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Diagnosis and management of anemia in clinical practice and its association with cardiovascular pathology

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Abstract

Anemia is a syndrome that can be presented in many medical conditions that primary healthcare professionals face during their practice. Anemia has become widespread (up to 25 % of the world's population), which makes this health issue highly relevant. The causes of anemia may include: acute and chronic blood loss, impaired absorption of iron and vitamins, hemolysis, inhibition of bone marrow hematopoiesis, impaired erythropoietin synthesis. Since the manifestations of anemia are nonspecific (weakness, shortness of breath during exercise, dizziness, tachycardia), they can be interpreted as chronic heart, lung or kidney disease that can lead to late diagnosis and treatment of this pathology. General practitioners have to be aware of the etiology, pathogenesis, and clinical signs of anemia as well as actively apply laboratory and instrumental diagnostic tools, and have a good understanding of the mechanisms of action of anemia medications and consider its indications and contraindications when prescribing.

The review focuses on the main causes of iron deficiency, differential diagnosis between anemias, treatment options for iron deficiency anemia.

Keywords: *iron deficiency anemia, anemia of chronic disease, hemoglobin, transferrin, hepcidin, iron preparations, erythropoietin.*

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Anemia is a clinical and laboratory syndrome characterized by the decrease of red blood cell count or hemoglobin per unit of blood volume due to various pathological (physiological) processes [1].

The most common causes of anemia in clinical practice include:

— iron deficiency — 29 %;
— chronic diseases — 27 %;
— acute bleeding — 17.5 %;
— hemolysis –17.5 %.

There is no generally accepted classification of anemia, but its severity can be classified by mean cell volume (MCV) of red blood cells:

- microcytic hypochromic anemia (MCV < 80 fL);
- normocytic normochromic anemia (MCV = 80–95 fL);
- macrocytic hyperchromic anemia (MCV > 95 fL).

Pathophysiologically, anemia can be:

- associated with decreased development of red blood cells and/or Hb;
- associated with increased breakdown of red blood cells.

Based on the hemoglobin level, anemia can be classified as:

- severe (Hb<70 g/l);
- moderate (Hb 70–100 g/l);
- mild (Hb > 100 g/l).

In clinical practice, it is convenient to divide anemia into the following groups in order to select the optimal treatment strategy:

Group 1 — "deficiency" anemia that is associated with iron (including post-hemorrhagic) or vitamin B12 (folic acid) deficiency;

Group 2 — anemia associated with chronic diseases such as chronic infectious, inflammatory, autoimmune and oncological diseases;

Group 3 — "hematological" anemia associated with bone marrow failure (hemoblastosis, aplastic anemia), or with increased breakdown of red blood cells (hemolytic anemia) [2].

Iron deficiency anemia

Iron deficiency anemia (IDA) is widely spread worldwide. It is the most common type of anemia (90 % among children, 80 % among adults).

IDA is polyetiological pathology that is mainly associated with iron deficiency due to impaired iron intake, absorption or increased loss of this element, characterized by microcytic hypochromic anemia.

It is widely known that anemias, including IDA, may be associated with socioeconomic status, nutrition, bleeding, parasitic diseases, etc. Experts from the World Health Organization found that anemia is commonly seen in developing countries, especially in infants and pregnant women (Table 1) [3].

Table 1. **The prevalence of anemia worldwide depending on age, gender, socioeconomic status**

Demographic group	Anemia prevalence, %		
	Developed countries	Developing countries	Worldwide
Children 0–4 years old	12	51	43
Children 5–12 years old	7	46	37
Men	2	26	18
Pregnant women	14	59	51
Women	11	47	35

Iron metabolism

Adult's organism contains approximately 3–5 g of bound iron, 70 % of which is stored in hemoglobin. Most of the iron that is absorbed in the intestine is then stored in the bone marrow, where it is used for proerythroblasts synthesis. The lifespan of erythrocytes ranges from 100 to 120 days, after which they clearance by macrophages in liver, spleen and bone marrow. The iron released in this process is then used for the synthesis of hemoglobin. Sufficient meat intake generally provides human organism with necessary amount of iron. When there is an iron deficiency (due to bleeding or impaired absorption), the depot activates. Ferritin is a protein of mass 474 kDa that stores and deposits iron.

