

Proper Management of Anemia (Iron Deficiency Anemia) in Primary Care with Family Physicians, Review

¹Eidah Mohammed Alahmari, ²Fatimah Ali Awad Alwadei, ³Ghadah Ali A Algadda

Abstract: There are not many similar studies discussing the management of anemia in primary setting by family physicians. Therefore, we conducted this review to assess the strategies and programs targeting the patients suffering anemia from any type, and the patient's management procedures that are available in primary care setting. Comprehensive review was conducted using electronic medical databases such as; Medline, PubMed, Embase, Search strategies were targeting all studies discussing Anemia in primary care, (Management, diagnosis, causes, and prevalence) published up to June, 2017. More than 100 conditions may cause anemia, yet 90% belong to three groups: nutritional shortages (iron, vitamin B12 and also folic acid), ACD (chronic swelling, lumps), as well as blood loss (leaving out chronic bleeding, which creates iron deficiency). Hemolytic anemia, although much less regular than the various other, is the last choice before considering the medical diagnosis of unusual illness. A couple of laboratory examinations, such as blood count, ESR, product ferritin, and product iron and also transferrin, are sufficient to focus the medical diagnosis. Management of iron deficiency anemia in family practice would be performed under based evidence guidelines, that could help family physicians to improve the quality of treatment provided to those patients with anemia.

Keywords: Proper Management of Anemia, Iron Deficiency Anemia, ACD (chronic swelling lumps).

1. INTRODUCTION

Anemia affects one-fourth of the globe's population, accounting for 8.8% of the total global burden of disease ^(1,2). Iron deficiency is the predominant reason for anemia throughout nations as well as in both sexes, with ladies much more commonly afflicted ^(2,3). The prevalence of anemia raises in the primary care setting. Anemia lowers the capacity for job and also enhances healthcare prices ^(4,5). Iron deficiency is also connected with agitated legs syndrome, lessened lifestyle, tiredness, damaged cognitive function, as well as the inability to conceive, every one of which may take place in the absence of anemia as well as may be turned around with iron treatment ^(5,6). Anemia often goes unrecognized, especially in those people who have non-specific signs and symptoms such as dyspnea, weak point, as well as tiredness. Historically, anemia has been taken into consideration an 'innocent onlooker', approved as typical in particular teams (e.g., menstruating females), or as an irregular lab worth connected with chronic ailments ⁽⁷⁾. The evidence is clear that anemia is connected with unfavorable end results in a number of professional setups such as persistent kidney illness ^(8,9,10).

Anemia is frequently treated with iron supplements, with or without erythropoiesis-stimulating agents. In spite of the effectiveness of this therapeutic approach, lots of anemic clients do not get ideal treatment ^(11,12). While UK renal divisions have reputable anemia clinics as well as therapy procedures, many various other medical facility departments and health care practices do not have access to these or equal services. Renal anemia facilities are generally restricted to patients with persistent kidney illness, and are unable to suit various other anemic patients due to high workloads.

In 2006, the Guy's and St Thomas' Trust (GSTT) established the Rapid-Access Anemia Clinic (RAAC) in order to fulfill the requirements of a variety of anemic Patients (**Table 1**), and also to address various healthcare improvement initiatives that were being implemented during that time, in particular the Department of Health's far better blood-transfusion

method⁽¹³⁾. Therefore, programs for management of anemia patients must be established and improved in all primary care clinics, and to help family doctors with the protocols towards those patients.

