MINISTRY OF PUBLIC HEALTH OF UKRAINE
HIGHER STATE EDUCATIONAL ESTABLISHMENT OF UKRAINE
«UKRAINIAN MEDICAL STOMATOLOGICAL ACADEMY»

V.I. POKHYLKO, S.M. TSVIRENKO, YU.V. LYSANETS

# AGE-RELATED FEATURES AND PATHOLOGY OF BLOOD IN CHILDREN

MANUAL FOR STUDENTS OF HIGHER MEDICAL EDUCATIONAL INSTITUTIONS OF THE III-IV ACCREDITATION LEVELS

Poltava
2017

**МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ**
**ВИЩИЙ ДЕРЖАВНИЙ НАВЧАЛЬНИЙ ЗАКЛАД УКРАЇНИ**
**«УКРАЇНСЬКА МЕДИЧНА СТОМАТОЛОГІЧНА АКАДЕМІЯ»**

**ПОХИЛЬКО В.І., ЦВІРЕНКО С.М., ЛИСАНЕЦЬ Ю.В.**

# ВІКОВІ ОСОБЛИВОСТІ ТА ПАТОЛОГІЯ КРОВІ У ДІТЕЙ

**НАВЧАЛЬНИЙ ПОСІБНИК ДЛЯ СТУДЕНТІВ ВИЩИХ МЕДИЧНИХ НАВЧАЛЬНИХ ЗАКЛАДІВ III-IV РІВНІВ АКРЕДИТАЦІЇ**

**Полтава**
**2017**

UDC: 616+616.15]-053.2(075.8)
BBC: 57.33я73

The manual highlights the issues of embryogenesis, age-related features, semiotics of lesion, examination methods and diseases of hemic system in children.

The manual is intended for students of higher educational institutions of III-IV accreditation levels, and can be used by medical interns and primary care doctors.

**Authors**:

Doctor of Medical Sciences, Professor of the Department of Pediatrics No.1 with Propedeutics and Neonatology **V.I. Pokhylko**

Candidate of Medical Sciences, Acting Head of the Department of Pediatrics No.1 with Propedeutics and Neonatology **S.M. Tsvirenko**

Candidate of Philological Sciences, Senior Lecturer of the Department of Foreign Languages with Latin and Medical Terminology **Yu.V. Lysanets**

**Reviewers**:

**O.S. Yablon' —** Doctor of Medical Sciences, Professor, Head of the Department of Pediatrics No.1, Vinnytsya National M.I. Pirogov Memorial Medical University of Ministry of Public Health of Ukraine.

**M.O. Honchar —** Doctor of Medical Sciences, Professor, Head of the Department of Pediatrics and Neonatology No.1, Kharkiv National Medical University.

## TABLE OF CONTENTS

## LIST OF ABBREVIATIONS

AA − aplastic anemia

ALT − alanine aminotransferase

APPT − activated partial thromboplastin time

AST − aspartate aminotransferase

ATG − antithymocyte globulin

G-CSF − granulocyte colony stimulating factor

ALL − acute lymphoblastic leukemia

AML − acute myeloid leukemia

ARF − acute renal failure

HUS − hemolytic uremic syndrome

DIC − disseminated intravascular coagulation

EBV − Epstein-Barr virus

ECG − electrocardiography

IDA − iron deficiency anemia

IDC − iron deficiency condition

TICS − total iron-binding capacity of serum

SI − serum iron

ITP − idiopathic thrombocytopenic purpura

CI − color indicator

LGM − lymphogranulomatosis (Hodgkin’s disease)

LDH − lactate dehydrogenase

LICS − latent iron-binding capacity of serum

LP − alkaline phosphatase

BW − body weight

SDG − succinate dehydrogenase

CML − chronic myeloid leukemia

CMV − cytomegalovirus

GIT − gastrointestinal tract

## FOREWORD

Blood system is a concept that embraces the blood itself, the organs of hematopoiesis and destruction of blood cells. Blood system in children of different age periods is constantly changing, both in quantitative and qualitative terms.

Blood is the most important integrating system of the human body which provides stability of metabolism, exchange of metabolites and information between cells and tissues, performs plastic and protective functions of the body. The total amount of blood in a newborn in relation to body weight is 15%, in children aged 1 year − 11%, in an adult − an average of 6-8%. Each day, this amount of blood passes through the heart more than 1000 times. However, only 40-45% of blood circulates in the bloodstream, since another part is located in the depot: the capillaries of the liver, the spleen and subcutaneous tissue − and is included into the bloodstream in hyperthermia, muscular work, blood loss, etc. Diseases of the blood system in children are quite common (16.6 cases per 1.000 of newly diagnosed diseases and 43.9 of all diseases). This is due to anatomical and physiological immaturity of the blood organs and their high sensitivity to the unfavorable environment.

Differential diagnosis of blood pathology in children is impeded by significant anatomical and physiological characteristics as compared with adults, especially early in life. In recent years, significant clinical experience has been accumulated, issues of pathogenesis have been explored, new methods have been developed that allow us to diagnose diseases of the blood system more accurately, but it still requires knowledge and data. The present manual is designed for the effective study of blood diseases in children and involves the assimilation of issues on anatomical and physiological characteristics of the blood system, semiotics of lesions, methods for objective and laboratory tests, etiology, pathogenesis, clinical manifestations, diagnosis, treatment and rehabilitation of children with the most common diseases of blood and blood-forming organs.

The manual is intended for students of higher educational institutions of III-IV accreditation levels. The authors hope that this work will be useful to readers. All possible criticisms will be accepted with deep gratitude.

# UNIT 1. EMBRYOGENESIS OF THE HEMATOPOIETIC SYSTEM

Hematopoiesis begins in the yolk sac on the 3rd week of embryogenesis. It contains stem cells that can give rise to all blood-forming buds. The formation of primary erythroblasts occurs within the vessels. After 6 weeks of fetal development, the first nuclear-free red blood cells are observed in the bloodstream. At the 3rd-4th week, the liver anlage occurs, and since the 5th-6th week, it becomes the principal organ of blood formation. During the hepatic hematopoiesis, erythropoiesis predominates, but starting from the 8th-10th week, the granulocyte precursors are also observed. Hematopoiesis in the liver reaches its maximum at the 19th-20th week and is terminated at the end of antenatal period.

Starting from the 3rd month of fetal life, the anlage of spleen and bone marrow occurs. In the spleen, blood formation begins from the 12th week: red blood cells, granulocytes, megakaryocytes are produced. Since the 20th week, intensive lymphopoiesis begins, which lasts throughout the life. Spleen gradually loses the functions of universal blood formation organs, and starts producing B-lymphocytes and immunoglobulins. In lymphopoiesis, an important role also belongs to the thymus. It determines the differentiation of T-lymphocytes. The development of peripheral lymphoid tissue starts from the 4th month of fetal development.

In the bone marrow, hematopoiesis begins from the 13th-14th week and initially occurs in all bones. Pluripotent stem cells appear which are capable of producing lymphoid and myeloid elements. With the development of skeleton, the foci of hematopoiesis shift to flat spongy bones.

Bone marrow of a newborn constitutes 1.4% of its weight and fills the cavity of almost all long bones. During the growth of the child, the mass of bone marrow increases and amounts to 1.4 kg, but it is gradually replaced by fatty tissue in the tubular bones. In the flat bones, marrow is stored throughout the life. In adults, the weight of bone marrow is 4.6% of body weight, but the red marrow is only 50% of its total mass. After the age of 30, hematopoiesis takes place only in the bone marrow of the sternum, ribs, and vertebral bodies. Differentiation and maturation time of erythroid cell is about

12 days, granulocytes − 13-14 days. Circulation time of different cells: red blood cells are in the bloodstream for 120 days, platelets − 10 days, neutrophils − about 10 hours. Reserve capacities of cells in the bone marrow are also different: the number of mature neutrophils is by 10 times more than in the bloodstream; there is a 3-day supply of reticulocytes.

Young children are characterized by functional lability of blood and possible return to the embryonic type, when hematopoiesis appears in the liver, spleen, lymph nodes. The appearance of myeloid or lymphoid metaplasia in the bone marrow is typical under the influence of exogenous and endogenous factors due to the relatively high content of undifferentiated cells that are easily converted to myelo- or lymphoid series. Children are also characterized by high regenerative ability, but rapid depletion of hemopoietic apparatus.

The process of hematopoiesis in accordance with the unitary theory is presented in the scheme of hematopoiesis by I.L. Chertkov and A.I. Vorobyev (1973, 1981), where hematopoiesis is seen as a series of successive cellular differentiations of a single stem cell (Figure 1). Depending on the type of final formation, formed elements of all cells of hematopoietic tissue are vertically divided into hematopoietic lineages (erythroid, myeloid and megakaryocytic). By the degree of differentiation (horizontally), the bone marrow cells are divided into 6 classes:

I − pluripotent progenitor cells (stem cells);

II − partly determined progenitor cells, which have a limited supply of information, namely lymphopoiesis progenitor cells and myelopoiesis progenitor cells;

III − unipotent poietic-sensitive progenitor cells that give rise to one of the lineages of blood formation, in other words, there are progenitor cells of erythropoiesis, myelopoiesis, thrombocytopoesis;

IV − morphologically recognizable proliferating cells that have certain morphological features;

V − maturing cells that are represented by all transitional forms;

VI − mature cells: red blood cells, granulocytes (neutrophils, eosinophils, basophils, monocytes) platelets.

*Erythropoiesis. The morphology of red blood cells*

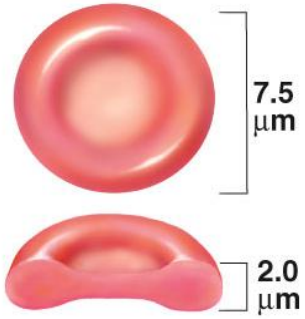
Erythropoiesis is regulated by erythropoietin − a hormone of glycoprotein nature, 90% of which is produced in the kidneys (synthesized by cells of juxtaglomerular apparatus and epithelial cells of renal glomeruli), a small portion is synthesized by hepatocytes. The kidneys produce proerythropoietin, which does not have a specific activity. Proerythropoietin in plasma under the action of a specific enzyme erythrogenin is converted into active erythropoietin. There are other regulators of erythropoiesis. Namely, androgens stimulate erythropoiesis (they increase the synthesis of erythropoietin). Vitamins and minerals also have the regulatory impact. The inhibitor of erythropoiesis − erythrocytic chalone, released from mature red blood cells − also takes part in the specific regulation. Its mechanism of action is to reduce the proliferative activity of erythron. In addition, in red blood cells, the erythrocytic anti-chalone has been detected, which stimulates erythropoiesis by feedback type.

Erythropoiesis under normal conditions undergoes the following steps: burst-forming unit → colony forming unit → erythroblast → pronormocyte → normocyte → erythrocyte. At the stage of normocyte, the denucleation of cells occurs. The remains in the erythrocyte nucleus are defined as Jolly bodies, Cabot's ring bodies, azurophil granules. Under physiological conditions, along with the loss of the nucleus hemoglobin accumulates in the cytoplasm of the erythrocyte. The active part of the life cycle of red blood cells takes place within the peripheral blood, where they come from bone marrow at the reticulocytes stage. Reticulocyte is a nuclear-free erythrocyte containing basophilic component that is shown in a grid during staining. Production of reticulocytes in the bone marrow is $3 \cdot 10^9$ cells/kg per day. In the bone marrow, reticulocytes are stored for 36-44 hours, then they go into the blood, and mature there within 24-30 hours. The entire life cycle from erythroblast to reticulocyte is from 3-4 to 5-7 days.

The number of formed red blood cells depends on age. Before the child's birth, the daily production of red blood cells is 3% of the total mass of circulating red blood cells. By the 5th day of life, the formation of red blood cells is reduced to 0.2% and on

the 10th day − to 0.1%. By 3 months of age, the production is 2% of the total mass of red blood cells and is kept at this level for the whole period of childhood.

Normally, a red blood cell has the shape of a biconcave disc of pink-red color which is lighter in the center. The average diameter of the erythrocyte is 7.2-7.5 μm, thickness − 2-2.5 μm. The discoid shape allows them to have a more extensive surface by 1.7 times than the spherical one, and it has a greater capacity for deformation in the capillaries. Normally, red blood cell can deform and pass through capillaries with lumen of 3 μm. This is due to the interaction between the proteins of membrane (segment 3, glycophorin) and cytoplasm (spectrums, ankyrin). Defects in these proteins cause morphological and functional changes in the erythrocyte.




Mature erythrocyte does not have cytoplasmic organelles and therefore is not able to synthesize proteins and lipids. The main way of energy metabolism in the erythrocyte is glycolysis. Glycolysis energy is used for active transport of cations through the cell membrane to maintain normal ratio between sodium and potassium ions in the red blood cells and plasma and to maintain the form of red blood cells.

The main function of red blood cells is the transport of oxygen from the lungs to the tissues, and carbon dioxide from the tissues to the lungs. This function is performed by hemoglobin (Hb) − a special protein found in red blood cells. Red blood cells play a certain role in hemostasis, they are involved in the formation of the primary hemostatic plug and transport the plasma factors of blood clotting, adsorbed on their surface.

Normally, the life span of red blood cells in adults is 110-120 days, the time of circulation in the bloodstream in term infants is 60-70 days, and in premature infants − 35-50 days. Under physiological conditions, the number of destroyed red blood cells is equal to the number of newly formed ones, therefore, their number remains constant. In

physiological conditions, the ageing RBCs are removed from circulation and are destroyed mainly in the spleen, liver and to a lesser extent − in the bone marrow. It is known that fraction of IgG serum contains antibodies against the old red blood cells. Their attachment to the erythrocyte leads to the phagocytosis of the latter. Products released in the intracellular destruction of hemoglobin are amino acids (from globin), iron (from heme) which are used in the body to build hemoglobin. Heme after detachment from iron in microtomes is converted using hemoxygenase at first into biliverdin and then into bilirubin. Bilirubin is released into the blood, where it binds to albumin and is transported to the liver. In hepatocytes, it is conjugated with glucuronic acid by means of enzyme glucuronosyl transferase, thus transforming into direct bilirubin, which then enters the intestine with bile.

Normally, a part of red blood cells is destroyed in the bloodstream, Hb is connected to the haptoglobin in the irreversible complex, which due to its size does not penetrate the liver filter, and is enzymatically broken down in the liver. If intravascular hemolysis is significant and haptoglobin cannot bind all released Hb, its surplus goes to the kidneys, and the portion is excreted in the urine (hemoglobinuria), a part is reabsorbed in the proximal section of tubule, and a part of hemoglobin iron is deposited in the tubular epithelium in the form of ferritin and hemosiderin, and is slowly excreted with urine.

*The structure, functions, biosynthesis features and types of hemoglobin*

Hemoglobin is the main component of red blood cells (about 98% of red cell mass). By its chemical nature, Hb belongs to chromoproteins, and incorporates protein (globin) and iron-group (heme). Heme is a complex compound of iron and protoporphyrin IX. Heme structure is the same for all types of hemoglobin. Only the protein part − globin − is different. The main component of human hemoglobin − HbA (95-98% of blood hemoglobin) consists of two α-and two β-chains. Other normal types of human hemoglobin are HbA2 (2-2.5%) and HbF (0.1-2%).

In red blood cells of embryo, fetus, child and adult, one can define 6 types of hemoglobin: embryonic (Gower-1, Gower-2 and Portland); fetal hemoglobin (HbF) and adult types HbA1 and HbA2. From the 8th week of gestational age, hemoglobin HbF is

the dominant type, which constitutes 90% of the total amount in the fetus up to 6 months. HbF level gradually decreases, and by birth is about 70% of the total amount. In the postnatal period, its level rapidly decreases, and at the age of 6-12 months only traces are detected.

