MINISTRY OF HIGHER EDUCATION, SCIENCE AND INNOVATIONS OF THE REPUBLIC OF UZBEKISTAN

MINISTRY OF HEALTH OF THE REPUBLIC OF UZBEKISTAN

SAMARKAND STATE MEDICAL UNIVERSITY

DIFFERENTIAL DIAGNOSIS OF DEFICIENCY ANEMIAS

(Monograph)

Akhmedova M.M.

Tashkent -2025

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The monograph is meticulously explores the underlying mechanisms (pathophysiology), outward signs (clinical presentation), identification methods (diagnosis), and treatment approaches (management) associated with primary deficiency anemias and their related disorders. A strong emphasis is placed on iron-deficiency anemia, widely acknowledged as the most frequently encountered type of anemia. The difficulties in accurately diagnosing and pinpointing the underlying causes of this prevalent condition are also scrutinized.

A differential diagnostic approach for hypochromic anemias is thoroughly outlined. Furthermore, the study proposes a structured method for identifying both cyanocobalamin (vitamin B12) deficiency anemia and deficiency Vit. B9 anemia, positioning megaloblastic anemias as a core focus of the discussion.

The crucial importance of prompt diagnosis is emphasized, highlighting the fact that early intervention is key to reversing neurological damage in cases of cyanocobalamin deficiency anemia. The necessity of routine screening for cyanocobalamin insufficiency is also considered.

This monograph is relevant for nephrologists, pediatricians and neonatologists. The materials of the monograph can be used for teaching subjects such as "Hematology", "Pediatrics", "Neonatology", for students of medical universities, as well as for postgraduate residents and clinical residents.

FOREWORD

The monograph is meticulously explores the underlying mechanisms (pathophysiology), outward signs (clinical presentation), identification methods (diagnosis), and treatment approaches (management) associated with primary deficiency anemias and their related disorders. A strong emphasis is placed on iron-deficiency anemia, widely acknowledged as the most frequently encountered type of anemia. The difficulties in accurately diagnosing and pinpointing the underlying causes of this prevalent condition are also scrutinized. A differential diagnostic approach for hypochromic anemias is thoroughly outlined. Furthermore, the study proposes a structured method for identifying both cyanocobalamin (vitamin B12) deficiency anemia and deficiency Vit. B9 anemia, positioning megaloblastic anemias as a core focus of the discussion.

The crucial importance of prompt diagnosis is emphasized, highlighting the fact that early intervention is key to reversing neurological damage in cases of cyanocobalamin deficiency anemia. The necessity of routine screening for cyanocobalamin insufficiency is also considered. The diagnostic steps for normochromic normocytic anemia are presented. The document delves into the specific manifestations of anemia associated with chronic diseases, chronic renal failure, and endocrine disorders. Anemia resulting from bone marrow infiltration (encompassing malignancies, hematological disorders, metabolic disorders, miliary tuberculosis, and sarcoidosis) is specifically highlighted. Hemolytic anemias and their diagnostic characteristics are addressed, with a demonstration of how schistocytosis can manifest in various conditions. A detailed description of the clinical presentation and diagnostic strategies for thrombotic thrombocytopenic purpura (TTP), a life-threatening disorder connected with thrombotic microangiopathies (TMA) and defined by a combination of low platelet counts and microangiopathic hemolytic anemia, is included. Finally, the appendices provide a concise overview of current concerns related to anemia in elderly individuals, liver diseases, and those infected with HIV

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LIST OF ABBREVIATIONS

BP – blood pressure

AIHA – autoimmune hemolytic anemia

ALG – antilymphocyte globulin

ALT – alanine aminotransferase

AST – aspartate aminotransferase

ACHB – anemia of chronic diseases

HIV – human immunodeficiency virus

WHO – World Health Organization

G6PD – glucose-6-phosphate dehydrogenase

GA – hemolytic anemia

HUS – hemolytic uremic syndrome

HC – homocysteine

DIC – disseminated intravascular coagulation

DC – diagnostic value

SA – sideropenic anemia

GIT – gastrointestinal tract

LDH – lactate dehydrogenase

MA – megaloblastic anemia

MAGA – microangiopathic hemolytic anemia

MDS – myelodysplastic syndrome

MMA – methylmalonic acid

NSAIDs – non-steroSAl anti-inflammatory drugs

TIBC – total ferrum-binding capacity of serum

ARF – acute renal failure

PZ – plasma exchange

PNH – paroxysmal nocturnal hemoglobinuria

RTR – soluble transferrin receptors

FFP – fresh frozen plasma

ESR – erythrocyte sedimentation rate

AIDS – acquired immunodeficiency syndrome

CRP – C-reactive protein

TSH – thyroid-stimulating hormone

FGS – fibrogastroscopy

FDA – deficiency Vit. B9 anemia

FCS – fibrocolunoscopy

CRF – chronic renal failure

CHF – chronic heart failure

Hb – hemoglobin

MCH – mean corpuscular hemoglobin content

MCV – mean corpuscular volume erythrocyte

RDW – red blood cell distribution by volume

Introduction

In the CIS nations, and especially in Uzbekistan, sideropenic anemia (SA) continues to be a significant medical and social issue [6]. This issue is significant not only because it is very common but also because it is linked to cellular, organ, and tissue disorders that develop with SA and cause a decline in IQ, frequent morbidity, internal organ dystrophy, and abnormalities in children's physical and sexual development [1, 2, 23]. SA has been shown to be the most prevalent illness. About 2 billion individuals worldwide suffer from ferrum insufficiency (FD), with half of them having SA, the severe type, according to the WHO [14,17].

The latter accounts for roughly 80% of all kinds of anemia [17]. The most susceptible sections of the population with respect to the development of SA are young children (under 3 years of age) and teenagers (mainly girls [7, 19, 20]. It has been demonstrated that the population's socio-domestic, social, and geographic circumstances affect the prevalence of SA. In Uzbekistan, 57% of school-age children, 60% of women of childbearing age, and 80% of pregnant women have SA [1, 3, 5].

Anemia is prevalent and steadily increasing in Central Asian countries, according to UNICEF data on the incidence of SA, particularly in women and children [7, 6, 8, 9]. It is amazing that the most vulnerable risk groups have manifest FD in the form of SA, according to epidemiological research carried out in different parts of Uzbekistan. Simultaneously, SA is very prevalent among risk groups in the Southern Aral Sea region, an area experiencing environment al hardship.

Given that hemoglobin (Hb) content in blood is analyzed as a screening method for ID in all epidemiological studies, allowing for the identification of only manifest (obvious) FD, it can be assumed that a significant portion of the population suffers from latent (hidden) forms of FD, which are not visible to researchers [21, 22, 29]. Consequently, it is evident that the actual frequency of FD is yet unclear[10, 14, 16].

Since the percentage of people with apparent SA exceeds 30% of the population, which corresponds to the critical threshold of disease transmission, we may infer that Uzbekistan is a high-risk location based on data from several studies on the detection of

SA among the population [22]. Given these statistics, immediate action is needed to avoid SA in the general public, particularly in youngsters[12, 13, 16, 27, 29]. It has been determined that up to 40% of young children and one-third of adolescents with SA are diagnosed during puberty[4, 6, 7, 9, 13, 23].

Adolescent females have much more severe "loss" as a result of menarche, and these age groups are known to be marked by an extreme growth rate. They need a lot of ferrum during these stages of life, and their diet doesn't always provide it [3, 4]. The prevalence of SA in young children varies between 8.2 and 39.5%, based on global figures. 33, 34 [3, 4], the frequency of LD ranges from 22.4-41% [2, 7, 8, 9], and in the Russian Federation, it is between 24.7-30%. The prevalence of SA in children in our Republic ranges from 17% to 62%, according to different writers, and it is believed that the Fergana Valley, Karakalpakstan, and Surkhandarya have the highest rates of this illness[10, 22, 25].

The prevalence of SA among school-age children in the Fergana Valley is still quite high (up to 32%) and, regrettably, does not appear to be declining. In terms of SA prevalence, older school-age children, adolescent conscripts, and females who have just begun their menstrual cycle are in a far worse condition. Unbalanced malnutrition, particularly in children and adolescents, who require higher ferrum intake to support growth and development, is the primary cause of SA in the Central Asian area[1, 2, 4, 5, 8, 9].

The health of the populace, particularly children, gradually deteriorates in tandem with unfavorable environmental circumstances. Studies on the impact of anthropogenic environmental elements on the blood system have been published recently by both local and international academics. It has been determined that every pathology has a unique "elemental portrait" that reflects both the involvement of certain components in the etiology of the illness and the condition in which it occurs. The current knowledge of the fundamentals of pathogenic processes is predicated on the identification of cell membrane destruction as the primary factor. Lipid peroxidation (LPO) is one of the processes that causes damage to the cell membrane [1, 4, 5].

Although LPO is now being researched in a number of disorders, including anemia, its role in the etiology of SA remains unclear. LPO-induced alterations in the functional state of erythrocytes have been demonstrated to be a characteristic of children with anemia from ecologically disadvantaged areas. The prognosis of the development of anemic syndrome is shown to be influenced by the indices of erythrocyte viscosity (VE) and erythrocyte peroxide hemolysis (EPH), as well as a rise in LPO activity and a reduction in the antioxidant protection of erythrocyte membranes.

The chronic effects of low doses of radiation [, which constitute a severe health concern to the entire population, and the toxic consequences of industrial contamination of the environment [5, 9] have both contributed to the emergence of a new environment al scenario in recent years. Certain parts of Uzbekistan, including the Tashkent and Surkhandarya regions, as well as parts of Andijan and Fergana have been demonstrated to have adverse endotoxin prevalence. Lead, mercury, cadmium, antimony, and nitrates are considerably more prevalent in the soil and water in these regions.

The frequency of SA in children under 15 has dramatically grown in the Republic of Belarus in recent years as a result of both the effects of low radiation doses and a decline in the socioeconomic level of life of the populace.

Unfavorable environment al variables have been demonstrated to affect healthy cells through the genome and cytoplasmic membrane damage, which can result in either cell death or structural and functional alterations. In light of this, researchers have recently placed a high value on a reduction in the lifespan of circulating erythrocytes, their hemolysis as a result of compositional disorders (impaired deformability), the structure of lipid membranes, and a lack of antioxidant defense enzymes when examining the genesis of SA in children of various ages[1, 2, 4, 5].

The fact that sideropenic anemia is so common and, more importantly, that it causes widespread organ pathology that disrupts the function of nearly every organ and system, resulting in a breakdown in adaptation and a rise in morbidity, makes the issue relevant. This is because ferrum in the body has a variety of functional qualities that guarantee every cell's necessary operation. Specifically, ferrum has been demonstrated to have a role in cellular respiration, oxidative phosphorylation, porphyrin metabolism, collagen formation, granulocyte and lymphocyte function, and the development of the body and nerves.

Since the ferrum concentration in the brain rises yearly for the first 20 years of life and reaches 21.3 mg per 100 g of tissue in the globus pallidum, whereas it only reaches 13–14 mg/100 g in the liver, the organ that stores ferrum, it has been demonstrated that the brain is highly sensitive to SA [24, 25]. Thus, the primary negative impact of SA is on brain function. Accordingly, a study conducted by international authors found that children with SA in their early years had a delayed psychomotor development, and that the more severe the anemia, the more noticeable the delay.

In children with SA, brain damage shows itself as emotional deprivation, a tendency toward negative moods, lethargy in games, impatience, and tearfulness. Children with severe SA lose all interest in their environment and are not even content to talk to their mother. They start talking, walking, and learning how to communicate with others later in life. It has been demonstrated that children with SA exhibit slower reflexes, inactivity, and decreased attention during play. Additionally, their cognitive capacities (memory, attention, and endurance) are significantly weaker than those of healthy children.

In Uzbekistan, Samarkand 102 schoolchildren aged 12 to 14 with SA (Hb = 101-114 g/l) and the same number of healthy children (Hb = 140-145 g/l) participated in a study on mental development using the Sowe Test of Basic Skills. The results showed that the former group solved all problems more slowly (4.08" versus 1.81" in the control group). Students with sideropenia were less able to examine assignments, had a lower vocabulary, and had poorer spelling [3, 7, 19, 28, 29]. youngsters with sickle cell anemia of the same severity, however, performed similarly to healthy youngsters in terms of speed and ability while finishing all tests and answering problems.

Children with SA show signs of exhaustion, weakness, agitation, difficulty focusing, inattention to objects around them, and a diminished enthusiasm for learning. Apathy and insufficient behavioral responses develop [28], social contacts are limited, and low cognitive functions of the central nervous system lead to functional isolation in society [7, 8, 29]. Adolescents with SA have been demonstrated to have a decline in cognitive and learning functions (memory and attention), which has a detrimental impact on academic performance. It is well recognized that a child's intellect and cognitive responses are connected[4, 5, 9, 13, 14, 15]. Children with lower IQs have been more prevalent in recent years [12, 16, 19]. About 15% of children between the ages of 3 and 15 have some kind of mental impairment (IQ), with 30 million of them suffering from significant mental retardation, according to the WHO. A moderate or mild intellectual impairment has been identified in about 80 million youngsters. Along with hypoxia, birth trauma, neuroinfection, hyperbilirubinemia, and social deprivation, dietary deficiencies (proteins, vitamins), as well as crucial microelements like ferrum, play a significant role in the development of intellectual impairment. It has been demonstrated that a lack of youngsters with ferrum has a very detrimental impact on their cognitive development.

The synthesis and metabolism of dopamine, catecholamines, serotonin, myelin, and other chemicals required to sustain the active growth of brain structures and higher functions of the central nervous system are disrupted, and brain hypoxia results against the backdrop of inadequate Fe consumption. As a result, it is thought that the majority of the negative physical effects of FD on children may be permanent in terms of cognitive abilities, which would restrict the capacity of whole generations to actively engage in life.

As a result of a reduction in the body's defenses, sideropenia has been linked to an increase in infectious morbidity, according to extensive clinical and experimental research now underway. Accordingly, studies have found that infants with SA had a higher prevalence of intestinal infections and acute respiratory virus infections [3,4,5,18,19,20]. Intestinal infections were shown to occur much more often (10–12 times). The percentage of children with chronic foci of infection is larger (37.4%) than that of children without FD (12.3% and 19.5%), and the number of often unwell children (23.4%) has increased, according to L.M. Kazakova et al. [3–13 infections, twice as commonly intestinal infections]. Significant dystrophic processes in the basement membrane, a decrease in the amount of melanin and glycogen in epithelial cells, parakeratosis in the oral mucosa, a decrease in saliva production, a decrease in the enzymes in its composition (Plomer-Wilson syndrome), and a decrease in the activity of mitochondrial ferrum-containing enzymes in the intestinal epithelium were found in individuals with SA. Additionally, an inflammatory process and areas of complete mucous membrane atrophy were observed in the stomach, duodenum, and jejunum[6, 7,18, 27]. The gastric acid-forming function, the pancreatic lipase, amylase, and trypsin activity, the development of inflammatory, dystrophic, and atrophic changes in the stomach, duodenum, and hepatobiliary system, and the presence of occult (hidden) bleeding, which was found in 34 to 57.7% of children, have all been shown to significantly decrease with SA. The breakdown and absorption of proteins, lipids, carbohydrates, vitamins, and minerals are thought to be hampered by SA in the gastrointestinal system, which shows up as maldigestion and malabsorption disorders.

The clinical symptoms of dyspepsia, including appetite loss, regurgitation, vomiting after eating, and perversion of taste and appetite (pica chlorotica), which manifests as an addiction to chalk, clay, lime, greens, ice, etc., are thought to be determined by these dystrophic changes in the mucous membranes of the oral cavity and gastrointestinal tract.

The protective barrier is weakened in FD due to dystrophic alterations in the epithelial tissue (skin, gastrointestinal mucosa, and respiratory system) and a reduction in secretory IgA production, which makes bacteria and viruses more prone to these organs [4]. IgE levels in the blood are markedly elevated in FD [6,7,8], indicating that the gastrointestinal mucosa is more permeable to foreign proteins[14]. Children with FD are far more likely to suffer from food allergies and atopic dermatitis [28]. Due to a decrease in ferrum-containing neutrophil enzymes, such as myeloperoxidase, acid phosphatase, cationic proteins, lactoferrin, and bio oxidants, the titer of complement and properdin is significantly reduced in sick children with SA, and the phagocytic and bactericidal activity of leukocytes is depressed. This is one of the factors contributing to the high incidence of sideropenia in children. According to contemporary science, ferrum deficiency-induced hemolysis (SA) is a clinical and hematological illness that manifests in a variety of physiological and pathological situations and is based on a violation of heme synthesis. Numerous factors can contribute to the development of SA in children, even older ones.

We were able to categorize the referenced sources of literature on this topic into the following categories after analyzing them: Increased blood loss from gastrointestinal tract hemorrhages (occult, per diapedes, gastric and duodenal ulcers, Meckel's syndrome, Crohn's disease, etc.), genital hemorrhages (dysmenorrhea), nosebleeds, bleeding from the mouth's mucous membranes, bleeding from teeth (blood diseases), bleeding from worms, and bleeding from parasitic invasions[15, 27]. Of the aforementioned factors, the following are important during adolescence: a rise in the prevalence of chronic gastrointestinal disorders (peptic ulcer, chronic gastritis, gastroduodenitis, and colitis) as a result of diet noncompliance; a rise in the percentage of menstrual cycle disorders in girls [1, 3, 5, 8]; and an increase in the invasiveness of worms in children of this age group (use of chewing gum, "kurtob") as a result of noncompliance with hygiene regulations [7, 8]; b) an imbalance in the body's ferrum intake and absorption due to a discrepancy between the ferrum intake from the diet and its expenditure in the body (intensive growth and development of adolescent children, therapeutic fasting, and intense sports activities).