Table 1: Types/causes of anemia

Anemia classification	Causes
Depressed RBC production from bone marrow	• Cancers (leukemia, lymphoma or secondaries)
	• Bone marrow shutdown (aplastic/drugs)
	• Anemia of chronic disease (eg, renal disease)
Nutritional anemia	• Iron deficiency
	• Vitamin B ₁₂ (pernicious anemia)
	• Folate deficiency (megaloblastic anemia)
Hemolytic anemia	• Sickle-cell disease
	• Thalassemia
Blood loss	• Acute (surgery, accidents)
	• Chronic bleeding (GI bleeds, menorrhagia, hematuria, epistaxis)
	• Autoimmunity
	• Infections/fevers
	• Drugs
Others	• Pseudoanemia (pregnancy)
	• Unexplained anemia

There are not many similar studies discussing the management of anemia in primary setting by family physicians. Therefore, we conducted this review to assess the strategies and programs targeting the patients suffering anemia from any type, and the patient’s management procedures that are available in primary care setting.

2. METHODOLOGY

Comprehensive review was conducted using electronic medical databases such as; Medline, PubMed, Embase, Search strategies were targeting all studies discussing Anemia in primary care, (Management, diagnosis, causes, and prevalence) published up to June, 2017. Restriction was applied to Only English language studies with human subjects. References list of each included study were manually screened for more relevant articles to our review study.

3. DISCUSSION

Anemia is defined as a less than typical hemoglobin focus. Low hematocrit is a subrogate value for anemia, but it is not determined directly by the hematological analyzer. Instead, it is calculated from hemoglobin and also other parameters. The erythrocyte count might be misinforming in the examination of anemia. In some instances of microcytic anemia, such as thalassemia, there is usually a raised erythrocyte matter (spurious polycythemia). To understand the etiology of anemia, a fundamental understanding of erythropoiesis, the procedure through which red cell (RBCs) are created, is essential. The primary governing hormone associated with erythropoiesis is Erythropoietin (EPO). This hormone is mostly generated by the kidney (small amounts are produced in the liver) and its release is contingent on the accessibility of oxygen for cells metabolic demands. When launched, EPO stimulates both the manufacturing and also maturation of erythroid forerunner cells in the bone marrow.

In order to make a generalized strategy to the medical diagnosis of anemia, the World Health Organization (WHO) has actually established a recommendation variety for regular blood hemoglobin concentration, depending on age and sex⁽¹⁴⁾. According to this criterion, anemia exists if the blood concentration of hemoglobin falls listed below 130 g/L in guys or 120 g/L in ladies. This regulation does not relate to infants, youngsters as well as expectant ladies, that have their own tables of lower restrictions of hemoglobin concentration. The WHO requirement has actually been approved widely for medical diagnosis as well as magazine, yet its global application has actually been questioned mostly because of racial distinctions. Beutler has suggested a reduced restriction of hemoglobin (1-2 g less) in African Americans compared to in

Caucasians. The recommendation range of hemoglobin concentration in blood could differ relying on the populace analyzed, age, sex, environmental problems as well as food routines ^(14,15).

Anemia causes tissue hypoxia as well as triggers making up mechanisms. Both procedures with each other generate the signs and also indicators qualities of anemic disorder. Individuals with anemia might present with dyspnea, exhaustion as well as dizziness; nonetheless, mild anemia reveals few clinical indications or symptoms. The sings of anemia consist of pallor of the conjunctivae, face, nail beds and palmar folds, although the absence of pallor does not rule out anemia ⁽¹⁶⁾. Anemia is one of one of the most frequent reasons for medical browse through because of the high occurrence in kids, girls and also elderly individuals, especially if malnutrition exists. Anemia is one of the leading sings in lots of illness or is the first proof of condition observed in routine blood cell list. Anemia is unusually prevalent in creating nations because of poor nutrition, and genetic, transmittable or parasitic illness ^(17,18).