# UNIT 2. ANATOMICAL AND PHYSIOLOGICAL FEATURES OF BLOOD FORMATION

## Blood in newborns

In the blood of newborns, there is a high content of red blood cells (5-7 • $10^{12}$/l) and hemoglobin (180-240 g/l). The main part of hemoglobin is HbF (80%). In addition, in the blood of some infants, abnormal forms of hemoglobin (Hb Baris, Lepore and others) can be observed. These hemoglobins have identical hemes and different structure of globin. Like HbF, they have high affinity to oxygen (easily attach it, but poorly give it away to the tissues). Therefore, the transport function of this hemoglobin is weak. Red blood cells in newborns have a higher hemoglobin content corresponding to a higher color indicator. At birth, it amounts to 1.1, indicating hyperchromia. These features are associated with fetal hypoxia during fetal development. After the birth, the oxygen supply becomes sufficient and red blood cells from HbF are destroyed. Throughout the neonatal period, the level of red blood cells and hemoglobin is gradually reduced, and by the end of the first month of life, the number of erythrocytes equals to 4.7 • $10^{12}$/l, and hemoglobin − 156 g/l.

For newborns, anisocytosis (sizes of red blood cells vary between 3-13 μm), poikilocytosis (red blood cells of irregular and varying shape due to different elasticity of the membrane), polychromatophilia (different color) are typical. Numerous reticulocytes (8-42 ‰) are characteristic. By the end of the 1st week of life, their number is reduced to 7-10 ‰. The average life span of red blood cells in the neonatal period is less than in adults. At the 2nd-3rd day after birth, it is 12 days. Red blood cells have a lower osmotic resistance: hemolysis in hypotonic NaCl solution is observed at higher concentrations of NaCl, than in adults.

Platelet count significantly ranges from 140 • $10^9$/l to 450 • $10^9$/l.

At birth, physiological leukocytosis is observed: 11-33 • $10^9$/l. Maximum rates of leukocytosis are observed in the first hours after birth, then during the 1st week of life, the number of leukocytes gradually decreases to 10 • $10^9$/l. Further, there is again a gradual increase in the number of leukocytes to 12 • $10^9$/l. The leukocyte formula at

birth is dominated by neutrophils − 60-70%, there is a shift of myelocytes to the left. The amount of lymphocytes at birth is 20-30%. By the end of the 1st day of life, neutrophil count is gradually reduced, while the amount of lymphocytes increases. By the 5th-7th day of life, there is the first intersection of neutrophils and lymphocytes curves when their percentage is equal and amounts to 43-45%.

Later on, during the neonatal period in the peripheral blood, the lymphocytes count increases and the amount of neutrophilic granulocytes decreases. At the end of neonatal period, promyelocytes and myelocytes disappear from the peripheral blood and generally only segmented ones are left, as well as a small percentage of stab neutrophils. The amount of monocytes after birth is up to 10%, and during the first two weeks, a slight increase is observed. The amount of eosinophilic granulocytes after birth may be 1-10%, but in the first days of life it reaches the usual level. Erythrocyte sedimentation rate in infants is 2-3 mm/hr.

*Factors affecting the features of the peripheral blood in newborns:*

1) insufficient oxygen supply of the fetus with compensatory increase of erythropoiesis;

2) changes in the biochemical composition of the blood;

3) termination of hormonal influence of the mother's blood;

4) relative blood thickening;

5) absorption of decay products from embryonic tissues;

6) massive bacterial invasion after birth;

7) the nature of feeding (lactotrophic);

8) a higher content of red blood cells than in adults.

## Blood in infants

Hb level and the amount of red blood cells reach the physiological minimum at the age of 3 months. Red blood cells are thus reduced to $3.0 \cdot 10^{12}$/l, hemoglobin − to 90 g/l, reticulocytes − to 1-2 ‰. This confirms the hypothesis that the physiological decline in red blood cells is based on the physiological immaturity of erythroid lineage of bone marrow (erythropoietin deficiency, poor development of receptors in the progenitor

cells to erythropoietin, intense disintegration of red blood cells containing fetal hemoglobin (HbF).

In the 2nd half year of life, Hb content is increased to 110-120 g/l, erythrocyte count to 4.0-4.5 • $10^{12}$/l, reticulocytes − to 5-10 ‰. However, iron deficiency anemia may develop in some infants due to the intense growth and insufficient exogenous supply with iron.

Platelet count is 180-350 • $10^{9}$/l.

The number of leukocytes ranges within 10-12 • $10^{9}$/l. From the age of 4-6 months, the leukocyte formula is dominated by lymphocytes (60-65%), neutrophil granulocytes amount to 25-30%. Among neutrophilic granulocytes, segmented forms make up the bulk of it. Eosinophilic granulocytes and monocytes do not significantly change in quantitative proportion.

ESR is 6-8 mm/hr.

**Blood in children above the age of 1 year**

At the end of the first year, the number of red blood cells, white blood cells and platelets is relatively constant and composition of peripheral blood gradually acquires features of an adult. After the age of 1 year, red blood cells amount to 4.0-5.0 • $10^{12}$/l, Hb − 120-160 g/l, reticulocytes 4-10 ‰. The diameter of red blood cells reaches the adult values until 5-6 years of age. Color index is 0.85-1.05.

Platelet count is within 180-320 • $10^{9}$/l.

The qualitative changes of white blood cells count take place. After the age of 1 year, the number of lymphocytes begins to decrease, while the number of neutrophils increases. During this process at the age of 5-6-years, their equal amount is again observed (the second intersection). The final composition of the blood is established in prepubertal age: neutrophil percentage − 60-65%, lymphocytes − 25-30%. In healthy children over 1 year of age, plasma cells disappear from the peripheral blood.

## UNIT 3. LESION SYNDROMES OF THE HEMATOPOIETIC SYSTEM

The main syndromes of blood system are:

- anemic;
- hemorrhagic;
- leukemoid reaction;
- lymphoproliferative;
- sideropenic.

Clinical signs of anemic syndrome:

1) asthenic-neurotic syndrome (drowsiness, adynamia, reduced intelligence and emotion, delay in the psycho-motor development);

2) epithelial syndrome (dystrophy and atrophy of barrier tissues − skin and mucous membranes, their inflammatory changes), taste disturbance;

3) immunodeficiency syndrome − frequent ARVI, intestinal disease, early formation of chronic foci of infection;

4) hypoxic syndrome − malaise, disturbance of consciousness, headaches, muscle pain;

5) cardiovascular syndrome − tachycardia, weakened heart tones, functional systolic murmur;

6) changes in the respiratory system − tachypnea;

7) hepatolienal syndrome − moderate enlargement of liver and spleen.

The triad of hemolytic anemia is as follows: hepatolienal syndrome, jaundice, anemia.

Clinical manifestations of hemorrhagic syndrome depend on the type of bleeding:

a) *hematomal* − occurs in coagulopathies (hemophilia A, B, C, Christmas disease); it is characterized by large, painful intramuscular hematomas and hemarthroses.

b) *petechial-spotted* − occurs is the pathology of platelets (thrombocytopathies, thrombocytopenia, thrombocytopenic purpura, Glanzmann thrombasthenia, leukemia). The skin spontaneously or after minor trauma develops punctulated hemorrhages

(petechiae) and larger ones − ecchymosis. Bleeding from the mucous membranes is characteristic. Bleeding in internal organs is also possible.

c) *mixed* − occurs in the pathology of factors of plasma and platelet links of homeostat (Willebrand disease).

d) *vascular purpuric* − is associated with pathology of vascular wall of primary (immunocomplex systemic vasculitis) and secondary genesis (acute infectious diseases, rheumatism). It is observed in hemorrhagic vasculitis, vitamin K deficiency, infectious and toxic shock.

e) *microangiomatous* − is observed in Rendu-Osler disease; resulting from reduced resistance and easy destruction of the vessel wall due to its focal (local) thinning and as a result of weak stimulation in these areas of platelet aggregation and coagulation, in hereditary telangiectasias; it is accompanied by persistent recurrent nasal, gastrointestinal, renal bleeding that occur in damaged telangiectasia.

Leukemoid response syndrome − is a clinical and hematological syndrome, accompanied by changes in the blood and blood-forming organs that resemble leukemia or other tumors of the hematopoietic system, but are always reactive in nature, do not transform into the tumor, which they resemble. They are more common in children aged 3-7 years; they occur more often in boys than in girls.

The reasons are as follows: a) the admission into the blood of endotoxin from the affected intestine, which is a powerful stimulant of granulocytopoiesis (neutrophilic type of leukemoid reaction);

b) massive collapse of cancer cells stimulates myelopoiesis with the release of leuko- and thrombopoietins;

a) infectious processes that are accompanied by a strong immune response, causing leukemoid reaction of lymphatic or monocytic type.

*Types of leukemoid reactions:*

1. Pseudoblastic reactions occur in neonates with a genetic defect in chromosome, at resolution of immune agranulocytosis; cells similar to blasts in the bone marrow are observed.

2. Promyelocytic reactions occur in toxinfection, allergic dermatitis, at resolution of immune agranulocytosis; a large percentage of promyelocytes is revealed in the points of the bone marrow without inhibition of platelet and erythrocytic lineages.

3. Neutrophilic reactions in septic conditions, in acute blood loss combined with toxinfection; neutrophilic leukocytosis with stab shift is observed.

4. Eosinophilic reactions − in helminthiasis, tumors, allergies, collagenoses, organ eosinophilias (lesions of lung, pleura), eosinophilic leukocytosis (20%), increased number of eosinophils in the bone marrow are observed.

5. The reactions of two or three myelopoiesis lineages − in cancer (hypernephroma), sepsis, cancer metastases in the bone marrow, acute immune hemolysis; neutrophilic leukocytosis, thrombocytosis, erythrocytoma, myelomia (myelocytes, erythrokaryocytes) are observed.

6. Lymphocytic − in infectious mononucleosis, viral infections, yersiniosis; the increase in peripheral blood lymphocyte count and the emergence of infectious mononucleosis cells (blast-transformed lymphocytes) are observed.

7. Monocyte-macrophage − in tuberculosis, rheumatism, yersiniosis, parasitic invasions; it is manifested by monocytosis in peripheral blood and monocyte-macrophage infiltrates (granulomas) in affected tissues (lymph nodes, spleen).

## UNIT 4. METHODS FOR EXAMINATION OF PATIENTS WITH BLOOD SYSTEM LESIONS

**Complaints**: pallor, increased fatigue, headache, dizziness, loss of appetite, irritability; frequent hemorrhages; arthralgia; abdominal pain; fever; taste disturbances.

**Anamnesis**: genetic anamnesis; adverse pregnancy course, childbirth; diseases in infancy; pathology of the digestive tract; inadequate care; adverse hygiene-and-sanitary conditions.

**Examination**: color, hemorrhages; enlarged lymph nodes, liver and spleen; increased joints (hemarthrosis), abdomen, swelling, defects.

**Palpation**: clinical examination of externally accessible lymph nodes, abdominal and thoracic areas (in their significant increase).

There are the following groups of lymph nodes: occipital; postaural; submandibular; submental; anterior cervical or tonsillar; posterior cervical; supraclavicular; subclavian; axillary; cubital; inguinal; popliteal. Palpation of lymph nodes should be sliding, systemic on both sides. One should characterize their size, number, mobility, relationship to surrounding tissue and with each other, tenderness. In healthy children, not more than 3 groups of lymph nodes (submandibular, axillary, inguinal) are palpated. The size from a lentil to a pea is considered normal (II-III degree). Consistency is elastic, palpation is not painful.

On objective examination, tubular bones and sternum are percussed, defining their painfulness, chest (increased mediastinal lymph nodes), abdomen (enlarged liver and spleen).

*The study of hematopoietic system includes:*

The study of peripheral (capillary) blood and study of bone marrow (myelogram).

*Laboratory examination methods of hematopoietic system:*

1) Complete blood count;

2) Osmotic resistance of erythrocytes;

3) ABO blood group system and the system of Rh;

4) Coagulogram;

*General rules for the collection of blood for analysis*.

a) at the same time of the day, usually in the morning;

b) on an empty stomach or one hour after a light breakfast;

c) before any medical procedures;

d) the child should be calm;

e) before morning exercises or other physical activities.

**Assessment of blood**

Red blood cell count

Normal fluctuations in the red blood cells count are:

- In children under 6 years: $3.66 \cdot 10^{12}/l - 5.08 \cdot 10^{12}/l$;

- Boys above the age of 7 years and older: $4.00 \cdot 10^{12}/l - 5.12 \cdot 10^{12}/l$;

- Girls above the age of 7 years and older: $3.99 \cdot 10^{12}/l - 4.41 \cdot 10^{12}/l$.

Increased values − in absolute and relative erythrocytoses:

- absolute − in hypoxic conditions (chronic lung disease, congenital heart disease);

- relative (when plasma volume is reduced while maintaining the amount of red blood cells) − with thickening of the blood (excessive sweating, vomiting, diarrhea, burns, growing swellings).

Reduced values: due to the deficiency of iron, protein and vitamins.

Hemoglobin contents

The optimal level of Hb in the capillary blood for children up to 6 years is higher than 120 g/l, for children over the age of 6 years − higher than 130 g/l.

Increased values: in diseases that are manifested by increase in the amount of red blood cells (primary and secondary erythrocytoses, congenital heart defects, cardiopulmonary failure); in blood thickening (dehydration, burns, vomiting, intestinal obstruction); due to physiological reasons (in the residents of highland areas, after increased physical activity).

Reduced values: in all types of anemia.

Color index (CI) reflects the relative content of Hb in erythrocytes. Normal values of CI are 0.85 − 1.05. The value of CI is important to determine the form of

anemia. Based on this value, anemias are divided into three types: hypochromic (CI is less than 0.85); normochromal (CI is within the normal range, i.e., from 0.85 to 1.05); hyperchromic (CI is more than 1.05).

The average content of Hb in the erythrocyte (mean corpuscular hemoglobin) (MCH) is the indicator that characterizes absolute hemoglobin content in one erythrocyte.

Normal rates of MCH are 24-33 picograms (pg).

The average concentration of Hb in the erythrocyte (mean corpuscular hemoglobin concentration) (MCHC) is the indicator that reflects the degree of erythrocyte's saturation with hemoglobin.

Normal values of MCHC are 30-38%.

The average volume of red blood cells (mean corpuscular volume) (MCV)

Normal values of mean corpuscular volume are 75-95 $\mu m^3$.

The average diameter of erythrocytes is 7.2-7.5 μm.

White blood cells

White blood cells perform protective functions, providing phagocytosis of microbes, foreign substances, decay products of cells, participating in the immune responses.

The normal white blood cells count is 4-9 • $10^9$/l (the amount of leukocytes in the age aspect is discussed in Unit 2).

Increased values (leukocytosis):

Absolute leukocytosis − in infants − 12-15 • $10^9$/l (neutrophils 60%), children from the age of 2 weeks to 2 years − 8-13 • $10^9$/l. Daily fluctuations (the content increases in the afternoon): in acute inflammatory and infectious diseases, acute and chronic leukemia, malignant tumors, burns, after blood loss (posthemorrhagic leukocytosis), in the postoperative conditions.

Reduced values (leukopenia) are observed in malnutrition (food deficiency), they are rarely hereditary; can be detected in certain viral and bacterial infections (influenza, viral hepatitis, sepsis, measles, malaria, rubella, mumps, tuberculosis, AIDS).

Leukocyte count is the index, which includes determining the 5 major types of white blood cells (neutrophils, eosinophils, basophils, lymphocytes, monocytes) that perform different functions in the body and represents their ratio (expressed as a percentage). WBC is counted by laboratory doctor via microscopy method of 100 cells in the blood smear or automatic hematology analyzer. It is important to remember that automatic meter does not divide the subpopulation of neutrophils into stab and segmented ones, which is a requirement for counting leukocyte formula under the microscope.

Normally, white blood cells are distributed in the following proportions: basophils − 0-1%, eosinophils − 0.5-5%, stab neutrophils − 1-6%, segmented neutrophils − 47-72%, lymphocytes − 19-38%, monocytes − 2-11%. In infants above the age of 2 weeks up to 4-5 years, lymphocytes amount is up to 50-60%. Up to 12 years of age, lymphocytes reduce to 25-48%, by 15 years − approach the adult rate.

In newborns, blood is characterized by 60-65% of neutrophils and 25-30% of lymphocytes. Starting from the 2nd day of life, the amount of neutrophils reduces and lymphocytes count increases. At the 5th-6th day, the first intersection occurs, when the amount of neutrophils and lymphocytes is the same. Further, the amount of lymphocytes increases to 60-65%. Subsequently, there is a gradual decrease in the amount of lymphocytes and increase of neutrophils count. At the age of 5-6 years, the second intersection occurs, then leukocyte count gradually approaches the formula of adults.