This set of variables accounts for a large portion of the causes of SA development in older kids. Because of their increasing development and muscular mass, children throughout puberty have a greater demand for ferrum. Additionally, higher blood loss after "menarche" and teenage boys who are passionate about extreme sports are linked to inadequate ferrum consumption in girls. In the latter instance, erythrocyte hemolysis and ferrum deficiency may coexist, exacerbating the severity and extent of SA. Teenagers' ferrum intake is also strongly impacted by their social standing.

The fact that SA is regarded as an alimentary deficiency syndrome globally and that its highest occurrence is seen in low-income households, as well as in homeless and neglected children and adolescents, is not a coincidence. This is because of the misalignment between their nutritional demands and their bodies. However, the addiction of contemporary adolescents to "fast food"—rapid food that disregards their physiological requirements for ferrum—must be noted [3, 8, 9, 29]. Early use of drugs, alcohol, or tobacco can also result in ferrum shortage during this stage of life, since it can reduce the body's ability to absorb ferrum from food [6, 8, 12, 13];

c) Both acquired and inherited malabsorption disorders (such as cystic fibrosis, enteropathy, gastrectomy, jejunectomy, celiac disease, and α1-antitrypsin deficiency). [14]. These include: d) genetic defects of erythrocytes or transferrin (thalassemia, hereditary hypo- and a transferrinemia [25]); d) hormonal changes in conjunction with psychophysiological instability of adolescent children against the backdrop of temporary (transient) depressions of the immune system [10, 28]; d) excessive consumption of coffee, cocoa, tea, and carbonated drinks, which significantly reduce the absorption of ferrum in the gastrointestinal mucosa, which is also important during school age [22]. It should be mentioned that, until recently, little was known about how endocrine glands contribute to the pathophysiology of SA in children, particularly when the disease strikes later in life. In this sense, the immunoregulation of hematopoiesis has garnered more attention in recent years. Data about B-lymphocytes' involvement in hematopoiesis regulation have been gathered [25]. It has been demonstrated that the immunological and hematopoietic systems are closely related, and that cellular and humoral immune components regulate both according to universal principles. Certain lymphokines and a subset of T-lymphocytes are suggested to have a role in regulating the growth of hematopoietic progenitor cells.

These findings closely match the clinical evidence that found a decrease in lymphocytes during children's rapid growth and development, particularly during adolescence, is accompanied by an increase in thymus gland reserves, nasopharyngeal lymphoid tissue, and blood growth hormone levels [11]. As is well known, the latter results in thymus gland enlargement as the adrenal glands' glucocorticoid action declines [18, 27]. Clearly, these characteristics are linked to an increased risk of acute respiratory virus infections, exacerbations of chronic infection foci, and an increase in adolescent anemia symptoms. [21, 23].

Adolescence is also a danger period for immunological and neuroendocrine issues, which seems to make SA worse during this time. The pathogenetic connections between SA in children and growth and development rates, however, are still not well understood in the field of pediatric hematology. Furthermore, the prevalence of chronic diseases of the genitourinary (primary and secondary pyelonephritis, glomerulonephritis, urinary tract infections), digestive (diseases of the stomach, duodenum, liver, and biliary tract), cardiovascular (rheumatic and non-rheumatic arthritis), and endocrine (thyroid hyperplasia, obesity) systems is markedly elevated in senior school age, in addition to the frequent exacerbations of chronic foci of infection. [2, 5]. As is known, anemia occurs in chronic illnesses owing to a long-term increase in the level of proinflammatory cytokines, such as TNF-α, IL-1, 6, 10, γ-interferon, which leads to a disturbance of ferrum metabolism and to the suppression of bone marrow hematopoiesis. At the same time, hepcidin excretion plays a major role in the development of anemia in chronic illnesses. In response to the action of bacterial lipopolysaccharides and IL-6, the liver produces hepcidin, an acute phase protein of inflammation.

ANAEMIA CLASSIFICATION

Anaemia is defined as a drop in the blood's hemoglobin (Hb) concentration relative to the normal level in individuals of a specific age and sex.

World Health Organization criteria for anemia:

Hb < 130 g/l for boys and < 120 g/l for girls.

Anemia can be categorized in a number of ways, one of which is determined by its causes:

1. anemia brought on by blood loss;
2. anemia brought on by the bone marrow's inadequate generation of red blood cells; and

3. anemia brought on by the bone marrow's reduced lifespan of red blood cells with adequate production.

It is common practice in clinical practice to categorize anemias according to the hemoglobin content of the erythrocyte or color index (the latter is presently exclusively used in the CIS):

Anemia that is hypochromic, normochromic,

Anemia that is hyperchromic.

Because blood analyzers are now widely utilized, anemias are grouped according to erythrocyte volume, which mostly overlaps with the prior categorization and is frequently coupled with it:

Three types of microcytic hypochromic, normocytic normochromic, and macrocytic hyperchromic are distinguished.

Anemia is categorized according to severity:

Severe: Hb < 69 g/l; moderate: Hb 89–69 g/l; and mild: Hb 120/110–89 g/l.

FERRUM DEFICIENCY HYPOCHROMIC MICROCYTIC ANEMIA (PART 1)

Hypochromic anemia categories:

1. Anemia due to ferrum deficiency,
2. sideroblastic anemia;
3. anemia linked to decreased porphyrin production or use, including acquired (lead poisoning) and inherited (erythropoietic porphyria); and
4. thalassemia.

Anemias with inadequate red blood cell production are associated with the first three categories, whereas hemolytic anemia, which has a shorter red blood cell life cycle, is associated with the fourth category.

Anemia in chronic diseases (ACD) frequently develops into hypochromic and microcytic conditions with time.

FERRUM DEFICIENCY/ SIDEROPENIC ANEMIA

In Uzbekistan, 63% of school-age children, 55% of women of reproductive age, and 76% of pregnant women have SA. According to UNICEF data, the prevalence of SA in Central Asian nations is significant and steadily rising, particularly in women and children. It is amazing that the most vulnerable risk groups have manifest FD in the form of SA, according to epidemiological research carried out in different parts of Uzbekistan. Simultaneously, SA is very prevalent among risk groups in the Southern Aral Sea region, an area experiencing environment al hardship.

Given that hemoglobin (Hb) analysis in the blood is the screening method used in all epidemiological studies to detect FD, allowing only manifest (obvious) FD to be identified, it can be assumed that a significant portion of the population suffers from latent (hidden) forms of ID, which are not visible to researchers.

FERRUM METABOLISM – The body's total ferrum content is controlled by the duodenum and proximal small intestine's controlled absorption of ferrum, which is linked to the fact that humans lack a mechanism to eliminate excess ferrum. Ferrum absorption from food ranges from less than 1% to more than 50%, depending on the body's ferrum requirements. Transferrin transports ferrum in the blood, and the protein transferrin receptor on the cell membrane then transfers it to the cell.(**Figure 1**)

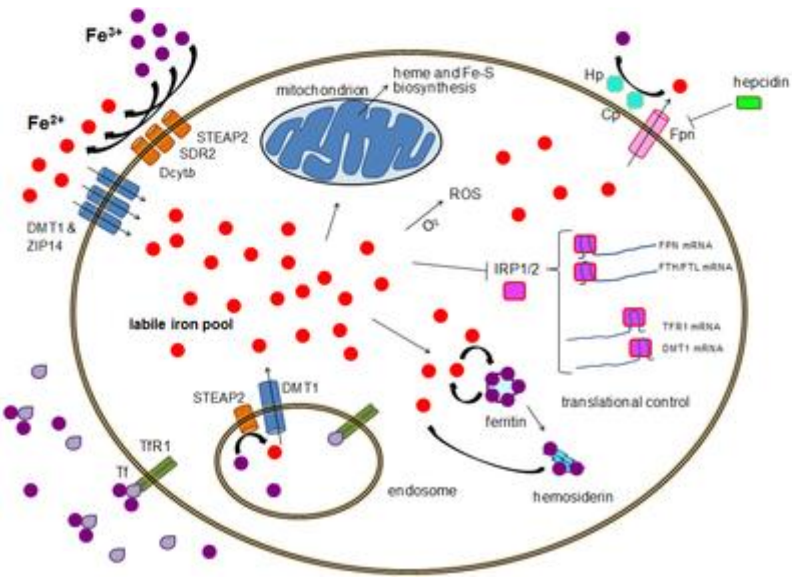


Figure 1

Hemostasin, an insoluble type of ferrum, or ferritin molecules are used to store excess ferrum. Desquamation of the gastrointestinal tract's (GIT) epithelial cells causes physiological ferrum losses in the body. The body's total ferrum concentration is 50 mg/kg for men and 42 mg/kg for women. Men who weigh 80 kg have 4 g of ferrum, while women who weigh 55 kg have 2.3 g.

Data on ferrum intake, its consumption, forms, and distribution in the body are contained in tables 2–4.

Table 2

EXPENDITURE OF FERRUM IN THE HUMAN BODY

Income	**Amount of ferrum**
Absorbed from food	no more than 2 mg per day
Physiological losses	1 mg per day
Lactation	30 mg per month
Pregnancy	700–800 mg
Menses	15–30 mg (30–60 ml of blood)

Table 3 FORMS OF FERRUM CONTAINED IN THE BODY IN CHILDREN

Form	Quantity, mg/kg body weight	
	boys	Girls
Ferritin	9	4
Hemosiderin	4	1
Transferrin	< 1	< 1
Hemoglobin	31	31
Myoglobin	4	4
Respiratory enzymes of cells	2	2

Table 4

FERRUM SPREADING IN THE BODY

Tissue/organ/cells (ferrum form)	**Amount of ferrum, mg**
Bone marrow	300
Macrophages	600
Liver	1000
Plasma (transferrin)	3
Muscles (myoglobin)	300
Circulating red blood cells (hemoglobin)	1800

1.1. FERRUM DEFICIENCY/SA CAUSES

I. LOSS OF BLOOD:

Metrorrhagia, heavy and protracted periods,

Blood loss in the gastrointestinal tract, renal losses (paroxysmal nocturnal hemoglobinuria, urolithiasis), and pulmonary losses (most frequently hemoptysis, but in idiopathic pulmonary hemosiderosis and Goodpasture's syndrome, there may be bleeding into the alveolar basement membrane),

nosebleeds,

Gum bleeding,

Hemodialysis, bloodletting, and donating.

II. INCREASED CONSUMPTION: pregnancy, puberty, lactation.

III. Inadequate ferrum intake from the mother results in congenital ferrum deficiency.

IV. MALABSORPTION:

small intestinal resection, duodenal switch gastrectomy, and celiac disease (gluten illness).

FOOD FERRUM DEFICIENCY (particularly critical for neonates).

Table 5 lists the features of the primary causes of SA as determined by the British Society of Gastroenterologists.

Table 5

MOST COMMONLY IDENTIFIED CAUSES OF SA

Reason	Frequency, %
Non-gastrointestinal bleeding	
Menstruation	20–30
Donation	5
Hematuria	1
Nosebleeds	< 1
Gastrointestinal blood loss	
Blood loss after taking aspirin	10–15
Carcinoma of the colon	5–10
Carcinoma of the stomach	5
Gastric ulcer	5
Angiodysplasia	5
Esophagitis	2–4
Esophageal carcinoma	1–2
Vascular ectasia of the antrum of the stomach	1–2
Tumors of the small intestine	1–2
Hookworm	< 1
Rectal carcinoma	< 1
Malabsorption	
Celiac disease	4–6
Gastrectomy	< 5
Helicobacter pylori	< 5
Bowel resection	< 1
Bacterial overgrowth	< 1

Let's take a closer look at some of the causes of ferrum deficiency.

LOSS OF BLOOD

Ferrum deficiency is caused by blood loss during menstruation that lasts longer than four to five days (more than 60 milliliters of blood) or happens at intervals shorter than twenty-six days. Ferrum loss will surpass dietary intake if monthly blood loss exceeds 60 milliliters. For instance, the monthly ferrum deficiency will be 10 mg, the annual ferrum shortfall will be 120 mg, and the ten-year ferrum shortage will be 1200 mg if 40 mg of ferrum/80 ml of blood is lost during menstruation (with the potential to replace 30 mg each month).

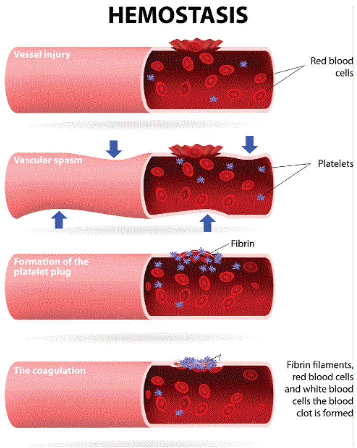


Figure 2.

SYSTEMIC RESPONSE: Beyond the local response designed to stop blood loss, the body also has mechanisms to improve blood flow to the brain in the event that mild to moderate loss does occur. The heart rate will increase as blood return to the heart decreases to ensure the arteries stay as full as possible. The arteries leading to the limbs and intestines will also vasoconstrict to ensure blood is routed to the brain.(**Figure 2.**) A woman's body should have 2310 mg of ferrum if she weighs 55 kg (55 (kg) x 42 (mg/kg)). The body will so lose half of its necessary ferrum reserve during a ten-year period if the amount of blood loss is taken into account. In affluent nations, the primary cause of SA in menopausal women and men is intestinal blood loss. Diverticula, Meckel's diverticulum, esophageal varices, tumors, polyps, ulcers, erosions, hemorrhoids, and hiatal hernias are among the causes of gastrointestinal bleeding, Drug-induced bleeding; diffuse hypertrophy of the gastric mucosa (Menetrier's disease); antrum vascular ectasia (necessary histological confirmation); alcoholic gastritis; angiodysplasia (can occur in any part of the gastrointestinal tract, but most frequently in the cecum or ascending colon); and antrum vascular ectasia. Chronic intestinal bleeding is linked to increased permeability of the small intestine wall; bleeding from aspirin or non-steroSAl anti-inflammatory medicines (NSAIDs) does not necessarily happen when an ulcer is present.

Blood loss during hemodialysis. – Annual blood loss during hemodialysis and blood sampling for testing can reach 2500 ml.

FERRUM MALABORATION

A prolonged resistance to the protein (gluten) of cereal gluten, along with the development of extensive atrophy of the small intestine mucosa and related malabsorption syndrome (malabsorption), are the hallmarks of celiac disease, also known as gluten disease. The atypical type of celiac disease, which has a typical to atypical symptom ratio of 1:2.5, frequently manifests without gastrointestinal symptoms.

The disease's sole symptom might be anemia. In most regions of the world, there is one instance of celiac disease for every 100–300 persons. In Europe, the proportion of celiac disease cases with a diagnosis to those without varies between 1:5 and 1:13. In St. Petersburg, two to five persons are diagnosed with celiac disease every week throughout the year. One patient out of every 184 is found to have celiac disease as a consequence of screening in a cohort of 28,000 adults in European nations.

THE FOLLOWING ARE RISK FACTORS FOR FERRUM DEFICIENCY:

- elevated ferrum intake: teenagers with fast development, pregnant women, and nursing mothers; - medicine intake: aspirin, other NSAIDs (like ibuprofen), and corticosteroids;

Vegetarianism and dieting; strenuous exercise, such as long-distance swimming and running.

Phases of the development of ferrum deficiency:

The ferrum reserve fund is exhausted at STAGE I (prelatent):

reduced serum ferritin levels; normal serum ferrum concentration.

Ferrum deficiency in stage II (latent):

Reduced transport and tissue ferrum:

Tissue ferrum deficiency symptoms include:

• a rise in serum total ferrum-binding capacity (TIBC);

• a reduction in serum ferrum concentration.

Sideropenic anemia, or STAGE III.

1.1. FERRUM DEFICIENCY/SA CLINICAL PICTURE

I. Anemic syndrome: exhaustion, weakness

- palpitations and shortness of breath while exerting oneself;
- lightheadedness and darkening of the eyes when standing up fast and in a crowded space;
- neck and temple pulsations;

headache; a potential deterioration in mental ability, memory loss, and concentration; Pale skin and mucous membranes; a systolic murmur during cardiac auscultation; a "whirring sound" on the jugular vein; and an exacerbation of ischemic heart disease.

II. Syndrome of sideropenia:

- perversion of scent and taste;
- skin: dryness, cracks on the soles and fingers; - mouth: cracks in the corners of the mouth; - tongue: fissures, maybe reddish;
- hair: drab, broken, and maybe falling out;
- teeth: enamel darkens, caries forms, and crumbles; - gastrointestinal tract: dysphagia;
- nails: exfoliation, transverse striation, waviness following manicure, and koilonychia;
- muscles: weakness, difficulty to contain pee while coughing or laughing;
- legs swelling;
- blue sclera;

-subfebrile fever (sometimes).

Restless legs syndrome, which is defined by the urge to move the legs because of discomfort, primarily in the evening and at night, has been linked to sideropenic anemia in certain individuals.