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Physiologically, the amount of ferritin is comparable to the amount of iron (when there is more ferritin, there is also more iron). Chief storage depots of iron are liver, spleen, and bone marrow.

About 10–20 % of iron from food is absorbed into the bloodstream in the small intestine. It is possible to assimilate only the bivalent iron (Fe2+), since trivalent iron (Fe3+) is practically not absorbed [4].

Transferrin and transferrin's receptors play pivotal role in iron transport. Transferrin have a molecular mass of 80 kDa and mediate the transport of iron through blood plasma to tissues (bone marrow, liver, spleen). It is produced in the liver in accordance with the amount of iron (iron deficiency activates transferrin synthesis). Transferrin transports both iron absorbed from food and iron released from depots (by macrophages). However, it cannot be transported from the transferrin–iron complex directly to the cell. This process requires another protein — the transferrin receptor. The transferrin-transferrin receptor complex is immersed into the cell, where iron releases.

Hepcidin in another key protein that is produced by the liver. Hepcidin is a regulator of iron release from monocyte–macrophage cells. It inhibits iron absorption from blood by intestine and its release from hepatic and splenic macrophages. Chronic inflammation is the main cause of hepcidin overproduction. It is often seen in patients with inflammatory bowel diseases that is accompanied by iron deficiency and anemia.

Only 10–15 % (about 2.5 mg) of iron that comes from food is absorbed, while about 1 mg of iron per day is excreted in stools, urine, hair, nails, and exfoliated epidermal cells. In young menstruating women this number is even higher. Therefore, in order to restore the daily loss of this element, the amount of absorbed iron should be 5–10 times higher.

The following stages of iron deficiency are identified:

I. Prelatent iron deficiency (iron stores are low or absent);

II. Latent iron deficiency (iron transport is low);

III. Iron-deficiency anemia.

Increased iron consumption leads to iron stores depletion followed by the reduction of ferritin, while transferrin saturation and serum iron as well as the level of red blood cells and hemoglobin remain within reference values, and the patient does not present clinical signs of anemia. This stage is called prelatent iron deficiency.

The continuation of iron consumption when iron stores are low leads to transferrin saturation and serum iron reduction, while hemoglobin and red blood cell count remain normal. This stage is called latent iron deficiency.

Finally, the stage of iron deficiency anemia is characterized by the drop of hemoglobin along with depletion of iron stores and the reduction of serum iron and transferrin saturation. At this stage patient usually have clinical signs of IDA.

Main IDA causes

According to the main mechanisms of iron deficiency, IDA can be caused by blood loss, increased iron need, insufficient dietary intake or malabsorption [6].

1. Blood loss:

a) uterine bleeding (uterine fibroids, cervical cancer, endometriosis, ovarian insufficiency, etc.);

b) gastrointestinal bleeding (peptic ulcer, hemorrhoids, cancer, ulcerative colitis, Crohn's disease, diverticular disease, NSAID-induced enteropathy, Meckel's diverticulum);

c) pulmonary hemorrhage (cancer, bronchiectasis, isolated pulmonary hemosiderosis);

d) kidney hemorrhage (urolithiasis, hematuric nephritis, tumors);

e) nosebleeds.

2. Increased iron need:

a) pregnancy, lactation;

b) growth and puberty;

c) chronic infections, tumors;

d) helminthiases.

3. Iron malabsorption:

a) stomach resection;

b) enteritis, sprue syndrome;

c) coeliac disease.

4. Impaired iron transport due to transferrin deficiency in patients with primary liver pathology.

5. Inadequate dietary intake:

a) children who are formula-fed without iron supplement;

b) vegetarian diet, malnutrition.

6. Iatrogenic causes:

a) blood and organ donation;

b) hemodialysis;

c) frequent blood sampling.

It should be also noted that IDA can have combined ethnology.

IDA progresses over the following stages:

Stage 1. Iron storage depletion due to excessive iron consumption and low intake. At this stage iron absorption usually increases.

Stage 2. Significant storage depletion (transferrin saturation <17.8 %, serum iron level <10.7 μmol/l).

Stage 3. Mild (compensated) anemia — hemoglobin level — 100–120 g/l.