Thrombocytes are blood platelets, cells non-nuclear with the diameter of 2-4 μm, of irregular rounded shape. They play an important role in blood clotting. The normal platelet count is $180 \cdot 10^9$-$320 \cdot 10^9$/l.

Increased values are observed in polycythemia, asphyxia, traumas, inflammation, anemia due to blood loss, after surgery.

Reduced values (thrombocytopenia) below $150 \cdot 10^9$/l are observed in thrombocytopenic purpura, infectious diseases, poisoning, leukemia.

Corpuscular volume (hematocrit − Ht) (ratio of formed elements volume to plasma volume). The normal hematocrit is 0.41-0.53 for men, and 0.36-0.46 − for

women. Hematocrit in neonates is about 20% higher, and in young children − about 10% lower than in adults.

**The features of myelogram in healthy children**

In the bone marrow of children under 3 years of age, there are significantly more lymphocytes, on average 6-16.5% (40%), while in children above the age of 3, their content is 2-8%.

In the myelogram of children under 3 years of age, there are significantly more granulocyte cells (60%) than in children above the age of 3 (35-40%).

Young children are characterized by lower content (5-10%) of myelocytes and metamyelocytes, while in older children and adults, the content of them is higher (15-20%).

An important myelogram indicator is the ratio of elements of myeloid and red blood cells, called myeloerythroblastic ratio (M/E). In neonates, M/E ratio is 1.2 : 1; in infants − 2 : 1; in children above the age of 10 years − 3 : 1; in adults − 3.5-4 : 1.

# UNIT 5. ANEMIAS IN CHILDREN

Anemia is a pathological condition characterized by a decrease in hemoglobin per unit of blood volume (less than 110 g/l in children under the age of 6 years and less than 120 g/l in children above the age of 6 years). Anemia is the most common group of blood diseases in children, of diverse etiology and pathogenesis. It can occur as an underlying disease and a syndrome of various diseases (systemic blood diseases, systemic connective tissue disease, and others). In this regard, oxidation processes in the body are disrupted and hypoxia develops.

According to WHO, 20% of the planet population suffer from iron deficiency anemia (IDA). The share of hemolytic anemia is about 11.5%. Aplastic anemia is observed much less frequently (10.6 per 1000 000 of child population per year), but is has a malignant course.

Classification of anemias

By the mechanism of development, anemias are divided into 4 groups:

I. *Posthemorrhagic anemias* (due to external or internal blood loss):

1. Acute.

2. Chronic.

II. *Anemia due to insufficient erythropoiesis:*

1. Hereditary aplastic anemias:

A. Pancytopenia (in conjunction with birth defects − Fanconi anemia, without congenital anomalies − Estren-Dameshek anemia);

B. With the partial damage of erythroid lineage (Blackfan-Diamond syndrome).

2. Acquired aplastic anemia:

A. With pancytopenia (acute, subacute, chronic forms);

B. With the partial damage of erythropoiesis, including transient erythroblastemia in neonates.

3. Dyserythropoietic anemias (hereditary and acquired).

4. Sideroblastic anemias (hereditary and acquired).

5. Deficiency anemia (due to deficiency of specific factors).

A. Megaloblastic anemias

a) folic acid deficiency (lack of folic acid in the nutrition or malabsorption);

b) vitamin $B_{12}$-deficiency (malabsorption or transport disruption);

c) orotic aciduria.

B. Microcytic anemias:

a) iron;

b) copper-iron;

c) in lead poisoning.

6. Physiological anemia in neonates.

7. Early anemia of premature infants.

*III. Hemolytic anemias*:

1. Hereditary:

A. Membranopathies:

a) deficiency or disruption in the structure of protein membrane (microspherocytosis, ovalocytosis, elliptocytosis, stomatocytosis et al.);

b) disruption of lipid membrane (acanthocytosis et al.).

B. Fermentopathies (disruption of enzyme activity of pentose-phosphate pathway, glycolytic cycle, metabolism of nucleotides, glutathione).

C. Defects of structural globin chains (hemoglobin S, C, D, et al., unstable hemoglobins) and synthesis of globin chains (thalassemia), mixed forms.

2. Acquired:

A. Immunopathologic (isoimmune − hemolytic disease of the newborns, transfusion of incompatible blood, autoimmune, hapten, drug-induced).

B. Infections (bacterial, viral, parasitic).

C. Vitamin-deficient (B-vitamin-deficient anemia in premature infants).

D. Toxic (poisoning by heavy metals and other chemical compounds, oxidants).

E. Paroxysmal nocturnal hemoglobinuria.

F. DIC of different etiologies and mechanical damage of red blood cells.

*IV. Anemias of mixed genesis:*

A. In acute infections, sepsis.

B. In burns.

C. In tumors and leukemia.

D. In endocrinopathies.

The classification given above takes into account only the leading pathogenetic factor. In many cases, anemia can be attributed to several groups. Chronic posthemorrhagic anemia is iron deficiency by pathogenesis. In chronic infections and inflammatory diseases, the demand for iron in reticulo-endothelial cells increases and iron deficiency anemia also develops, while treatment with iron in this case has a minimal effect on hematopoiesis.

Clinical manifestations of anemia

Clinical course of anemia depends on the etiology, rate of its progression and adaptive capacities of the child. Due to reduction in hemoglobin, symptoms caused by tissue hypoxia occur. Patients complain of fatigue, drowsiness, tinnitus, dizziness, decreased performance, drowsiness or insomnia. Along with general symptoms of anemia, each option has its own specific symptoms: sideropenic syndrome − in iron deficiency anemia, jaundice − in hemolytic anemia, neurological disorders − in $B_{12}$-deficiency anemia, hemorrhagic syndrome − in aplastic anemia.

An important role in the differential diagnosis of anemic belongs to anamnestic data. In collecting the history, one should clarify the following issues:

- The occurrence and rate of anemia progression (usually hereditary anemia is manifested at an early age, anemia with the course of crises over the years can also indicate a hereditary process);

- Information about the pregnancy of the mother, nutrition, presence of preeclampsia, the threat of termination, medications during pregnancy, industrial hazard, bad habits;

- The nature and dates of delivery;

- The possibility of chronic hemorrhage (bleeding);

- The presence of anemia, jaundice in the maternal and paternal lines, health condition of other children in the family;

- The nature of the child’s feeding, especially in the first year of life;

- The possibility of the child's contact with various toxins and poisons (mercury, lead, benzine, pesticides, etc.).

The child's objective examination displays the signs typical of anemias of different genesis.

*The skin and mucous membranes*

Pale skin and mucous membranes are the typical manifestations of anemia of non-hemolytic nature. Pale skin combined with icterus is typical of hemolytic anemia. Pale skin along with hemorrhagic rash (petechiae, purpura) indicates anemia combined with thrombocytopenia (hypo- and aplastic anemia). Dryness, trophic disorders of the skin and its appendages are most characteristic for iron deficiency anemia. Smoothing of lingual papillae occurs in megaloblastic anemia.

*Lymphatic system*. Severe lymphadenopathy is not characteristic of anemia as an underlying disease and suggests the diagnosis of anemia syndrome in other diseases, such as leukemia, lymphoma, or infectious diseases (tuberculosis, AIDS, toxoplasmosis, etc.).

*Cardiovascular system*. Tachycardia, the appearance of systolic murmur of functional nature, muffled heart tones, expanded boundaries of the heart to the left indicate the severe and prolonged course of anemia.

*The organs of gastrointestinal tract*. Hepatosplenomegaly is characteristic of hereditary and autoimmune hemolytic anemia with a prolonged course.

*Nervous system*. Ataxia, paresthesia, clonus, appearance of pathological reflexes are typical of $B_{12}$-deficiency anemia.

**Deficiency anemias in children**

80% of hematological diseases account for deficiency anemias. In modern classification, deficiency anemias are divided into:

1) primarily iron deficiency,

2) primarily vitamin deficiency,

3) primarily protein deficiency.

There has recently been a redistribution of deficiency anemias toward poly-deficiency, which is especially important for children during the first 3 years of life.

**Iron deficiency conditions** (IDC − ICD-10: D50) are most often observed in childhood.

Classification of iron deficiency anemias (IDA):

1. By the form: alimentary; posthemorrhagic; due to increased consumption of iron; disrupted transport of iron (atransferrinemia) and others.

2. By the stage: pre-latent iron deficiency; latent iron deficiency; iron deficiency anemia.

3. By the severity: mild anemia (Hb 110 − 91 g/l); medium severity anemia (Hb 90 − 71 g/l); severe anemia (Hb 70 − 51h/l); extremely severe (Hb less than 50 g/l).

The relevance of the problem of iron deficiency in children goes beyond the phenomenon of anemia. In addition to hemoglobin, the iron is found as a part of many enzyme systems which provide tissue respiration and immune reactions; iron also takes part in the biosynthesis of collagen and DNA.

According to WHO statistics, approximately 1 billion of people in the world suffer from iron deficiency. Iron deficiency anemia and iron deficiency conditions (IDC) have always been common among children and adolescents.

Causes of IDC.

*Antenatal*:

- Disorders of utero-placental circulation (toxicosis, threatened miscarriage, somatic and infectious diseases of the mother);
- Feto-maternal and feto-placental bleeding;
- Prematurity, multiple pregnancy;
- Deep and prolonged iron deficiency in pregnancy.

*Intranatal*:

- Fetoplacental transfusion;
- Intrapartum bleeding.

*Postnatal*:

- Insufficient intake of iron from food (early artificial feeding, dairy-and-vegetarian diet, unbalanced diet);

- Increased need for iron in children (premature infants; neonates with high birth weight; children of the second half year and the second year of life, prepubertal and pubertal age);

- Increased loss of iron through bleeding, disorder of intestinal absorption (malabsorption syndrome, chronic bowel disease);

- Disrupted metabolism of iron in the body due to hormonal changes in the transport of iron.

In children with IDC, Hb content in the blood is not beyond the age norm and is usually located at the lower limits: 110-118 g/l − in children during the first 5 years of life; 120-128 g/l − in children above the age of 5 years (as recommended by WHO). In this regard, one can observe the disappearance of reserve iron and reduction of its content in the tissues. In IDC, further depletion of tissue iron continues and the reduction of hemoglobin iron begins, leading to anemia.

The main localizations of iron in the body are: 1) Hb of erythrocytes; 2) brain cells; 3) myoglobin of muscles, liver, spleen, bone marrow; 4) enzymes of oxidizing group.

Iron in the body is represented in the form of *heme* and *non-heme* compounds (Table 2).

Heme compounds of iron.

*Hemoglobin* (translated as “blood corpuscle”) is a complex protein-pigment complex which is found in erythrocytes. It transports oxygen from the lungs to the tissues and carbon dioxide from the tissues to the lungs.

*Heme* is a complex compound of pigment protoporphyrin with ion of ferrous iron. Heme is a non-protein molecule of Hb. It is also a part of myoglobin and enzymes (cytochromes, catalase, etc.). Iron, which is included in these compounds, is called heme iron. Heme iron is much better absorbed by the body than ionized one or iron, which is not a part of protoporphyrin compounds. Protoporphyrin is a pigment, which is synthesized in the body from succinic acid and glycine and has the affinity for ions of ferrous iron.

*Myoglobin* is a pigment heme-containing proteid that is found in muscle tissue. Myoglobin transports oxygen and is deposited in muscle tissue.

*Catalase* is a heme-containing enzyme that catalyzes the redox reaction, whereby the disintegration of hydrogen peroxide to form oxygen and water occurs. The physiological role of catalase is to protect the body from excess peroxides.

*Cytochromes* are heme-containing proteids, which provide tissue respiration.

*Peroxidases* are heme-containing enzymes that catalyze the oxidation of compounds using hydrogen peroxide. Their physiological role consists in protecting the body from excess peroxides.

Non-heme iron compounds

*Xanthine oxidase* is the enzyme that catalyzes the oxidation of xanthine, hypoxanthine and aldehydes with the absorption of oxygen and the formation of urinary and carboxylic acid, xanthine.

Acetyl-coenzyme-A dehydrogenate is the enzyme that catalyzes the oxidation of macroergic compounds of acetyl coenzyme A, participates in the metabolism of fatty acids.

*Succinate-dehydrogenase* is the enzyme that catalyzes the reverse reaction of oxidation of succinic acid into fumaric. It participates in the citric acid cycle.

*NAD-H dehydrogenase* is the enzyme that is involved in restoring NADP, catalyzes the transfer reaction of hydrogen atoms.

*Transferrin, ferritin and hemosiderin* are non-heme compounds of iron, taking a direct part in the metabolism of iron.

The functions of iron in the body. The main function of iron is the transport of oxygen and participation in oxidative processes (using 72 enzymes that contain iron). Iron plays an important role in maintaining the high level of immune resistance of the body. Adequate iron content in the body promotes the proper functioning of factors of nonspecific defense, cellular and local immunity. Indirect stimulating effect of iron on myeloperoxidase and enzyme systems by $H_2O_2$ generation contributes to the maintenance of phagocytosis activity at the required “protective” level. Iron through the system of ribonucleotide reductase supports the normal proliferation and mitotic activity

of T-lymphocytes. Regulation of the expression of class II surface antigens of the major histocompatibility complex on T-cells occurs in the obligatory participation of iron enzymes. In sideropenia, the number of T-lymphocytes is reduced by 50%, their functionality is disrupted, the synthesis of secretory component of IgA in the mucus of nasopharynx and digestive tract is disturbed, which impairs the barrier function. The phagocytic activity of neutrophils is disrupted as well.

According to new data, after Hb of erythrocytes, the largest amount of iron is found in the cells of the brain. Iron deficiency in them leads to the disruption of neuropsychiatric features, reduced performance of intelligence quotient (IQ), delayed formation of logical thinking, language deterioration, learning deviations in the child's psyche.

Many authors believe that simultaneously with the development of sideropenia and its progression, the glucocorticoid and androgen functions of adrenal glands are impaired.

Thus, IDC leads to the profound dysfunction of four major systems: the blood, the nervous, immune and adaptive systems. In addition, in iron deficiency, degenerative changes develop in the epithelium of the skin, mucous membranes of the mouth, gastrointestinal tract, the respiratory tract. Clinically it is manifested by dryness of the skin, dryness, fragility and hair loss. Peeling and brittle nails are observed, less frequently – celonychia, angular stomatitis, atrophy of lingual papillae, glossitis, dysphagia, and chronic gastroduodenitis develop. The amount of gastric juice, its acidity, the activity of gastric and pancreatic enzymes are reduced, the absorption of amino acids, vitamins, trace elements is disrupted.

In other words, iron deficiency leads to enteropathy and is accompanied by malabsorption syndrome. An important aspect of sideropenic enteropathy is the intestinal bleeding with the volume is 0.5-2.0 ml/day. The role of these bleedings in the exacerbation of iron deficiency in children is significant. Enteropathy is clinically manifested by the decrease in appetite.

Diagnostics of IDC. *Pre-latent iron deficiency* in the body is characterized by the depletion of tissue iron stores. Levels of transport fund of iron and Hb are within the age

norms. In children with the decreased tissue iron stores, its absorption from the food is not increased, but decreased. It is associated with the reduction of enzyme activity of ferrum absorption in the child's intestine.

*Latent iron deficiency* develops against the background of depletion of tissue iron stores and is characterized by the reduction of the deposited iron and transport pool without reducing Hb and development of anemia.

*Iron deficiency anemia* is the clinically manifested iron deficiency condition. It develops only in depleted iron stores of the body. Hb concentration reduces and anemic hypoxia develops. Enzyme activity of tissue respiration is inhibited, and degenerative processes in tissues develop.

Symptoms of IDC: sideropenic; generally anemic.

*In young children*, the following symptoms predominate:

1) pale skin;

2) growth delay or weight loss;

3) frequent ARVI.

In 10% of infants with IDC, hepato- or splenomegaly is found.

*In older children* (7-12 years), the skin-and-epithelial syndrome is in foreground: dry skin; peeling skin on the elbows and knees; darkened and brittle hair; atrophy of lingual papillae ("varnished" tongue); cracked tongue, painful cracks in the corners of the mouth (angular stomatitis).

One simple test to identify the IDC is beeturia symptom (pink color of urine after consumption of red beet salad). The reason is that with a sufficient amount of iron, the liver can completely desaturate the beet colors by enzymes that iron contains.