Anemia can be classified from three viewpoints: pathogenesis, red cell morphology, as well as scientific discussion. Every little thing is necessary to assist the diagnosis. Pathogenic mechanisms associated with the production of anemia are very simple: insufficient manufacturing and loss of erythrocytes an outcome of blood loss or hemolysis. Based on these pathogenic mechanisms, anemia can be divided right into 2 types. (A) Hypo-regenerative: when bone marrow production is reduction as a result of damaged feature, decreased variety of forerunner cells, minimized bone marrow infiltration, or lack of nutrients; (B) Regenerative: when bone marrow reacts appropriately to a low erythrocyte mass by enhancing manufacturing of erythrocytes. In practice, category based on standard criteria of red cell morphology such as mean corpuscular volume (MCV), enables a quicker analysis technique. Anemia also can be categorized inning accordance with the type of professional presentation as intense (usually bleeding or hemolysis) or chronic.

Anemia can be identified as microcytic, normocytic or macrocytic, relying on MCV. As mentioned above, it can be hypo-regenerative or regenerative, which depends on the variety of reticulocytes. Using both, the listing of feasible diagnoses in the individual client is decreased substantially. Both parameters can be provided regularly by a lot of the automatic hematological cell counters.

There are many types of anemia, often named for their origins, such as: (**Table 2**)

Table 2:

• Anemia of chronic disease
• Aplastic anemia
• Bone marrow anemia
• Hemolytic anemia
• Iron deficiency anemia
• Pernicious anemia
• Sickle cell anemia
• Vitamin deficiency anemia

○ **Diagnosis:**

The World Health Organization defines anemia as a degree of Hb listed below 13.0 g/dL in male grownups, listed below 12.0 g/dL in women adults that are not expectant, and also below 11.0 g/dL in pregnant women ⁽¹⁹⁾. Hb degrees could differ across age and race, so treatment should be taken, especially in the interpretation of borderline values. Cigarette smokers and also occupants of greater altitudes might have greater standard Hb degrees, and also involvement in endurance sports might change Hb degrees ^(20,21,22,23).

The mean corpuscular Hb as well as suggest corpuscular quantity identify macrocytic anemia from iron shortage anemia, which is normally microcytic as well as hypochromic. Shortages of multiple nutrients (eg, malabsorption) or the use of thiopurine drugs (eg, azathioprine in IBD) can lead to a mix of iron shortage anemia and also macrocytosis, with resultant normocytic anemia. In this scenario, a broad red cell circulation size aids recognition of the iron deficiency component ⁽²⁴⁾. The platelet and leukocyte matters aid to dismiss pancytopenia. Thalassemia qualities likewise offer with microcytic, hypochromic anemia as well as should be taken into consideration in populaces where these characteristics are highly common. Additional specifications to diagnose iron shortage are the transferrin saturation (TfS), which shows the iron readily available for erythropoiesis, and also the lotion degree of ferritin, an iron storage protein ^(25,26). A TfS listed below

20% and a ferritin degree below 30 ng/mL are a sign of iron deficiency. Ferritin is an intense stage protein that enhances throughout swelling. Inflammatory specifications such as C-reactive protein help identify these situations. Different cutoff worths are utilized in the presence of inflammatory comorbidities such as IBD (<100 ng/mL)^(25,26), CKD (<500 ng/mL plus TfS <30%), and CHF (<100 ng/mL or <100-299 ng/mL plus TfS <20%) to detect iron shortage. If the diagnosis continues to be uncertain, the soluble transferrin receptor (sTfR) and also sTfR/log ferritin index (<1) can be made use of to distinguish between iron shortage anemia and also ACD due to the fact that the sTfR is elevated just in iron deficiency anemia^(27,28,29).

o **Management of Iron Deficiency Anemia in family practice:**

There is clear evidence to sustain prompt treatment in all people with iron deficiency anemia in family practice, because it is known that treatment enhances quality of life as well as physical problem as well as alleviates fatigue and cognitive shortages^(30,31,32). Clear proof is doing not have, iron deficiency without anemia is connected with RLS and also persistent fatigue, and therapy minimizes these symptoms^(33,34). In CHF, iron substitute therapy has been revealed to be useful, even when anemia is absent^(30,33). Thus, the choice to treat iron shortage in a person without manifest anemia have to be made on an individual basis^(24,26).