Stage 4 — Moderate (subcompensated) anemia — hemoglobin level < 100 g/l.

Stage 5 — Severe anemia — hemoglobin level 60–80 g/l with the development of tissue hypoxia and vascular lesions.

IDA diagnosis is based in the clinical picture and laboratory parameters of absolute iron deficiency.

The main IDA clinical signs are sideropenia and hypoxia [7]. Sideropenia symptoms are typical for IDA. Particular changes are seen in tissues that constantly regenerate: skin has pale color, becomes dry and covered with fissures. There is usually a slight jaundice of nasolabial triangle and fingers, associated with carotene metabolism impairment in patients with iron deficiency. Angular cheilitis with red, swollen patches in the corners of the mouth may develop.

Nails may become concave in shape or spoon-shaped with peeling (the condition is called "koilonychia").

Tongue may develop glossitis (redness and soreness, as well as atrophy of the papillae).

Hair turns gray, falls out, becomes brittle and dry.

Muscle weakness develops even during low physical activity. Dysuria or involuntary urination may develop due to sphincter weakness.

Picachlorotica — taste and smell perversions — the patient has desire to consume inedible substances, such as: chalk, earth, sand, raw cereals; inhale substances with pungent odor: gasoline, acetone, etc.

Hypoxia can lead to the impairment of cardiovascular system (CVS), central nervous system, gastrointestinal tract (GIT).

Cardiovascular symptoms may include:

- tachycardia;
- hypotension;
- dyspnea;
- cardialgia;
- lower extremity edema;
- exacerbation of angina pectoris and cardiac decompensation, especially in elderly patients.

Chronic IDA can lead to myocardial dystrophy that can manifest as systolic heart murmur at the apex and pulmonic areas [8, 9].

Nervous system impairment can present with headache, dizziness, poor concentration, fatigue during exercising, and decreased intelligence in children.

Changes in the **gastrointestinal tract** are associated with tissue hypoxia due to iron deficiency and can manifest as gastritis, dysphagia, poor appetite, achlorhydria, bloating, diarrhea, or constipation. At the same time, the decrease in hydrochloric acid secretion and in chronic gastritis is considered as the consequence, and not as the cause of iron deficiency, and can be explained by dysregenerative processes in the gastric mucosa. It is assumed that iron deficiency can cause increased absorption of iron antagonist metals in the intestinal wall followed by its accumulation, such as cadmium [10].

Despite the bright clinical picture of IDA, laboratory parameters are superior in the IDA diagnosis [11].

Laboratory parameters of IDA

1. Complete blood count (CBC). CBC determine hemoglobin, the red blood cell count and calculate the average amount of hemoglobin in RBCs (MCH), hematocrit (Hct) and the level of immature red blood cells (reticulocytes). In patients with IDA all the above indicators decrease, and morphological examination show microcytic hypochromic anemia.

2. Biochemical makers of iron metabolism determine the iron serum level, transferrin, the transferrin saturation (TS), the total iron-binding capacity (TIBC), and ferritin. IDA is characterized by low ferritin level that indicates iron storage depletion, increased levels of TIBC and transferrin. The iron serum level and the TS are usually reduced.

3. It is necessary to exclude celiac disease in patients with impaired iron absorption in the small intestine and the development of anemia that resistant to treatment with oral preparations. Therefore, it is essential to assess antibodies to tissue transglutaminase (anti-tTG) and endomysium (Anti-EMA). In case when leukopenia and thrombocytopenia are present in CBC, a bone marrow aspiration is indicated [12].

4. In order to verify the diagnosis, patients with IDA should undergo the following instrumental investigations:

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— endoscopy (esophagogastroduodenoscopy and colonoscopy, to exclude a possible causes of blood loss and impaired iron absorption);

— abdominal, pelvic and thyroid ultrasound;

— electrocardiography (ECG);

— echocardiography (Echo-CG);

— X-ray or computed tomography of the chest.

The conducted instrumental investigations allow to determine the cause of blood loss in the gastrointestinal tract, however, it should be kept in mind that IDA can develop in patients with nosebleeds, hematuria (with urolithiasis, nephritis and nephropathy), and iatrogenic causes (frequent blood sampling for research and bloodletting). Iron deficiency can also develop due to injuries, tumors and endometriosis.

