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# COORDINATION OF TREATMENT GUIDELINES FOR IRON DEFICIENCY AND B12 DEFICIENCY ANEMIA ASSOCIATED WITH HELICOBACTER PYLORI

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**Abstract:**

Iron deficiency is a common complication of Helicobacter pylori infection and can be asymptomatic or with symptoms of sideropenia, up to the development of anemia.

One of the mechanisms for the development of iron deficiency is chronic inflammation, as a result of which the expression of the iron-regulating protein hepcidin increases. Increased expression of hepcidin leads to the development of iron deficiency in patients infected with Helicobacter pylori.

Effective treatment of iron deficiency is possible only after the suppression of the inflammatory syndrome and a decrease in the increased level of gypsidine with successful eradication of H. pylori. This article presents scientific theoretical views on this topic.

**Key words:** Helicobacter pylori, IDA, Lactobacillus and Bifidobacterium, sorbifer-durules (Fe sulfate + ascorbic acid), ferroplex (Fe sulfate + ascorbic acid), tardiferon (Fe sulfate + ascorbic acid), Fenuls (Fe sulfate + ascorbic acid + riboflavin + nicotinamide + pyridoxine + calcium pantothenate), hemofer prolangatum (Fe sulfate), ferrogradumet (Fe sulfate), gynotardiferon (Fe sulfate + folic acid), actiferrin (Fe sulfate + serine), actiferrin compositum (sulfate Fe + folic acid + serine), ferro-foil gamma (Fe sulfate + folic acid + cyanocobalamin).

**Introduction:**

In the treatment of IDA, there is poor control and documentation of efficacy, late diagnosis and violation of treatment standards [26-2], which explains the modest global results in reducing the incidence of IDA: when studying the dynamics over the past 20 years, it was found that among the child population (compared with the situation among women of fertile age and pregnant women) there was the least improvement in the IDA situation [13-14]. It is extremely important to study the real clinical practice in relation to IDA with the search and elimination of possible reasons for deviation from the guidelines.

In connection with the above problems, it becomes necessary to improve the provision of assistance to children with iron deficiency in primary health care, to develop new organizational forms of medical care to this part of the child population, which determines the goal and objectives of this study.

**The main results and findings:**

The methodology of the research is based on the study and generalization of literature data on the problem of iron deficiency in children; conducting a retrospective study of the health status of children with IDA; cohort prospective study of children from birth to 1 year. In the work, modern clinical-statistical, laboratory and instrumental research methods were used.

1. To assess the state of iron metabolism in patients infected with H. pylori.
2. To study the level of hepcidin in patients infected with H. pylori.
3. Based on the results of the study, single out a group of patients with iron deficiency and establish the etiology of iron deficiency.

4. To assess the effect of H. pylori eradication on the indicators of iron metabolism and the effectiveness of therapy for iron deficiency.
5. To develop an algorithm for prescribing iron preparations for the treatment of iron deficiency in patients infected with H. pylori on the basis of its etiopathogenetic cause.

Considering the treatment of ID and IDA in patients with H. pylori infection, it is important to note that eradication therapy is just as important as the appointment of iron supplements. In the studies described above, the relationship between eradication therapy and the resolution of railway and IDA was studied. In many cases, after successful eradication therapy, the levels of hemoglobin, ferritin, and transferrin increased. In addition, the levels of TIBC and hepcidin in patients decreased after successful eradication therapy. Based on this, it can be assumed that in the treatment of ID and IDA in patients suffering from H. pylori infection, eradication therapy can lead to the resolution of ID and IDA. Also, control of H. pylori infection over time in patients after successful eradication therapy can prevent the development of ID and IDA. When considering iron therapy, it is necessary to take into account comorbidities that can lead to the development of ID and IDA. In some cases, treatment of the underlying disease can lead to the resolution of railway and IDA. Iron treatment should be started immediately, even in the absence of anemia, especially if patients develop characteristic symptoms [4, 81]. A systematic review of the efficacy of iron supplementation in non-anemic individuals with iron deficiency has shown that treatment (of any type) increases hemoglobin and ferritin levels and decreases fatigue in patients, but does not improve physical performance, nor does it provide maximum oxygen saturation [10].