Iron Therapy:

Premenopausal ladies with an unfavorable examination for uncommon uterine bleeding can be given a trial of iron therapy. In youngsters and also expectant women, iron therapy should be tried at first. Present guidelines advise empiric treatment in children approximately 2 years old as well as in pregnant ladies with iron shortage anemia; nevertheless, if the hemoglobin degree does not increase by 1 g per dL (10 g per L) after one month of treatment in kids or does not boost in pregnant females, further evaluation might be shown^(35,36). In expecting individuals, inadequate conformity or intolerance need to be thought about, and also parenteral iron could generate a better action⁽³⁵⁾.

The action to treatment should be meticulously kept track of. The Hb degree should raise by 2 g/dL within 4 to 8 weeks, although some individuals might report an enhanced feeling of health after a few days. If the Hb degree does not react properly within this moment frame, treatment ought to be changed (changed to intravenous iron) and the source of the lack of feedback examined (**Figure 1**). Depending on the severity of the deficiency and also underlying reason, normalization of the Hb level might take up to 3 months, and it could take longer to replace iron shops (ferritin > 100 µg/L).

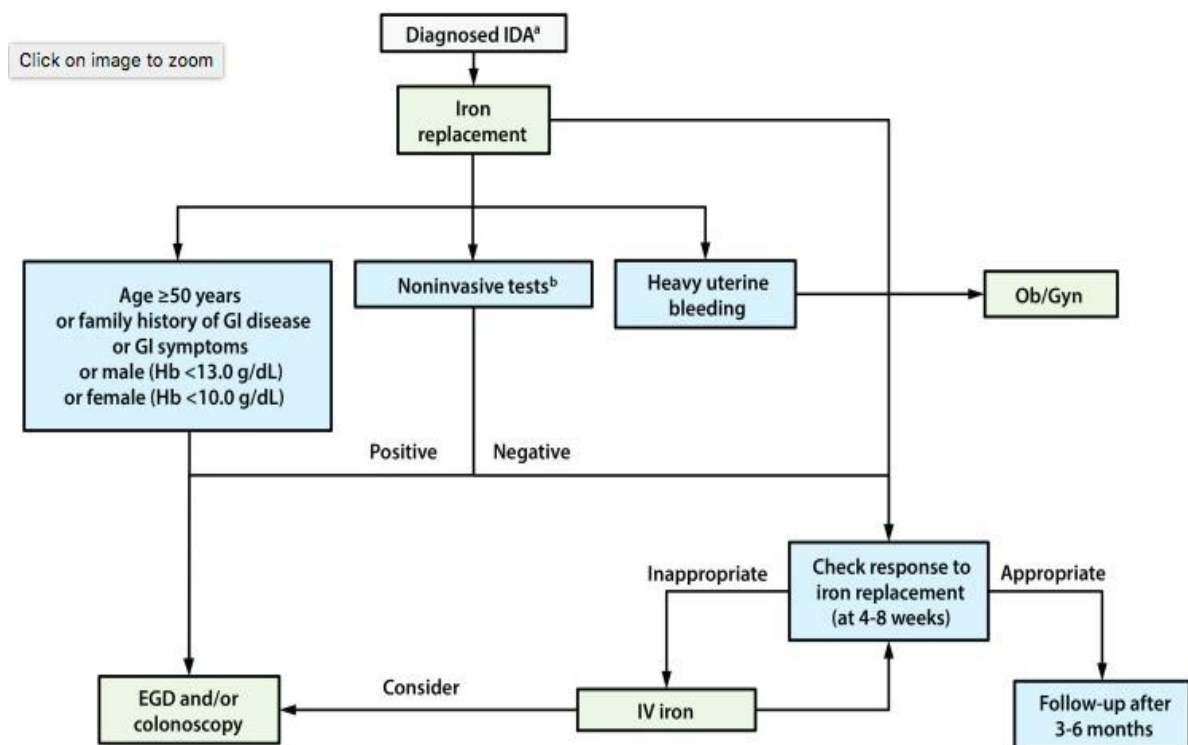


Figure 1: A proposed algorithm for the management of iron deficiency anemia (IDA)