Differential diagnosis of IDA

Differential diagnosis of IDA should be carried out in patients with anemia and chronic inflammatory and neoplastic diseases ("anemia of chronic diseases" and hypochromic anemia with iron overload: α- and β-thalassemia, porphyria).

Differential diagnosis between iron deficiency anemia and anemia of chronic disease (ACD) is presented in Table 2.

Table 2. **Differential diagnosis between iron deficiency anemia and anemia of chronic disease**

Parameters	Reference values	IDA	ACD
Serum iron level	10.7–32.2 μmol/l	↓	↓ N
TIBC	46–90 μmol/l	↑	N or ↓
TS	17.8–43.3 %	↓	N↓↑
Serum ferritin	11.0–306.8 ng/ml	↓	N or ↑

Comment. N — parameter is within the reference values; ↓ — decreased level of the parameter; ↑ — increased level of the parameter.

IDA treatment

The main principles of IDA treatment have been formulated by L.I. Idelson in 1981 and remain valid today:

— it is impossible to treat IDA only with diet;

— first-line treatment is oral iron supplements that should be prescribed in sufficient dosages (100–200 mg/day) and for at least 3 months;

— the improvement of Hb level is not the reason to stop treatment, it is necessary to restock iron storages (determined by the level of serum ferritin);

— blood transfusion in case of IDA should be performed only for health reasons [13].

There are two groups of iron supplements: those containing divalent iron (ionic, saline) and trivalent iron (non-ionic) based on hydroxide polymaltose complex (HPC) and protein succinylate [14]. The daily dosage of iron should range between 100 and 200 mg. The degree of absorption of divalent iron salts is higher compared with trivalent form, therefore they have faster effect and improves Hb levels more quickly. Preparations with hydroxide polymaltose complex (trivalent iron) are better tolerated by the gastrointestinal tract, thus, they are preferable for the treatment of patients with gastroenterological pathology and in children [15].

Parenteral iron preparations are prescribed for patients with intolerance to oral forms, or with the need for rapid restock of iron storages (severe IDA, postoperative period), impaired absorption of iron (for example, with celiac disease, inflammatory bowel disease). It is recommended to administer parenteral forms of iron intravenously, since intramuscular administration is less effective and may cause post-injection infiltrates [16].

Anemia of chronic disease (ACD): focus on CHF

ACD is ranked second in the prevalence after IDA and develops in patients with acute and chronic diseases (especially common in elderly and senile patients). It is usually mild, normochromic microcytic anemia with Hb level between 90 and 120 g/L and hematocrit of 30–40 %. In chronic and long-term course, this anemia becomes hypochromic [17].

ACD develops in many diseases and conditions: infections (bacterial, viral, fungal), autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, systemic scleroderma, hemoblastosis and malignant neoplasms, inflammatory bowel disease, sarcoidosis, chronic kidney disease, diabetes mellitus). The main mechanism of the ACD development is the formation of the hepcidin protein, which is produced by hepatocytes during inflammation. Hepcidin inhibits the absorption of iron from the small intestine and its re-utilization from iron depots, leading to the decrease of the serum iron level. In addition, the synthesis of erythropoietin in kidneys decreases due to elevation of pro-inflammatory cytokines — interferon-α (IFN-α), tumor necrosis factor-α (TNF-α) and interleukins (IL-1.6) [18,19].

Cardiovascular diseases are often associated with anemia, the prevalence of anemia increases along with the progression of heart failure and reaches 80 % in patients with class IV New York Heart Association (NYHA) clinical classification of heart failure. Anemia is an additional risk factor for mortality and complications (due to impaired exercise tolerance and low cardiac ejection fraction). The progression of CHF contributes to renal dysfunction leading to the activation of the renin-angiotensin system, vasoconstriction, and decreased erythropoietin synthesis. Timely treatment of anemia can prevent heart failure complications and renal dysfunction (cardiorenal continuum) that decreases the frequency of admissions and allow to reduce the dosage of diuretics and subsequently improves patient's quality of life [20].

