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Anemia of critical illness: a narrative review

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Abstract

The prevalence of anemia in patients admitted to the intensive care unit (ICU) reaches 66%. Moreover, numerous patients develop anemia during ICU hospitalization. In fact, anemia is the most common hematologic disease in the ICU.

The majority of patients hospitalized in the ICU present with acute systemic inflammation, so called systemic inflammatory response syndrome (SIRS). These patients may develop anemia of inflammation (AI). In crtitically ill patients AI may present acutely (acute systemic inflammation) or chronically (comorbidities associated with prolonged systemic inflammation), here we describe both presentations of AI as 'anemia of critical illness' (ACI). The second most frequent type of anemia in critically ill patients is iron-deficiency anemia (IDA). A mixed type of anemia (ACI + IDA) may also be present in these patients.

The three major pathophysiological mechanisms leading to ACI are: iron restriction, decreased erythropoiesis, and decreased erythrocyte lifespan. Cytokines synthesized during SIRS induce the production of hepcidin that inhibits the only transmembrane iron exporter (ferroportin) present in the duodenum and macrophages.

Etiological classification of anemia in critically ill patients poses a significant challenge to clinicians, as there is a multitude of tests available, and there are various reference ranges for these tests reported in the literature in the patient population in question. Pure ACI or mixed ACI + IDA can be diagnosed using a single laboratory test — complete blood count with analysis of reticulocytes — which provides Hb concentration in erythrocyte and reticulocyte.

The management of ACI incorporates discontinuation with erythropoiesis-stimulating agent causing anemia, reduction of iatrogenic blood loss, parenteral iron, and combined therapy of parenteral iron with erythropoiesis-stimulating agents in approved indications.

Key words: anemia of inflammation, anemia of critical illness, critically ill patients, hepcidin, iron-deficiency anemia, intensive care unit, reticulocyte hemoglobin equivalent

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Introduction

The prevalence of anemia in patients admitted to the intensive care unit (ICU) reaches 60–66% [1, 2]. Moreover, numerous patients develop anemia during ICU hospitalization, which is caused by disease processes, but may also be iatrogenic (e.g. phlebotomy, extracorporeal treatment procedures). By day 3 of ICU hospitalization, up to 90% of patients are anemic [3]. Lower hemoglobin (Hb) concentrations are associated with higher mortality rates and longer stays in the ICU, and in hospital in general [4].

The majority of patients hospitalized in the ICU present with acute systemic inflammation (SI), so called systemic inflammatory response syndrome (SIRS). These patients may develop anemia of inflammation (AI). AI, previously known as anemia of chronic disease (ACD), is also the most common

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Table I. Prevalence of anemia of inflammation in chronic conditions

Study	Year	Patient population	Anemia [%]
Birgegård et al. [9]	2006	Cancer (lymphoma + multiple myeloma)	72.9
Macciò et al. [7]	2015	Cancer (solid tumors)	63
Ambrosy et al. [10]	2019	Heart failure	57.1
Coiffier et al. [11]	2001	Cancer (chemotherapy)	54.1
Gaskell et al. [12]	2008	Older people (>65 years)	17-47
St Peter et al. [13]	2018	Chronic kidney disease (dialysis)	6.7–22.2
Boutou et al. [14]	2013	Chronic obstructive pulmonary disease	15.6

type of anemia in hospitalized chronically ill patients [5] and may be present in the following conditions: infection, autoimmune disease [6], cancer [7], chronic kidney disease (CKD), congestive heart failure, chronic obstructive pulmonary disease, pulmonary arterial hypertension, chronic liver disease, obesity, advanced atherosclerosis, and old age [8]. The prevalence of AI in different chronic conditions is presented in Table I [7, 9–14]. Patients with the aforementioned diseases are frequently hospitalized in the ICU. These factors make AI the most common type of anemia in critically ill patients [15]. In critically ill patients AI can present acutely (acute systemic inflammation) or chronically (comorbidities associated with prolonged systemic inflammation), so we decided to call both presentations of AI in critically ill patients 'anemia of critical illness' (ACI). The second most frequent type of anemia in critically ill patients is iron-deficiency anemia (IDA). A mixed type of anemia (ACI + IDA) may also be present in these patients.

Moreover, deficiency of vitamin B12, folic acid, and vitamin D, may also be present in critically ill patients.