Laboratory test results:

Red blood cell hypochromia (color index < 0.8 or mean corpuscular hemoglobin content (MCH) < 24 pg);

• microcytosis: a reduction in the mean corpuscular volume (MCV) to less than 85 fl femtoliter (10 liters);

• a widening of the dispersion of red blood cells

(RDW) > 16%; thrombocytosis (in individuals with severe blood loss); leukopenia up to 3.0x109 l (sometimes);

• thrombocytopenia, which may happen to adults but is more common in children and teenagers;

• reduced blood ferrum concentration;

• elevated TIBC;

• reticulocytes (the number is typically normal, but may rise during bleeding or at the start of ferrum preparation therapy);

• a higher concentration of zinc protoporphyrin in erythrocytes;

• a decrease in serum ferritin concentration;

• an increase in soluble transferrin receptors (STR), which is crucial for the diagnosis of ferrum deficiency during pregnancy and for the differential diagnosis of anemia in chronic diseases (the test is not widely available in our country);

(the test is not widely accessible in our nation);

• a 15% reduction in the bone marrow's sideroblast count.

SA, or HYPOCHROMIC MICROCYTIC ANEMIA, is typified by elevated TIBC, reduced serum ferritin content, and decreased serum ferrum concentration.

PREGNANT WOMEN'S FERRUM DEFICIENCY

WHO standards for pregnancy-related anemia:

Hb < 110 g/l is considered anemia; Hb < 70 g/l is considered severe anemia; and Hb < 40 g/l is considered extremely severe anemia (an emergency situation that carries a risk of congestive heart failure).

The American Centers for Disease Control and Prevention (1998) established the following criteria for anemia in pregnancy:
Hb < 110 g/L, hematocrit <33% in the first trimester, Hb < 105 g/L, hematocrit <32% in the second

• Third trimester: hematocrit <33%, Hb < 110 g/L.

The frequency of SA during pregnancy is 44% in Uzbekistan and 33% in developed countries. Tests for measuring serum ferrum and TIBC also have low sensitivity during pregnancy. Determining soluble transferrin receptors or the concentration of zinc protoporphyrin in erythrocytes can be useful for diagnostics, but these tests are not yet widely available in our country. The first trimester is crucial for detecting anemia and assessing ferrum stores in the body because the ferritin concentration is unreliable in the second and third trimesters—it remains normal even in the presence of signs of ferrum deficiency in the bone marrow.

COMPLICATIONS OF FERRUM DEFICIENCY

Mild iron deficiency anemia usually doesn't cause complications. However, left untreated, iron deficiency anemia can become severe and lead to health problems, including the following:

- **Heart problems.** Iron deficiency anemia may lead to a rapid or irregular heartbeat. Your heart must pump more blood to compensate for the lack of oxygen carried in your blood when you're anemic. This can lead to an enlarged heart or heart failure.
- **Problems during pregnancy.** In pregnant women, severe iron deficiency anemia has been linked to premature births and low birth weight babies. But the condition is preventable in pregnant women who receive iron supplements as part of their prenatal care.
- **Growth problems.** In infants and children, severe iron deficiency can lead to anemia as well as delayed growth and development. Additionally, iron deficiency anemia is associated with an increased susceptibility to infections.

1.1. DIAGNOSIS OF FERRUM DEFICIENCY/SA

FIRST STAGE OF DIAGNOSIS:

identification of risk factors, symptoms, causes of Ferrum deficiency/SA.

I. THOROUGH INTERVIEW OF THE PATIENT

Ask the patient the following questions:

A. How long has the patient had Ferrum deficiency/SA (Ferrum deficiency/SA in early childhood, school, adolescence, and during pregnancy)?

B. Have you identified risk factors or causes of Ferrum deficiency/SA?

Did you eat earth, clay, sand, coal, or chalk as a child or during pregnancy?

4. Did you have nocturnal enuresis as a child (in girls)?

B. Identification of risk factors/causes of Ferrum deficiency/SA:

1. Does your mother have anemia?

If so, what kind?

2. How many children did your mother have?

If not the first, how old are you compared to your older siblings?

3. How many days does your period last?

How severe is it?

How long does it last?

4. How many births have you had? How long does it last?

5. Do your gums bleed when you bite your food or brush your teeth?

How often? How many years?

6. Are you experiencing nosebleeds? How frequently? How many years?

7. Melena, have you ever had "coffee ground" vomiting?

8. Have you ever observed blood in your bowel movements?

9. Do you have black or bloody urine?

10. Have you ever had a bloody cough?

11. Do you donate blood?

1. Have you ever used any nonsteroidal anti-inflammatory medications, such as aspirin?
2. Are you on a diet?
3. Have you undergone a stomach removal? Resection of the stomach?
C. Recognizing Ferrum deficiency/SA symptoms:
1. Is it necessary for you to consume chalk, cereals, uncooked pasta, dough, ash, ashes (from cigarettes or burned paper), or rubber?
2. Do you enjoy odd scents like paint, acetone, gasoline, lime, bleach, dampness, exhaust fumes, and so on?
3. Are the corners of your mouth cracked?
4. Is water necessary when consuming dry food?
5. Do you break or flake your nails?
6. Are you experiencing hair loss?
7. Do you have crumbling or broken teeth?
8. When you cough or laugh, do you hold your pee?

I. **ANALYSIS OF THE SURVEY RESULTS**
(explanation of Ferrum deficiency/SA's cause):
1. Having three or more older siblings and/or having an age gap of fewer than three years with the elder sibling.
2. Determining the cause of blood loss (responses to II.1–9):
2.1. periods that are heavy and frequent (> 4–5 days; > 60 ml of blood) or that occur less frequently than 26 days;
2.2. childbirth: four or more births or less than three years between births;
2.3. nosebleeds (the length of time must be considered);
Gum bleeding (2.4); vomiting "coffee grounds," melena (2.5);
2.6. blood in the stool, hemorrhoids;
2.7. urine that is crimson or black;
Hemoptysis (2.8); donation (frequency and length of blood donation); 2.10 Hemodialysis.

3. Using medications that reduce inflammation.

1. A lack of Ferrum in food (vegetarianism, diet).

2. Gastrectomy, or stomach removal.

I. Identifying Ferrum Deficiency in the Lab.

The following laboratory tests are used to diagnose Ferrum deficiency/SA:

1. serum ferritin concentration;

2. TIBC;

3. serum soluble transferrin receptors; and

4. serum Ferrum concentration.

If a patient exhibits anemia together with clinical and/or test indicators of Ferrum deficiency, SA is diagnosed.

It is required to go on to the second step of diagnosis, which is based on the secondary nature of Ferrum deficiency/SA and aims to find and clarify the reason, if the cause of the condition is not disclosed during questioning.

Finding and confirming the etiology of Ferrum deficiency, or SA, is the second stage of diagnosis.

I. COELASIA SCREENING:

all SA patients (evidence level B; see Appendix 4) should be screened.

A small intestine sample performed during fibrogastroduodenoscopy (FGDS) confirms the diagnosis if endomysia antibodies are found or if testing is not feasible.

II. GASTROINTESTINAL TRACT EXAMINATION:

1. Testing is required for girls going through menopause and boys of any age:

• Barium enema or FCS (level A proof). Note: Barium enema is a valid alternative diagnostic procedure (evidence level B), and FCS has an advantage in identifying angiodysplasia and permits a biopsy at any place.

• FGDS (level A evidence).

2. Girls before to menopause:

• FGDS (if symptoms are present).

• FGS (family history, if symptoms are present; two near relatives have been diagnosed with colon cancer, or one relative has had the disease before the age of 45)

(evidence level B).
Note: Because upper and lower gastrointestinal tract pathology frequently coexist, FGS is required if pathology is found by FGDS (apart from cancer and celiac disease).
2. It is advised that patients who experience ongoing Ferrum deficiency after receiving Ferrum preparation therapy and addressing potential causes of the condition (diet, menorrhagia, or donation) have FGDS + FGS.
3. All patients must have a proctologist examination, albeit this may usually wait until FGS.
4. NSAID discontinuation followed by hemoglobin level monitoring. The symptoms of persistent small intestinal inflammation may not usually go away right away after taking this action. Switching to cyclooxygenase-2 inhibitors (nimesulide, meloxicam, and celecoxib) is advised if cancelation is not feasible since this will lessen the adverse effects. Their usage does not, however, totally prevent enteropathy from developing.
5. Small intestine X-rays are rarely performed, with the exception of probable Crohn's disease.
6. To rule out Ancylostoma duodenale invasion, a stool test for helminth eggs is required if the patient has traveled to Central Asia, the Caucasus, or tropical nations.
7. SA can result from Helicobacter pylori colonization, which can interfere with Ferrum absorption. The problem of H. pylori eradication can be settled if FGDS and FCS do not show pathology (level of proof C).
8. The small intestine is examined using capsule endoscopy if the findings of FGDS and FCS are negative.
9. The following research is required if transfusion-dependent SA develops:
• diagnostic laparotomy with intraoperative endoscopy; mesenteric angiography to identify vascular alterations.
Note: Because stool testing for occult blood has limited sensitivity and specificity, it is useless for diagnosing SA.
KIDNEY EXAMINATION:
1. Since 1% of individuals with SA have a urinary tract tumor, a general urine analysis is advised for all patients.

2. If microhematuria is seen in the urine, a renal ultrasound, intravenous urography, and/or computed tomography may be required.
3. Hemostasin analysis of urine.
II. LUNG EXAMINATION:
Lung biopsy to detect idiopathic pulmonary hemosiderosis in particularly challenging cases; Sputum analysis for hemosiderin (or, in the absence of sputum, analysis of bronchial lavage water for hemosiderin) is required when pulmonary symptoms coexist with Ferrum deficiency or when the cause of blood loss is unclear.

1.1. TREATMENT OF FERRUM DEFICIENCY/ SA
First principle: SA cannot be cured by diet!
Principle 2: The cause of SA must be addressed.
I. Reduction of blood loss during menstruation, which can be caused by:
• blood coagulation system pathology (thrombocytopathy, von Willebrand disease), which may be the only symptom of the condition and requires a hemostasiogram and a hematologist consultation for diagnosis;
• gynecological pathology, including tumors, endometrial dysplasia, vaginitis, and endometriosis.
II. Modification of diet.
WHO dietary guidelines from 2001:
• wait one to two hours after meals before consuming tea, coffee, or cocoa;
Improve the absorption of non-heme Ferrum:
• heme Ferrum;
• ascorbic acid (fruits, juices, potatoes, vegetables);
• fermentation (fermentation as a cooking process) of food, sprouting grains lower the amount of phytates, increase the bioavailability of Ferrum;
• incorporate juices, tubers, cabbage, carrots, and cauliflower into your diet;
• eat dairy products in between meals;
• combine foods containing Ferrum absorption inhibitors with products with low Ferrum content (bread, cornflakes with tea or dairy products);

• Phytates (found in cereal bran, grains, legumes, nuts, and seeds);
• foods high in inositol (such as peanut butter, whole grains, milk, yeast, cantaloupe, and citrus fruits);
• phenolic compounds that bind Ferrum (found in tea, coffee, cocoa, some spices (like oregano), red wine, berries, and apples);
• calcium in large amounts (found in milk exceeding one liter per day, dairy products);
• carbonated drinks. The body gets enough Ferrum from a well-chosied vegetarian diet!

Principle 3: The primary treatment method is oral Ferrum preparations. Ferrum(II) sulfate is a classic preparation; a depot form is produced, characterized by a slow release of the preparation. Some preparations contain additives to improve absorption (ascorbic acid, serine, mucoproteose), or vitamin B9for use during pregnancy. II. Cancellation of aspirin, NSAIDs, if possible. III. Surgical treatment of tumors, gastrointestinal polyps, and hemorrhoids. IV. Deworming. V. Eradication of H. pylori with antibiotics and elimination of gluten-containing disease.

Fumarate and gluconate of Ferrum (II) have worse absorption but superior tolerance.

It is advised to take Ferrum (II) salt preparations empty-handed and to wash them down with water or juice. Milk, tea, coffee, chocolate, and cola all hinder the absorption of Ferrum!

Ferrum(III) hydroxide polymaltose complex preparations have recently surfaced; in this instance, Ferrum absorption is independent of food consumption and is characterized by high tolerance.

100–200 milligrams of elemental Ferrum daily is the regimen.

Principle 4: After the hemoglobin level returns to normal, do not immediately discontinue therapy!

Therapy will last for three months until Ferrum stores are restored at half the dosage, or until the hemoglobin level returns to normal.

1. Treatment should be maintained for up to six months if tissue Ferrum deficient symptoms persists.
2. Ferrum, ferritin, and TIBC levels should be checked after three months of maintenance therapy (the ideal ferritin level is at least 50 pg/l).

3. If blood loss is due to menstruation, additional treatment is administered for one week following each menstruation.

Data on the main groups of oral Ferrum preparations are presented in Table 6.

Table 6

FERRUM PREPARATIONS FOR CHILDREN AND FOR PATIENS WITH IRON DEFICIENCY ANEMIA

Supplements	**Preparation**	**Form**	**Dose, mg ferrum**
Ferrum(II) sulfate			
–	Ferrogradumet	pill	105
–	Hemofer prolongatum	pill	105
Ascorbic acid	Sorbifer Durules	pill	100
Ascorbic acid	Ferroplex	tablet	10
Ascorbic acid Vitamin B9(350 mcg)	Ginotardiferon	tablet	80
Vitamin complex	Fenuls	capsule	45
Mucoprotease	Tardiferon	tablet	80
Serine	Aktiferrin	capsule drops syrup	34,5/ caps. 0,53/ drop. 34/5 ml
Vitamin B9(500 mcg) Cyanocobalamin (300 mcg)	Aktiferrin compositum	capsule	34,5/ caps.

Serine			
Vitamin B9(5 mg) Cyanocobalamin	Ferro-folgamma	capsule	37
Ferrum (II) gluconate			
Manganese gluconate Copper gluconate	Totem	ampoule per os	50
–	Ferronal-35	syrup	35/ 5 ml
Ferrum (II) fumarate			
Vitamin B9(500 mcg)	Ferretab	capsule	50
–	Heferol	capsule	100
Polymaltose complex of ferrum (III) hydroxide			
Vitamin B9(350 mcg)	Maltofer-fol	tablet	100
–	Maltofer	tablet drop syrup	100 2,5/drop. 50/ 5 ml
–	Ferrum Lek	tablet syrup	100 50/ 5 ml

Hemosiderosis, hemochromatosis, reduced Ferrum utilization (lead anemia, sideroachrestic anemia), and heightened sensitivity to Ferrum preparations are among the conditions that exclude the use of Ferrum preparations.

Ferrum preparation side effects include diarrhea, constipation, nausea, vomiting, and epigastric discomfort, which is often dose-dependent.

In the event of adverse effects, it is advised to:

1. Take the preparation after eating;
2. Lower the dosage;
3. Change the preparation if p. 1 and p. 2 don't work. The Ferrum preparation's dosage determines any side effects.

Interaction with other medications: Ferrum preparations hinder d-penicillamine and tetracycline absorption.

INDICATIONS FOR PARENTERAL FERRUM PREPARATIONS:

Table 7 lists the characteristics of parenteral Ferrum preparations. Polymaltose and polyisomaltose are isomers, and polymaltose causes fewer side effects, including anaphylactic ones. Other factors that affect Ferrum absorption include: celiac disease, extensive small intestine resection, gastrectomy with exclusion of the duodenum, intolerance to oral medications, acute duodenal ulcers, uncontrollable vomiting in pregnant women, and swallowing disorders.

Table 7 PARENTERAL USE OF FERRUM PREPARATIONS

Preparation	**Chemical name**	**Form/ content**	**correct use of medicine**
Ferrum-Lek	Polyisomaltose complex of ferrum hydroxide III (ferrum dextran) 2 ml	100 mg IM	100–200 mg per day

Preparation	Chemical name	Form/ content	correct use of medicine
Maltofer	Polymaltose complex of ferrum III hydroxide (Ferrum Dextrin)	2 ml/ 100 mg	i/m 100–200 mg per day
Venofer	Ferrum hydroxide sucrose complex III (Ferrum sugar)	5 мл/ 100 мг	i/v 100–200 mg 2–3 per a week

Dose of parenteral Ferrum preparations: calculated using the formula (for patient body weight >35 kg):

Mx(150-Hb)x0.24+500

A =

100

where A is the number of ampoules, M is the patient's body weight, Hb is the patient's hemoglobin.

Example: a patient with a body weight of 60 kg and hemoglobin of 80 g/l will need 15 ampoules:

60x(150-80)x0.24+500

A = = 15.08

100

The dependence of the dose of intravenous Ferrum preparations on the patient's body weight and hemoglobin level is shown in Table 8.

Table 8 INTRAVENOUS USE OF FERRUM PREPARATIONS

Body weight, kg	Total number of ampoules			
	Hb–60 g/l	Hb–75 g/l	Hb–90 g/l	Hb–105 g/l
30	9,5	8,5	7,5	6,5

35	12,5	11,5	10,0	9,0
40	13,5	12,0	11,0	9,5
45	15,0	13,0	11,5	10,0
50	16,0	14,0	12,0	10,5

Body weight, kg	Total number of ampoules			
	Hb–60 g/l	Hb–75 g/l	Hb–60 g/l	Hb–105 g/l
55	17,0	15,0	13,0	11,0
60	18,0	16,0	13,5	11,5
65	19,0	16,5	14,5	12,0
70	20,0	17,5	15,0	12,5
75	21,0	18,5	16,0	13,0
80	22,5	19,5	16,5	13,5
85	23,5	20,5	17,0	14,0
90	24,5	21,5	18,0	14,5

100 mg of intramuscular Ferrum formulations are given every day. At the initial administration, a test is conducted by administering 1/4 to 1/2 of the dose; if, after 15 minutes, there is no reaction, the full mixture is provided. A single dosage cannot exceed 200 mg. The computed number of ampoules should not be exceeded by the total dosage. Side effects include discomfort, injection site redness, allergic responses, local hemosiderosis that persists if the administration method is done incorrectly, and maybe a risk of developing sarcoma.