Intravenous iron is really effective in the therapy of iron shortage anemia and also must be thought about when dental iron is ineffective^(37,38,39,40). The efficiency of oral iron is reduced when uptake with the digestive tract suffers (eg, in celiac condition, autoimmune gastritis, ACD, or post-gastric or duodenal resection) or when iron losses are big and/or continual (eg, with menorrhagia, stomach blood loss, or post-surgery). Diminished individual compliance because of negative effects likewise restricts the efficiency of oral iron. In these circumstances, intravenous iron treatment is liked since the intestine is bypassed, enabling faster repletion (**Table 3**)⁽⁴¹⁾. Ferritin expression enhances soon after administration and gets to higher degrees than with oral iron which could diminish the reoccurrence of iron shortage anemia in the long term^(40,41,42,43).

Table 3: Oral Vs Intravenous Iron

Oral Iron	
<p>Pros</p> <ul style="list-style-type: none"> • Available over the counter • Convenient • Inexpensive • Effective when intestinal absorption is not impaired 	<p>Cons</p> <ul style="list-style-type: none"> • Limited daily intestinal absorption results in slower iron repletion. • Dose-dependent gastrointestinal side effects (nausea, vomiting, abdominal pain, constipation) may limit patient compliance. • Uptake is impaired in the setting of disease (eg, celiac disease, anemia of chronic disease, autoimmune gastritis). • Mucosal injury and/or potential exacerbation of disease activity may occur in inflammatory bowel disease. • Alteration of microbiota and tumorigenic potential have been observed.
Intravenous Iron	
<p>Pros</p> <ul style="list-style-type: none"> • Fast repletion of iron stores • Safe if formulations with dextran are avoided • Effective even when intestinal absorption is impaired 	<p>Cons</p> <ul style="list-style-type: none"> • Requires administration by a health care professional, with associated increased costs • Potential for iron overload and transient increase in oxidative stress • Potential for anaphylactic reactions with dextran-containing formulations

The called for dosage of parenteral iron was traditionally computed with the Ganzoni formula, where complete iron deficiency in mg = [body weight in kg x (target Hb-- actual Hb in g/dL) x 0.24] + 500⁽⁴⁴⁾. This formula is bothersome as well as inconsistently made use of, and also it takes too lightly iron needs^(43,44). The FERGIcor (FERinject in GI Disorders to Correct Iron Deficiency) test compared an easier application system with Ganzoni-calculated dosing and located far better efficacy as well as conformity for the simpler regimen⁽⁴⁵⁾. The therapy of iron shortage without anemia can be carried out with 500 to 1000 mg (**Table 4**)⁽⁴⁶⁾.

Table 4: Simple Scheme for the Estimation of Total Iron Need

Degree of Iron Deficiency	Hemoglobin Level, g/dL	Dose for Body Weight <70 kg, mg	Dose for Body Weight ≥70 kg, mg
No anemia	Normal	500	1000
Moderate	10-12 (women) 10-13 (men)	1000	1500
Severe	7-10	1500	2000
Critical	<7	2000	2500

Iron balance is managed by modifying digestive uptake, without any active excretion. Hence, care should be taken not to trigger iron overload when this regulation is bypassed. Within the very first 8 weeks after mixture, the serum ferritin degree is highly raised and also does not associate well with body iron shops⁽⁴⁷⁾. Analysis of the ferritin degree need to be considered 8 to 12 weeks after the end of treatment. A TfS going beyond 50% is an indication of iron overload, and treatment should be changed appropriately⁽⁴⁸⁾. The Hb degree ought to increase by 2 g/dL within 4 to 8 weeks of iron replacement.