The peculiarities of clinical manifestations of IDC in teenagers include dizziness, syncope, hypotension. Clinical course of IDC is similar to vegetative dystonia since the asthenia syndrome is distinct (weakness, shortness of breath on exertion, fatigue, headache, inability to focus, reduced academic performance). On the ECG of these children, the degenerative changes in the heart muscle are determined (sideropenic myopathy). It can be suspected at the lowered voltage of QRS complex and the T wave,

in tachycardia. Phonocardiogram (PCG) indicates the weakening of the papillary muscles.

Laboratory criteria for IDC diagnosis:

*Microscopic changes* in red blood cells undergo the following steps:

- isolated microcytes appear among the red blood cells;
- anisocytosis occurs (erythrocytes of various sizes);
- hypochromia of red blood cells;
- poikilocytosis (erythrocytes of various shapes);
- basophilic stippling of red blood cells;
- normoblastosis.

Laboratory parameters that characterize the status of iron metabolism

Iron metabolism in the body is characterized by the parameters of the transport fund and iron stores parameters. Iron transport fund is determined by the following factors: serum iron (SI), total iron-binding capacity of serum (TIBC), latent iron-binding capacity of serum (LIBC), ratio of transferrin saturation (RTS).

*Serum iron (SI)* is the amount of non-heme iron in serum. Non-heme serum iron is a part of transferrin and ferritin serum.

Age-standardized values of serum iron:

- In neonates: 5.0-19.3 μmol/l;
- In infants over the age of 1 month: 10.6-33.6 μmol/l.

*Total iron-binding capacity of serum (TIBC)* is an indicator that characterizes the total amount of iron that can bind with plasma transferrin.

Normal values of TIBC are 40.6-62.5 μmol/l.

*Latent iron-binding capacity of serum (LIBC)* is an indicator that reflects the mathematical difference between the values of TIBC and SI: LIBC = TIBC − SI

In the norm, the value should not be less than 47 μmol/l.

*The ratio of transferrin saturation (RTS)* is an indicator that indicates the proportion of TIBC to SI:

RTS = (SI: TIBC) × 100%

Normally, RTS value should not be less than 17%.

SI in normal conditions is ⅓ of TIBC. When SI reduces, TIBC increases. This is due to the increase in the LIBC values. At the same time, the coefficient of transferrin saturation is reduced due to decreased proportion of “transferrin bound to iron”.

The indicators of body iron stores

Body iron stores are characterized by the parameters of desferal test and serum ferritin levels.

*Desferal test* is based on the ability of desferal to form compounds with iron, which is a part of hemosiderin, ferritin and is excreted in the urine. By daily urinary excretion of these complexes, the iron stores in the body are assessed. Normally, the desferal test result is 0.3 − 0.4 mg/day.

*Serum ferritin* characterizes the iron stores in the body.

Normal levels of serum ferritin in infants are 175 mg/l, in children aged from 1 to 14 years − 32-36 mg/l. Regardless of age, the serum ferritin below 10-12 μg/l is considered the criterion of iron stores depletion.

Treatment of IDC

Important elements of treatment are: elimination of etiologic factors, clinical nutrition (for infants − breastfeeding, and in the absence of milk in the mother − adapted infant formula fortified with iron, early introduction of complementary foods, meat, especially beef, innards (meat by-products), oatmeal and buckwheat groats, fruit and vegetable mash, hard cheese, reduced intake of phytates, phosphates, tannin, calcium that impair iron absorption), pathogenetic treatment with iron.

Correction of iron deficiency in mild anemia is carried out mainly by good nutrition, adequate period of staying outdoors. Prescription of iron supplements at the level of hemoglobin 100 g/l and above is not indicated.

Classification of iron supplements

*I. Monocomponent*.

1. Iron sulphate: hemofer prolongatum, ferrogradumet, conferon.

2. Iron fumarate: cheferol.

3. Iron chloride: hemofer.

*II. Combined*.

1. With folic acid: feromed, fefol.

2. With serine: aktiferrin.

3. With ascorbic acid: sorbifer durules, ferroplex.

4. With ascorbic acid and mucoproteasa: tardyferon.

5. With folic acid, calcium, vitamins C and B: vi-fer, natabsk.

6. With folic acid and amino acids: irravit, irradian.

7. With vitamins of group B and nicotinic acid: fesovit.

It is advisable to prescribe trivalent iron preparations due to their optimal absorption and lack of side effects.

Calculation of daily doses of iron preparations

Daily therapeutic doses of oral iron supplements in medium and severe IDC are as follows:

- up to 3 years − 3-5 mg/kg/day of elemental iron;

- from 3 to 7 years − 50-70 mg/day of elemental iron;

- above the age of 7 years − 100 mg/day of elemental iron.

The daily dose of iron supplements is given to a child in three ways. Treatment should start with ½-¼ of a therapeutic dose, gradually (for 7-14 days) bringing it to the full therapeutic one. This reduces the risk of side effects in ferrotherapy; in case of their development, it allows time to detect the initial signs and take appropriate actions.

*When prescribing iron supplements, one should observe the following rules:*

1. They should be taken in the intervals between meals, to prevent the formation of insoluble salts, unable to be absorbed from food components.

2. It is advisable to combine them with the prescription of ascorbic acid (0.1 g), which increases the absorption of iron.

3. It is advisable to start therapy with a single dose to identify the body's tolerance to iron supplements which can prevent adverse reactions, the full daily dose is prescribed only at the end of the week after the initiation of treatment.

4. Treatment must be controlled by studies of peripheral blood with calculation of reticulocyte count before treatment and two weeks after treatment.

Parenteral administration of iron preparations is indicated only: in the syndrome of impaired intestinal absorption and after major resection of the small intestine, nonspecific ulcerative colitis, chronic enterocolitis and severe dysbacteriosis, intolerance to oral medications.

Recovery of normal Hb − is only a part of IDC treatment. After normalization of Hb, it is necessary to restore iron levels in the muscles, nervous system, and depot. For treatment of infants under the age of 1 year, it is needed to use the liquid form. Children above the age of 1 year can be prescribed any iron supplements.

After 2.5-3 weeks of iron preparations intake, one should evaluate the effectiveness of treatment.

Criteria of treatment effectiveness:

1) development of the reticulocytes crisis on the 12th-14th days of treatment (increase in young cells to 20-100 ‰ at the rate of 4-8 ‰);

2) normalization of the morphological features of erythrocytes (elimination of anisocytosis, poikilocytosis);

3) daily increase in hemoglobin by 2 g/l or more;

4) improvement and normalization of the laboratory evidence of iron balance in the body;

5) improvement or normalization of ECG and PCG;

6) disappearance or significant weakening of abnormal murmurs in the heart;

7) improvement in the clinical presentation: reduced muscle weakness, improved memory, elimination of paresthesias in the extremities and others.

*Parenteral iron supplements* should be used only by highly specific indications, due to the high risk of local and systemic adverse reactions.

The daily dose of elemental iron for parenteral administration is:

- infants aged 1-12 months − up to 25 mg/day.
- infants aged 1-3 years − 25-40 mg/day.
- above the age of three years − 40-50 mg/day.

The course dose of elemental iron is calculated by the formula:

WT • (78-0.35 • Hb), where WT − body weight (kg), Hb − hemoglobin (g/l)

The toxicity of iron supplements. The range between therapeutic and toxic dose of iron is large, therefore iron poisoning during the treatment is rare, but it should be taken into account. The poisoning by iron preparations may be caused by their use in large quantities, wrong dose of parenteral administration. In addition, children may face increased sensitivity to iron (even at low doses). Poisoning is manifested by the following criteria: ceaseless vomiting; recurrent diarrhea; general growing dehydration; ulceration of the mucous membrane of the digestive tract and the appearance of blood in fecal masses; increase of pronounced pallor; development of soporose condition; gradual symptoms of shock and coma.

If there are signs (or history) of the intake of excessive doses of iron, one should:

1. Conduct the gastric lavage with a short period of time by 2% aqueous solution of soda.

2. After the gastric lavage, it is necessary to drink 100-150 ml of soda solution. It promotes the formation of iron carbonate, which is very poorly absorbed. After that, gastric lavage should be conducted once again.

3. Give almagel, thereby preventing the necrotic effect of iron salts on the mucosa of the gastrointestinal tract.

4. Anti-shock treatment by generally accepted method.

Since 50-100% of premature babies develop late anemia, from the 20-25 days of life at gestational age of 27-32 weeks, in body weight 800-1600 g (in reducing the concentration of hemoglobin below 110 g/l, and erythrocyte count below $3.0 \cdot 10^{12/}$l, reticulocytes less than 10 ‰), apart from iron supplementation (3-5 mg/kg/day) and sufficient protein supply (3-3.5 g/kg/day), erythropoietin is prescribed s/q, 250 units/kg/day three times a week for 2-4 weeks with vitamin E (10-20 mg/kg/day) and folic acid (1 mg/kg/day).

Diet in anemia

The diet of the child must be balanced so as to include foods rich in iron (Table 4). Iron, which is included in products containing heme (e.g., meat) is better absorbed than iron, which is a part of ferritin (liver) or hemosiderin (fish). Culinary processing does not affect the properties of heme iron, therefore there is no need to give the child

meat or liver in semifinished condition, as some may recommend “meat with the blood”. In total, the diet made of products listed in the table provides the intake of 15-20 mg of iron per day, but only 3-5% (0.8-1 mg) of it will be absorbed. In IDC, the diet is not able to provide the body’s need for iron.

Iron absorption sharply increases in the presence of ascorbic, citric, glutamic acid, fruit juice, therefore the consumption of dogrose, black currant, strawberry garden, spinach, oranges, lemons, grapefruit, gooseberry enhances the absorption of iron from food (even of plant origin) by almost 5 times. The diet that includes meat, fish, increases the efficiency of absorption of iron from grains and vegetables. Dairy products should be limited because they are poor in iron and calcium in the milk forms poorly soluble iron salts. It is necessary to limit flour products, since phytin which they contain, complicates the absorption of iron. Drinks containing tannin (tea, coffee) lead to the decrease in absorption of iron from food.

Feeding young children is based on general principles. In the first months of life, when breastfeeding, one should draw attention to maternal nutrition, and if necessary, conduct the correction of nutrition for both mother and child. The first solid foods (vegetable puree) should be administered at the age of 4-5 months. Among the cereals (the second supplemental feeding), preference is given to buckwheat, oats. In artificial feeding of children with anemia, the iron deficiency is moderately balanced out by milk formula enriched with iron.

Prophylaxis. *Antenatal*: women since the 2nd half of pregnancy are prescribed iron supplements or multivitamins fortified with iron. *Postnatal* prophylaxis for children at high risk of IDA: prematurely born children; children born of multiple and complicated pregnancies; children with intestinal dysbiosis, food allergies; bottle-fed children; children who grow ahead of generally accepted standards of physical development.

## Vitamin deficiency anemias

Vitamin deficiency anemias are often represented by deficiency of folic acid (ICD-10: D52) and vitamin $B_{12}$ (ICD-10: D51).

*Deficiency of folic acid* occurs in celiac disease, chronic diseases of the gastrointestinal tract, hemolytic process, prolonged use of anticonvulsants, malnutrition (in infants who consume mainly goat's milk, in which the content of folate is very low), diseases that are accompanied by loss of folate (liver and kidney diseases), and in premature infants.

*Deficiency of cyanocobalamin* (vitamin $B_{12}$) in children is rare. Malabsorption of vitamin $B_{12}$ may be observed in disorders of absorption, major surgeries on the gastrointestinal tract, family defect of vitamin $B_{12}$ absorption (Imerslung-Gräsbeck syndrome).

Vitamin $B_{12}$ is deposited in mitochondria, it comes to the bone marrow as often as required, where it stimulates the DNA in the nuclei of erythropoietic cells. Lack of vitamin $B_{12}$ leads to the cessation of mitoses in the early stages of erythrocyte development, resulting in premature hemoglobinization of a cell, its "early" maturation and exit into the blood of megalocytes − large, functionally imperfect, short-lived cells. Most of these cells are destroyed in the bone marrow, at the megaloblast stage.

Asthenia, anorexia, glossitis, pale skin with lemon tinge, subicteric sclera, and hepatomegaly are clinically defined. Hemorrhagic manifestations are possible in infants due to thrombocytopenia or infection against the background of neutropenia.

In the blood analyses: hyperchromic megaloblastic anemia, basophilic stippling of erythrocytes, poikilocytosis, macrocytosis, the presence of red blood corpuscles with Jolly bodies, Cabot rings and nuclear forms of erythroblasts (megalocytes and megaloblasts). Moderate leuko- and thrombocytopenia is possible. Folic acid deficiency anemia is characterized by macrocytosis, red blood cells normally are hemoglobinized, in severe cases − aniso- and poikilocytosis, hypersegmentation of neutrophils nuclei.

Specific therapy: vitamin $B_{12}$ (50-100 mg every other day, 10-15 injections) and folic acid (0.25-2 mg/day depending on the age).

### *Protein deficiency anemias*

Protein deficiency anemias develop as a result of starvation or predominantly carbohydrate feeding of children, leading to the disrupted synthesis of hemoglobin, protein transport compounds, reduced production of erythropoietin, hormones and

enzymes (tissue and gastrointestinal tract). The result is not only malabsorption of iron, but many trace elements and vitamins. Therefore, protein deficiency anemia is always pandeficient in nature. Clinic course is commonly characterized by severe degenerative changes and signs of hypopolyvitaminosis. In hemogram: normoregenerative, mainly normocytic anemia. The life span of red blood cells is reduced by 2-fold (without evidence of hemolysis). Biochemical blood tests reveal hypoproteinemia mainly due to hypoalbuminemia, dysproteinemia.

Treatment of protein deficiency anemia is similar to malnutrition therapy, including vitamins and iron supplements.

## Hemolytic anemias in children

This is a group of diseases in which there is the premature destruction of red blood cells and reduced duration of their life. The frequency of hemolytic anemia is about 11.5%.

*Classification of hemolytic anemia*

I. Hereditary hemolytic anemias.

A. Hereditary hemolytic anemias, related to disorder of erythrocyte membranes: hereditary microspherocytosis, hereditary elliptocytosis, hereditary stomatocytosis.

B. Hemolytic anemia, caused by disturbance of lipid structure of erythrocyte membranes:

1. Hereditary acanthocytosis.

2. Hereditary hemolytic anemia, caused by deficiency of activity in lecithin-cholesterol acetyltransferase and others.

C. Hereditary hemolytic anemia, related to disorder of erythrocyte enzyme activity:

1. Hereditary hemolytic anemias, related to disorder of enzyme activity in pentose phosphate cycle:

a) deficiency of activity in glucose-6-phosphate dehydrogenase;

b) deficiency of activity in 6-phosphogluconate dehydrogenase.

2. Hemolytic anemia, related to disorder of the glycolysis enzymes:

a) deficiency of pyruvate kinase activity;

b) deficiency of activity in hexokinase and others.

3. Hemolytic anemia, caused by deficiency of enzymes of glutathione cycle:

a) deficiency of glutathione synthetase activity;

b) glutathione reductase activity deficiency and others.

4. Hemolytic anemia, caused by metabolic porphyrins.

5. Hereditary hemolytic anemia, caused by disturbance of the metabolism of nucleotides:

a) deficiency of adenylate kinase activity;

b) hyperactivity of adenosine deaminase and others.

6. Hereditary hemolytic anemias, associated with disruption of the structure or synthesis of hemoglobin:

a) hemolytic anemia, related to the disrupted synthesis of globin chains: alpha-thalassemia; beta-thalassemia, etc.;

b) anemias, associated with disruption of the structure of globin chains: anemias caused by carriership of stable abnormal Hb S, C, D, E, etc.; anemias, caused by carriership of unstable abnormal hemoglobins.

II. Acquired hemolytic anemias.

A. Isoimmune hemolytic anemias.

1. Hemolytic disease of the newborns.

2. Posttransfusion hemolytic anemias.

B. Autoimmune hemolytic anemias.

1. Anemias, associated with incomplete warm antibodies (idiopathic, symptomatic in patients with leukemia, myelofibrosis, Hodgkin’s disease, etc.).