The aim of this work was to summarize the current knowledge on the pathophysiology, diagnosis, and management of ACI, and to present our perspectives on this important topic.

Pathophysiology

There are three major pathophysiological mechanisms leading to ACI: iron restriction, decreased erythropoiesis, and decreased erythrocyte lifespan.

Iron-restricted erythropoiesis

The activation of immune cells leads to synthesis of cytokines. The most important here are interleukin (IL) 6 and 1β as they induce the production of hepcidin in the liver, which is the master regulator of the iron metabolism [16]. Hepcidin is a 25-amino acid protein that exerts its effects by inhibiting the only transmembrane iron exporter — ferroportin, either through internalization [17] or direct occlusion [18]. These ILs also decrease production of the only iron-transporting protein — transferrin. Bacterial lipopolysaccharide (LPS) and interferon gamma (IFN-γ) also block the transcription of ferroportin [19]. Ferroportin is present in the duodenum where dietary iron is absorbed, and in macrophages from where over 90% of daily iron comes from. All these mechanisms lead to iron-restricted erythropoiesis (IRE) and its typical laboratory profile: low iron, low transferrin, and high ferritin.

Decreased erythropoiesis

This effect is mainly caused by decreased erythropoietin (EPO) production. EPO is produced by fibroblasts in the renal cortex. Decreased EPO is caused by the negative effect of IL-1 and tumor necrosis factor alpha (TNF-α) on EPO expression [20], and decreased erythropoietin biological activity caused by IL-1 and IL-6 [21]. Erythropoietin is responsible for proliferation and differentiation of erythrone and induces erythroferrone that inhibits hepcidin synthesis. Numerous cytokines (mainly IFN-γ) induce apoptosis of erythroid progenitor cells in the stem.

Decreased erythrocyte lifespan

This effect is caused by: enhanced phagocytosis by hepatic and splenic macrophages caused by deposition of antibody and complement on erythrocytes, activation of macrophages, and mechanical damage from fibrin deposits in microvasculature [22]. An overview of the pathophysiology of AI is presented in Figure 1 [23]. The organs involved are the bone marrow, liver, duodenum and kidneys, the most important regulator being hepcidin.

There can be other causes of anemia in critically ill patients, including mineral (iron) and vitamin (vitamin B12, folic acid, vitamin D) deficiency. Iron deficiency (ID) leads to impaired erythropoiesis, vitamin B12 and folic acid deficiency (megaloblastic anemia) leads to impaired erythropoiesis and hemolysis, and vitamin D increases hepcidin concentration leading to even greater IRE.

Etiological classification of anemia

The World Health Organization defines anemia as a condition in which the number of erythrocytes, or their oxygen-carrying capacity, is insufficient to meet the body's