The choice of the form of iron and the method of its administration largely depends on the presence and degree of anemia, the reversibility of the underlying cause of ID and IDA, clinical status (age, gender, long-term or recent onset), and in some cases, on the patient's preference. Oral iron supplementation, such as ferrous sulfate, fumarate, and ferrous gluconate, remains the mainstay of therapy for absolute iron deficiency.

A growing body of evidence indicates that low doses are more effective and better tolerated than the traditionally recommended 100–200 mg of oral iron per day. Since the absorption of non-heme iron is very low (from 5% to 28%) [40], high doses can lead to toxicity, due to the ROS of unabsorbed iron on the intestinal mucosa. Common side effects such as nausea, vomiting, constipation or diarrhea can lead to non-adherence in 30–70% of cases [24] and compromise planned long-term (several months) treatment. It is important to note that even a small increase in serum iron activates hepcidin, limiting iron absorption. This physiological response was factored into the development of the most appropriate oral iron dose and regimen for women with iron deficiency without anemia.

In short-term studies using stable isotopes of iron, the addition of iron sulfate (60–240 mg) caused an increase in hepcidin for up to 48 hours, limiting the absorption of subsequent doses [16]. In another study, participants were randomized into 2 groups: 60 mg iron per day for 14 days and 60 mg iron every other day for 28 days. Iron absorption was significantly higher in the latter group. In a study comparing 2 groups of women who received 120 mg of ferrous sulfate per day in either 1 or 2 doses, the first group showed a smaller increase in serum hepcidin [23].

In general, these studies demonstrate that changing the regimen from daily to alternating and from divided doses to single doses increases the effectiveness of treatment in people with iron deficiency without IDA and can improve the tolerance of therapy. A current study in women with iron deficiency anemia [22] assesses the feasibility of an alternating regimen in the presence of anemia [21], given that hypoxia further increases intestinal iron absorption and completely suppresses hepcidin [5].

Other negative effects of unabsorbed iron include changes in the composition of the gut microbiome with a decrease in the beneficial bacteria Lactobacillus and Bifidobacterium, an increase in the number of potential pathogens (Enterobacteriaceae), and increased inflammation and diarrhea, as shown in a

study in African children [12, 164]. The minimum dose of iron supplementation is 60 mg per day. Lower doses (37.5 mg per day) of oral iron have been found to be beneficial to blood donors in limiting the delay in donating blood [3]. Prophylactic treatment with iron sulfate (60 mg for adults and 30 mg for children) is recommended in regions of the world with a high prevalence of iron deficiency anemia [25]. However, the validity of universal iron supplementation in countries with high prevalence of malaria and other infections is controversial. Epidemiological studies in vitro [7] have shown that iron deficiency is an adaptation process that protects the body from plasmodial virulence, and that its correction can increase the severity of infection [20, 37]. Recent data indicate that ferroportin expressed in erythrocytes is a functional protein and is decreased when iron-induced hepcidin levels are high. This will increase the iron content of the red blood cells, promoting the growth of parasites [7]. In these cases, iron administration should be combined with antimalarial treatment [17]. Other problems associated with iron intake are intestinal dysbiosis and diarrhea. To solve this problem in the future, it is planned to develop iron compounds that are available only to humans, and not to intestinal pathogens. There is also great interest in developing compounds that are better tolerated than iron salts. Many compounds have been proposed (eg, sucrosomal iron, heme iron polypeptide, iron-containing nanoparticles), but research is limited [6]. Sucrosomal iron has been tested in patients with CKD [18], but the mechanism of absorption and real benefits have not been determined. Under the same conditions, iron citrate, which binds phosphates, simultaneously corrects hyperphosphatemia and iron deficiency; its dual effect is being tested in clinical trials with CKD [11]. A phase 3 study of iron maltol yielded positive results for iron deficiency anemia in inflammatory bowel disease [5]. Further clinical trials are required to confirm the effectiveness of these iron preparations.