2. Anemias, associated with heat hemolysins.

3. Anemias, associated with cold agglutinins.

4. Anemias, associated with two-phase cold hemolysins by Donath-Landsteiner type (paroxysmal cold hemoglobinuria) and others.

C. Hemolytic anemias, associated with mechanical damage to red blood cell membrane and anemias due to the collision with prosthetic heart valves (march hemoglobinuria, etc.).

D. Hemolytic anemia, associated with changes in the structure of erythrocytes membranes (paroxysmal nocturnal hemoglobinuria − Marchiafava-Micheli disease).

E. Hemolytic anemias, caused by chemical damage to red blood cells (in poisoning with acids, lead and other heavy metals).

F. Hemolytic anemias, caused by lack of vitamins (vitamin E).

G. Hemolytic anemias, caused by lesions of erythrocytes by parasites (malaria).

In hereditary anemias in children, microspherocytosis is most often observed, less frequently − deficiency of glucose-6-phosphate dehydrogenase. In tropical countries, β-thalassemia and sickle cell anemia are common.

Among the acquired anemias, hemolytic disease of newborns is most often observed; in tropical countries − anemias, caused by vitamin deficiency against the background of parasitic infestations.

## Hereditary hemolytic anemias associated with a defect in erythrocyte membrane structure

### Minkowski-Chauffard disease (hereditary microspherocytosis)

Inherited microspherocytosis is a common disease (2-3 cases per 10 000 of population).

*Etiology*. Inherited microspherocytosis is transmitted by the autosomal dominant type. Typically, one parent shows signs of hemolytic anemia. There are sporadic cases (25%), which represent new mutations under the influence of teratogenic factors. The main feature of the disease is the appearance of microspherocytes in the peripheral blood.

*Pathogenesis*. The disease is associated with a defect or lack of spectrin of erythrocytes membranes, resulting in its disrupted density, excessive penetration of potassium in erythrocytes. As a result of these processes, red blood cells lose their ability to deform, making it difficult to pass in the narrow sites of blood flow. These red blood cells are partially eliminated, and partially destroyed in the spleen. It explains the nature of hemolysis, and as a result, the development of hypoxia, hyperbilirubinemia, and anemia.

The disease occurs by the type of alternating exacerbations and remissions. Aggravation is called hemolytic crisis. The crisis is caused by hypothermia, overheating, trauma, intercurrent infection, vaccination, aggravation of chronic infection, medicines and others. The main pathogenetic mechanisms in the period of crisis are: hypoxia, cerebral edema, hyperbilirubinemia, hemodynamic disturbances, acidosis and hypoglycemic changes.

*Clinical presentation*. The first symptoms are observed in childhood. There is jaundice, spleen enlarges gradually and anemia increases. The degree of anemia depends on the intensity of hemolysis and compensatory reaction of erythropoiesis. The development of hemolytic crisis leads to the aggravation of anemia, accumulation of indirect bilirubin in the blood, development of calculous cholecystitis.

*Clinical manifestations of crisis*. Rapid deterioration of general condition, weakness, headache, fatigue on insignificant exertion, palpitations. Sometimes there are abdominal pain, diarrhea. The main symptoms are jaundice (lemon yellow color), splenomegaly, some children may have enlarged liver. On objective examination: muffled tones, systolic murmur, expanded boundaries of the relative cardiac dullness. Jaundice is not characterized by discolored feces and beer-colored urine.

*The diagnosis* is confirmed by laboratory data: in clinical analysis of blood, the number of red blood cells decreases, but the content of hemoglobin does not change, therefore the CI is normal. The shape of red blood cells changes: they become spherocytes. The increasing number of microspherocytes is up to 20-30%. Price-Jones curve is often used for differential diagnosis (the curve reflects the presence of red blood cells of different diameters and it displays the shift to microcytes).

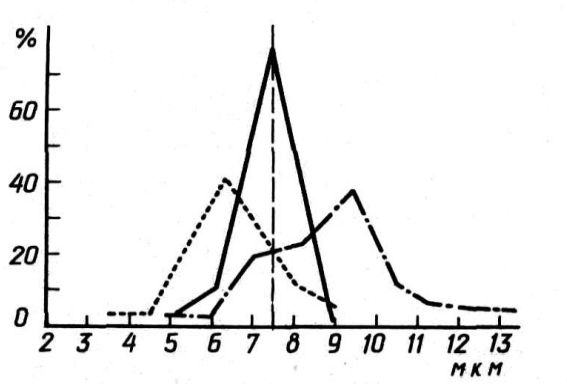



**Fig. 1. Histogram of red blood cells distribution by diameter**

----- − predominance of microcytes

─ ● ─ ● ─ ● ─ predominance of macrocytes in the blood

——— erythrocytes of normal diameter

In the peripheral blood, immature cells of erythroid line appear, the number of reticulocytes increases up to 50 ‰. Leukogram changes only in times of crisis (leukocytosis with neutrocytosis, leukocyte count shifts to the left), erythrocyte sedimentation rate is accelerated during the crisis. Platelet count is normal.

A characteristic feature of inherited microspherocytosis is the reduction of minimum osmotic resistance of red blood cells − hemolysis starts at the concentration of NaCl 0.6-0.7% (the norm is 0.44-0.48% NaCl). To confirm the diagnosis, the significant reduction in the minimum osmotic resistance is of importance. Maximum resistance can be increased (the norm is 0.28-0.3% NaCl).

*Treatment*. Treatment in the hemolytic crisis period is always conducted in a hospital and is aimed primarily at the elimination of anemic syndrome, hypoxia, hyperbilirubinemia and bilirubin intoxication, hypoglycemia, acidosis, edema, swelling of the brain. Strict bed rest for the entire acute period and diet No.5 (liver) are prescribed. Drinking a large amount of liquid depending on the age of the patient is indicated.

During the hemolytic crises, medical care consists in rapid decrease of bilirubin concentration (detoxification therapy), infusion therapy with solutions of 10% glucose with insulin (1 unit of insulin per 50 ml of 10% glucose solution) in the early days, then 5% glucose solution, 0.9% solution of NaCl, cocarboxylase, ascorbic acid. If necessary, plasmapheresis is used along with infusion therapy. Antispasmodics and choleretic agents are prescribed. Phenobarbital, which has bilirubin- conjugating action, induces the glucuronosyl transferase activity of the liver, is prescribed 10-15 mg/kg 3 times a day for 7-10 days. Antioxidants: vitamin E. Washed red blood cells transfusion is performed only at lowered Hb below 50-60 g/l at a dose of 8-10 ml/kg.

In case of aregeneratory crisis, replacement transfusion therapy and stimulation of hematopoiesis are required (erythromass transfusion, prednisolone 1-2 mg/kg/day, vitamin $B_{12}$ before the appearance of reticulocytosis etc.).

Radical treatment of hereditary spherocytosis is splenectomy, which provides practical recovery, despite preservation of spherocytes and reduced osmotic resistance (degree of severity is reduced). This surgery is the method of choice that can dramatically cut the occurrence of crises in the future, as hemolysis develops due to the fact that red blood cells get stuck in the sinuses of the spleen. The optimum age for this surgery is 5-6 years. However, age cannot be considered as a contraindication to the surgery. Severe hemolytic crises, their frequent relapses, and aregeneratory crises are indications for splenectomy even in young children.

The prognosis for hereditary spherocytosis is favorable.

## Hereditary anemias associated with a defect or deficiency of erythrocyte enzyme systems

The main representative of this group is hemolytic anemia associated with deficiency of the enzyme − glucose-6-phosphate dehydrogenase (H6PDH). It was established that the lack of this enzyme affects the synthesis of ATP, condition of glutathione shield, metabolic processes in erythrocytes. Inheritance type is partly autosomal dominant part and partly bound to gender. The disease also occurs in the form of crises and remissions. The crisis is caused by action of chemical factors, and drugs in particular (NSAIDs, certain antibiotics, vitamins, sulfonamides, etc.). Triggers can also include infections and hypothermia.

**Favism** is found mainly in Southeast Asia. The crisis is provoked by intake of beans.

Clinically, the disease can occur at any age. In infants, the development of kernicterus is at high risk. The course of the condition is chronic. During the crisis, jaundice, combined with bleaching stool and dark urine are observed. Common symptoms are palpitations, lethargy, and loss of appetite.

Laboratory diagnosis: reduced number of red blood cells, Hb, normal CI, high reticulocytosis (100 ‰). The decisive method for the diagnosis is the study of G-6PDH activity in the erythrocyte.

*Treatment*. It is necessary to withdraw the drug that triggered the crises. Infusion therapy, blood transfusion can be applied. Splenectomy is not conducted in this case.

## Anemias caused by the inherited defect in hemoglobin metabolism

In humans, there are 7 options of Hb. Hemoglobin consists of 2 parallel pairs of α and β chains. In case of point mutations, Hb defect consists in the disrupted placement of amino acid residues sequence in the beta chain. In case of mutation in the area of regulatory loci, serious disorders occur: one of the chains is not synthesized at all or the chain length is reduced.

Thalassemia is a heterogeneous group of hemoglobinopathies, based on the decrease in the synthesis of polypeptide chains within the structure of normal HbA. The pathogenesis of thalassemia is associated with mutation of the 11th pair of chromosomes, resulting in disturbed synthesis of one of the globin chains. The inheritance of the pathology occurs from one (heterozygosity) or both parents (homozygosity), the type of chain disturbances determines the severity of clinical symptoms.

In 1925, the American pediatricians Cooley and Lee described thalassemia for the first time. Severe homozygous form of thalassemia was named Cooley's disease or major thalassemia. In addition, by the severity of anemia and other clinical symptoms, intermediate, low and minimum thalassemias are distinguished. Apart from the Mediterranean countries, thalassemia occurs in France, Yugoslavia, Switzerland, England, Poland, and the inhabitants of the Caucasus and Central Asia, where in some regions the carriership frequency reaches 10-27%. Isolated cases occur in all parts of the globe, they are sporadic mutations. Since homozygotes die before reaching the reproductive age, the selection goes in favor of heterozygotes.

Thalassemia is a target-like anemia with impaired ratio of HbA and HbF by biochemical indicators; the partial failure of a certain chain or its complete lack with dominance of another chain is possible. Hence, in disrupted synthesis of β-chain, α-chain will prevail, and vice versa. Beta-thalassemia is caused by reduced production of β-chains of hemoglobin. Intact α-chain are excessively accumulated in the cells of erythropoiesis, leading to membrane damage and destruction of both erythroid cells in the bone marrow and red blood cells in the peripheral blood; ineffective erythropoiesis,

hypochromic anemia and erythrocyte hemolysis develop, because hemoglobin in red blood cells is insufficient.

In thalassemia, HbF accumulates, which has great affinity for oxygen and its impeded release to tissues, leading to hypoxia. Ineffective erythropoiesis promotes the expansion of blood formation area, which affects the skeletal structure; at the same time, destruction of erythrokaryocytes in the bone marrow leads to increased iron absorption and pathological overload of the body with iron.

*Clinical presentation* of major thalassemia is already manifested in childhood. Patients have a specific "tower-like" shape of the skull, Mongoloid face with enlarged upper jaw. Early signs of Cooley's disease are spleno- and hepatomegaly, developing due to extramedullary hematopoiesis and hemosiderosis. Over time, patients develop liver cirrhosis, diabetes due to pancreatic fibrosis, and myocardial hemosiderosis leads to congestive heart failure.

*Homozygous β-thalassemia (Cooley's anemia)* is characterized by the dramatic decrease in the formation of HbA1, significant increase in the content of HbF, low, normal or high content of HbA2. Content of HbF can range from 30 to 90%.

The course of the disease is characterized by severe hemolytic anemia in the first months of life, hepato- and splenomegaly, retarded physical development of the child, jaundice and pallor of the skin. In some patients, sores in the area of legs develop. Radiological findings reveal the symptom of "hedgehog" or "brush" which is positive when HbF content increases, and negative when HbA2 increases. In infants aged from 6 months to 1 year, thinning of the cortical layer of bone is revealed in the small bones of the feet and hands, swelling of the bones and the formation of mesh structure of the bone marrow. Since the 1st year of life, impaired bone development is observed, which progresses until puberty. Prolonged hemolysis (reticulocytosis, increased free fraction of bilirubin in the blood, urobilinuria, hypersideremia) and frequent transfusions of packed red blood cells lead to hemosiderosis of the liver and spleen. The formation of bilirubin stones in the biliary tract often occurs. In severe homozygous thalassemia, patients die in the first year of life.

*Heterozygous β-thalassemia* occurs in the form of both asymptomatic and manifested forms with slightly enlarged spleen, specific bone changes, and often severe hypochromic anemia. On examination of patients' relatives, minimal form of β-thalassemia is often revealed.

There are such forms of *α-thalassemia*: fetal hydrops with Hb Bart's (y4), hemoglobinopathy H (β4), α-thalassemia-1 and α-thalassemia-2. Fetal hydrops is a homozygous state (by genes a-th-l) and is often incompatible with life. Pregnancy in such cases is arbitrarily interrupted; brain dropsy and hepatomegaly are found in the fetus. Electrophoretic studies reveal Hb Bart's (80-90%), combined with traces of HbH.

Hemoglobin H is one of the variants of α-thalassemia, which is manifested by hemolytic anemia, enlarged spleen, bone changes. The clinical presentation of the peripheral blood is characterized by reduction of Hb, hypochromia and multiple inclusions in erythrocytes (HbH sediment).

α-thalassemia-1 (minor form of the disease) occurs when a-th-1 gene is combined with a normal gene of α-chain synthesis. It is characterized by slight anemia, moderate anisocytosis, interior erythrocytic inclusions, increased osmotic resistance of red blood cells.

α-thalassemia-2 (minimum form of the disease) develops when a-th-2 gene is combined with a normal gene of α-chain synthesis. Clinical manifestations are absent.

*Diagnostics of thalassemia*

In the blood test, hypochromic anemia with high reticulocyte count of varying severity is determined. In the blood smear, hypochromic erythrocytes of small sizes and different shapes, target-like red blood cells are detected; numerous normocytes. In the biochemical analysis of blood, hyperbilirubinemia due to free fraction is found, hypersideremia, reduced total iron-binding serum capacity, increased LDH activity. In erythrocytes, the level of fetal hemoglobin is increased.

α-thalassemia is widespread mainly in Southeast Asia, China, Africa and the Mediterranean. Synthesis of α-chains is encoded by 4 genes, therefore, the degree of synthesis disruption is smaller than in β-thalassemia; pronounced imbalance develops only when all 4 genes are affected. At the same time, β-chain aggregates whose number

in α-thalassemia is in abundance, are more soluble than aggregates from α-chains, therefore hemolysis in α-thalassemia is less pronounced than in β-thalassemia and erythropoiesis is more effective. Thus, clinical and laboratory data in α-thalassemia are less pronounced than with β-thalassemia; their main difference consists in the biochemical composition of erythrocytes hemoglobin.

*Treatment of thalassemia:*

Transfusion of red blood cells. In severe forms of thalassemia, the need for transfusion of erythrocytic preparations arises from the first months of life and persists for life, developing the so-called transfusion dependence. This means that Hb in the blood of patients constantly continues to decline and there are no other real ways to improve it, except for such transfusions. It is desirable that a patient's blood Hb content does not fall to the low level; it is better to conduct repeated transfusions while it is still at the satisfying levels − 95-100 g/l. The fact is that in the marked reduction of Hb, pathological processes, characteristic for thalassemia, are activated, such as abnormal increase in the size of the liver and spleen; deteriorating function of all organs, reduced resistance to infections due to increased oxygen starvation.

In major β-thalassemia, the lack of red blood cells in the circulating bloodstream is managed, in addition to the replacement via transfusions of red blood cells, by inhibition of its own excessive, but ineffective hematopoiesis in the patient's bone marrow. Iron absorption in the intestine also decreases. Thus, the observation of patients with thalassemia is important to prevent episodes of pronounced drop in hemoglobin − which, firstly, may directly threaten the life, and secondly, contributes to the progression of pathological manifestations of thalassemia.

At the same time, transfusion of erythrocytic blood products has significant disadvantages. It is known that in blood transfusions one must take into account the compatibility of donor's and recipient's blood type, Rh factor. However, since there are no genetically identical people in nature, in the repeated transfusions the patient sooner or later begins to produce antibodies that react with other, more complex parts of the membranes of red blood cells transfused. Therefore, after some time (usually 3-4 years), the patient's body becomes biologically compatible not with any donor, relevant by

blood group and Rh factor, but only with certain donors that have a specific set of protein antigens on red blood cells.