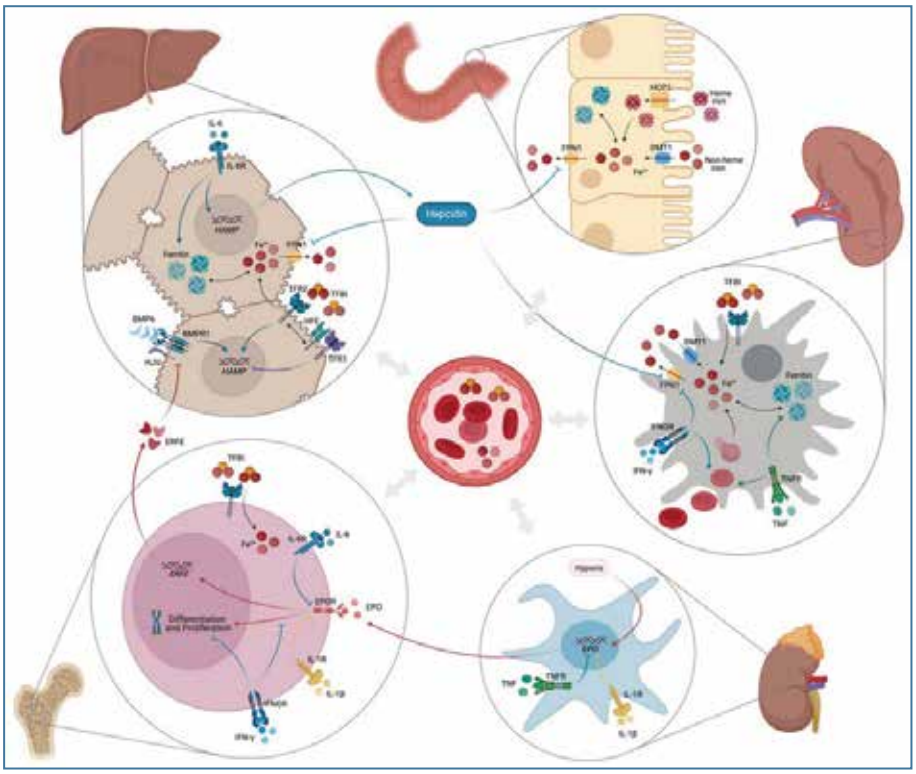

Figure 1. Pathophysiology of anemia of inflammation ['Pathophysiology of anemia of inflammation (created with Biorender)' by Lanser et al. (no modification), available at: https://doi.org/10.3390/nu13113732, under licence CC BY 4.0]

physiological needs [24]. The diagnostic criterion for anemia is a Hb concentration <12 g/dL for women and <13 g/dL for men. In clinical scenarios with potential blood loss (e.g. the perioperative period), there is a consensus to use a Hb cut-off value of <13 g/dL for both sexes, as women have lower blood volumes, yet bleed as much as men [25, 26].

Exclusion of nutrient deficiencies

ACI is a diagnosis of exclusion, so as a first step other causative/contributory factors of anemia ought to be excluded. These include at least mineral (iron) and vitamin (vitamin B12, folic acid, vitamin D) deficiencies, as these can be easily remedied.

The order of laboratory tests in diagnosis of ACI is presented below.

Erythrocyte parameters

Complete blood count (CBC) is the first line test to diagnose anemia. It is the only test that should be used to precisely determine Hb concentration. Assessment of Hb concentration, both in capillary blood [27, 28] and non-invasively [28], is not accurate and should be avoided. Anemia of critical illness typically presents as normocytic and normochromic anemia, IDA as microcytic and hypochromic anemia, and megaloblastic as macrocytic and normochromic anemia, however analysis of erythrocyte indices is not conclusive. Low mean cell volume (MCV), mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC) can be seen in thalassemias, however these conditions are quite rare and their prevalence varies by geographical region. MCV has been found to be within a reference range in up to 40% of patients with ID or mixed hematinic deficiency [29]. MCV is affected by pre-analytical factors such as sample temperature or storage time [30]. To conclude, in the absence of thalassemia, low MCV, MCH or MCHC suggest ID, whereas their normal values do not exclude ID. CBC should be the first test for screening and preliminary classification of anemia [26].

Reticulocytes

A decreased number of reticulocytes is present in ACI, IDA, megaloblastic anemia, and bone marrow aplasia/hypoplasia. An increased number is present in hemolysis, polycythemia, hemorrhage, and when hematopoietic agents are used.

Reticulocyte Hb content

The name of the test varies with the analyzer: reticulocyte Hb equivalent — Ret-He (Sysmex XE/XN), mean reticulocyte Hb content — MCHr (Abbott Sapphire), reticulocyte Hb equivalent — RHE (Mindray BC6800), and reticulocyte Hb content calculated — RHCc (ABX-Horiba Petra) [31]. Reticulocytes circulate in the peripheral blood for 1–2 days and then they

mature into erythrocytes. Determination of reticulocyte Hb shows if there is enough iron available for erythropoiesis at the time. Due to the short lifespan of reticulocytes, these parameters change within a few days and can be used to monitor iron availability and treatment progress. In patients with CKD, CHr can predict response to iron even when ferritin is increased as high as 800 µg/L [32]. Patients with sepsis or septic shock with serum ferritin even above 800 µg/L with low Ret-He, can positively respond to parenteral iron (unpublished data, clinicaltrials.gov identifier: NCT05217836). The Ret-He test was introduced in 2005. This test generally is rapid, convenient and cost-effective. It has been used to identify IDA in inflammatory conditions: rheumatoid arthritis [33], cancer [34], chronic disease [35], and gastroenterological disease [36]. CHr cannot distinguish IDA from thalassemia; however, in populations with a low prevalence of thalassemia, the Mentzer index may be used to identify thalassemia [37]. The Mentzer index is calculated by dividing MCV by RBC, with a value <13 suggesting thalassemia with a sensitivity of 98% [38]. Different cut-off values of reticulocyte Hb have been proposed for diagosis of IDA: 25 pg [39], 28 pg [40], 29 pg [32], and 30 pg [41, 36]. The current guidelines recommend a cut-off value of 29 pg in adults (excluding pregnancy) and children, until further data is available [42].