Intravenous iron is an alternative for patients with intolerance or refractoriness to oral forms of iron [9]. This route of administration, limited by the risk of severe hypersensitivity reactions, is now more widely used due to the improved safety profile of the latest generation of components. The established indications for intravenous iron administration are decreased absorption capacity in gastrointestinal diseases or after bariatric surgery, severe anemia (Hb, 7–8 g / dL), high hepcidin levels as a result of concomitant inflammation, and, in rare cases, iron-resistant iron deficiency anemia. Also, the intravenous route of administration of iron is preferred when a quick recovery is required. The advantages of intravenous iron administration are faster action and less gastrointestinal toxicity [24]. Intravenous iron is more effective than oral iron in CKD patients treated with drugs that stimulate erythropoiesis [15, 97]. The oral route of iron administration is recommended for patients with inactive diseases and mild anemia [19], who are more likely to have an absolute iron deficiency. Intravenous iron is available in various forms. The stable carbohydrate shell of the latter compounds prevents the release of free iron, which increases their safety [1].

Thus, iron deficiency is not only a condition that often occurs in the population, but also has a close pathogenetic relationship. Further studies are needed to clarify the role of pathogenic factors in the occurrence of iron deficiency in patients with H. pylori. This interaction requires the development of approaches to the joint therapy of H. pylori and iron deficiency.

The most common (80–95% of all anemias) in therapeutic practice are chronic iron deficiency anemia (IDA) - a painful condition caused by a violation of hemoglobin synthesis due to iron deficiency.

The condition is observed in 10-30% of the adult population, more often in women. Children get sick less often than adults. In ICD-10 it corresponds to the heading -D50 - Iron deficiency anemia.

*Treatment.* Treatment goals: it is necessary to eliminate the cause of IDA (identify the source of bleeding or restore the process of Fe assimilation), replenish the Fe deficiency in the body, prevent the development of dystrophic changes in internal organs and maintain their functional capacity in full.

*Diet.* It is impossible to eliminate IDA only with the help of a diet, since the absorption of Fe from food is no more than 2.5 mg / day, while it is absorbed from drugs 15-20 times more. However, for patients