○ **Blood Transfusion:**

Blood transfusion should be extremely limited in chronic iron shortage anemia. It may be taken into consideration for patients with energetic bleeding who are hemodynamically unpredictable, or for people with vital anemia (Hb level <7 g/dL), acute myocardial ischemia, or if all other therapies fail to deal with the anemia^(49,50,51). In individuals with substantial cardiovascular disease, higher cutoff values (Hb <8 g/dL) may use⁽⁴⁹⁾. Transfusions are just a temporary solution, and also correct administration should consist of the recognition and also therapy of the underlying condition.

There is no globally approved threshold for transfusing stuffed red blood cells in individuals with iron shortage anemia. Standards commonly define particular hemoglobin worths as indicators to transfuse, yet the patient's professional condition and signs and symptoms are a crucial part of choosing whether to transfuse⁽⁵²⁾. Transfusion is advised in expectant women with hemoglobin degrees of less than 6 g each dL as a result of potentially irregular fetal oxygenation resulting in non-reassuring fetal heart lookings up, low amniotic liquid quantities, fetal cerebral vasodilation, and fetal death (40). If transfusion is performed, 2 devices of stuffed red cell must be given, then the scientific situation needs to be reflected on to lead more treatment⁽⁵²⁾.

4. CONCLUSION

More than 100 conditions may cause anemia, yet 90% belong to three groups: nutritional shortages (iron, vitamin B12 and also folic acid), ACD (chronic swelling, lumps), as well as blood loss (leaving out chronic bleeding, which creates iron deficiency). Hemolytic anemia, although much less regular than the various other, is the last choice before considering the medical diagnosis of unusual illness. A couple of laboratory examinations, such as blood count, ESR, product ferritin, and product iron and also transferrin, are sufficient to focus the medical diagnosis. Management of iron deficiency anemia in family practice would be performed under based evidence guidelines, that could help family physicians to improve the quality of treatment provided to those patients with anemia.

REFERENCES

- [1] de Benoist B, cLean E, Egli I, Cogswell M, editors. WHO Global Database on Anaemia. Geneva, Switzerland: World Health Organization; 2008.
- [2] Kassebaum NJ, Jasrasaria R, Naghavi M et al. A systematic analysis of global anemia burden from 1990 to 2010. *Blood*. 2014;123(5):615–624.
- [3] Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood*. 2004;104(8):2263–2268.
- [4] Nissenson AR, Wade S, Goodnough T, Knight K, Dubois RW. Economic burden of anemia in an insured population. *J Manag Care Pharm*. 2005;11(7):565–574.
- [5] Haas JD, Brownlie T. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. *J Nutr*. (4th) 2001; 131(2S-2):676S–688S.discussion 688S-690S.
- [6] Allen RP, Auerbach S, Bahrain H, Auerbach M, Earley CJ. The prevalence and impact of restless legs syndrome on patients with iron deficiency anemia. *Am J Hematol*. 2013;88(4):261–264.
- [7] Goodnough LT, Dubois RW, Nissenson AR. Anemia: not just an innocent bystander? *Arch Intern Med* 2003;163:1400-4
- [8] Maeda K, Tanaka Y, Tsukano Y, et al. Multivariate analysis using a linear discriminant function for predicting the prognosis of congestive heart failure. *Jpn Circ J* 1982;46:137-42
- [9] Collins AJ, Ma JZ, Ebben J. Impact of hematocrit on morbidity and mortality. *Semin Nephrol* 2000;20:345-9
- [10] Low-Friedrich I, Grutzmacher P, Marz W, et al. Therapy with recombinant human erythropoietin reduces cardiac size and improves heart function in chronic hemodialysis patients. *Am J Nephrol* 1991;11:54-60
- [11] Barroso F, Allard S, Kahan BC, et al. Prevalence of maternal anaemia and its predictors: a multi-centre study. *Eur J Obstet Gynecol Reprod Biol*. 2011;159(1):99–105.
- [12] Goodhand JR, Kamperidis N, Rao A, et al. Prevalence and management of anemia in children, adolescents, and adults with inflammatory bowel disease. *Inflamm Bowel Dis*. 2012; 18(3):513–519.