Iron studies (iron, transferrin, transferrin saturation, ferritin)

Serum iron determination is required for the calculation of transferrin saturation (TSAT) and, due to high diurnal variability, should not be measured in isolation. Transferrin concentration variability is lower than for iron. Nevertheless, transferrin synthesis is impaired in malnutrition and chronic disease, therefore specificity of transferrin in diagnosis of ID remains inadequate. TSAT is the ratio of serum iron to transferrin. ACI presents as low iron, transferrin and variable TSAT. IDA presents as low iron, increased transferrin, and low TSAT. The most useful differentiating parameter here is serum ferritin. Whereas a ferritin level <30 µg/L signifies typical IDA, ferritin 30–100 µg/L and TSAT <20% may suggest ID. Patients with ACI may present with normal or increased ferritin levels (>100 µg/L); the degree of elevation depends on the underlying condition. With ferritin >100 µg/L and TSAT >20%, we still cannot be sure if there is ID accompanying ACI [43]. Ferritin and transferrin are acute response proteins, and therefore they lose their diagnostic utility in the critically ill. Ferritin and transferrin saturation cannot be used for a precise diagnosis of absolute (ACI + IDA) or functional (ACI) ID in critically ill patients [44]. A wide range (20–85%) of patients with AI have absolute ID (AI + IDA) which may be caused by bleeding episodes related/unrelated to primary diagnosis and/or iatrogenic blood loss, mainly associated with laboratory sampling or extracorporeal procedures [45].

Hepcidin

As hepcidin is the master regulator of iron metabolism, its concentration may be useful to discriminate between IDA and AI. In AI, there is increased concentration of hepcidin, whereas in IDA its concentration is low. There is variation in hepcidin concentration depending on fasting status, circadian rhythm, and the time of the day [46]. Moreover, renal function influences hepcidin concentration, as hepcidin is also produced by the kidneys and clearance of hepcidin is through the kidneys [47]. There are different hepcidin assays available. Mass-spectrometry and radioimmunoassays are specific, but lack adequate sensitivity [48]. Enzyme-linked immunosorbent assays (ELISA) seem to overcome these problems and are more widely available. Although serum hepcidin may help differentiate AI from AI + IDA, for a precise diagnosis it should be combined with biochemical markers (ferritin) [49] or hematological indices (CHr) [33]. Hepcidin and Ret-He are used in a two-step diagnostic pathway in gastroenterology in- and outpatients. Based on hepcidin concentration, anemia has been classified as IDA (low hepcidin <6 ng/mL), IDA and/or AI (normal hepcidin 6–46 ng/mL), or AI (high hepcidin >46 ng/mL). Then, in the second mixed group, Ret-He was determined and further differentiation into IDA (Ret-He <30 pg) or AI (Ret-He >30 pg) was possible [36]. Hepcidin cannot be used for a preliminary differentiation between AI and AI + IDA in dialysis patients because its level is increased due to impaired renal excretion [50]. Moreover, hepcidin can be used to predict response to oral iron in patients with IDA [51, 52]. There have been no studies using hepcidin to identify ID in critically ill patients. This interesting topic deserves further investigation in a prospective clinical manner (clinicaltrials.gov identifier: NCT05217836).

Other tests used in anemia diagnostics are presented in Table II.

Management of anemia of critical illness

The best treatment for ACI would be resolution of the primary condition that led to ACI. Disease-specific treatments can correct anemia in certain conditions, e.g. anti-TNF agents in inflammatory bowel disease [54] or rheumatoid arthritis [55].