Therefore, it is preferable to carry out transfusion of erythrocyte concentrate in thalassemia on individual selection, at a special isoserology laboratory of blood transfusion station. In addition, erythrocyte concentrate for patients with thalassemia should be specially purified from other biological components contained in the blood (white blood cells, plasma proteins) as they are the cause of transfusion complications. Whole blood is not currently used for transfusion. Transfusion of erythrocyte concentrate, untreated by additional methods is also not desirable. One can also use filtered or washed red blood cells, which are much less likely to cause reactions.

In milder forms of thalassemia, or when patients have mild anemia or normal hemoglobin, and most importantly, hemoglobin is consistently kept at the same level for a long time, transfusion of blood products is not conducted.

*Desferal*. An important part of treatment is removing excess iron from the body with medicines from the "chelates" group, by the drug desferal. Currently, treatment with subcutaneous hours-long injections is accepted, the use of special devices (pumps) is the most convenient. From the syringe, fixed in the pump, desferal is gradually injected subcutaneously to the patient within a few hours. Ideally, patients with severe thalassemia should receive lifelong desferal 5 days a week, but in real life it is hardly achievable.

In some countries with high prevalence of thalassemia (e.g., Italy), there are special government programs aimed at helping patients with thalassemia, which provide them, apart from other treatments, with desferal and pumps for its administering. A similar program exists in Azerbaijan.

Desferal is kept in a dark place at temperature +8-15$^0$C, it must be diluted immediately before administration. Infants under 2 years of age are prescribed desferal treatment with caution. In these children, desferal treatment is started, once about 15-20 blood transfusions have already been conducted. To improve the quality of life, it is better to administer desferal infusion at night. It is necessary to systematically change the places of subcutaneous injection for preventing the local damage to the skin and

underlying soft tissues. As with any treatment, desferal therapy has side effects. The most common are allergic reactions to the drug.

*Splenectomy*. This surgery does not cure thalassemia itself, although it can alleviate the symptoms. Operation is not feasible before the age of 5 years; the age of 8-10 years is the best period for surgery. In the first year, there is usually a beneficial effect, but further on, the recurrence of thalassemia manifestation can be observed, hepatomegaly can progress. In addition, the risk of infection increases, especially regarding the overlay of pneumococcal disease, such as sepsis, pneumonia.

*Bone marrow transplantation* is the only method for radical treatment of thalassemia.

Patients with thalassemia should follow the diet No.5. Useful beverages containing tannin are: tea, cocoa, as well as nuts and soy. These products reduce the absorption of iron. To improve the liver function, hepatoprotectors, lipoic acid, vitamin E, Essentiale, courses of choleretic herbs, etc. are prescribed. The output of iron from the body is improved by ascorbic acid 50 mg/day up to 10 years and 100 mg/day in children above the age of 10 years.

*Prevention of thalassemia* is based on the screening programs for carriership. For example, in Greece, Cyprus, Iran and Italy, the screening for thalassemia before marriage is compulsory. In the UK, Ireland and other countries of northwestern Europe, where prenatal diagnostics is widespread, the screening is conducted during pregnancy.

## Sickle cell anemia

Sickle cell anemia is a representative of hemoglobinopathies. In this regard, in case of homozygous carriership, sickle cell anemia is implied, while in heterozygous carriership − sickle cell abnormality. The disease was first described in 1910 by the American physician James B. Herrick in a black American student from the West Indies. Sickle cell anemia is the most common in Central Africa. It is common among some peoples of India, on the island of Ceylon, in Turkey, Iran, Iraq, Algeria, Tunisia, Kuwait, on the island of Cuba.

Sickle cell phenomenon is a consequence of low solubility of hemoglobin, which gave away oxygen. Hemoglobin A, deprived of oxygen, is dissolved twice less than

hemoglobin A, saturated with oxygen. The solubility of hemoglobin S, when deprived of oxygen, decreases by 100 times. This leads to the formation of gel. At microscopy, crystals sized 15 μm are revealed, resembling the sickle-shaped red blood cells that disappear after the integration of oxygen.

*Homozygous form of hemoglobinopathy S.* Clinical course of homozygous form of hemoglobinopathy S consists of moderate normochromic anemia and thrombotic complications. The disease starts to manifest itself several months after birth, since the fetal hemoglobin does not contain the pathological chain. In addition, the high level of fetal hemoglobin in young children after the onset of pathological chain reduces the sickle-shaped phenomenon through the increased affinity for oxygen. The most common symptom of sickle cell anemia in young children is the damage of skeletal system: sharp pain in the joints, swelling of the feet, hands, legs. These changes are associated with thrombosis of blood vessels that supply bones. Quite often there is aseptic necrosis of head of femur and humerus. Thromboses often cause pulmonary infarction. Patients are often tall, thin, with a curved spine, they often have a high "tower-like" skull, teeth are changed; infantilism, sometimes signs of eunuchoidism are present. Abdominal pain can imitate various diseases of the abdominal cavity.

A frequent complication of sickle cell disease is vision disorder, related to changes in blood vessels of the retina. Thrombosis leads to the development of arteriovenous anastomoses; peripheral vascular and fibrous proliferates with areas of black pigmentation may be on the retina. Bleeding in the vitreous and retinal detachment often leads to blindness. Thrombosis of large vessels leads to renal, pulmonary infarctions; frequent thromboses of the brain vessels.

The spleen in young children is large, but further it decreases and after the age of 5 years, enlargement of the spleen is rare. This is caused by "autosplenectomy" due to fibrosis of the spleen. The liver in sickle-cell anemia is also increased. Sometimes in the periods of exacerbation, children develop severe hemolytic or aplastic crises. Moreover, in sickle cell anemia, sequestration crises are described, in which a significant portion of red blood cells is temporarily deposited in internal organs and is not destroyed. This can lead to serious collapse.

*Heterozygous form of hemoglobinopathy S (sickle cell anemia)*

Patients never know about their disease; hemoglobin count and general condition are normal. The only symptom in some patients is hematuria which is associated with minor infarctions in renal vessels. The content of pathological Hb in erythrocytes of patients with heterozygous form of hemoglobinopathy is low, and clinical manifestations of the disease are observed only during hypoxia, in case of severe pneumonia, during anesthesia. Thromboses on significant exertion, when climbing in the mountains, thrombotic complications when diving have been described.

There is often a combination of heterozygous form of sickle-cell anemia with β-thalassemia. The disease is considerably milder than homozygous thalassemia and homozygous form of sickle cell anemia. The combination of thalassemia and hemoglobinopathy S is characterized by significant enlargement of the spleen, expressed hypochromia and target-like red blood cells. Thrombotic complications may occur, but much less frequently than in sickle cell anemia. In this form, the disease is characterized by joint pain, severe episodes of abdominal pain.

*Diagnostics of sickle cell anemia*. Anemia is insignificant in most cases, Hb content does not fall below 60-80 g/l. CI is normal. In the blood, sickle-shaped erythrocytes are detected, the amount of reticulocytes and erythrokaryocytes in the bone marrow is increased. Sickle-shaped red blood cells are detected using metabisulfite test: in Hb electrophoresis, two major fractions − HbA and HbS − are defined. Hyperbilirubinemia by indirect fraction is characteristic.

*Treatment of sickle cell anemia*. Most often, one has to deal with thrombotic crises. Treatment requires, above all, adequate fluid supply. Sickle-shaped phenomenon decreases with reduced concentration of Hb in erythrocytes. It is recommended to consume sufficient amount of fluid, in crisis condition, it is necessary to administer diluted 2-fold isotonic sodium chloride solution. It is very important to manage the infectious complications. Oxygen therapy is recommended, in severe anemia − transfusion of packed red blood cells.

In most cases, treatment of heterozygous condition by HbS is not necessary.

## Aplastic anemia

ICD ciphers − 10: D 61.1, D 61.2, D 61.3

Aplastic anemia is a disease, the leading clinical feature of which is peripheral pancytopenia (reduced amount of blood cells), accompanied by a decrease in bone marrow cellular structure without evidence of its abnormal infiltration.

*Classification of aplastic anemias*:

I. Hereditary aplastic anemias.

1. Hereditary aplastic anemias with the total lesion of hematopoiesis:

a) genetic hypoplastic anemia with the total lesion of hematopoiesis and congenital anomalies of development (Fanconi anemia);

b) genetic familial hypoplastic anemia with the total lesion of hematopoiesis without congenital anomalies (Estren-Dameshek anemia);

c) partial genetic hypoplastic anemia with the selective lesion of erythropoiesis (Blackfan-Diamond syndrome).

II. Acquired aplastic and hypoplastic anemias.

1. With the total lesion of hematopoiesis: acute, subacute, chronic.

2. With the selective lesion of erythropoiesis − acquired red blood hypoplastic anemia.

The severity of aplastic anemia is determined by the level of granulocytes $<0.5 \cdot 10^9$/l, platelets $<10 \cdot 10^9$/l, and reticulocytes <1%; in myelogram: few cells; non-hematopoietic cells amount to > 65%. By the amount of neutrophils, a very severe form is distinguished, when the neutrophils count is $<0.2 \cdot 10^9$/l, and medium severe, when the amount of neutrophils varies within $0.2\text{-}0.5 \cdot 10^9$/l.

Etiological factors of aplastic anemia are: genetic defects of stem cells; idiopathic aplasias (87% according to the European registry for bone marrow transplantation); toxic environmental factors (benzene compounds, the effect of ionizing radiation); hepatitis viruses A, B, C, (posthepatitis aplasia (6%), cytomegalovirus, Epstein-Barr virus); drugs (cytotoxic drugs, tetracycline, sulfonamides, analgin).

Fanconi anemia

This is the hypoplastic anemia with the total lesion of hematopoiesis and congenital abnormalities. The disease was described by Fankoni in 1927 in 3 children from the same family. Since that time, numerous family cases have been described. Inheritance of the disease is autosomal recessive, it is manifested in homozygotes. It is more common in boys.

*Pathogenesis*. In Fanconi anemia, there is a defect in stem cells. There is a defect in the DNA repair system in fibroblasts of patients with Fanconi anemia. Most likely, this is due to the slight damage to chromosomes by ultraviolet radiation, low doses of cytotoxic drugs.

*Clinical course* is manifested at the age of 4-10 years. Anemia progresses gradually, first symptoms are hemorrhages and bruising. Skin hyperpigmentation, congenital malformation of bones, kidney defects, and congenital heart defects are the obligatory symptoms. Along with these symptoms, increased susceptibility to infections develops. The liver, spleen, lymph nodes are not enlarged. Neurological disorders are identified (strabismus, deafness, mental retardation and others), genital lesions (absence of one or both testicles, hypospadias), which is a manifestation of polyglandular endocrine insufficiency.

*Diagnosis*. The blood pancytopenia and progressive decrease in Hb concentration are noted. The amount of reticulocytes decreases. In the bone marrow punctuate, the impairment of all three links is observed, leading to pancytopenia and replacement of blood-forming cells by the adipose tissue. In 50% of children, high content of amino acids in urine is revealed.

Estren-Dameshek anemia

Hereditary hypoplastic anemia with total lesion of hematopoiesis without congenital anomalies. It is characterized by progressive bone marrow hypoplasia and panhemocytopenia in the peripheral blood. Clinical and hematological pattern is similar to Fanconi anemia, but unlike it, this anemia is not accompanied by developmental abnormalities.

Blackfan-Diamond syndrome

Hereditary hypoplastic anemia with selective lesion of erythropoiesis. The autosomal dominant and autosomal recessive inheritance has been proven. In the blood test: pronounced anemia, which has normochromic character, the number of reticulocytes is reduced. The leukocytes and platelets count is normal. In myelogram, there is a sharp decrease in the amount of elements of erythroid series.

Acquired AA can develop as a result of chemical agents (benzene), medications, infectious agents and ionizing radiation. In many cases, the cause of the disease is unknown; such anemia is regarded as idiopathic.

*The acute form of AA* begins suddenly and has a rapid course; it is characterized by the manifested hemorrhagic syndrome and septic-necrotic processes. Necrotic lesions of the mucous membranes develop early, there is often necrotic angina, rarely − necrosis of the skin, the total intoxication increases. The course of acquired hypoplastic anemia can be acute, subacute and chronic.

*Acute hypoplastic anemia* has a longer course than acute aplasia. Pallor, weakness, hemorrhagic syndrome, and progressive necrotic lesions of the mucous membranes are intensifying for several months.

*Subacute hypoplastic anemia* begins gradually. At first, one can observe pallor, fatigue, dizziness, subfebrile temperature with periodic rises to 38-39°C. Hemorrhagic rash, accompanied by bleeding, appears on the skin.

*Chronic hypoplastic anemia* is characterized by a long course. The disease develops slowly. The earliest clinical signs are: gradually increasing fatigue, loss of appetite, pallor. Hemorrhagic syndrome, necrotic skin and mucous membranes occur less frequently.

*Treatment of aplastic anemias*

I. Treatment of acquired AA should be administered only after the full scope of diagnostic procedures and reference of the bone marrow specimens to the research center, which has the ability to confirm/establish the diagnosis in accordance with standard criteria.

In severe/very severe AA, patients who have HLA-identical family donor must receive stem cell transplantation. With no possibility of transplantation, treatment may

include immunosuppressive therapy with combination of antithymocyte globulin (ATG) and cyclosporine A. In order to accelerate the regeneration of neutrophils, granulocyte colony stimulating factor (G-CSF) is administered at a dose of 5.10 mg/kg/day for 28-42 days. At the time of treatment, patients require isolation, strict rules of hygiene, antibiotics, antifungal and antiviral drugs.

II. Treatment of congenital hypoplastic anemias.

1. In Fanconi anemia, the combination of glucocorticoids (at a dose of 2-3 mg/kg/day) and androgens (testosterone propionate 1.2 mg/kg/day) is used. Currently, the only method for definitive cure of hematological syndrome is allogenic transplantation of hematopoietic stem cells (HSCT).

2. In Blackfan-Diamond syndrome, highly effective is early administration of glucocorticoids (2.5 mg/kg/day). If there is no response to this therapy, immunosuppressant treatment is used (cyclosporin A + antilymphocytic immunoglobulin). Bone marrow transplantation or transfusion of stem cells derived from cord blood is also prescribed. Transfusions of packed red blood cells is indicated.

*Prognosis*. Using bone marrow transplantation, it is possible to cure 50% of patients with severe AA. In some patients, aplastic syndrome becomes the onset of acute leukemia. Sometimes the signs of hemoblastosis are revealed only a few years after the onset.

# UNIT 6. HEMOBLASTOSES

Hemoblastoses include: acute leukemia, myeloproliferative tumors (chronic myeloid leukemia, polycythemia, essential thrombocytopenia, idiopathic myelofibrosis), Hodgkin's disease and non-Hodgkin's lymphomas.

## Acute leukemia

Acute leukemia is a malignant neoplasm of the blood system. The tumor, arising from hematopoietic cells, affects primarily the bone marrow.

Myeloproliferative tumors is the group of hematologic diseases, characterized by proliferation of all hematopoiesis lineages in the bone marrow (excluding lymphopoiesis) and resulting from early destruction of myelopoiesis progenitor cells.

Acute leukemia is the most common cancerous disease in children. It accounts for 1/3 of all new cancers that occur each year. In childhood, acute lymphoblastic leukemia (ALL) is the most common. It occurs in 76-82% of total leukemia cases. Acute non-lymphoblastic leukemia occurs in 17-21% of cases and chronic myelogenous leukemia − in 3% of cases.

Leukemia occurs with a frequency of 4-5 cases per 100 000 children, most often it occurs at the age of 3-5 years. The second peak of high frequency is observed at the age of 20-30 years. Boys suffer more often than girls. Leukemia mostly affects children from families of middle and high income levels. Recently, there have been more cases of leukemia among children from rural areas. This makes it possible to examine the relationship of leukemia with the use of pesticides, herbicides and exposure to viruses. There is evidence of increasing numbers of leukemia cases after flu epidemic. It is believed that infections contracted in childhood (rubella, measles, chicken pox, whooping cough) to some extent prevent the occurrence of leukemia.