Intravenous Ferrum preparations are given by intravenous injection or infusion at a dose of 100–200 mg two–three times per week. At the initial administration, a test is conducted: 1–2.5 ml (20–50 mg) is given; if no adverse effects are observed after 15 minutes, the whole amount is given. Facilities for cardiopulmonary resuscitation must be accessible. For injections, the maximum single dose is 200 mg; for infusions, it is 7 mg/kg, but not more than 500 mg. Convulsions, nausea, hypotension, and, in rare cases, anaphylactic responses are side effects.

INDICATIONS FOR HEMOTRANSFUSIONS:

• Risk of cardiovascular instability (especially if endoscopy is necessary before receiving the effect of treatment with Ferrum preparations).

• Urgent preparation for childbirth, surgery.

RISK GROUP:

If ferritin concentration cannot be determined, the following factors establish the risk group:

• anemia or ferrum deficiency symptoms in anamnesis,

With several pregnancies separated by fewer than three years,

• more than one pregnancy,

• menstruation lasting more than five days or less than twenty-six days,

• birth of the fourth and subsequent child, etc.

Evaluating the effectiveness of therapy It is crucial to properly evaluate the outcomes of SA treatment

ASSESSMENT OF TREATMENT EFFECTIVENESS

Therapy result/research	Duration of therapy
Decreased muscle weakness	48 hours
Reticulocytosis	5th–12th days
Increased hemoglobin, sometimes abrupt	3 weeks
Normalization of hemoglobin levels	5–6 weeks
Ferritin monitoring	2–3 months

Strategies in the event that the therapy has no impact after four to six weeks. It is essential to identify the cause:

1. another hypochromic anemia that was misdiagnosed,
2. inflammation
3. continuous blood loss;
4. poor small intestine absorption of Ferrum; and
5. irregular intake as a result of medication side effects.

A switch to parenteral preparation treatment is recommended in cases of reduced absorption and Ferrum preparation sensitivity. Resuming the search for the cause of blood loss is important if the explanation for the lack of impact is unclear. This includes ruling out pulmonary hemosiderosis, blood loss with urine, blood loss in closed cavities (such as endometriosis or glomical tumors), and blood loss from the small intestine. Antibacterial or anti-inflammatory treatment should be used when inflammation is present.

FERRUM DEFICIENCY PREVENTION is indicated:

2. during pregnancy in the risk category (details in Table 10); 3. regular donors, particularly women (within 2 weeks after blood collection); and 4. for women with severe periods and polymenorrhea (within 7 days after menstruation).

1. DIFFERENTIAL DIAGNOSIS OF HYPOCHROMIC ANEMIA

Figure 1 shows the differential diagnostic algorithm for hypochromic anemia. Anemia in chronic diseases (ACD) and SA may be distinguished, and their combination can be found, by measuring the soluble transferrin receptors and evaluating the blood ferritin levels (Table 11). Table 11 compares the features of sideropenic anemia with anemia in chronic illnesses.

Table 11

DIFFERENTIAL DIAGNOSIS OF SA AND HChA

Biochemically or clinically proven inflammation		
Transferrin saturation < 16%		
Research Diagnosis	Ferritin concentration, ng/ml	Definition of RTR
SA	< 30	< 30
HChA+SA	30–100 RTP/log	ferritin>2
HChA	30–100	RTR/log ferritin<1

HChA	> 100	

Table 12

CHARACTERISTICS OF SA AND HChA

Index	SA	HChA
Serum ferrum concentration	Decreased	Decreased
TIBC	Increased	Norm/Decreased
Serum ferritin concentration	Decreased	Norm/Increased
Transferrin	Increased	Decreased/Norm
Transferrin saturation	Decreased	Decreased
Soluble transferrin receptors	Increased	Norm
PTR/log ferritin ratio	> 2	< 1
Cytokine levels	Normal	Increased

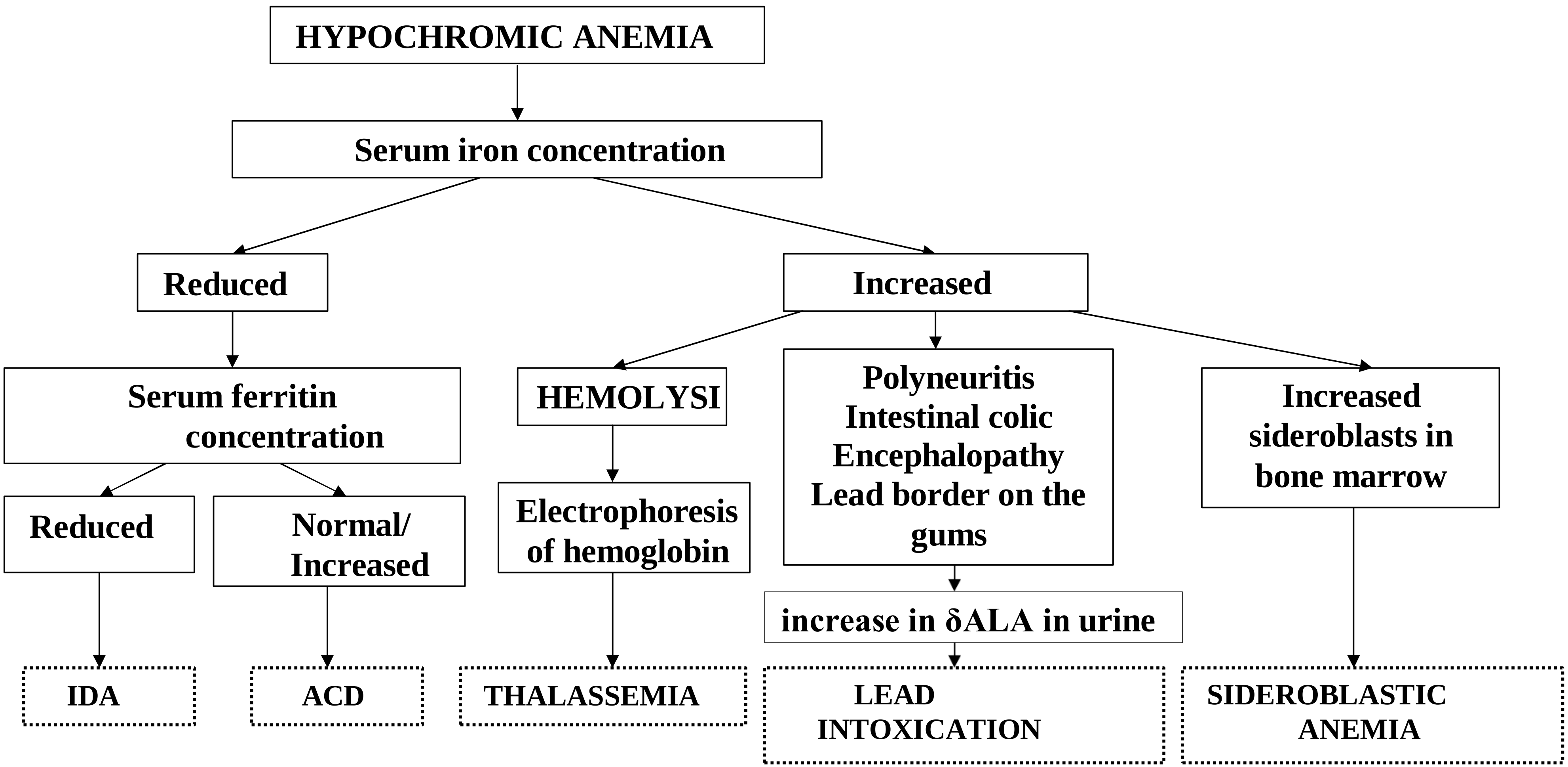


Figure 1. ALGORITHM FOR DIAGNOSTICS OF HYPOCHROMIA

Section II: MACROCYTIC HYPERCHROMIC ANEMIA

There are two types of macrocytic anemia: **megaloblastic** and **non-megaloblastic**.

Liver disorders, heavy alcohol misuse, malignancies, aplastic anemia, myeloproliferative illnesses, and hypothyroidism can all cause non-megaloblastic macrocytic anemia. Megaloblastic cells are a hallmark of MEGALOBLASTIC ANEMIA, a class of macrocytic anemias brought on by compromised DNA synthesis. The two main forms of megaloblastic anemia are deficiency Vit. B9 anemia and cyanocobalamin deficiency anemia.

Megaloblastic anemias also include **drug-induced anemia** (5-fluorouracil, azathioprine, methotrexate, hydroxyurea, anticonvulsants, zidovudine), anemia in **myelodysplastic syndrome** (MDS), and anemia in orotic aciduria. The blood and bone marrow exhibit the same alterations in both forms of anemia.

CYANOCOBALAMIN DEFICIENCY/VITAMIN B12-DEFICIENCY ANEMIA

Twelve to fifteen percent of those over 60 have cyanocobalamin (Vit.B 12) laboratory deficiencies. Research on older people in hospitals found that 30–40% of them had cyanocobalamin insufficiency. Cyanocobalamin levels in the body reach 2–5 mg, which is enough for three to five years after absorption stops. The body needs between 2 and 5 mcg every day.

CYANOCOBALAMIN (cobalamin) ABSORPTION IN THE GASTROINTESTINAL TRACT:

• The stomach:

Intrinsic factor (IF) is produced by parietal cells; free B12 binds to R protein (B12–R–complex); and B12 is released from food under the impact of gastric juice.

• DUODENUM: Pancreatic enzymes cause the B12–R–complex to cleave; free B12 attaches to IF (IF–B12) in an alkaline environment ; and IF carries cobalamin to the terminal ileum.

• TERMINAL ILEUM: The VF-B12 complex attaches itself to certain mucosal cell receptors; cyanocobalamin is taken up by the cell, attaches itself to transcobalamin-II, and enters the bloodstream.

passive diffusion in which VF (1–5% of cyanocobalamin) is not involved.

THE CYANOCOBALAMIN FUNCTIONS Table 13 lists the features of metabolic processes using cyanocobalamin.

Table 13 CYANOCOBALAMIN-DEPENDENT BIOCHEMICAL REACTIONS

Reaction	Homocysteine Methionine	Methylmalonyl coenzyme A Succinyl coenzyme A
Enzyme	Methionine synthetase	Methylmalonyl coenzyme A
Coenzyme	Methylcobalamin	Adenosylcobalamin
Consequence of cyanocobalamin deficiency	Homocysteine accumulation	Accumulation of methylmalonic acid

Along with cyanocobalamin, vitamin B9participates in the first reaction (homocysteine methionine), which transforms into an active form required for DNA synthesis by giving up a methyl group for methionine synthesis. This guarantees the gastrointestinal tract's epithelial cells reproduce and undergo regular hematopoiesis. Erythrocyte death in the bone marrow (ineffective erythropoiesis) and the gastrointestinal tract epithelium due to a disruption of DNA synthesis (induced by a lack of cyanocobalamin and/or Vitamin B9) are the outcomes of the first response violation.

For certain fatty acids that are a component of myelin to normally break down and synthesize, the second reaction (methylmalonyl coenzyme A succinyl coenzyme A) is required.

1.1. The accumulation of methylmalonic acid (MMA) in the body and its harmful effects on nerve cells are the outcome of the second reaction being violated.

VITAMIN B12 DEFICIENCY CAUSES

I. INSUFFICIENT FOOD INTAKE:

1. persistent malnourishment,

2. Strict vegetarianism, which forbids the use of any animal products, such as dairy or eggs.

II. CYANOCOBALAMIN INADEQUATE ABSORPTION:

The inability to release cyanocobalamin from food or intestinal transport proteins, particularly in hypochlorhydria, when the absorption of unbound cobalamin is normal, is the first sign of inadequate absorption of cyanocobalamin from food or intestinal transport proteins2 (ITP or R-protein):

Atrophic gastritis, whether or not H. pylori is present

1.2. prolonged usage of proton pump inhibitors, H2-blockers,

In chronic pancreatitis, cyanocobalamin cannot be released from the R-protein and join the BF due to a lack of pancreatic enzymes.

1.2. gastrectomy;

1.3. Zollinger-Ellison syndrome (cyanocobalamin is not released from the R-protein and does not connect to the IF because to low pH in the duodenum);

2. Lack of an inherent factor

Pernicious anemia (2.1)

2.2. removal of the stomach,

2.3. IF secretion genetic disease;

3. insufficient intestinal absorption:

3.1. removal of the small intestine at the end,

3.2. The illness Crohn's

3.3. lymphoma of the intestinal

3.4. TB,

3.5. Amyloidosis

3.6. Scleroderma

3.7. Disease of Whipple,

3.8. drugs (cholesteramine, colchicine),

3.9. Immerslund-Gräsbeck syndrome, a congenital impairment of the HF cubilin receptor,

CONSUMPTION IN COMPETITIVENESS:

2. "Blind loop" syndrome (growth of cyanocobalamin-destroying microflora):

2.1 Blind pockets are sections of the gut where food cannot flow through following surgery.

2.2. minor intestinal diverticulosis; 3. widespread tapeworm invasion.

II. ADDITIONAL CAUSES:

A metabolic disorder caused by certain substances (nitric oxide used during anesthesia, with prolonged exposure, destroys methylcobalamin, causing acute megaloblastic anemia; the clinical picture develops after 6 hours, pronounced changes in the bone marrow – after 12-24 hours, disappear spontaneously) and 1. impaired transport of cyanocobalamin in the body (congenital deficiency of transcobalamin-II).

The primary cause of cyanocobalamin deficiency is atrophic gastritis. causes of senior cyanocobalamin insufficiency. Table 14 lists the characteristics of cyanocobalamin deficiency in the elderly.

CYANOCOBALAMIN DEFICIENCY IN THE TEENAGERS Table 14

Cause of Cyanocobalamin Deficiency	Frequency, %
Insufficient absorption of cyanocobalamin from food	60–70
Pernicious anemia	15–20
Dietary deficiency	< 5
Insufficient absorption of cyanocobalamin in the intestine	< 5
Hereditary metabolic abnormalities	< 1

The majority of elderly people with cyanocobalamin insufficiency have inadequate vitamin absorption from meals (60–70%), and a sizable portion of these patients have pernicious anemia (15–20%).

A low or nonexistent amount of HF is a characteristic of PERNICIOUS ANEMIA, an autoimmune illness that destroys the stomach mucosa, particularly the fundus.

Typical antibodies to parietal cells (specificity > 90%, sensitivity < 50%) and HF (specificity – 98%, sensitivity – 50%). Moderate to occasionally high hypergastrinemia is seen (specificity < 50%, sensitivity > 80%).

The mucosa does not contain H. pylori in pernicious anemia.

Pernicious anemia accounts for more than 80% of the structure of cyanocobalamin deficiency (up to 20% in older individuals).

Pernicious anemia is associated with autoimmune diseases (autoimmune thyroiditis, vitiligo, primary adrenal insufficiency, diabetes mellitus, Sjogren's syndrome).

Increased risk of developing gastric tumors.

1.2. CYANOCOBALAMIN DEFICIENCY CLINICAL PICTURE

CLINICAL SYMPTOMS OF CYANOCOBALAMIN DEFICIENCY:

I. Hematological symptom clinical manifestations:

1. Anemic syndrome (for further information, see page 9):

When cardiological symptoms become apparent, patients are admitted to the cardiology department.

When anemic coma develops, hemoglobin levels can drop significantly to 30–40 g/l, especially in older patients.

2. jaundice;
3. dark urine;
4. spleen enlargement;

II. The digestive system:

1. Hunter's glossitis (tongue discomfort and burning),
2. appetite loss (often severe weight loss), and
3. stomatitis (rare);

III. Symptoms related to the nervous system:

1. paresthesia
2. impaired proprioceptive sensitivity, vibration sensitivity (leg stiffness, instability),
3. subacute combined degeneration of the spinal cord (funicular myelosis (ataxia, spastic gait)),
4. optic atrophy (rare),
5. fecal and urinary incontinence (rare);

IV. Psychiatric symptoms:

1. instability, personality change,
2. memory loss,
3. dementia,
4. psychosis,
5. depression;

V. Cardiovascular symptoms: the risk of myocardial infarction and stroke may increase. In a significant portion of patients (28–40%), neurological and/or psychiatric symptoms are the only indication of vitamin B deficiency, and damage to the nervous system is irreversible if treatment is not initiated promptly.

LABORATORY SYMPTOMS OF CYANOCOBALAMIN DEFICIENCY:

I. Hematological symptoms include macrocytosis (MCV > 100 fl) and anemia primarily characterized by a reduction in red blood cells.

- hyperchromia (color index > 1.0; MCH > 35 pg);
- thrombocytopenia;
- leukopenia; - reduced or normal reticulocyte count;

II. Peripheral blood smear: Jolly bodies and Cabot rings; hypersegmentation of neutrophils; anisocytosis; poikilocytosis; macroovalocytosis;

Schistocytes, rare fragmented erythrocytes, and erythrocaryocytes.

III. Bone marrow: hypercellularity, nuclear-cytoplasmic asynchrony, and megaloblastosis.

IV. Biochemistry: elevated bilirubin (indirect); elevated LDH (isoenzyme 1), decreased serum cyanocobalamin, elevated serum MMC, elevated serum homocysteine (HC), and decreased holotranscobalamin. Serum cyanocobalamin levels can be determined with high sensitivity (level < 200 pg/ml, which is present in 97% of cases of clinical cyanocobalamin deficiency), but low specificity (Tables 15-16).