with IDA, foods containing sufficient amounts of well-absorbed protein and Fe are recommended. Meat products contain Fe, which is part of heme (heme Fe), which is absorbed by 25-30%. Fe (liver, eggs, fish), which is part of hemosiderin and ferritin, is absorbed by 10-15%. Fe, which is a part of plant products (legumes, soy, spinach, dill, lettuce, apricots, prunes, bread, rice), is absorbed by 3 - 5%.
The intake of a large number of apples, pomegranates, buckwheat is unjustified from the point of view of the limited absorption of Fe ions from them.
Blood transfusions are carried out to patients only for health reasons, and the indication is not the level of Hb, but the general condition of the patient and hemodynamics. Most often, they resort to blood transfusions (transfusions of erythrocyte mass) when Hb falls below 40 - 50 g / l.
*Drug therapy for IDA.* It is carried out only with Fe preparations, mainly oral, less often parenteral, for a long time under the control of a detailed blood test. The rate of recovery of red blood counts does not depend on the route of administration.
The main principles of the treatment of iron deficiency anemia with oral Fe preparations include:
• prescribing Fe preparations with a sufficient content of bivalent Fe2 + (200-300 mg / day);
• when using new forms, one should focus on the average therapeutic dose;
• appointment of Fe preparations together with substances that enhance their absorption (ascorbic and succinic acid);
• avoid the simultaneous intake of substances that reduce the absorption of Fe (antacids, tannin, oxalates);
• use preparations that do not contain vitamin components (especially B6, B12);
• convenient dosing regimen: 1 - 2 times / day;
• good bioavailability, absorption, tolerability of Fe preparations;
• sufficient duration of therapy for at least 6-8 weeks until the hemoglobin level normalizes;
• continue taking the half dose for another 4–6 weeks after the hemoglobin level has returned to normal;
• it is advisable to prescribe short monthly courses of therapy (3-5 days) at an average therapeutic dose for women with polymenorrhagias;
The criterion for the effectiveness of treatment with iron preparations is the increase in reticulocytes (reticulocytic crisis) by 3-5 times on the 7-10th day from the start of therapy (with a single control, they are not always recorded).
Fe preparations are divided into: ionic ferro-preparations, which are salt or polysaccharide compounds of Fe2 + and non-ionic compounds, consisting of a hydroxide-polymaltose complex of trivalent Fe3 +.
Fe sulfate, which is part of mono-component and combined ferro-preparations, is well absorbed (up to 10%) and is tolerated by patients. Fe chloride compounds are absorbed worse (up to 4%) and have more undesirable effects: metallic taste in the mouth, darkening of teeth and gums, dyspepsia.
Preparations containing ferrous sulfate: sorbifer-durules (Fe sulfate + ascorbic acid), ferroplex (Fe sulfate + ascorbic acid), tardiferon (Fe sulfate + ascorbic acid), Fenuls (Fe sulfate + ascorbic acid + riboflavin + nicotinamide + pyridoxine + calcium pantothenate), hemofer prolangatum (Fe sulfate), ferrogradumet (Fe sulfate), gynotardiferon (Fe sulfate + folic acid), actiferrin (Fe sulfate + serine), actiferrin compositum (sulfate Fe + folic acid + serine), ferro-foil gamma (Fe sulfate + folic acid + cyanocobalamin)
Other Fe preparations: hemofer (ferric chloride), ferretab (ferrous fumarate),
Iron (III) preparations polymaltose hydroxide - ferrum-lek, maltofer.
Indications for parenteral administration of Fe preparations. In accordance with the Federal Clinical Guidelines, parenteral (intravenous and intramuscular) iron preparations in the treatment of IDA are indicated for:
■ severe form of IDA (at present it is quite rare, in less than 3% of cases);

■ intolerance to oral iron preparations;
■ resistance to treatment with oral iron preparations; ■ the presence of gastric ulcer or duodenal ulcer or gastrointestinal surgery, even in history;
■ anemia associated with chronic inflammatory bowel diseases (ulcerative colitis, Crohn's disease);
■ chronic kidney disease for the treatment and prevention of anemia during the pre-dialysis and dialysis periods;
■ the presence of contraindications to red blood cell transfusion, including for religious reasons (for example, representatives of the Jehovah's Witnesses sect);
■ the need to quickly saturate the body with iron (emergency surgery).
Other indications include: impaired intestinal absorption (bowel resection, malabsorption syndrome), extensive ulcerative surfaces on the gastrointestinal mucosa; treatment with erythropoietins, when the need for Fe increases sharply, but for a short time (2-3 hours after administration of erythropoietin) due to its active consumption.
With parenteral administration, in the case of an incorrectly established diagnosis, the development of hemosiderosis with multiple organ failure is possible.
Fe preparations for parenteral administration. For intramuscular administration, iron III polymaltose hydroxide (ferrum lek, maltofer, ferrompharm) is used. For intravenous administration: iron III in the form of a hydroxide of a sucrose complex (venofer, irondext, irongard, argeferr, velferrum, vialfer), iron III hydroxide dextran (cosmofer), iron III hydroxide polyisomaltosate (monofer), iron carboxymaltose (ferinject).
*B12-deficiency anemia* is caused by a violation of hematopoiesis due to a lack of vitamin B12 in the body. It is more common in old and senile age.
In ICD-10 it corresponds to the heading - D51 - Vitamin-B12-deficiency anemia.
*Treatment of B12-deficiency anemia.* Before starting treatment, it is advisable to confirm the diagnosis with the help of bone marrow punctate examination, which reveals megaloblastic hematopoiesis in the bone marrow and allows excluding myelodysplastic syndromes and hemoblastosis.