There is some geographic dependence − the lower incidence of ALL I is observed in Africa and Central Asia, relatively high − in China, Japan, USA and Europe. High risk of disease is detected in patients with chromosomal disorders (Down syndrome, etc.). Children who are under the influence of ionizing radiation and X-rays, as well as

in children with high birth weight (more than 4000 g) are at risk for the development of ALL. Some role is certainly played by infectious diseases, especially viral in nature.

The causes of tumors in children have not been sufficiently studied. The role of endogenous carcinogens of transplacental action, radiation effects, genetic susceptibility factors for tumor occurrence, and effect of specific viruses and agents have been discussed. Leukemia genesis in a person has the multifactorial character, where external factors such as exposure and viral infections interact with the constitutional ones.

Environmental factor, that may influence the occurrence of leukemia, is the effect of X-ray or γ-radiation. Clinical data indicate that exposure increases the incidence of leukemia. Mechanisms of radiation leukemia genesis are multifaceted and can be considered as follows: radiation acts directly on cells; leukemia develops from damaged cells after the direct effect of radiation on the genetic apparatus of cells and increased susceptibility to infectious or other exogenous influences.

Leukemia does not necessarily develop directly from the irradiated cell but is also due to: a) normal instability processes of cell division (radiation kills cells, alters cellular environment, promoting the instability of genetic division processes); b) radiation increases susceptibility to infections or exogenous agents, changing the immunological response and detoxification mechanisms.

An important role in the occurrence of leukemia belongs to genetic factors. The role of heredity is proved in chronic lymphocytic leukemia, which accounts for a high percentage (43%) of disease in relatives. There are many cases of family leukemia in brothers and sisters or a parent. There are families in which leukemia occurs in several generations. In patients with chronic myeloid leukemia, chromosomal changes were discovered that were called “Philadelphia chromosome” (Ph-chromosome), by the name of the city where the abnormal chromosome was discovered. For the “Philadelphia chromosome”, deletion (loss) of the long arm of group G chromosome is typical.

A number of authors believe that the main causes of acute leukemia in children are the spontaneous mutations, since the unique properties of high proliferation are inherent to precursors of lymphocytes.

Retroviruses are of particular importance in the study of the mechanism of leukemia genesis. By the example of the model of the latter, it was found that the genome of cancer-causing viruses contains specific genes or their proteins that are directly responsible for the transformation of normal cells into tumors. The discovery of reverse transcriptase has proven the impact of retrovirus genome, consisting of RNA, on the DNA of the host cell. Reverse transcriptase synthesizes the molecule that contains the same genetic information encoded in the viral RNA. RNA can be integrated into the genome of the host cell. Since RNA of the virus carries the information required for the synthesis of viral components, its activation can lead to the emergence of new viruses (productive infection), chromosomal aberrations (disorder of proliferation and differentiation, leading to malignant growth) and death of the host cell.

Data on viral induction of leukemia in animals and birds have given rise to search for oncogenic viruses in humans.

*Pathogenesis*. Tumors of the hematopoietic system undergo in their development two major stages. The first phase is the emergence of mutant cells and autonomously proliferating offspring − clone. At this stage, the cell has no signs or polymorphism, or atypism. In the second phase, due to recurrent mutations clones (subclones) appear, usually already with dramatically increased inclination to mutations, and tumor transforms into the polyclonal one. At this stage, cellular polymorphism appears. Thus, maturation of all or parts of cells is disturbed and there are atypical elements.

According to the clonal theory, the development of leukemic population occurs from a single cell, and the rate of growth depends on the proportion of actively proliferating cells. Leukemic population is divided into two subsets: proliferating and currently non-proliferating. The first one consists of cells that are in mitotic cycle. This population constitutes 6-10% of the weight of leukemic cells. The most part are represented by leukemia cells which are beyond the mitotic cycle in the phase of “rest” ($G_0$). Thus, the rapid proliferation of cells in acute leukemia occurs. An important feature of cells that are in the state of “rest” is the significant extension of their life as compared to normal ones and their ability to exit from the state of “rest” in the mitotic cycle under autonomous impulses emanating from the proliferating subpopulation.

It is estimated that one proliferating leukemia cell, having lost the ability to differentiate, but maintaining the potential for the uncontrolled number of cell divisions, on average over the period 3 months provides a huge number of cells − $10^{12}$, which weigh around 1 kg. It is believed that with this number of leukemia cells, clinical manifestations of ALL appear. In fact, the accumulation of leukemia cells is much slower, because the mitotic cycle involves only proliferating subpopulation. A. Maner has calculated the time required for the formation of a single abnormal cell of leukemic clone weighing 1 kg, i.e., for the manifestation of the disease − 3.5 years. This period of time is consistent with clinical data − the peak of ALL in children is accounted for the age of 3-5 years. Thus, the leukemic cells in the majority of cases occur in the antenatal period, when there is an intensive development of the lymphatic system of the fetus.

It is important to point out that in ALL, there is a close connection between the proliferating subpopulation and that of at "rest" phase. Replenishing of cells in proliferating pool is possible by means of cells staying at rest which indicates at certain autonomy of leukemic cell population in general and its ability of self-renewal. When leukemic population reaches a certain critical mass, the division of normal stem cells is inhibited and their production is significantly reduced. Inhibition of normal hematopoiesis may also be due to the release of normal hematopoiesis inhibitors by tumor cells which is manifested by the development of anemia, thrombocytopenia, and neutropenia. Increased number of mitotic cycles in proliferating cells subpopulation and the accumulation of non-proliferating leukemic subpopulation cells are the basis for the development of leukemic hyperplasia, clinically manifested by hyperplastic syndrome (increased liver, spleen, lymph nodes).

To understand the dynamics of the process in ALL, one should recall another pathogenetic mechanism: the ability of leukemic cells to metastasize by the "feeling of home" principle. In the early stages of the process, many colonies of leukemia cells are formed.

Classification of leukemias

In order to unify the cytochemical and morphological signs of differentiation of acute leukemia, hematologists of France, USA and England created classification,

known as the FAB: France-America-British. According to the FAB classification, acute leukemias are divided into 3 groups:

1) acute non-lymphoblastic (myeloid) leukemia (M0 − undifferentiated leukemia, M1 − myeloblastic undifferentiated, M2 − myeloblastic differentiated, M3 − promyelocytic, M4 − myelomonoblast leukemia, M5 − monoblast leukemia, M6 − erythremic myelosis, M7 − megakaryocytic leukemia).

2) acute lymphoblastic leukemia (L1, L2, L3):

• L1 − acute microlymphoblastic leukemia dominated by small lymphoid cells (84-88% of all cases of ALL).

• L2 − acute leukemia with typical lymphoblasts (more common in adults and in 8-15% of cases in children).

• L3 − acute leukemia lymphoblasts with large basophilic, vacuolated cytoplasm (0.7-1.5% of all cases of ALL).

3) myelopoietic dysplasia (4 types).

ALL has immunocytological options: O-cell, B-cell, T-cell, neither A- nor B, or “Common” type.

“Common” ALL (C-ALL) is the most widespread in children (80% of all cases), and it is usually observed at the age of 3-5 years. The course it less aggressive, neuroleukemia and hyperleukocytosis are rarely seen.

T-lymphoblastic leukemia (T-ALL) − 15-25% of all cases of ALL, boys suffer more often; the course is more aggressive, more pronounced signs of hyperplastic syndrome: high leukocytosis, tumor proliferation of lymph nodes, especially in the mediastinum, enlarged liver, spleen, high frequency of neuroleukemia.

O-lymphoblastic leukemia (O-ALL) − 1% of all cases, it is heterogeneous by its course, there can be both mild and aggressive variants.

B-lymphoblastic leukemia (B-ALL) occurs in 1% of cases, it is distinguished by major malignancy and resistance to treatment, and characterized by significant hepato- and splenomegaly, total infiltration of bone marrow, extramedullary proliferation of the tumor. In the blood: anemia, thrombocytopenia, hyperleukocytosis. Prognosis is highly unfavorable.

Diagnosis is based on ALL cytochemical features of cells: they have a negative reaction to peroxidase.

*Clinical and hematological manifestations of acute leukemia*

Clinical manifestations of acute leukemia at primary active stage of the disease are different and there are no specific pathological manifestations. Children develop general symptoms of physical ailment (fatigue, loss of appetite, lethargy and so on). However, it is necessary to remember the main symptoms that are characteristic for ALL:

1. Proliferative syndrome − swollen lymph nodes. Cervical and submandibular lymph nodes are affected most often; there may be an increase of several groups at the same time. Affected lymph nodes are of elastic consistency, painless at palpation, not glomerate to surrounding tissues, mobile, skin over them is not changed.

2. Hepatolienal syndrome − isolated enlargement of the liver and spleen.

3. Hemorrhagic syndrome (55-60% of children) is caused by thrombocytopenia, leukemic vascular lesions, secondary coagulation disorders. There may be skin hemorrhages, bleeding of mucous membranes.

4. Anemic syndrome − anemia, most often normochromic or hypochromic.

5. Pain syndrome − pain in bones due to infiltration of bones with leukemic cells. Young children cease walking. Arthralgia may be observed.

6. Immune dysfunction syndrome − children develop necrotic tonsillitis, stomatitis and other infections.

In the remission period, it is very important not to miss out the bone marrow manifestations of ALL that may be in the form of neuroleukemia, leukemic infiltration of the testicles, ovaries, eyes, liver, spleen, gums and other organs. The most common complication of ALL is affected CNS − leukemic infiltration of the cerebral vessels (leukemic meningitis, meningoencephalitis). Clinical manifestations of hypertensive syndrome are: headache, vomiting, photophobia, decreased visual acuity, positive meningeal symptoms.

T-cell variant of leukemia is characterized by a marked increase in lymph nodes, thymus.

The clinical presentation of myeloid leukemia (especially M5) is characterized by the presence of infiltrate on the face, in the cerebral cranium, in the ribs, in retroorbital area. Sometimes leukemids appear along the vessels. In the presentation of the peripheral blood in the developed clinical course, there are severe anemia, thrombocytopenia. The amount of leukocytes may be different: from leukopenia ($2.0 \cdot 10^9$/l) to hyperleukocytosis (up to $400.0 \cdot 10^9$/l), the presence of blasts and mature cells in the absence of intermediate forms is characteristic.

*Stages of ALL*

1. Primary-active stage (primary acute period) is characterized by the sharp inhibition of normal hematopoiesis, significant blast infiltration of bone marrow.

2. Remission.

3. Recovery.

4. Relapse.

*Diagnosis of acute leukemia* is based on the study of bone marrow. The diagnosis of acute leukemia cannot be made only in the presence of blast cells in peripheral blood. Blast cells in the blood may occur due to leukemoid reaction in response to infection, hemolysis (especially in infants). Thus, the presence of blast cells is not an accurate marker of acute leukemia and, conversely, the lack of blast cells in peripheral blood does not exclude the diagnosis of acute leukemia.

*The criteria for full remission:*

1) in myelogram: blast cells are less than 5%

2) lack of local leukemic infiltrates

3) lack of leukemic cells in the lumbar punctate on the 29th day of protocol treatment.

*Treatment of leukemia*. Basic therapy of ALL is based on protocols of German cooperative group BFM (Berlin, Frankfurt, Munster), whose therapeutic concept today is one of the most effective. Protocol therapy is performed with the aim of induction and consolidation of remission and prevention or treatment of neuroleukemia with initial CNS lesion. The principle of treatment consists in the use of alternating chemotherapy with various cytotoxic drugs with the account of the division of blast cells and in the

therapeutic possibilities of complete eradication of leukemic clone. The therapy is conducted in a differentiated manner according to the risk groups of patients.

*Definition of risk groups*

To determine the treatment strategy (the choice of treatment protocol), the risk groups need to be distinguished, taking into account the risk factors. There are three risk groups: low, medium and high. The criteria determining the risk groups include: the child's age; the amount of leukocytes in the peripheral blood; the amount of blasts in the peripheral blood in 1 $mm^3$ on the 8th day of treatment with prednisolone; remission on the 33rd day of protocol treatment.

The zero risk group will include children with the following indicators:

1. Age 1-6 years;

2. The initial amount of leukocytes in the peripheral blood is less than 20 000 in 1 $mm^3$.

3. The amount of blasts in the peripheral blood on the 8th day of protocol treatment with prednisolone is less than 1000 to 1 $mm^3$.

4. Complete remission on the 33rd day of treatment according to the protocol.

The group of medium-risk will include children with the following parameters:

1. Age under 1 year and above 6 years.

2. The initial amount of leukocytes in the peripheral blood is more than 20 000 in 1 $mm^3$.

3. On the 8th day of treatment with prednisolone, blast cells in the peripheral blood are less than 1000 in 1 $mm^3$.

4. Complete remission on the 33rd day of treatment according to the protocol.

The group of high-risk will include children with the following parameters:

1. Regardless of age.

2. On the 8th day of treatment with prednisolone, blast cells in the peripheral blood are more than 1000 in 1 $mm^3$.

3. Lack of complete remission after 33 days of treatment according to the protocol.

The general direction of the effect of cytostatic drugs is interference with the intracellular metabolism of leukemic cells with the aim of stopping the synthesis or destruction of substances vital for them, ending in the cell death. Each cytostatic drug has its place of action in the intracellular metabolism, therefore they sensitize the cell that is in a certain phase of the life cycle. By their action on cell kinetics, cytotoxic drugs are divided into two groups:

1. Compounds which have a selective effect on a certain phase of the mitotic cycle, causing cell death in any stage of the cycle (non–cycle-specific agents). The most typical representatives of this group are alkylating compounds and anticancer antibiotics.

2. Chemotherapy drugs that are characterized by a selective effect on a certain phase of the mitotic cycle (cycle-specific agents). This group includes antimetabolites entering into a competitive relationship with the relevant metabolites and leading to cell death in one of the stages of DNA synthesis, i.e., substances act in a certain phase of DNA synthesis (S-phase, M-phase, etc.).

Cytostatics are most active against the proliferating cells (phases S, M, $G_1$, $G_2$) and to a much lesser extent affect non-proliferating pool, ($G_0$), which is the bulk of the tumor's pathological substrate. This determines the difficult treatment of leukemia, since it is impossible to effectively destroy cells in the resting phase (phase $G_0$). Application of non–cycle-specific agents is limited by their high toxicity, which manifests itself equally both in relation to leukemic and healthy somatic cells.

Currently, the superiority of polychemotherapy over monochemotherapy has been proven. Combination therapy is intended to capture tumor cells to the fullest extent, in whatever phase of the mitotic cycle they are.

For performance of current aggressive chemotherapy programs, it is mandatory to ensure the reliable long-term central venous access. According to the BMF-protocols, patients of the lowest risk group are initially treated according to the protocol No.1, and then M protocol and protocol No.2 in conjunction with brain radiation to prevent neuroleukemia. Irradiation of the brain during the protocol No.1 is indicated only in case of primary lesion of CNS.

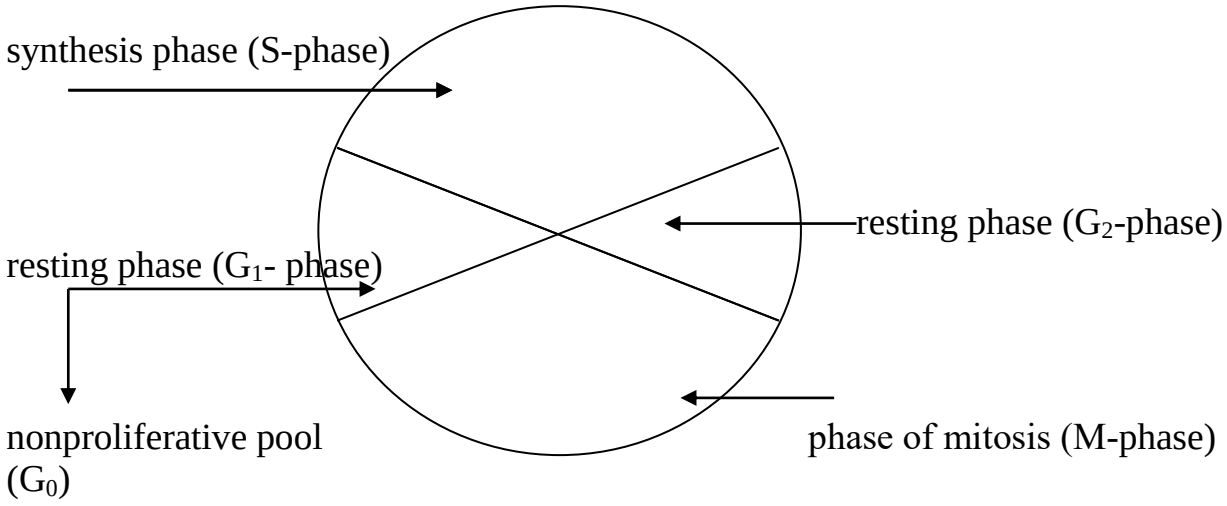



**Fig. 2. Phases of mitotic cycle life of leukemic cells.**

Patients from groups of middle and high risk receive treatment according to the same protocol, but with mandatory irradiation of the brain.