Parenteral iron

It is imperative to identify patients who are iron-deficient because these patients would benefit from iron supplementation. Indiscriminate use of iron supplementation should not be used because mild anemia and ID may be beneficial in patients with infectious diseases [56]. The contraindications for parenteral iron, according to the manufacturers, include: hypersensitivity, decompensated cirrhosis and/or hepatitis, and acute or chronic infection. This latter contraindication is questionable, as causative anemia treatment is recommended by numerous organizations (e.g. British Society of Gastroenterology, American Gastroenterological

Table II. Other laboratory tests in anemia diagnostics

Laboratory test	Definition	Usefulness	Limitations
Percentage of hypochromic erythrocytes (%HypoHe)	Percentage of erythrocytes with Hb content ≤17 pg (subpopulation of mature erythrocytes with insufficient iron content)	Used to identify absolute ID in patients with AI (AI + IDA) with a cut-off value of 1.8% [35]	Relates to iron status in last three months, does not reflect acute changes in iron availability
Percentage of microcytic erythrocytes (% MicroR)	Percentage of erythrocytes with MCV <60 fL (subpopulation of mature erythrocytes with insufficient iron content)	Can be used to identify IDA in patients with AI with a cut-off value of <25.0% [35]	This parameter does not reflect acute changes in iron availability
Zinc protoporphyrin (ZPP)	Lack of iron leads to incorporation of zinc into porphyrin during hemosynthesis	Not recommended for diagnosis of ID (IIB) [42]	Limitations due to measurement technique (hyperbilirubinemia; CKD); false increase with Hb <100 g/L
Soluble transferrin receptor (sTfR)	Elevated concentration in majority of IDA and AI + IDA, within reference range in pure AI, decreased sTfR provides reliable diagnosis of IDA	Not recommended to identify ID [42]	Increased concentration may be associated with hemolytic anemia, deficiency of vitamin B12 or folic acid, hematological malignancies; confounded by inflammation — several cytokines affect sTfR levels independently of iron status
Ferritin index	Calculated as sTfR/log ferritin	Some discrimination between AI (<1) and AI + IDA (>2) [53]	Overlap between values

Hb — hemoglobin; ID — iron deficiency; AI — anemia of inflammation; IDA — iron-deficiency anemia; MCV — mean cell volume; CKD — chronic kidney disease

Association, National Blood Authority Australia), and transfusion of allogeneic erythrocytes leads to increased morbidity and mortality, including sepsis and infection [57, 58]. Increased risk of infection with parenteral iron remains a theoretical threat unsupported by studies [59]. Parenteral iron has been shown to successfully correct ID in different populations of AI patients [60]. There have been calls to revise approval for parenteral iron and widen its indications [61]. The parenteral iron formulations available in Poland are set out in Table III. Different doses of these formulations have been used in critically ill patients: iron sucrose 100 mg three times per week [62], iron sucrose 1,000 mg (single dose) [63], ferric carboxymaltose 500 mg once every five days [64], and ferric carboxymaltose 1,500 mg (single dose) [63]. In the setting of infection, divided doses (e.g. 200 mg) as opposed to single total doses of intravenous iron, should be preferred.

Table III. Parenteral iron formulations available in Poland

Iron formulation	Pharmacological agent	Brand name (manufacturer)
Iron-carbohydrate	Ferric gluconate	No i.v. agent available
	Iron(III)-hydroxide sucrose complex	Venofer® (Vifor)
	Iron(III)-hydroxide dextran complex	CosmoFer® (Pharmacosmos)
		Ferrum Lek® (Sandoz)
Glycan-coated	Iron(III)-hydroxide carboxymaltose complex	Ferinject® (Vifor)
	Iron(III)-derisomaltose	Diafer® (Pharmacosmos)
		Monover® (Pharmacosmos)
	Ferumoxytol	No i.v. agent available

i.v. — intravenous

Agents affecting erythropoietin and proinflammatory cytokines

Higher mortality with erythropoiesis-stimulating agents (ESA) has been reported in cancer patients [65], in dialysis patients not responding to ESA [66], and in pre-dialysis patients [67]. The official approval for ESA in the European Union market is for preoperative autologous donation, pre-dialysis/dialysis end stage CKD, and chemotherapy-induced anemia. There are calls to revise the approval for ESA and widen its indications, as commonly reported complications may in fact be attributable to other factors [68]. Hypoxia-inducible factors stabilizers (prolyl hydroxylase inhibitors) (clinical trials) act through endogenous erythropoietin formation and iron delivery from enterocytes and macrophages, and may be a viable therapeutic option in AI [69].