Table 15 CONDITIONS AFFECTING CYANOCOBALAMIN LEVELS

False positives (low cyanocobalamin)	False Negative (false normal cyanocobalamin level)
Excessive vitamin C	Intraintestinal excess bacterial proliferation
Progressive multiple myeloma	Lymphoma
Vitamin B9 deficiency	Acute liver diseases
–	Myeloproliferative diseases
Oral contraceptives	Alcoholism

Assessment of MMC and HC levels: – Higher serum MMC and HC levels are a better indicator of cyanocobalamin deficiency than lower levels. The findings of these investigations are particularly significant for diagnosis when the cyanocobalamin level is intermediate, between 200 and 400 pg/ml (Table 16). However, the methods for measuring the MMC and HC levels are costly and not commonly accessible in our nation.

Table 16

DIAGNOSIS OF CYANOCOBALAMIN DEFICIENCY IN NEUROLOGICAL, SYMPTOMATICS

	Cyanocobalamin deficiency	Cyanocobalamin deficiency (if levels normalize with treatment)	No cyanocobalamin deficiency	No deficiency
Cyanocobalamin, pg/ml	< 200	200–400	200–400	> 400
Vitamin B9	norm	norm	norm	norm
MMC			Increased levels of any metabolite	
HC	norm	norm		

Serum holotranscobalamin assay: conflicting information regarding the efficacy of a novel test for the early detection of cyanocobalamin insufficiency. In the absence of a characteristic clinical and hematological picture, megaloblastic anemia (Fig. 2) can be diagnosed by sternal puncture. If a sternal puncture is decided upon, cyanocobalamin medication should be stopped before to the surgery since bone

marrow megaloblastosis can be eliminated with a single injection (vitamin B9and prednisolone have the same effect).
There is currently no "gold standard" test for diagnosing cyanocobalamin deficiency, but in certain patients with normal levels of cyanocobalamin, MMC, and HC in serum, cyanocobalamin therapy can act as an indicator of cyanocobalamin deficiency. It should be noted that neurological and psychiatric symptoms are irreversible if treatment is not received promptly (within a few months of the onset of the disease's first symptoms).

The diagnosis is still made based on the patient's reaction to cyanocobalamin therapy.

1.2. CYANOCOBALAMIN DEFICIENCY DIAGNOSIS

Finding a cyanocobalamin shortage is the first step in the diagnosis process, which serves as the foundation for starting treatment.

1. When clinical symptoms are present, a cytocobalamin level of less than 200 pg/ml provides an adequate basis for diagnosis and treatment.

2. An rise in the level of at least one of the metabolites (MMC or GC) provides the foundation for therapy when the cyanocobalamin level is between 200 and 400 pg/ml; the diagnosis is made when MMC or GC returns to normal following treatment.

1. Clinical symptoms may be regarded as treatment indications if cyanocobalamin, MMC, or HC testing is not feasible or if the test result is normal. Hyperchromic macrocytic anemia with reticulocytopenia and dysmyelopoiesis (Jolly bodies, Cabot rings, hypersegmentation of neutrophils, erythrocytes in the blood) is a common clinical and hematological picture. This is particularly true when combined with leukopenia, thrombocytopenia, hyperbilirubinemia, enlarged spleen, paresthesia, and glossitis, which are all hallmarks of cyanocobalamin deficiency anemia.
1.2. Megaloblastic anemia is a type of macrocytic anemia. An anemia is a red blood cell defect that can lead to an undersupply of oxygen.[1] Megaloblastic anemia results from inhibition of DNA synthesis during red blood cell production.[2] When DNA synthesis is impaired, the cell cycle cannot progress from the G2 growth stage to the mitosis (M) stage. This leads to continuing cell growth without division, which presents as macrocytosis. Megaloblastic anemia has a rather slow onset, especially when compared to that of other anemias. The defect in red cell DNA synthesis is most often due to hypovitaminosis, specifically vitamin B12 deficiency or folate deficiency. Loss of micronutrients may also be a cause.
1.3. Damage to the nervous system without the development of anemia (paresthesia, impaired vibration sensitivity, ataxic gait, mental disorders) may be the only manifestation of cyanocobalamin deficiency. The observation of a large number of

megaloblasts in the bone marrow puncture allows us to make a preliminary diagnosis of megaloblastic anemia and start therapy with cyanocobalamin under the control of reticulocytes. The development of a reticulocyte crisis as a result of the treatment provides grounds for the diagnosis of cyanocobalamin deficiency anemia.

Identifying the etiology of cyanocobalamin insufficiency is the second stage of diagnosis.

1. To rule out H. pylori, FGDS is used in conjunction with a mucosal biopsy to detect tumors and atrophic gastritis. 2. The following symptoms may indicate pernicious anemia:

- antibodies to HF and/or stomach parietal cells,

higher amounts of gastrin,

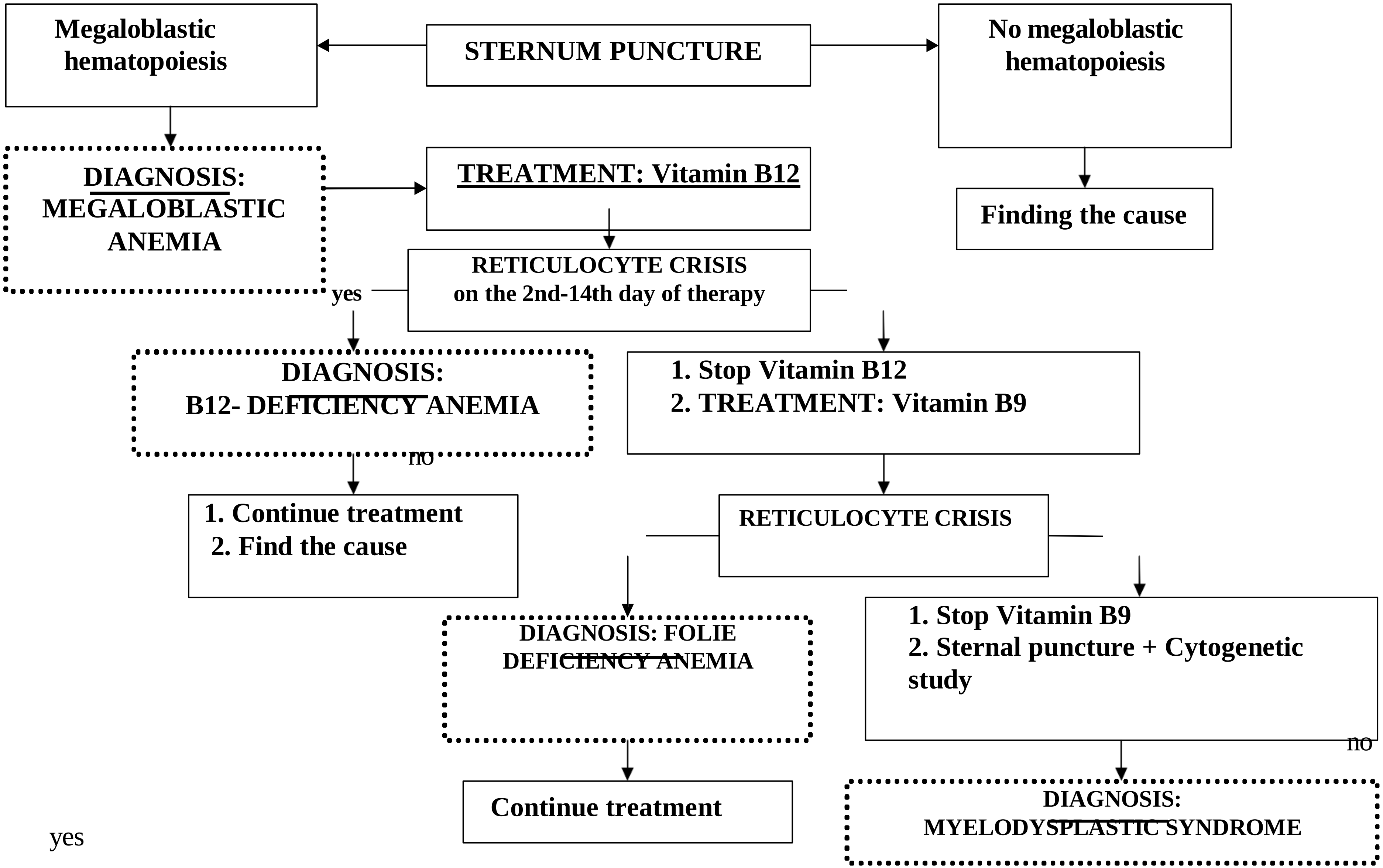

STERNUM PUNCTURE
Megaloblastic hematopoiesis
No megaloblastic hematopoiesis
DIAGNOSIS: MEGALOBLASTIC ANEMIA
TREATMENT: Vitamin B12
Finding the cause
RETICULOCYTE CRISIS on the 2nd-14th day of therapy
yes
DIAGNOSIS: B12- DEFICIENCY ANEMIA
no
1. Stop Vitamin B12
2. TREATMENT: Vitamin B9
1. Continue treatment
2. Find the cause
RETICULOCYTE CRISIS
DIAGNOSIS: FOLIE DEFICIENCY ANEMIA
1. Stop Vitamin B9
2. Sternal puncture + Cytogenetic study
no
Continue treatment
DIAGNOSIS: MYELODYSPLASTIC SYNDROME
yes

Figure 2. ALGORITHM FOR DIAGNOSTICS OF PERNICIOUS ANEMIA

– concurrent autoimmune disease.

2. Since stool testing does not always detect the invasion, it is crucial to determine the fact that strobila (in the form of noodles) has passed in order to diagnose diphyllobothriasis.

3. It is advised to use serial radiography and barium transit in the small intestine to rule out blind loops, interintestinal anastomoses, jejunal diverticulosis, and other small intestine pathologies:

- in the absence of atrophic gastritis; - in patients who have had minor intestinal resection following a full or partial gastrectomy.

4. Finding pancreatic calcification on plain radiography is typically enough to diagnose chronic pancreatic insufficiency; endoscopic retrograde cholangiopancreatography might be helpful in this regard.

5. FCS to rule out cancer.

Differential diagnostics is the third stage of diagnosis. Deficiency in Vitamin B9The clinical picture of cyanocobalamin deficiency is practically indistinguishable from the clinical picture of vitamin B9 deficiency, with the exception of the characteristic nervous system lesion (funicular myelosis) with cyanocobalamin deficiency. In half of the cases, determining the level of cyanocobalamin and vitamin B9can help in diagnostics. If the study does not provide grounds for making a diagnosis, then trial therapy with cyanocobalamin is indicated.

Starting vitamin B9treatment is absolutely prohibited since it may cause signs of nervous system damage to arise or worsen.

This outcome results from Vitamin B9's involvement in the HC to methionine conversion process, which draws cyanocobalamin and increases its deficit in the MMK conversion reaction.

The symptoms of hemolysis, such as jaundice from indirect bilirubin and an enlarged spleen, can indicate hemolytic anemia. Cyanocobalamin deficiency anemia is characterized by the absence of reticulocytosis, but we frequently deal with patients who are referred to a hematologist after being prescribed medications (such as cyanocobalamin, Vitamin B9, or prednisolone) that result in an increase in reticulocytes (even a single injection of cyanocobalamin can cause reticulocytosis) and the loss of megaloblasts.

A small number of megaloblasts are often detected in the myelogram due to vitamin B9 deficiency in hemolysis; determining the level of cyanocobalamin, Vitamin B9, in the serum can facilitate diagnosis, provided that the patient has not started taking these drugs; the Coombs test allows to exclude autoimmune hemolytic anemia; and this greatly complicates the diagnosis, especially in the absence of data on the number of reticulocytes prior to starting to take the listed drugs.

PNH, or paroxysmal night hemoglobinuria In PNH, pancytopenia with hemolysis may occur. PNH is characterized by reticulocytosis in the blood, hemosiderin will be detected in the urine, and intravascular hemolysis, which might show up as dark urine. Hyperchromia and macrocytosis are hallmarks of megaloblastic anemia. In PNH, histological analysis of the bone marrow typically shows a reduction in cellularity. Megaloblastic anemia can be diagnosed by measuring megaloblastic hematopoiesis. A sucrose test, a Hema test, or information gathered from immunophenotyping on the reduction or lack of CD55 and CD59 expression on erythrocytes are used to establish the diagnosis of PNH.

IDIOPATHIC THROMBOTIC THROMBOCYTOPENIC PURPURA (THROMBOTIC THROMBOCYTOPENIC PURPURA (ITTP):

Patients with megaloblastic anemia who also have hyperbilirubinemia, increased LDH, thrombocytopenia, and impaired consciousness (stupor, precoma) may have schistocytes (fragmented erythrocytes) in a blood smear. Megaloblastic anemia is characterized by hyperchromia, macrocytosis, and the absence of hemorrhagic syndrome.

Normally, the myelogram shows megaloblastic hematopoiesis, which eliminates all doubts, though a small number of megaloblasts may also be present in ITTP due to hemolysis.

The signs and symptoms of ITTP may at first be subtle and nonspecific. Many people experience an influenza-like or diarrheal illness before developing ITTP. Neurological symptoms are very common and vary greatly in severity. Frequently reported symptoms include feeling very tired, confusion, and headaches. Seizures and symptoms similar to those of a stroke can also be seen. Other symptoms include, but are not limited to jaundice or paleness of the skin, a fast heart rate or shortness of breath, or dots on the skin known as petechiae. High blood pressure has also been observed as a symptom.

As ITTP progresses, blood clots form within small blood vessels (microvasculature), and platelets (clotting cells) are consumed. As a result, bruising, and rarely bleeding can

occur. The bruising often takes the form of purpura, while the most common site of bleeding, if it occurs, is from the nose or gums. Larger bruises (ecchymoses) may also develop. The classic presentation of ITTP, which occurs in less than 10% of people, includes five medical signs. These are:

- Fever
- Changes in mental status
- Thrombocytopenia
- Reduced kidney function
- Hemolytic anemia (microangiopathic hemolytic **Figure 3.** anemia).

CYANOCOBALAMIN DEFICIENCY TREATMENT PRINCIPLES

1: If a sternal puncture has been planned prior to the procedure, cyanocobalamin therapy should be avoided! PRINCIPLES

2: It is strictly prohibited to begin therapy with Vitamin B9! EMERGENCY THERAPY – Red blood cell transfusions are performed for vital indications. PRINCIPLES
3: The only way to ensure reversibility of neurological and psychiatric symptoms is to treat them promptly. PRINCIPES
4: Cyanocobalamin monotherapy with subsequent evaluation of the effect. BASIC AND MAINTENANCE THERAPY (Tables 17–18) – Therapy is primarily administered with injectable cyanocobalamin preparations (cyanocobalamin and oxycobalamin). Recently, oral, sublingual, and intranasal forms of cyanocobalamin have been used abroad.

Cyanocobalamin treatment regimens are given in Table 17.

Table 17

CYANOCOBALAMIN TREATMENT (IM or SC)

Initial therapy	Support Therapy
Stage 1	
200–500–1000 mcg/day until blood levels are normalized and neurological symptoms disappear –	500 mcg per month 500 mcg in 2 weeks

SIDE EFFECTS OF THERAPY:

1. Deworming for diphyllobothriasis;
2. Surgery to remove anatomical defects (blind pockets, diverticulosis);
3. Drug withdrawal (restoration of cyanocobalamin absorption occurs two weeks after drug withdrawal);
4. Treatment of pancreatitis;
5. Elimination of H. pylori;
6. Antibiotic therapy for "blind loop" syndrome (cephalexin + metronidazole).

Principle 6: If the cause of cyanocobalamin deficiency cannot be corrected, treatment should be lifelong.

MAINTENANCE THERAPY. – In case of an irreparable cause of cyanocobalamin deficiency (atrophic gastritis, condition after gastrectomy, etc.), maintenance therapy is prescribed for life (Tables 17–18).

Table 18 MAINTENANCE THERAPY IN THE TEENAGERS

Form/route of administration of the drug B12	Maintenance dose
IM injection	100–1000 mcg/1–3 months
Oral form	500–2000 mcg/day
Sublingual form	2000 mcg/day
Intranasal form	500 mcg/week

Principle 7: The effectiveness of cyanocobalamin monotherapy must be well evaluated.

ACHIEVEMENT OUTCOMES Analysis of the dynamics of clinical and laboratory symptoms is used to determine how successful a therapy is (Table 19). After one to two days, there is a noticeable improvement in wellbeing.

Table 19

LABORATORY EVALUATION OF THERAPY EFFECT

Laboratory data	Duration of therapy
Reticulocyte crisis	2nd–14th day peak – 5th–8th day
Hemoglobin and erythrocyte growth - 20–30 g/l per week	from 2nd week
Normalization of blood parameters	4–8 weeks

Restoration of MMC, HC and cyanocobalamin levels	3 months

Leukocyte and platelet counts recover quickly (7–10 days), but neutrophil hypersegmentation continues until the 10th–14th day after therapy. Due to an increase in reticulocytes, MCV rises after 3–4 days before falling and returning to normal over 25–78 days.

Clinical symptoms are eliminated. - The irreversibility of neuropsychiatric symptoms that arise from delayed treatment necessitates consideration of the significance of early diagnosis and treatment decisions. Within three to six months, neurological symptoms go away, however gait abnormalities could not completely go away.

EVALUATION OF THERAPY EFFICACY

1. A considerable rise in reticulocytes over days 2–14 of treatment signifies a response to treatment and establishes the diagnosis of cyanocobalamin deficient anemia.

