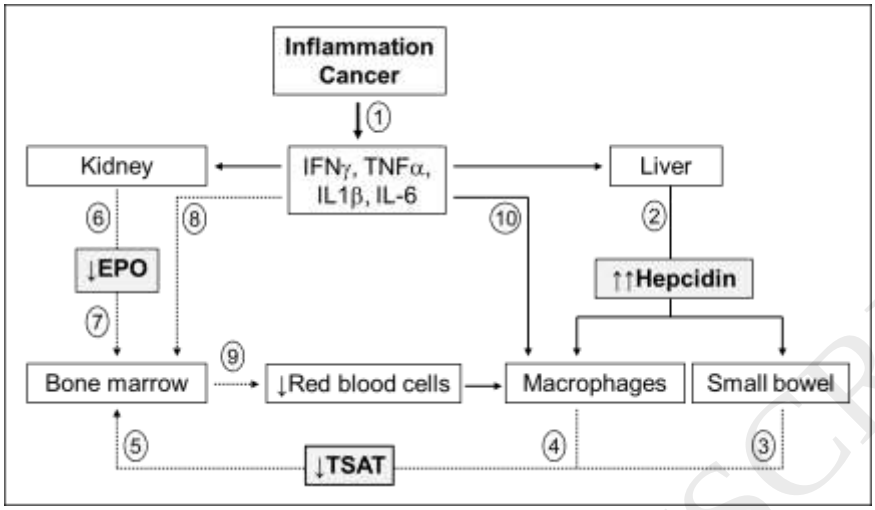
ACI, anemia of chronic inflammation; AntiH_2, histamine H_2 receptor antagonists; DMTI1, divalent metal transporter 1; IRIDA, iron-refractory iron deficiency anemia; PPI, proton pump inhibitors.

Figure 1. Main causes of perioperative anemia



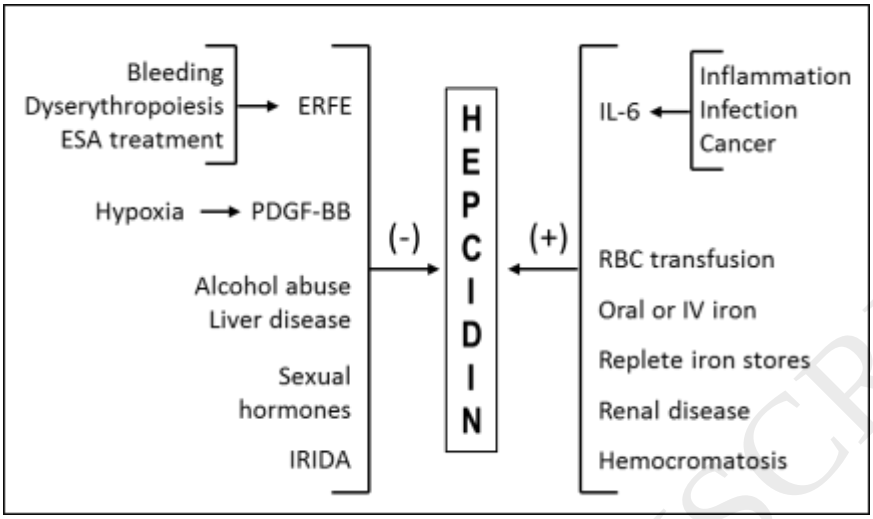
EPO, erythropoietin; Hb, hemoglobin; RBC, red blood cell.

Figure 2. Pathophysiological mechanisms involved in anemia of chronic inflammation



Keys: 1, activation of immune system with release of immune and inflammatory cytokines; 2, IL-6 induced hepcidin synthesis and release by hepatocytes, which binds ferroportin at enterocytes and macrophages, promoting its internalization and degradation; 3&4, decreased release of iron via ferroportin, leading to decreased transferrin-bound iron (reduced transferrin saturation, TSAT); 5, decreased iron availability for the bone marrow; 6, decreased erythropoietin (EPO) production; 7, decreased EPO stimulatory effect on erythroid progenitors; 8, inhibition of erythroid cell proliferation; 9, reduced hemoglobin and erythrocyte production; 10, augmented erythrofagocytosis by macrophages (modified from Muñoz et al. [34]).

Figure 3. Main regulators of hepatic hepcidin synthesis



ERFE, erythroferrone; ESA, erythropoiesis stimulating agents: IL-6, interleukin-6; IRIDA, iron-refractory iron-deficiency anemia; IV, intravenous; PDGF-BB, platelet derived growth factor BB; RBC, red blood cell; (-) inhibition; (+), stimulation (modified from Girelii et al [44]).