- [13] Department of Health Better blood transfusion: safe and appropriate use of blood 2007 Available from: http://webarchive.nationalarchives.gov.uk/20120405095111/http://www.dh.gov.uk/prod_consum_dh/groups/d_h_digitalassets/documents/digitalasset/dh_080803.pdf
- [14] Nutritional anaemias. Report of a WHO scientific group. World Health Organ Tech Rep Ser. 1968; 405:5–37.
- [15] Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? *Blood*. 2006;107:1747–1750.
- [16] Patel KV, Harris TB, Faulhaber M, Angleman SB, Connelly S, Bauer DC, Kuller LH, Newman AB, Guralnik JM. Racial variation in the relationship of anemia with mortality and mobility disability among older adults. *Blood*. 2007;109:4663–4670.
- [17] Irwin JJ, Kirchner JT. Anemia in children. *Am Fam Physician*. 2001; 64:1379–1386.
- [18] Hercberg S, Galan P. Nutritional anaemias. *Baillieres Clin Haematol*. 1992; 5:143–168.
- [19] *Assessing the Iron Status of Populations*. 2nd ed. Geneva, Switzerland: World Health Organization; 2007.
- [20] Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? *Blood*. 2006;107(5):1747–1750.
- [21] Cook JD, Boy E, Flowers C, Daroca MC. The influence of high-altitude living on body iron. *Blood*. 2005; 106(4):1441–1446.
- [22] Nordenberg D, Yip R, Binkin NJ. The effect of cigarette smoking on hemoglobin levels and anemia screening. *JAMA*. 1990;264(12):1556–1559.
- [23] Dickson DN, Wilkinson RL, Noakes TD. Effects of ultra-marathon training and racing on hematologic parameters and serum ferritin levels in well-trained athletes. *Int J Sports Med*. 1982;3(2):111–117.
- [24] Oustamanolakis P, Koutroubakis IE, Messaritakis I, Kefalogiannis G, Niniraki M, Kouroumalis EA. Measurement of reticulocyte and red blood cell indices in the evaluation of anemia in inflammatory bowel disease. *J Crohns Colitis*. 2011;5(4):295–300.
- [25] Gasche C, Berstad A, Befrits R et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm Bowel Dis*. 2007;13(12):1545–1553.
- [26] Dignass AU, Gasche C, Bettenworth D et al. European Crohn's and Colitis Organisation [ECCO]. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. *J Crohns Colitis*. 2015;9(3):211–222.
- [27] Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int*. 2012;2012(suppl 2012):2279–2335.
- [28] McMurray JJ, Adamopoulos S, Anker SD et al. ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2012;33(14):1787–1847.
- [29] Beguin Y. Soluble transferrin receptor for the evaluation of erythropoiesis and iron status. *Clin Chim Acta*. 2003;329(1-2):9–22.
- [30] Anker SD, Comin Colet J, Filippatos G et al. FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med*. 2009;361(25):2436–2448.
- [31] Wells CW, Lewis S, Barton JR, Corbett S. Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. *Inflamm Bowel Dis*. 2006;12(2):123–130.
- [32] Evstatiev R, Marteau P, Iqbal T et al. FERGICor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease. *Gastroenterology*. 2011; 141(3):846–853. e1-2.
- [33] Avni T, Leibovici L, Gafter-Gvili A. Iron supplementation for the treatment of chronic heart failure and iron deficiency: systematic review and meta-analysis. *Eur J Heart Fail*. 2012;14(4):423–429.