Vitamin B9should be prescribed in place of cyanocobalamin if there is no reticulocyte crisis with good management, which occurs two to three times per week from day two to day fourteen of therapy (see Fig. 2, page 38).

2. The effect of hematological parameters is evaluated one month after the start of treatment, and in some cases after two to three months. A decrease of at least five fold in MCV (with an initial value of more than 98 fl) and an increase in hemoglobin, erythrocyte count, and hematocrit in cases where they initially decreased prior to the start of therapy are indicators of significant improvement.

3. The neurological response is evaluated one to three months, and in some cases after six months from the start of therapy. If the response to therapy is positive, it is important to:

1. clearly document the effect of therapy in the patient's outpatient card,

2. diagnose cyanocobalamin deficiency anemia or neuropathy due to cyanocobalamin

deficiency,

3. In the event that cyanocobalamin deficiency has an irreversible cause, prescribe lifelong maintenance therapy.

PREVENTION OF CYANOCOBALAMIN DEFICIENCY

Patients require preventive therapy in the following situations:

1. following gastrectomy;
2. following "major" small intestine resection; and
3. following strict vegetarianism. Therapy is given in maintenance doses for preventive purposes (refer to Tables 17–18).

When symptoms point to a cyanocobalamin deficit, get tested right away.

I. Patients between the ages of 50 and 65; first testing at age 50:

Test every five years if the cyanocobalamin level is greater than 400 pg/ml; test MMC and GC if the level is between 200 and 400 pg/ml.

200 pg/ml cyanocobalamin level: treat (if symptomatic).

II. Annual screening for patients over 65

III. Every patient in mental health facilities.

2. ANEMIA OF FOLIC DEFICIENCY

Red blood cells with a folate content of less than 102.6 ng/ml or blood serum with a folate content of less than 2.6 ng/ml are considered to be deficient in Vitamin B9.

According to a UK research of 1,562 adults 65 and older, the risk of folate insufficiency in the elderly is 10% between the ages of 65 and 74 and 20% above the age of 75. A considerable percentage of elderly individuals with low folate levels also had low cyanocobalamin levels: around 10% of patients aged 65 to 74 and 20% of patients aged 75 and beyond.

The body needs 150 mcg of vitamin B9per day, which is found in almost all foods, but particularly in fresh fruits and vegetables. It is absorbed in the duodenum and jejunum and is transported in the blood by albumin. The body stores 10–12 mg of Vitamin B9, which is sufficient for four months. In the intestine, vitamin B9is transformed into 5-

methylhydrotetraVitamin B9, which loses its methyl group during the synthesis of methionine. It contributes to DNA synthesis during cyclic metabolism.

2.1. VITAMIN B9 DEFICIENCY CAUSES

I. VITAMIN B9 DEFICIENCY IN DIETS with a particular diet (particularly in elderly and senile individuals, while supplying goat's milk to infants).

II. A GROWTH IN THE NEED FOR VITAMIN B9(in foetuses, hemolysis, exfoliative dermatitis, and during pregnancy and breastfeeding).

III. MALABORTION accompanied by amyloidosis, tropical sprue, Crohn's disease, celiac disease (gluten disease), and occasionally following small intestine resection.

IV. Elevated loss of vitamin B9in patients receiving hemodialysis, heart failure, and active liver disorders.

V. Congenital enzyme deficiencies, or metabolic disorders in cells.

VI. DRUG DEFICIENCY brought on by trimethoprim, oral contraceptives, cytostatics, and anticonvulsants.

VII. ALCOHOLISM (low nutrition combined with decreased vitamin B9metabolism).

2.2. FOLIC DEFICIENCY ANEMIA CLINICAL PICTURE Vitamin B12 or folate deficiency anaemia can cause a wide range of symptoms. These usually develop gradually, but can worsen if the condition goes untreated.

Most symptoms are the same whether they are caused by either folate deficiency or vitamin B12 deficiency.

Symptoms of vitamin B12 and folate deficiency anaemia include:

- rapid breathing or shortness of breath
- headaches
- indigestion
- loss of appetite
- palpitations

- problems with your vision
- feeling weak or tired
- diarrhoea
- a sore or red tongue, sometimes with mouth ulcers
- problems with memory, understanding and judgment (cognitive changes)

Some of these symptoms can also happen in people who have a vitamin B12 or folate deficiency but have not developed anaemia.

Vitamin B12 deficiency can also cause symptoms that affect your brain and nervous system (neurological symptoms), including:

- numbness
- muscle weakness
- psychological problems, which can range from mild depression or anxiety, to confusion and dementia
- problems with balance and coordination
- pins and needles
- incontinence

2.1. FOLIC DEFICIENCY DIAGNOSIS

The FDA's anemia diagnosis procedure is shown in Figure 2 (p. 37). The following forms the basis of the FDA's diagnosis: 1. Megaloblastic anemia accompanied by low serum and/or red blood cell folate levels and normal cyanocobalamin levels.

2. Megaloblastic anemia that improves with vitamin B9treatment.

2.2. FOLIC DEFICIENCY ANEMIA TREATMENT PRINCIPLE:

Verifying that there isn't a cyanocobalamin deficit is crucial before starting FDA medication! Even in cases where vitamin B9absorption is compromised, treatment is carried out with oral drugs (although calcium folinate, often known as leucovorin, is also available as an injectable form). BASIC THERAPY: vitamin B91–15 mg daily for 4 months; EVALUATION OF THERAPY EFFECTIVENESS: reticulocyte crisis occurs 5-8 days after therapy, although fast recovery is seen.

MANAGING THE FOLIC DEFICIENCY CAUSE Anemia:

- dietary adjustment;
-removing gluten from the diet in cases of celiac disease;
- tetracycline therapy for tropical sprue;
- stopping the medication (if at all feasible) to enhance vitamin B9loss.

MAINTENANCE THERAPY is carried out taking into account the underlying disease (0.4-1.0 mg/day).

LIFELONG THERAPY is necessary:

- in congenital hemolytic anemia,
- after resection of the small intestine,
- in subleukemic myelosis,
- in all cases when the cause of vitamin B9 deficiency cannot be established.

PREVENTION of vitamin B9 deficiency is necessary:

– pregnant and lactating women – 0.4 mg/day
– with hemolytic anemia
– with subleukemic myelosis 0.4–1 mg/day
– after small bowel resection
– patients with chronic renal failure on dialysis

Part III. NORMOCYTIC ANEMIA CLASSIFICATION OF NORMOCHROMIC NORMOCYTIC ANEMIA:

1. Anaemias resulting from decreased bone marrow production of red blood cells (hypoproliferative anemias):

1.1. anemias with decreased erythropoietin production:

1.1.1. anemia in chronic renal failure,

1.1.2. anemia in endocrine pathology,

1.1.3. anemia in exhaustion;

1.2. anemias with decreased erythropoietin sensitivity:

1.2.1. anemia in chronic diseases,

1.2.2. anemia in infiltrative processes, anaplastic anaemia,

1.2.4 partial red cell aplasia of bone marrow,

1.2.5. dyserythropoietic anaemias;

Diagnosis of NORMOCHROMIC NORMOCYTIC ANEMIA First Stage of Diagnosis:

- reticulocyte count:
- if reticulocytosis is present, tests are needed to rule out hemolysis (bilirubin, LDH, ultrasound to measure spleen size);
- if hemolysis is not present, blood loss should be ruled out. THIRD STAGE OF DIAGNOSIS:
- if reticulocyte count is normal or reduced, the following tests are required to identify SA, cyanocobalamin-deficiency anemia, FDA, and ACB with atypical laboratory symptoms or with combined genesis: serum ferrum concentration, TIBC, serum ferritin concentration, serum cyanocobalamin level, vitamin B9concentration, serum cyanocobalamin concentration, serum cyanocobalamin concentration, serum cyanocobalamin level, serum cyanocobalamin concentration, serum ferritin concentration, serum cyanocobalamin concentration, serum cyanocobalamin concentration, serum cyanocobalamin-deficiency anemia,

In order to detect or rule out CRF, creatinine analysis is required. Liver tests are conducted in order to detect or rule out liver pathology. Thyroid stimulating hormone (TSH), cortisol, and testosterone should be measured in order to detect or rule out endocrine disorders. The third step comes if the research conducted did not enable a diagnosis to be made. Third-stage diagnostic procedures include trephine biopsy, if required, and external puncture to detect tumor metastases, myelofibrosis, dyserythropoietic anemia, Gaucher disease, aplastic anemia, PKCA, leukemia, multiple myeloma, MDS, and tumor metastases.

ANEMIA DUE TO REDUCTION OF ERYTHROPOIETIN BONE MARROW

ANEMIA WITH REDUCED PRODUCTION OF ERYTHROPOIETIN

ANEMIA IN CHRONIC RENAL FAILURE

Ferrum deficiency during hemodialysis is linked to significant blood loss (annually exceeding 1000 mg of ferrum) during the procedure; frequently occurring uremic thrombocytopathy can cause blood loss in the gastrointestinal tract; contact with dialysis fluid during hemodialysis destroys Vitamin B9; secondary hyperparathyroidism, which develops in CRF, can suppress erythropoiesis.

The clinical picture of anemia in CRF includes the following features: normochromic, normocytic, low reticulocyte count, echinocytes perhaps visible in the blood smear, normocytic bone marrow, and typically normal serum ferrum content (prior to hemodialysis).

ANEMIA DIAGNOSIS IN CRF

Anemia of chronic kidney disease (CKD), also known as anemia of chronic renal disease, is a type of normocytic normochromic anemia and hypoproliferative anemia. This condition is common in patients with renal disease and is associated with poor outcomes and increased mortality risk in CKD. Although it shares many similarities with the chronic inflammation aspects of anemia of CKD, a key distinction is the severe erythropoietin deficiency in anemia of CKD. Consequently, treatment focuses on improving renal function when possible, reducing functional iron deficiency, and increasing red blood cell production. Diagnosis requires a complete blood count with differential, peripheral smear, and tests to rule out other causes of anemia, including B12, folate, haptoglobin, thyroid studies, and iron indices (iron, ferritin, total iron-binding capacity, and transferrin saturation).

Erythropoiesis-stimulating agents (ESAs) and iron supplementation currently constitute the backbone of treatment for anemia of chronic renal disease. Guidelines have evolved significantly since the initial use of ESAs and intravenous iron formulations, and many new therapeutic interventions are currently available or being studied in advanced-phase clinical trials. This activity reviews the evaluation and management of anemia of chronic renal disease. This activity also highlights the role of the interprofessional healthcare team in caring for individuals affected by this condition to achieve optimal patient outcomes.

Anemia combined with elevated creatinine > 0.2 mmol/l and glomerular filtration < 30 ml/min in non-diabetic patients and glomerular filtration < 45 ml/min in diabetic individuals.

1. Chronic renal failure therapy (hemodialysis, kidney transplant);
2. erythropoietin: 80–120 units/kg weekly subcutaneously until the Hb level reaches 110–120 g/l, at which point the dosage is lowered to 50–100 units/kg weekly subcutaneously (since erythropoietin inefficiency can be linked to ferrum deficit, vitamin B9 deficiency, and hyperparathyroidism);
3. Hemodialysis patients are prescribed:
- ferrum preparations (this patient group does not absorb the oral version well). – Vitamin B9; – venofer – 1–3 g (IV) annually while ferritin levels are monitored;

4. If required, blood transfusions are administered. Recombinant erythropoietin includes darbepoietin alpha (Aranesp), erythropoietin alpha (Eprex, Epocrinum), erythropoietin beta (Recormon, Erythrostim), and erythropoietin omega (Epomax).

1.1.1. ENDOCRINE DISEASES AND ANEMIA

Erythropoietin production is modulated by thyroid hormones, androgens, and cortisol, which are produced by the anterior pituitary gland's hormones. Anemia results from a lack of any one of these components. Hypothyroidism, chronic adrenal insufficiency, hypogonadism, and hypopituitarism can all cause anemia. Typically, hemoglobin levels are not less than 80 g/l. Treatment of endocrine pathology-related anemia: sluggish response to medication, successful with replacement therapy. moderate normochromic, normocytic anemia brought on by a toxic excess of parathyroid hormone in the bone marrow in hyperparathyroidism.

1. 2. ANEMIA WITH REDUCED SENSITIVITY TO ERYTHROPOIETIN

1.2.1. ANEMIA IN CHRONIC DISEASES

CHARACTERISTICS OF ACHB. – ACHB is the second most common anemia.

Diseases associated with ACHB

Acute infections include sepsis, pneumonia, septic endocarditis, and peritonitis; chronic infections include osteomyelitis, tuberculosis, lung abscess, and HIV (more on page 78); autoimmune diseases include rheumatoid arthritis, systemic lupus erythematosus, vasculitis, sarcoidosis, Crohn's disease, and nonspecific ulcerative colitis; and tumors.

The causes of ACHB have recently been expanded to include critically sick individuals (those in intensive care) and chronic heart failure (anemia is found in 17% of patients with newly diagnosed CHF and is an independent predictive factor for death).

The pathophysiology of ACHB Cytokines are generated and macrophages are activated when the immune system is stimulated (due to infection, autoantibodies, or tumors). There are several repercussions from these processes.

1. A compromised metabolism of ferrum. Hepcidin, an acute phase protein, prevents the intestines from absorbing ferrum. Additionally, macrophages are absorbing more ferrum, but they are unable to export ferrum, mostly to the bone marrow. This leads to a drop in the serum's ferrum content (which is normal in the body); erythropoiesis requires too little ferrum.
2. Erythrocyte lifetime reduction as a result of macrophage activation.
3. Impaired erythropoiesis: the bone marrow's erythroid precursors' ability to differentiate and proliferate is hindered.
4. Reduced erythropoietin synthesis and erythroid cells' sensitivity to erythropoietin.

CLINIC OF ACHE: Usually, the underlying disease's symptoms outweigh anemia; nevertheless, anemic syndrome may occasionally be the initial sign of the illness (further information is provided on page 9).

It is challenging to determine the primary diagnosis in such a scenario. The laboratory symptoms of ACB include: - normochromia, which is characterized by hypochromia as the process progresses; - normocytic, which is characterized by a long-term process that results in microcytic (in 20–50% of patients, the MCV index is reduced); - Hb, which is 70–110 g/l; - reticulocytopenia; - decreased serum ferrum concentration; - decreased TIBC; - normal or increased ferritin concentration. The following may be identified: leukocytosis with a neutrophilic shift to the left, accelerated ESR, and elevated C-RP.

ACB DIAGNOSIS After ruling out alternative causes of anemia (such as hemolysis, cyanocobalamin or vitamin B9insufficiency, or ferrum deficiency), the diagnosis is predicated on the existence of an anemia-causing illness. Typically, ACB is a normochromic, normocytic anemia that lasts for at least one to two months and is characterized by a normal or elevated serum ferritin content, a reduced TIBC, and a decreased serum ferrum concentration. As the illness progresses, anemia changes into hypochromic microcytic.

DIFFERENTIAL DIAGNOSIS:

An SA differential diagnosis is necessary when the ferrum content in ACB decreases. TIBC and serum ferritin levels enable the differential diagnosis of SA and ACB.

Figure 1 (p. 27) shows the differential diagnostic algorithm.

The treatment of anemia in chronic diseases necessitates ACB treatment for the following reasons:

1. Anemia can be dangerous in and of itself, requiring an increase in cardiac output to maintain systemic oxygenation; 2. When effective treatment of the underlying disease is not possible, an alternative strategy is required, which includes: - intravenous ferrum preparations; - erythropoietin: I regimen: 10 thousand units three times a week subcutaneously; - erythropoietin: I regimen: 30–40 thousand units once a week; - blood transfusions (which can be used as one-time measures, without becoming a means of permanent therapy).

Ferrum preparations were thought to be inappropriate for treating anemia until

recently. The following suggestions about the use of ferrum preparations in ACB were released in 2006 by specialists from the USA and Europe:
- using intravenous ferrum preparations in conjunction with erythropoietin boosts its effectiveness and can speed up or improve the response to erythropoietin; - using intravenous ferrum preparations can lower the amount of erythropoietin needed to provide the desired effect;
Intravenous delivery of ferrum preparations devoid of erythropoietin can occasionally result in notable improvement; nevertheless, it should not be employed in situations of active sepsis.
Because of their limited effectiveness and potential negative effects, oral and intramuscular ferrum treatments should not be utilized in ACB.
Evaluation on the effectiveness of the therapy (four weeks later):
1. Reevaluate ferrum status if the Hb rise is less than 10 g/l.
2. After achieving the maintenance dosage of 120 g/l of Hb,
3. Refractoriness to erythropoietin if, after 8 weeks of treatment, there is no improvement and there is no ferrum deficit.

1.2.1. INFILTRATIVE PROCEDURE CAUSES OF ANEMIA

Anemia is linked to granuloma, fibrosis, or tumor infiltration of the bone marrow (sarcoidosis, military tuberculosis). The most frequent reason is when cancer spreads to the bone marrow. Furthermore, metabolic disorders like Gaucher disease and other lipid accumulation disorders, as well as hematological disorders like leukemia, may be the reason.