Allogeneic red blood cell transfusion

Red blood cell (RBC) transfusion is an allogeneic tissue transplantation and should be viewed as a treatment of last resort in anemic critically ill patients. It is associated with multiple complications: sepsis, infection, multi-organ dysfunction, thromboembolic events, cardiac events, respiratory failure, acute kidney injury, and prolonged hospitalization [58]. RBC transfusion at a restrictive Hb threshold is safe and potentially reduces in-hospital mortality in critically ill adults compared to a liberal strategy (transfusion at Hb <7 g/dL vs. <9 g/dL) [70]. As transfusion of RBC at restrictive triggers still may not improve oxygen delivery in some patients, and may in fact be deleterious, so called 'physiological transfusion triggers' have started to be used in RBC transfusion decision making [71]. Even elderly patients may tolerate very low Hb concentrations [72].

Direct hepcidin inhibitors and agents preventing binding of hepcidin to ferroportin (clinical trials)

These agents may act through different mechanisms: inhibition of hepcidin production, neutralization of circulating hepcidin, protection of ferroportin from hepcidin inhibition, and inhibition of hepcidin-inducing signals (e.g. IL-6) [73].

Potential role of erythroferrone (pre-clinical investigation)

Erythroferrone (ERFE) inhibits liver hepcidin synthesis during stress erythropoiesis, ensuring sufficient iron supply for bone marrow erythroblasts, and therefore ERFE has been suggested to protect against AI [74]. Some experimental research has confirmed the inhibitory effect of ERFE on hepcidin [75], however the inhibitory effect of ERFE on hepcidin was not evident in a population of rheumatoid arthritis patients [76].

Contributory factors

It is wise to correct modifiable patient factors contributing to anemia. Vitamin deficiencies should be replenished: vitamin B12, folic acid, and vitamin D. However, we must remember that vitamin deficiencies are rare in patients hospitalized in the ICU: in one study only 2% of patients had a vitamin B12 deficiency and another 2% had a folic acid deficiency [77], while in another study 2.4% of surgical patients had a vitamin B12/folic acid deficiency [26]. If possible, pharmacological agents leading to anemia should be discontinued: nonsteroidal anti-inflammatory drugs, antiplatelet agents, heparins, angiotensin-converting enzyme inhibitors, proton pump inhibitors, neuroleptics, penicillin derivatives (e.g. piperacillin), cephalosporins (e.g. ceftriaxone), and trimethoprim-sulphametoxazole [78, 79].

Iatrogenic blood loss (e.g. phlebotomy, stress-related gastrointestinal bleeding) is an important factor in the ICU and should be minimized. Phlebotomy blood loss can be reduced by ordering fewer laboratory tests (only tests that potentially could change the clinical management of patients) [80], by using low-volume sampling tubes [81], by drawing the minimum amount of blood for a particular test, by applying in-line blood conservation devices allowing reinfusion of blood that would otherwise be wasted [82], by the more common use of point-of-care micro-analytic tests, and by non-invasive monitoring [83].

Conclusions

The high prevalence of anemia in critically ill patients should encourage clinicians to implement proactive measures to prevent, detect, diagnose and treat anemia. In fact, anemia is the most common hematologic disease in the ICU. Taking into account the availability of tests, their limitations, uncertainty, cost, and iatrogenic blood loss, a diagnosis of pure ACI or mixed ACI + IDA can be established using solely complete blood count with analysis of reticulocytes (a standard 2 mL EDTA test tube) which provides Hb concentration in erythrocyte and reticulocyte. Before reticulocyte Hb content can be used as an indicator of ID, thalassemia should be excluded either by checking the patient's history or by calculating the Mentzer index (MCV/RBC). The management of ACI should incorporate discontinuation of pharmacological agents causing anemia, reduction of iatrogenic blood loss, dividing doses of parenteral iron when reticulocyte Hb content is below the reference range, and combined therapy of divided doses of parenteral iron with ESA in approved indications. Reticulocyte Hb content, determined twice a week, is useful for monitoring treatment. Transfusion of RBC should remain a treatment of last resort.

Authors' contributions

PC — conceptualization; writing of paper. ŁK — revision, writing of paper.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to biomedical journals.

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