Diagnosis of ACD

ACD is usually diagnosed in patients chronic diseases of cardiovascular, autoimmune, infectious origin [21]. The diagnosis of ACD can be considered in patients with long lasting anemia that is refractory to treatment with oral iron preparations. ACD can be differentiated from IDA by the level of serum ferritin, that stores iron. Ferritin level is reduced in patients with IDA while in patients with ACD it is within the reference values or even increased, since ferritin increases during inflammation. The level of transferrin (iron binding protein) is significantly increased in patients with IDA, and, conversely, reduced in patients with ACD.

Since the clinical signs of anemia are nonspecific (weakness, shortness of breath while exercising, dizziness, tachycardia), the additional examination in order to exclude or confirm cardiovascular pathology is necessary. In addition to medical history assessment and objective examination, it is necessary to conduct laboratory and instrumental investigations (ECG, Holter-ECG monitoring, Echo-CG, 24-hour BP monitoring, etc.)

ACD treatment

The main principle of ACD management is the treatment of the disease that caused it [22]. It has been proven that ACD aggravate the course of many chronic diseases (autoimmune diseases, inflammatory bowel disease, cardiovascular diseases, diabetes mellitus, etc.) and serves as the predictor of high mortality. It has been established that patients with AHD have 2 times higher risk of death compared with patients with mild anemia. The management of anemia can significantly improve the course of the disease.

There are 3 main types of ACD treatment [23]:

- blood components transfusion;
- administration of iron supplements;
- administration of erythropoiesis stimulants.

Blood components transfusion is widely used therapeutic intervention with rapid effect. Blood transfusion is indicated for patients with life-threatening anemia (Hb<65 g/l). It can also be used in patients with severe (Hb<80 g/l) or complicated by bleeding ACD. However, it should be noted that blood components transfusion give short-term effect, and due to the destruction of red blood cells in the bloodstream can lead to immune complications up to anaphylactic shock. In addition, it is impossible to exclude the transmission of blood borne infections (HIV, viral hepatitis, etc.). Repeated blood transfusions can lead to endogenous erythropoietin synthesis suppression and erythropoiesis inhibition.

Iron supplements administration

The treatment of ACD with iron supplements has low effectiveness, since hepcidin produced by hepatocytes disrupts iron absorption from the intestine. Only in patients with ACD and concomitant iron deficiency oral supplements has positive effect [24].

Considering the pathogenesis of ACD, the use of intravenous iron therapy seem more effective, however, even in this case, it is not always possible to achieve treatment targets, since the production of erythropoietin decreases in patients with ACD. Therefore, the most effective treatment for ACD is the combination of erythropoietin and intravenous iron preparations. Modern parenteral iron therapy allow to achieve good results with 1–2 infusions and to maintain the level of hemoglobin for a long time.

Erythropoiesis stimulants administration

Recombinant human erythropoietin medications were implemented into clinical practice in the 1980s and are used to replace endogenous erythropoietin that is insufficiently produced in patients with ACD. Erythropoietin stimulates the growth and differentiation of erythroid precursor cells in the bone marrow, and counteracts antiproliferative effect of cytokines [25].

Subcutaneous injections of erythropoietin at the dosage of 150 IU/kg 3 times a week are recommended, followed by dosage increase up to 300 IU/kg 3 times a week in patients who did not respond to previous treatment. The use of 10.000 IU 3 times a week is considered optimal and allow to control the development of possible side effects and discontinue treatment when needed (arterial hypertension and thrombosis development). Currently, the subcutaneous administration of erythropoietin at the dosage of 40.000 IU per week is recommended.

Conclusion

Thus, anemia of various origin has high prevalence and significantly impairs not only life quality and physical activity of patients, but also aggravates the course of concomitant diseases. It is of special importance to establish the cause of anemia in order to choose treatment strategy that can be done with correct interpretation of laboratory data. Primary measures should aim to exclude etiological factor of anemia with varying severity. The optimal approach for patients with mild to moderate IDA are the prescription of oral iron supplements and for patients with severe anemia — the combination of intravenous iron and erythropoietin medications. Adequate treatment of anemia result in cardiovascular pathology improvement (decompensation of heart failure decreases: shortness of breath, edema, tachycardia), exercise tolerance increase according to the 6-minute walk test, self-assessment of the general health state (life quality) improvement, the progression of CHF slow down, functional class according to NYHA decrease.

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