CLINICAL PICTURE OF ANEMIA IN BONE MARROW INFILTRATION

I. Anemic syndrome (more information is provided on page 9), II. Infiltrative disease symptoms include ossalgia, pathological bone fractures, and manifestations of hypercalcemia, such as nausea, muscle weakness, and stupor. The characteristics of anemia include:

• mild to moderate anemia;

• the presence of teardrop-shaped erythrocytes;

• the presence of immature leukocytes, erythroblasts (normoblasts), and megakaryocytes, also known as the "leukoerythroblastic blood picture," and

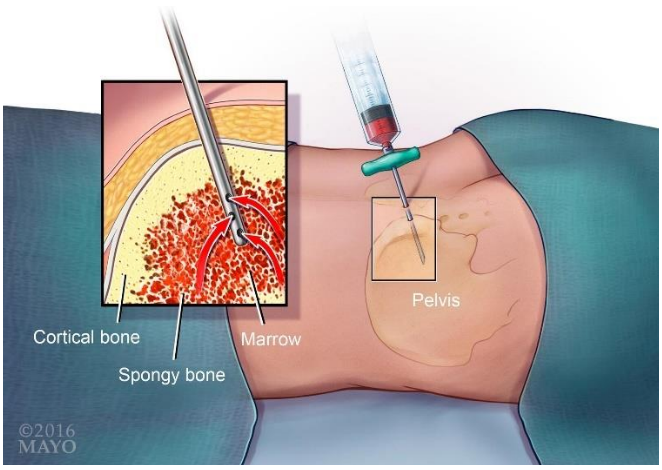
• a low or high leukocyte and platelet count.

DIAGNOSIS OF ANEMIA

IN BONE MARROW INFILTRATION

The following tests can help diagnose aplastic anemia:

- **Blood tests.** Normally, red blood cell, white blood cell and platelet levels stay within certain ranges. In aplastic anemia all three of these blood cell levels are low.
- **Bone marrow biopsy.** A doctor uses a needle to remove a small sample of bone marrow from a large bone in your body, such as your hipbone. The sample is examined under a microscope to rule out other blood-related diseases. In aplastic anemia, bone marrow contains fewer blood cells than normal. Confirming a diagnosis of aplastic anemia requires a bone marrow biopsy.



TREATMENT: The underlying illness must be treated. Erythropoietin treatment can be beneficial in certain situations (10 thousand units three times a week or 40 thousand units subcutaneously each week).

PROGNOSIS Poor if the tumor spreads to the bone marrow. If therapy is effective in treating hematological cancers, hematopoiesis can be fully restored.

Bone marrow exam

In a bone marrow aspiration, a health care provider uses a thin needle to remove a small amount of liquid bone marrow, usually from a spot in the back of your hipbone (pelvis). A bone marrow biopsy is often done at the same time. This second procedure removes a small piece of bone tissue and the enclosed marrow.

1.3. ANEMIA CAUSED BY INSUFFICIENCY IN BONE MARROW

1.3.1. ANEMIA APLASTIC

Bone marrow aplasia and peripheral blood pancytopenia are hallmarks of APLASTIC ANEMIA.

Aplastic anemia occurs in 1-2 incidences per million people annually.
Autoimmune hostility toward hematopoiesis is the basis for pathogenesis.
There are two types of aplastic anemia: acquired (linked to radiation, chemicals (benzene), medications, and viral infections; more frequently, idiopathic); and congenital (Fanconi anemia, etc.).

CLINICAL APLASTIC ANEMIA PICTURE

I. Anemic syndrome (page 9 for further information).
II. Thrombocytopenia-induced hemorrhagic syndrome:

Hematuria, nasal, gingival, uterine, and less frequently, gastrointestinal bleeding; hemorrhages on the skin, mucous membranes, fundus, and sclera.
I. Necrotic angina, pneumonia, sepsis, and other infectious consequences brought on by neutropenia.
Aplastic anemia symptoms in the lab:
reticulocytopenia; granulocytopenia-induced leukopenia; thrombocytopenia; anemia, which is frequently normochromic;

Cellularity is drastically decreased after a sternum puncture, albeit this can be normal if it enters the so-called "hot pocket"; in a bone marrow trephine biopsy, fat cells diffusely fill the bone marrow cavities.
Diagnosis of aplastic anemia: The diagnosis is made solely based on the finding of aplasia in the bone marrow trephine. The diagnosis is deemed reliable if two of the three parameters are present along with bone marrow hypoplasia in the trephine.
DIFFERENTIAL DIAGNOSIS IMMUNE CYTOPENIAS: The diagnosis is made based on normal or increased cellularity in the trephine.

ACUTE LEUKEMIA AND T-CELL LYMPHOMA APLASTIC VARIANTS
Aplastic anemia (AA) is a disease characterized by bone marrow hematopoietic dysfunction and peripheral blood pancytopenia, which is thought to be mediated by an abnormal T cell-induced immune response. T cell receptor (TCR) signaling is pivotal for T cell development and function. An aberrant TCR signaling leads to an unbalanced immune system that can result in a range of immune-related disorders, including autoimmune diseases, chronic infections, and tumors. In this article, we briefly review the T cell immune pathophysiology of AA, the physiology of normal TCR signaling and its regulatory factors, and clinical and laboratory findings of TCR signaling molecules and their regulatory factors in AA.

3. Immunosuppressive therapy (antilymphocyte globulin (ALG): 15–20–40 mg/kg – 5 days) in conjunction with cyclosporine A (5–10 mg/kg for at least a year) and methylprednisolone (during the first month of therapy); the first month of treatment is conducted in a sterile ward. The first treatment option for APLASTIC ANEMIA is bone marrow transplantation, which is performed on patients under 45 with a related donor who is compatible with HLA.

Symptomatic treatment includes platelet mass, blood transfusions, and

- granulocyte colony-stimulating factor; - therapy of infectious problems.

The efficacy of therapy The five-year survival rate is 72% with BMT and around 50% with immunosuppressive treatment.

1.3.1. A portion of the red cell MARROW OF THE BONE APLASIA
RED PARCIAL CELL Erythroid precursors in the bone marrow are either absent or reduced in APLASIA (PRCA), a group of disorders.
PKCA can be acquired (acute, caused by parvovirus B19, and chronic) or congenital (Diamond-Blackfan disease). Both primary and secondary chronic PKCA are possible. Thymoma, tumors, hemoblastoses, collagenoses, etc. can all result in secondary PKCA.
The clinical picture of PKCA includes the following characteristics: anemia: normochromic; Hb < 50 g/l; reticulocytopenia; reduction or absence of red germ in bone marrow; Diagnosis of PKCA: - Diagnosis is based on anemia and isolated reduction of red germ in bone marrow puncture; Treatment of PKCA: - If thymoma is present, surgical removal; immunosuppressive therapy (glucocorticosteroids, cyclosporine, cyclophosphamide, splenectomy), plasmapheresis, and blood transfusions.

Prognosis.
Complete remissions over an extended period of time are seen in primary chronic types. Stunny recovery in parvovirus B19.
1. Anemia due to hemolysis
1.1. OVERALL SPECIALITIES

A shorter lifespan of red blood cells with normal or enhanced bone marrow production is the hallmark of hemolytic anemia. Table 20 lists the characteristics of a few different forms of hematopoiesis.

The primary types of hemolytic anemia are:

I. Congenital or hereditary hematopoiesis:

1. Membrane abnormalities: 1.1. inherited spherocytosis,

Table 20

THE MOST COMMON FORMS OF HEMOLYTIC ANEMIA:

Hereditary (congenital) forms of hemolytic anemia:

Red blood cell membranopathy (erythrocyte structure disorder):

microspherocytic,

ovalocytic,

acanthocytic.

Enzymopenic (fermentopenic) - anemias associated with a deficiency of an enzyme.

associated with a deficiency of pentose phosphate enzymes,

associated with a deficiency of glycolytic enzymes,

associated with a deficiency of enzymes involved in the formation, oxidation and reduction of glutathione,

associated with a deficiency of enzymes involved in the use of ATP,

associated with a deficiency of enzymes involved in the synthesis of porphyrins.

Hemoglobinopathies:

qualitative hemoglobinopathies (sickle cell anemia)

thalassemia (impaired synthesis of one of the polypeptide chains of hemoglobin).

Acquired forms of hemolytic anemia:

Immunohemolytic anemias:

autoimmune,

isoimmune.

Acquired membranopathy:

paroxysmal nocturnal hemoglobinuria,

spur cell anemia.

Associated with mechanical damage to red blood cells:

march hemoglobinuria,

Moszkowitz disease (microangiopathic hemolytic anemia),

occurring with prosthetic heart valves

Toxic.

hemolytic anemias caused by taking medications and hemolytic poisons.

Other hemolytic anemias

hemolytic jaundice of the newborn, in which maternal antibodies destroy the red blood cells of the fetus or child,

idiopathic (approximately 50% of cases of hemolytic anemia),

secondary (for example, in lymphoma, and anemia can be the first manifestation of lymphoma)

1.1, 1.2, and 1.3: Hereditary elliptocytosis, Stomatocytosis, and Acanthocytosis

2. The primary categories of metabolic abnormalities (enzyme faults) are:

2.1. Lack of pyruvate kinase,

2.2. 90% of enzyme deficiencies are caused by a deficit in glucose-6-phosphate dehydrogenase (G6PD).

3. Hemoglobinopathies, or hemoglobin defects:

3.1. Thalassemia

Sickle cell anemia (3.2)

Hemoglobins that are unstable (3.3).

II. Defects in acquired hemoglobin:

1. Hemoglobin deficiencies acquired by the immune system:

1.1. Autoimmune (AIHA):

- paroxysmal cold hemoglobinuria,
- warm hemolysins,
- warm incomplete antibodies,
- cold agglutinins;
- isoimmune (alloimmune):
- hemolytic transfusion responses,
- neonatal hemolytic illness.

2. Acquired HA that is not immune:

2.1. Red blood cell fragmentation syndrome (Table 21),

2.2. PNH,

2.3. infection-related anemia (malaria, babesiosis, clostridium sepsis),

2.4. toxic anemia caused by substances including arsenic, copper, lead, chlorates, and the venom of snakes and spiders,

2.5. Wilson's disease (HA, which affects 15% of patients, may be the initial sign of the illness),

2.6. In liver disorders, spur cell anemia

2.7. hypophosphatemia,

2.8. anemia brought on by radiation or heat burn, and

2.9. hypersplenism.

There are two types of hemolysis:

intravascular and intracellular (extravascular).

Increased indirect bilirubin is a sign of hemolysis.

- elevated fecal stercobilinogen and urine urobilin,
- reduced serum haptoglobin,

A greater quantity of reticulocytes,

- blood normoblasts,
- bone marrow erythroid hyperplasia.

Intravascular hemolysis is selective for hemoglobinuria, hemosiderinuria, methemoglobinemia, and free hemoglobin in the blood.

Blood transfusions that are incompatible with the ABO and Rh antigens, hemolysin AIHA, PNH, hemolytic crises with G6PD deficiency, and cold hemoglobinuria can all result in intravascular hemolysis.

The condition known as microangiopathic hemolytic anemia (MAHA) is characterized by mixed hemolysis, which starts in the vasculature, erythrocyte fragmentation, macrophage capture of the pieces (schistocytes), and intracellular hemolysis.

1.1. Hemolytic anemia clinical picture

The degree of hemolysis determines the clinical picture of HA, which can range from acute, life-threatening situations (AIHA, crisis with G6PD) to compensated illnesses (spherocytosis, heterozygous β-thalassemia) that only show up as hyperbilirubinemia and an enlarged spleen with normal hemoglobin.

I. Anemic syndrome;

II. Syndrome of hemolysis:

- elevated indirect bilirubin (beer-colored, black urine), icterus of the skin, mucous membranes, and sclera,
- elevated levels of stercobilin in the stool and urobilin in the urine,

splenic enlargement (in the majority of intracellular hemolysis instances),

Reticulocytosis,

- elevated levels of lactate dehydrogenase (LDH) - a trait but not a particular indication,

reduced levels of haptoglobin,

In the bone marrow, there are more erythroid cells.

- blood's free hemoglobin (in intravascular hemolysis),

Hemoglobin in the urine causes it to look dark or brown (in intravascular hemolysis),

Urine containing hemosiderin (in intravascular hemolysis).

Certain HA types could present with particular clinical symptoms. Hereditary spherocytosis frequently results in the development of bilirubin stones in the gallbladder. People with sickle cell anemia may develop leg ulcers. PNH may result in mesenteric vascular thrombosis. Autoimmune hemolytic anemia is characterized by elevated body temperature.

1.1. Hemolytic anemia diagnosis

Diagnostic phases when hemolysis is present (anemia with reticulocytosis, hyperbilirubinemia (indirect)).

Initial Diagnosis Stage:

The first step in a comprehensive analysis of the blood smear is to evaluate the morphology of the red blood cells! The question of ruling out MAHA and counting schistocytes (fragmented erythrocytes) must be brought up in every instance of recently discovered hemolysis.

When looking at a smear, schistocytes must be counted and the doctor should be notified right away if schistocytosis is seen.

Findings from the study:

Schistocytes: semi-disk, triangular, tiny, irregularly shaped fragment, with two or three sharp protrusions (helmet-shaped).

- spherocytes (hereditary spherocytosis and AIHA),

Elliptocytes serve as the foundation for the diagnosis of hereditary elliptocytosis (similar alterations may be seen in relatives' blood),

The diagnosis of hereditary stomatocytosis is based on stomatocytes (identical alterations might be seen in relatives' blood), and acanthocytes (congenital and acquired acanthocytosis).

The Coombs test is the second stage of diagnosis.

1. Positive direct reaction: This is the foundation for diagnosing AIHA. When AIHA is combined with cold agglutinins in a test tube, erythrocyte autoagglutination is shown, which goes away when the temperature is raised to 37 °C.
2. The diagnosis of hereditary spherocytosis is based on the presence of spherocytes and a negative Coombs test.

The third diagnosis stage:

1. Infections that induce hemolysis must be ruled out when fever is present, particularly after visiting southern nations:
A thick blood drop and blood smear are examined to rule out malaria, and blood cultures are used to rule out Clostridium Perfringens infection.
2. PNH must be ruled out when intravascular hemolysis and/or pancytopenia are present:
Hem and sucrose tests; immunophenotyping of CD55 and CD59 erythrocytes.
3. Do a blood test for hemolytic toxins if poisoning is suspected.
4. To rule out Wilson's disease, check for ceruloplasmin in blood, copper levels in serum, urine, and liver tissue, as well as the presence of Kayser-Fleischer rings on the cornea when examined under a slit light.

STAGE FOUR OF DIAGNOSIS:

1. after ruling out immune forms of HA and PNH, G6PD deficiency must be ruled out in hemolytic crises involving intravascular hemolysis;
2. hemoglobin electrophoresis aids in the diagnosis of hemoglobinopathies (thalassemia, sickle cell anemia); and
3. other enzymopathies must be ruled out. The nosological form is necessary for the diagnosis.

1.1. Schizocytosis is the presence of small fragments of red blood cells, or degeneratively altered cells of irregular shape.

Causes:

microangiopathic hemolytic anemia;
vasculitis;
glomerulonephritis;
uremia;
hemoglobinopathy;
DIC syndrome;
myelodysplastic syndrome.

Red blood cells (RBCs) start to break down early in hemolytic anemia, which can be chronic or life-threatening. It should be considered while determining if normocytic or macrocytic anemia is present. Hemolysis in the reticuloendothelial system may happen intravascularly, extravascularly, or both. It accounts for a broad spectrum of laboratory and clinical situations, both physiological and pathological. Whenever the frequency of RBC breakdown is rapid enough to lower hemoglobin levels below the normal range, hemolytic anemia occurs. Microangiopathic hemolytic anemia (MAHA) is a term used to describe non-immune hemolysis induced by intravascular RBC fragmentation caused by substances in the tiny blood arteries that generate schistocytes in the peripheral circulation. Microvasculature abnormalities, such as small arterioles and capillaries, are usually involved. Furthermore, MAHA can also be brought on by intravascular devices like a prosthetic heart valve or assistive technologies. Poor deformity results in entrapment, phagocytosis, antibody-mediated elimination through phagocytosis or direct complement activation, fragmentation brought about by microthrombi or acute mechanical stress, oxidation, or spontaneous cellular death. Hemolysis may cause acute anemia, jaundice, hematuria, dyspnea, tiredness, tachycardia, and possibly hypotension. Thrombotic MAHA or thrombotic microangiopathy (TMA) is the term used to describe the co-occurrence of MAHA with thrombocytopenia.

1.2. Thrombotic microangiopathy (TMA) (Thrombocytopenia + Microangiopathic Hemolytic Anemia) Features of the TMA clinical syndrome include:

1. Microangiopathic hemolytic anemia (MAHA);

2.thrombocytopenia:

3. terminal arteriole and capillary microvascular thrombosis;

4.impairment of various organs.

Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (ITTP) are the two main conditions that are included in TMA.

Hemolytic-uremic mode. The condition was initially discovered in children who had thrombocytopenia, acute renal failure (ARF), MAHA, and bloody diarrhea as prodromes. It has been determined that Escherichia coli 0157:H7 is linked to the condition. Adult patients are diagnosed with the condition far less commonly. Although HUS can occur after diarrhea (D+), there is also an unusual variant with a poorer prognosis known as "non-diarrheal" (D-)/idiopathic/sporadic/primary. The combination of TMA and ARF is what defines HUS. The illness can occasionally show up as polyorgan pathology, which includes damage to the liver, heart, and nervous system.

HUS and ITTP have similar clinical signs, and it can be challenging to distinguish between the two, particularly when there is nervous system impairment. According to some specialists, ITTP and HUS are one illness, known as ITTP-HUS (the estimated frequency of ITTP-HUS is 2.2 in Great Britain and 6.5 in the USA per million inhabitants annually).