In cases where it is impossible to determine the concentration of vitamin B12 and conduct a sternal puncture, prescribe vitamin B12 subcutaneously or intramuscularly daily, one ampoule with any content of vitamin B12 (200 or 500 mcg) for 4-6 weeks. Confirmation of the diagnosis of B12-deficiency anemia in this case is the reticulocytic crisis - a 5-10-fold and even 20-fold increase in the percentage of reticulocytes in the blood test on the 8-10th days from the start of treatment.
Thrombocytopenia and leukopenia are often observed before treatment. Both symptoms disappear with effective treatment.

After a course of treatment and normalization of red blood counts for 2 months, cyanocobalamin is administered weekly in 1 ampoule, and then for life 2 times a month in 1 ampoule (or in courses of 20 injections per year).
After gastrectomy, even with a normal level of hemoglobin and erythrocytes, they begin lifelong therapy with maintenance doses (20 injections, 1 ampoule per year). Ineffectiveness of treatment indicates an incorrect diagnosis, very rarely about the formation of antibodies (AT) to cyanocobalamin.
Transfusion of blood and its components is carried out only for health reasons (with unstable hemodynamics, the threat of anemic coma) in a hospital setting.
The prognosis is favorable. Patients with B12-deficiency anemia are subject to lifelong dispensary observation by a hematologist.
The most natural way to prevent iron deficiency and IDA is to eat iron-rich foods and reduce the intake of iron absorption inhibitors. Increasing dietary iron intake can be achieved by changing dietary habits,

processing and cooking patterns. Educational programs with varying degrees of reliability have shown their effectiveness, but all of them were conducted in economically underdeveloped countries and it is impossible to assess their impact on the development of iron deficiency in countries with a higher level of development.

In connection with all of the above, the most rational recommendations for the prevention of iron deficiency are probably as follows: full-term breastfed babies from 4-6 months should receive 1 mg / kg / day of iron mainly from food, i.e. 2 meals a day should be represented by fortified porridge or meat. If children cannot be provided with at least two iron-rich meals per day, they should receive supplemental iron in the form of a medication.

Timely treatment of B12-deficiency anemia in most cases can completely eliminate the hematological disorder. Already on 4-5 days, you can find changes in the test results, an increase in hemoglobin, the number of erythrocytes is observed on day 7. These indicators are completely normalized after 8 weeks.

Neurological symptoms can go away for quite a long time, up to six months. Spinal cord injuries associated with anemia are irreversible, therefore it is very important to consult a doctor in a timely manner: a hematologist or a therapist.

Increased attention to the prevention of this ailment should be paid to patients who have undergone bariatric surgery, gastrectomy. At risk are vegetarians, people who adhere to strict diets with limited meat and offal, pregnant women and women who have recently given birth. Prevention consists in the use of B12 in the form of tablets or injections, the doctor will select a prophylactic safe dose.

**Conclusion:**

At the end of the research, the following conclusions were drawn:

— Thus, in the modern foreign and domestic literature there is a large number of works devoted to iron deficiency and IDA. However, there is no single point of view on any of the aspects related to this problem, which is reflected in the extremely cautious conclusions of the Cochrane Review.

— Despite the fact that the presence of the influence of IDA on the physical and neuropsychic development of children can be considered proven, the question of whether the deficiency, the severity and duration of what extent can cause negative effects remains unstudied.

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— Based on the results of a study of literature, it can be concluded that most of the recommendations for the management of children with IDA and iron deficiency were mechanically transferred from foreign sources without assessing the real situation in Uzbekistan. The problem of integrating the existing theoretical knowledge on the diagnosis and treatment of IDA into the practical activities of primary health care remains unresolved, which may be due to the underestimation of the severity of the problem by practicing doctors.

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— Usually, intramuscular administration of large doses of vitamin B12 is prescribed for a course of up to 2 months. Then they switch to supportive therapy with a decrease in dosage (its duration depends on the severity of the deficiency and the cause that caused it, in rare cases it can be lifelong). Taking pills is possible if it is established that cobalamin deficiency is caused by its insufficient intake with food, and no other pathological reasons have been identified.

— In severe cases, a blood transfusion is required. A diet enriched with foods high in vitamin B12, folate and iron is also prescribed.

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