- [34] Favrat B, Balck K, Breymann C et al. Evaluation of a single dose of ferric carboxymaltose in fatigued, iron-deficient women—PREFER a randomized, placebo-controlled study. *PLoS One*. 2014;9(4) e94217.
- [35] American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 95: anemia in pregnancy. *Obstet Gynecol*. 2008;112(1):201–207.
- [36] Baker RD, Greer FR; Committee on Nutrition, American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0–3 years of age). *Pediatrics*. 2010; 126(5):1040–1050.
- [37] Koutroubakis IE, Oustamanolakis P, Karakoidas C, Mantzaris GJ, Kouroumalis EA. Safety and efficacy of total-dose infusion of low molecular weight iron dextran for iron deficiency anemia in patients with inflammatory bowel disease. *Dig Dis Sci*. 2010;55(8):2327–2331.
- [38] Onken JE, Bregman DB, Harrington RA et al. A multicenter, randomized, active-controlled study to investigate the efficacy and safety of intravenous ferric carboxymaltose in patients with iron deficiency anemia. *Transfusion*. 2014; 54(2):306–315.
- [39] Rozen-Zvi B, Gafer-Gvili A, Paul M, Leibovici L, Shpilberg O, Gafer U. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: systematic review and meta-analysis. *Am J Kidney Dis*. 2008; 52(5):897–906.
- [40] Lindgren S, Wikman O, Befrits R et al. Intravenous iron sucrose is superior to oral iron sulphate for correcting anaemia and restoring iron stores in IBD patients: a randomized, controlled, evaluator-blind, multicentre study. *Scand J Gastroenterol*. 2009; 44(7):838–845.
- [41] Schroder O, Mickisch O, Seidler U et al. Intravenous iron sucrose versus oral iron supplementation for the treatment of iron deficiency anemia in patients with inflammatory bowel disease—a randomized, controlled, open-label, multicenter study. *Am J Gastroenterol*. 2005; 100(11):2503–2509.
- [42] Kulnigg S, Stoinov S, Simanenkov V et al. A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial. *Am J Gastroenterol*. 2008;103(5):1182–1192.
- [43] Khalafallah AA, Dennis AE, Ogden K et al. Three-year follow-up of a randomised clinical trial of intravenous versus oral iron for anaemia in pregnancy. *BMJ Open*. 2012;2(5) e000998.
- [44] Ganzoni AM. Intravenous iron-dextran: therapeutic and experimental possibilities [in German] *Schweiz Med Wochenschr*. 1970;100(7):301–303.
- [45] Evstatiev R, Marteau P, Iqbal T et al. FERGICor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease. *Gastroenterology*. 2011;141(3):846–853. e1-2.
- [46] Favrat B, Balck K, Breymann C et al. Evaluation of a single dose of ferric carboxymaltose in fatigued, iron-deficient women, PREFER a randomized, placebo-controlled study. *PLoS One*. 2014;9(4) e94217
- [47] Ali M, Rigolosi R, Fayemi AO, Braun EV, Frascino J, Singer R. Failure of serum ferritin levels to predict bone-marrow iron content after intravenous iron-dextran therapy. *Lancet*. 1982;1(8273):652–655.
- [48] Novacek G, Weltermann A, Sobala A et al. Inflammatory bowel disease is a risk factor for recurrent venous thromboembolism. *Gastroenterology*. 2010;139(3):779–787. 787.e1.
- [49] Carson JL, Grossman BJ, Kleinman S et al. Clinical Transfusion Medicine Committee of the AABB. Red blood cell transfusion: a clinical practice guideline from the AABB. *Ann Intern Med*. 2012; 157(1):49–58.
- [50] Villanueva C, Colomo A, Bosch A et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med*. 2013;368(1):11–21.
- [51] Hébert PC, Wells G, Blajchman MA et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340(6):409–417.
- [52] Murphy MF, Wallington TB, Kelsey P, British Committee for Standards in Haematology, Blood Transfusion Task Force, et al. Guidelines for the clinical use of red cell transfusions. *Br J Haematol*. 2001;113(1):24–31.