1.2. Moshkowitz disease, or thrombotic thrombocytopenic purpura

Given the severity of the acute illness, its rapid onset, its extremely aggressive course, and the fact that it will quickly cause death if proper treatment is not received (the mortality rate without prompt, appropriate treatment approaches 100%, while modern therapy cures 70–91%), the doctor must act quickly to diagnose the illness and begin treatment as soon as possible. In this context, we shall examine the characteristics of Moshkowitz illness in depth.

The disease's foundation is the development of platelet thrombi in the capillaries and terminal arterioles, which causes internal organ failure.

Narrowing of the vessel lumen results in the death of red blood cells. The illness mostly affects young people (median age: 16 years old), and it disproportionately affects women.

Table 22

FORMS AND TYPES OF ACQUIRED ITTP (Uzbekistan registry)

Form/Type of ITTP	**Share, %**
Idiopathic ITTP	50,70
Secondary ITTP, including:	49,30
– pregnancy-related	4,25
– autoimmune diseases	20,19
– drug-induced	3,76
– after BMT	8,92
– malignant tumors	4,55
– other types of ITTP	2,35

ITTP'S CLINICAL PICTURE

Moshkowitz disease patients don't have any particular clinical signs. On a backdrop of perfect health, the quickly developing illness appears out of nowhere. The prodrome that frequently manifests is similar to a cold-like, viral illness. A considerable percentage of patients (35%) with ITTP have abdominal syndrome, which is brought on by abdominal ischemia and manifests as severe abdominal pain, nausea, and vomiting. The traditional pentad (frequency: 34–77%) is what defines

ITTP:

1. microangiopathic hemolytic anemia (MAHA);
2. thrombocytopenia (frequently severe);
3. neurological conditions;
4. renal damage;
5. fever.

A detailed description of the elements of the classical ITTP pentad is given in Table 23.

Table 23

CHARACTERISTICS OF THE CLASSICAL ITTP PENTAD

Pentad Element	Characteristic
Thrombocytopenia (often severe)	platelet count < 30x109/l – in most patients (avg. – 18x109/l);
	hemorrhagic syndrome (skin hemorrhages (petechiae), nasal, gingival and, less commonly, gastrointestinal bleeding, menorrhagia, subarachnoid hemorrhage, profuse hemoptysis)
Microangiopathic hemolytic Anemia	decreased hemoglobin (40–80 g/L);
	reticulocytosis;
	schistocytes (fragmented red blood cells) in a blood smear (> 1% of the total number of red blood cells)83; on average, the number of schistocytes in ITTP is 8.35% of the total number of red blood cells (1–18.4%), the norm is 0.05–0.08% (0– 0.27%); during the first two days of ITTP, there may be no increase in the number of schistocytes.
	hyperbilirubinemia (due to the indirect fraction);

	negative direct antiglobulin test (negative Coombs test);
	increased LDH levels (reflects both the degree of hemolysis and tissue ischemia)
Neurological disorders	impaired consciousness up to coma – common
	headache, convulsions
	focal disorders (hemiplegia, visual impairment, aphasia, paresis) – less common
Kidney damage	microhematuria – most common
	proteinuria – most common
	Cylindruria
	increased creatinine – about half of patients
	acute renal failure – less common
	nephrotic syndrome – very rare
Fever	often irregular in shape, very high temperature with severe chills is uncommon

DIAGNOSIS OF ITTP.

Diagnostic dyad:

1. thrombocytopenia;
2. microangiopathic (non-immune) hemolytic anemia.

As long as there are no other clinically proven causes of the illness, the combination of these symptoms is thought to be adequate justification for ITTP diagnosis and prompt treatment beginning. In certain instances, differential diagnosis, which includes sepsis, diffuse connective tissue disorders, malignant arterial hypertension, and catastrophic antiphospholipid syndrome, persists despite the initiation of treatment.

ITTP treatment. The acquired ITTP treatment algorithm is based on the J.N. George-developed treatment plan and takes into consideration the British Society for Haematology's and the British Committee for Standards in Haematology's recommendations. Individual ITTP treatment regimen components are shown by a dotted line.

ITTP'S BASIC THERAPY

Starting therapy during the first 24 hours of the illness is advised; plasma exchange (PE) should be a part of the treatment: Every day, 40–60 ml/kg body weight A patient weighing 60 kg needs between 2400 and 3600 milliliters of plasma each day. Alternatively, if PE cannot be obtained right away, large amounts of cryosupernatant or fresh frozen plasma (FFP) should be infused: Every day, 25–30 ml/kg body weight Although this therapy is often as successful as PE, around 30% of patients require transfer to PE because of fluid overload.

Many treatment plans advise employing glucocorticosteroids and antiplatelet medications in conjunction with PE, making them part of the basic therapy even though their necessity in treating ITTP has not been shown.

Glucocorticosteroids: Some regimens include glucocorticosteroids (prednisolone (1 mg/kg body weight) / methylprednisolone (2 mg/kg body weight IV) or pulse therapy (1 g IV - 3 days) in addition to PZ from the first day of ITTP treatment.

After achieving a full response, hormonal therapy is continued; after that, a gradual dosage reduction is initiated until the treatment is stopped. Antiplatelet drugs (disaggregants): if the platelet count is more than 50x109/l, modest doses of acetylsalicylic acid (75–375 mg/day) are administered, frequently in conjunction with 400 mg/day of dipyridamole. The term "adjustive therapy" Transfusions of red blood cells are administered based on clinical indications. Transfusions of platelets are generally not recommended! can result in the patient's rapid decline and eventual death. They are only carried out when the bleeding is life-threatening. Some researchers believe that vitamin B9should be prescribed to every patient. Patients with renal failure may require hemodialysis.

ASSESSMENT OF RESPONSE TO THERAPY:

Following seven days of treatment, the efficacy of basic therapy is evaluated. The platelet count is the most crucial metric for evaluating the effectiveness of treatment. Reaction to treatment: Restoring LDH levels, normalizing the platelet count (>/= 150x109/l), and removing neurological symptoms The level of hemoglobin is stabilized. PZ should be done every day until a response to treatment is seen, and then for at least two more days after that.

The ideal length of treatment is not determined by any clinical factors. There is usually a very quick exacerbation after stopping plasma replacement therapy, which is indicated by a decrease in platelets and necessitates starting daily plasma replacement therapy again (relapse rates range from 29 to 82%). It is objectively assessed if eachpatient can stop receiving plasma replacement treatment.

THERAPY CONSOLSATING

Following a response, several clinics reduce the frequency of plasma replacement therapy to two or three times per week in order to avoid the patient's condition from worsening. For two to four weeks, consolidation is carried out.

Exacerbation: a rise in thrombocytopenia, the development of additional illness symptoms following a therapeutic response during plasma replacement therapy, and the recurrence of thrombocytopenia within a month of stopping plasma replacement therapy. Treatment must be intensified in cases of exacerbation. After seven days of treatment, persistent thrombocytopenia (< 150x109/l) or increased LDH levels indicate a poor response to basic therapy.

There is no one treatment method for refractory patients. If PZ is not working, cryosupernatant plasma should be used; if the condition is life-threatening, the amount of plasma to be replaced should be doubled; if glucocorticosteroids were not part of the therapy prior to this stage of treatment, they are prescribed after refractoriness has been established; various protocols combine different medications with PZ and glucocorticosteroids.

Treatment options for vincristine include: regimen I: four injections of 1 mg every three days (1st, 4th, 7th, 10th days); regimen II: 0.02 mg/kg (1st, 5th, 9th, 13th days); regimen III: 2 mg once a week103; regimen IV: first course: day 1–2 mg, days 4 and 7–1 mg, and a week later, the second course is performed. Vincristine is used to treat diseases that are not responsive to plasma exchange therapy. After the first week of treatment, or perhaps even two days after the initial vincristine injection, the response is observed.

Cyclophosphamide: In severe instances that are not responsive to PZ, daily dose of cyclophosphamide (1.5 mg/kg body weight) or pulse treatment (1 g/m2) is useful. Cyclosporine A: regimen I: 5 mg/kg body weight; regimen II: 150 mg daily; despite the elevated risk of post-transplant TMA with cyclosporine medication, there is evidence of its efficacy in treating extreme refractoriness. Although the ideal length of therapy has not been established, clinical and hematological response is observed 7–14 days following the initiation of medication administration. Rituximab: In limited series of individuals with severe refractory/recurrent ITTP, rituximab therapy (monthly 375 mg/m2 IV (2–8 doses)) has been observed to be successful.

REMISSION: Symptoms are resolved and PZ is stopped within 30 days. **Treatment of ITTP recurrence:** Relapses usually happen within a year, but cases of disease recurrence up to 10 years after the initial episode have been reported. The relapse rate for patients who have achieved remission is 11%–36%110. Relapse treatment is similar to initial therapy and is generally successful because of accelerated diagnostic workup and timely PZ initiation. Regrettably, some patients suffer from multiple relapses.

Prevention of ITTP recurrence: Although its role in treating ITTP is still up for debate, splenectomy is used to lower the risk of relapse. In addition to PZ, the following medications are used for the second and subsequent relapses: rituximab, azathioprine, and cyclophosphamide (1.5 mg/kg body weight for 6–12 months)112, rituximab.

Treatment of hereditary ITTP: Plasma infusions every two to three weeks without PZ should prevent relapse.

Symptom dynamics throughout therapy. Data on the amount of time needed to eradicate the disease's symptoms (35 ITTP patients, 41 episodes) are provided by C.E.Thompson et al.

• Symptoms related to the nervous system:
The median improvement period is two days (1–7 days).
The median recovery period is three days.
• a 50% reduction in LDH levels during a median of three days (1–20 days);
- median time for normalization: 5 days (2–22 days);
• platelet count increase: – when the platelet count increased to 50x109/l, the median time was 7 days (3–28 days); – when the platelet count increased to 150x109/l, the median time was 10 days (3–32 days);

• Renal function recovery:
The creatinine level decreased significantly over a period of 5 days (2–25 days), and it returned to its baseline/normal level over a period of 15 days (8–36 days). To eradicate the disease's symptoms, 3 to 36 PZ are needed (mean: 15.8). The length of time between the beginning of plasma replacement therapy and the development of the disease's initial symptoms affects survival.

PLASMA EXCHANGE THERAPY'S EFFICACY FOR ITTP:

ITTP linked to pregnancy, acute idiopathic ITTP, and acute immune-mediated drug-induced ITTP (ticlopidine, clopidogrel, quinine-associated) are examples of high plasma exchange efficiency; average plasma exchange efficiency includes
ITTP linked to autoimmune conditions (SLE, APS, Sjogren's disease, rheumatoid arthritis, scleroderma, periarteritis nodosa): PZ is used as a supplement to intensive immunosuppressive therapy; HIV-associated ITTP: PZ is the primary treatment option; patients with ITTP linked to AIDS have a 57% survival rate; highly active antiretroviral therapy is advised, though the prognosis is uncertain with this treatment option;
• Poor plasma exchange efficiency:

ITTP following bone marrow transplantation: since PZ is typically ineffective, immunoadsorption is carried out using columns that contain highly purified staphylococcal protein A; ITTP in oncological diseases: extracorporeal immunoadsorption is also utilized because these conditions are frequently resistant to plasma exchange therapy;

Drug ITTP that is dose-dependent (mitomycin, cyclosporine, tacrolimus, cyclophosphamide): PZ may not be effective; in certain cases of ITTP linked to cyclosporine and tacrolimus, drug withdrawal is enough to induce remission. Potential side effects during plasma exchange include:

- complications related to a central venous catheter (pneumothorax/hemorrhage:

4%; infections: 15%; thrombosis: 10%);

- allergic reactions to plasma administration (4%);

- problems resulting from hardware apheresis (decrease in circulating blood volume, alkalosis); - infections linked to plasma transfusions;

- side effects of citrate toxicity (paresthesia, seizures, or tetany with the emergence of hypocalcemia).

Blood smears having a higher concentration of schistocytes should draw particular attention from laboratory professionals. When looking at the smear, if broken red blood cells are seen, they need to be counted. At least two symptoms must be present in order to make a clinical diagnosis of ITTP (assuming no other causes have been found).

-thrombocytopenia Hemolytic anemia microangiopathic. If a diagnosis of ITTP is suspected, the patient must:

- start medication very once, including plasma exchange (40–60 ml/kg body weight per day) or, at the very least, FFP infusion (up to 30 ml/kg body weight per day);

-see a hematologist right away.

Anemia in children with immunodeficiency. Seventy to ninety percent of AIDS patients with a noticeable clinical presentation have anemia.

Anemia types in immunodeficiency: The most prevalent form of anemia in immunodeficiency infection is ACB. Seldom is autoimmune hemolytic anemia identified. TMA (ITTP and HUS) is more common in immunodeficiency patients than in the general population; it often appears in the latter stages of the illness but can potentially be the major sign of immunodeficiency. Immunodeficiency -related causes of anemia include: One of the primary causes of anemia (22%) in this patient group is medication therapy for immunodeficiency and associated side effects (zidovudine, ganciclovir, amphotericin B, trimethoprim, dapsone, and delaviridine); parvovirus B19 can result in severe chronic anemia in immunodeficiency;

The main treatment for immunodeficiency -associated ITTP is PZ. With significant hematopoiesis depression, infection with Mycobacterium avium, Mycobacterium tuberculosis, and Hystoplasma capsulatum can be assumed. Whether immunodeficiency -associated ITTP is caused by immunodeficiency itself or by cytomegalovirus (in immunodeficiency -associated TMA, CMV infection is 50%), Escherichia coli 0157:H7, and secondary tumors is unknown.

TREATMENT: Antiretroviral therapy, in some cases, erythropoietin is effective.

ANEMIA DUE TO DAMAGE TO INTERNAL ORGANS.

Anemia can range from mild to moderate, or be normocytic, in chronic liver diseases. Liver diseases may also present with mild macrocytic anemia.

Spur cell hemolytic anemia (SCHA), characterized by acanthocytes in the blood, often occurring with thrombocytopenia, may develop in advanced liver disease. Other types of SCHA can occur, including:

transient SCHA with hypertriglyceridemia and fatty liver; transient SCHA with stomatocytosis; SCHA with echinocytes (in malnourished alcoholics with severe hypophosphatemia); and autoimmune SCHA.

In cirrhosis, anemia due to hypersplenism, linked to portal hypertension and secondary splenomegaly, can occur alongside leukopenia and thrombocytopenia.

Anemia can be caused by bleeding from esophageal varices.

Aplastic anemia may result from acute viral hepatitis.

Direct toxic effects of alcohol can lead to suppressed bone marrow function. Alcoholism can also cause sideroblastic anemia and vitamin B9 deficiency.

Anemia in the elderly is linked to reduced survival, increased frailty and need for assistance; increased risk of treatment complications (such as toxicity) from chemotherapy; higher risk of coronary mortality; increased risk of congestive heart failure; and increased risk of dementia.

In older individuals, anemia substantially deteriorates their health and shortens their life expectancy. The hemoglobin level should not be less than 120 g/l while administering cytostatic chemotherapy to individuals who are older than 45. Allowing the hemoglobin level to drop below 100 g/l might result in the patient losing their ability to function independently and necessitating medical attention.

The criteria for anemia were maintained even though the need to update the criteria for anemia in the elderly has been brought up time and time again in support of raising the lower limit of the normal hemoglobin level to 140 g/l for men and 130–135 g/l for women (specifically, the Women's Health and Aging Studies data about the severe consequences of hemoglobin levels below 135 g/l in women over 65: the need for patient care, an increased risk of mortality).

In Uzbekistan, the prevalence of anemia in adults over 15 is 10.2% in girls and 11.0% in boys. Up to the age of 75, anemia is more common in women, and after that, it is more common in males. The chance of getting anemia rises with age (Table 24).

Table 24

FREQUENCY OF ANEMIA DEVELOPMENT IN THE CHILDREN

Gender	Frequency, %	
Age	Boys	Girls
5-10 years	5	8
Over 10 years	12	15

The characteristics of the main causes of anemia and its types in children are given in Table 25.

Table 25

COMMON CAUSES/TYPE OF ANEMIA IN CHILDREN

Cause/Type of anemia	Frequency, %

ACHB	30–45
SA	15–30
Anemia caused by blood loss	5–10
Vitamin B12 and deficiency Vit. B9	5–10
Chronic leukemia or lymphoma	5
MDS	5
Unclear cause	15–25

Anemia Diagnosis in the Children

I.Investigations required:

Anamnesis that focuses on: illnesses linked to anemia; - use of medications (NSAIDs, including aspirin);

2.Physical assessment;

3.Absolute reticulocyte count and complete blood count with platelets;

4. Ferrum assays (concentrations of ferritin and ferrum in the serum, soluble transferrin receptors, and TIBC);

5. Tests for cyanocobalamin deficit (levels of homocysteine, methylmalonic acid, and serum cobalamin);

6.Creatinine

7.Biochemistry of blood;

8.Erythropoietin in serum.

I.Further research:

Tests for inflammation (ESR, C-reactive protein);

1. Serum levels of T4, TSH, and testosterone;

2. Bone marrow puncture, biopsy, and cytogenetics (particularly in cases where MDS is suspected);

4. the amount of vitamin B9in erythrocytes or serum;

5. Helicobacter pylori detection;

6. FCS and FGDS.

ANEMIA TREATMENT IN THE TEENAGERS

Even minor anemia needs to be corrected since teenagers do not handle it well. During periods of active growth, stressful situations and in teenage girls during menstruation, this treatment should be carried out actively. This is particularly true for secondary anemias in kidney, liver, and endocrine organ disease, as well as AChB. When the first symptoms of weakness develop, post-cytostatic anemia in the teenagers should be treated. The primary function of erythropoietin is to treat this kind of anemia.

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