The main drugs used in the protocols are cytostatics. All drugs under the protocol are prescribed per $m^2$ of the body surface. On the first day after the diagnosis the doctor must begin the treatment. The child is prescribed prednisolone 60 mg/$m^2$ from day 1 to 7. On the 8th day, complete blood count is conducted, if the number of blasts in the peripheral blood is less than 1000 $mm^3$, treatment begins under protocol No.1.

Phase 1: Prednisolone is prescribed at the same doses from the 8th to 28th day, from day 28, the dose of prednisolone is reduced three times by half every 3 days. Vincristine is administered at a dose of 1.5 mg/$m^2$ intravenously at days 8, 15, 22, 29 of the protocol. Daunorubicin (rubomycin) 30 mg/$m^2$ intravenously at days 8, 15, 22, 29 of the protocol. L-asparaginase 10 000 U/$m^2$ on days 12, 15, 18, 21, 24, 27, 30, 33 of the protocol. On the 29th day of the protocol treatment, lumbar puncture is conducted. On the 33rd day, sternal puncture is performed to determine remission.

Phase 2: Cyclophosphamide 1000 ml/$m^2$ on days 36 and 64. With the administering of the drug, acute renal failure may develop, therefore, it is necessary to monitor urine output, fluid infusion 24 hours before the administration, the use of furosemide 0.5 mg/kg after administration of cyclophosphamide. 6-mercaptopurine 60 mg/$m^2$ per day in 3 divided doses on days 36 and 63 of the treatment (28 days in total).

Cytosar 75 mg/m$^2$ intravenously in 4-day blocks: from day 38 to 41; from day 45 to 48; from day 52 to 55; from day 59 to 62. Methotrexate is administered by endolumbal route on days 38, 49 and 59.

After the end of Protocol No.1, a break for 2 weeks is made and Protocol M begins with the duration of four weeks, then after a 2-weeks break, Protocol No.2 starts. Two weeks after Protocol No.2, supportive therapy starts, which lasts up to 24 months of total duration of treatment. Maintenance therapy: 6-mercaptopurine 50 mg/m$^2$ orally once a day in the evening, methotrexate 20 mg/m$^2$ orally 1 time a week.

After the completion of treatment protocol, the child is at the dispensary follow-up list for 5 years. Complete remission that lasts five years or more is considered as recovery. However, relapse of ALL can occur in 6-7 years and even in 16-20 years afterwards.

*Relapse* is a condition in which there is the returning of active stage of the disease after complete remission. This recurrence may be of extramedullary character (neuroleukemia, lesions of eyes, gonads, etc.) or of bone marrow nature. Since the current treatment can cure up to 70% of children with ALL, it is especially important to prevent infection, bleeding and metabolic disorders during the induction of remission.

*Features of acute myelogenous leukemia (AML).* Clinical manifestations of AML, apart from general symptoms of intoxication, have a tendency to more pronounced hemorrhagic syndrome due to thrombocytopenia. Unlike ALL, there are no clear criteria for AML risk. Treatment is also carried out according to the protocols, but these children need prophylaxis of bleeding, infections, more severe isolation. Corticosteroids are not used for treatment. Prevention of neuroleukemia is provided by intrathecal administration of cytosar (30 mg, single dose) every 2 weeks during the intensive course and cranial irradiation after its completion with the total dose of 18 Gy.

Complications of chemotherapy. Polychemotherapy is naturally accompanied by severe neutropenia, thrombocytopenia, which last for 1-3 weeks. The most common manifestations of the disease are cytostatic agranulocytosis with septicemia, gastrointestinal lesions − mucositis, neutropenic enterocolitis. In this regard, it is

mandatory to conduct selective oral decontamination by the complex of antibiotics and prevention of mucositis (polymyxin-M, nystatin, biseptol, amphotericin B).

It is essential to ensure adequate substitution therapy: thromboconcentrate (6-12 doses per 1 $m^2$ weekly) to maintain the level of platelets > $20 \cdot 10^9$/l, and in the development of abdominal symptoms or pneumonia > $50 \cdot 10^9$/l.

For the treatment of infectious complications in neutropenic period, it is necessary to use cephalosporins of III generation with antipseudomonal activity and (or) β-lactam penicillins with aminoglycosides, metronidazole, amphotericin B. Multiple bacterial studies of blood, urine, culture tests from mucous membranes, skin and catheter are mandatory. Fungi of the genus Candida, Aspergillus, Criptococus are increasingly defined as the cause of sepsis and death in children during the anticancer therapy. Depending on the cause of infection, it is necessary to prescribe antibiotics, antifungals, antiviral drugs.

Granulocytopoiesis stimulants are used − G-CSF (granulocyte colony stimulating factor); GM-CSF (granulocyte-macrophage), known as leukomax (3-5-10 mg/kg sq No.7-14-30), neupogen, and high-dose immunoglobulins (sandoglobulin, intraglobulin-F − 200-400 mg/kg No.1-2).

Neuroleukemia is a specific lesion of CNS, which is found in all forms of acute leukemia, but most often complicates the course of ALL. This is due to several reasons: 1) the increase in the life expectancy, especially of children with ALL; 2) cytotoxic drugs do not cross the brain-blood barrier, and thus the tumor area in the nervous system has the ability to progress. It is noted that neuroleukemia often develops in patients with high leukocytosis and marked proliferative syndrome at the primary active phase of the disease.

Symptoms of neuroleukemia usually appear in remission, sometimes they are the first manifestations of ALL. The clinical course of neuroleukemia consists of symptoms of meningoencephalitis, hypertensive syndrome. In the early period, children develop the phenomena of general fatigue. They become sluggish, capricious, and sleepy. The behavior of the child is changing; he/she becomes avoidant, irritable. Further clinical course depends on the nature of leukemic lesion of CNS.

There are several forms of neuroleukemia: lesions of mainly meninges (meningeal form), brain substance (encephalitic form), mixed (meningocephalitic form), lesions of the peripheral roots of the nervous system.

An important role, especially in the early diagnosis of neuroleukemia, belongs to additional methods of study. The most informative is spinal fluid analysis. In the liquor, cytosis is determined. Absolute criterion is identifying blast cells. High pressure, increased protein levels, and lower blood sugar are typical. In the development of neuroleukemia, endolumbar administration of drugs (methotrexate, cytosine-arabinoside, prednisolone) and cranial irradiation are used.

**Chronic myeloid leukemia (CML)**

This is a tumor of hematopoietic tissue, which comes from progenitor cell of myelopoiesis, the main morphological substrate of this tumor are mature granulocytes. CML constitutes 2-5% of all leukemia cases in children, and it is the only tumor process in which chromosomal abnormalities are clear − the defect of the 22nd pair (Philadelphia Ph'-chromosome). The presence of Ph'-chromosome is considered as a pathognomonic sign of CML. As a result of extensive research, two groups of diseases have been distinguished: CML version with Ph'-chromosome (Ph'-positive variant) and the version in which Ph'-chromosome is not detected (Ph'-negative variant). The feature of CML is the lack of Ph'-chromosome in the child.

There are two stages of CML: 1 − expanded benign (monoclonal), chronic and 2 − terminal (polyclonal), sometimes called “blast”, accelerated. There are 4 stages of the disease: 1) initial, pre-clinical, chronic; 2) expanded clinical manifestations; 3) the transition period (acute phase); 4) blast crisis (end-stage).

CML in childhood has specific features of clinical course. There is the adult (mature) type which is not different from that of the adults, and juvenile type which is characterized by the lack of Ph'-chromosome. This version is distinguished by malignant course. Adult version of CML occurs predominantly in older children, juvenile − at the age of 3-5 years.

The initial period may be asymptomatic with minor hematological changes (leukocytosis, shift to the left). The initial period can give no manifestation of the

disease for a long time. The disease develops gradually and is usually diagnosed in the expanded phase of the disease. General condition of patients is deteriorating. The spleen is enlarged; there are characteristic changes in the blood.

With modern therapy, the expanded stage can last for several years. The long course is typical for adult type, the course of juvenile form is more malignant. In CML of adult type, there are the following periods: initial, expanded, and terminal. In the initial period, the overall condition of the child is slightly disturbed; condition is satisfactory, although occasionally there may be weakness, fatigue. In most children, there is no loss of appetite, but anorexia may be observed. No pale skin, hemorrhagic syndrome, hyperplasia of organs. However, the insignificant enlargement of the spleen may be observed.

In the initial period, leukocytosis of varying degrees (20-50·$10^9$/l) is observed in the peripheral blood, leukocyte count shifts to the left, there may be increased number of eosinophils and basophils (eosinophilic-basophilic association), while the number of red blood cells, hemoglobin level, erythrocyte sedimentation rate are normal. Platelet count is often normal, but there may be slight thrombocytosis within 500-600·$10^9$/l. In myelogram, normal amount of blast cells remains, promyelocytic-myeloid reaction is observed; index of granulocytes maturation is increased. The duration of the initial period is 6-12 months.

The period of expanded clinical presentation is characterized by the increase of symptoms caused by generalization of the neoplastic process. The condition of patients significantly worsens, due to intoxication and damage to the nervous system. Children complain of weakness, loss of appetite, weight loss. Fever, increased sweating, and pain syndrome appear. The spleen is enlarged to enormous size (it can go up to the pelvis, causing reconfiguration of the abdomen). On palpation, spleen is of rocky density. The liver is also enlarged, but less than the spleen. A typical feature of this period is bone ache.

In the peripheral blood, leukocytosis increases (up to 100-200·$10^9$/l). In leukogram, there are all forms of myeloid cell: from myeloblasts to stab granulocytes. Severe lymphocytopenia is typical. Compared with the initial period, basophilia is

observed, but to a lesser extent, the number of eosinophils increases. ESR is increased. Platelet count remains within normal limits. In myelogram, there is the significant hyperplasia of granulocytic lineage. The duration of this period is 3-5 years.

The shift of tumor in the terminal stage is logical, and at the same time the malignant properties of the tumor are revealed. As a rule, blast crisis suddenly arises against the background of the therapy. This is accompanied by progressive leukocytosis, further enlargement of the spleen, there is resistance to therapy. The child's condition is dramatically deteriorating due to intoxication, fever, weight loss up to cachexia. Further on, the lymph nodes are involved in the pathological process. Necrotic lesions of the skin, mucous membranes are characteristic, hemorrhagic syndrome and CNS lesions appear. The spleen and liver are progressively enlarging, despite the therapy. Abdominal pain is typical.

Hematologic sign of terminal stage is the blast crisis characterized by the increase in the number of blast cells (over 10%) and in the bone marrow (20%). The cell substrate of the tumor at the end-stage displays the polyclonality of malignancy process. In morphological and cytochemical terms, one can distinguish young shapes of cells: myeloblasts, monoblasts, undifferentiated lymphoblasts, erythroblasts, megacaryoblasts, and atypical forms of cells. Anemia is progressing, eosinophilic-basophilic association disappears, ESR is accelerated.

*Juvenile variant of CML* in children has a number of features. This form occurs mainly in children under 5 years of age. In karyotypic analysis, the specific marker − Ph'-chromosome − is not determined. The main difference is its more aggressive course that resembles the terminal stage of CML of adult type.

The early symptoms are the following: loss of appetite, lack of weight gain, sleep disturbance. In the early stages of the disease, there is hemorrhagic syndrome. A long period of relative well-being is not observed. Severe hemorrhagic symptoms are typical: nasal and gastrointestinal bleeding, hematuria, the appearance of infiltrates of hemorrhagic character on the skin. Enlargement of all groups of lymph nodes is a characteristic feature of juvenile variant. There are signs of skeletal system lesion − severe pain in the tubular bones. The liver and the spleen are enlarged.

Normochromic anemia and thrombocytopenia are observed in the peripheral blood. Red blood cells contain increased amounts of fetal hemoglobin − 30-40%, sometimes up to 100%. Leukocytosis is typical, but it is less pronounced than in the adult version. The number of leukocytes rarely exceeds $100 \cdot 10^9$/l. In leukogram, eosinophilic-basophilic association is observed, there are all transitional forms of granulocytic series, blast cells. Juvenile form is characterized by unresponsiveness to therapy, life expectancy of patients is less than 1 year.

The cause of death in CML is general intoxication, secondary infections (pneumonia, sepsis), complications caused by hemorrhagic syndrome. Treatment of CML is also carried out using polychemotherapy; prescription of myelosan at a dose of 0.6-2.0 mg/m$^2$ is the basis of therapy.

## Lymphogranulomatosis

Lymphogranulomatosis (LGM), or Hodgkin's disease, is the malignant tumoral disease of the lymphatic system. The disease is characterized by hyperplasia of lymphatic tissue and the presence of atypical Berezovsky-Sternberg cells. Hodgkin's disease in children ranks first among the malignant lymphomas and second only to leukemia among hemoblastoses. Hodgkin's disease in the age aspect has two peaks. One of them occurs in childhood, the second − at the age of 50. Hodgkin's disease is the most frequently encountered at the age of 4-6 and 12-14 years. Boys suffer from it more often.

*Etiology and pathogenesis*. The theory of tumor origin of LGM is currently the most pathogenetically accepted. LGM is not a primary generalized process. It is considered to be a tumoral disease of unicentric origin. Further on, the process spreads, metastasizing from the primary focus. Generalization is mainly lymphatic, however, hematogenous way is also possible. Tumor progression is in two stages: the first stage is benign, characterized by monoclonal tumors; the second stage is the formation of polyclonality that leads to malignancy. The pathological substrate of the disease is granuloma.

Cytological studies of lymph nodes punctate indicate polymorphic cellular composition of granulomas. Lymphocytes, plasma cells, eosinophils and neutrophil

cells are observed. Against the background of the polymorphic clinical presentation, there are Berezovsky-Sternberg cells. These cells are characterized by their large size − from 25 to 70-80 μm, irregularly shaped, multi-nuclear. There are no clear ideas about the origin of Berezovsky-Sternberg cells, but it has been found that they carry immunoglobulins on their surface. This fact suggests the B-cell origin of giant cells, and one can consider LGM as a B-cell lymphoproliferative disease. LGM is characterized by high activity of enzymes − acid phosphatase, succinate dehydrogenase, lactate dehydrogenase.

*Morphological presentation* of the lymph node in LGM varies depending on the stage of cancer. Progression of the process is morphologically expressed by the development of fibrosis, increased number of Berezovsky-Sternberg cells, decrease in the number of lymphocytes. Morphological classification provides prognostic information based on the proportion of cellular elements and the nature of sclerosis in the affected lymph node.

By histological classification based on the contents of various cells in the specific granuloma, there are four main types of LGM: lymphocytes-enriched version (nodular or diffuse); nodular sclerosis version (type 1 and 2, by the degree of malignancy); version of mixed cellularity; lymphocytes-depleted version (variant of lymphocytic depletion).

According to REAL classification, Hodgkin's disease variant of lymphocytic predominance is entitled "Hodgkin's disease, enriched with lymphocytes of classical type", which is characterized by proliferation and infiltration of lymphocytes. This corresponds to the first stage of the clinical course of Hodgkin's disease. Nodular sclerosis is characterized by the appearance of fibrin strands, lymph node fragmentation into separate bundles (noduli) containing Berezovsky-Sternberg cells. In the mixed-cellular variant, the presence of multiple sclerosis and polymorphic composition of cellular elements are observed. Numerous Berezovsky-Sternberg cells are typical. The variant with lymphoid depletion includes two varieties − diffuse fibrosis and reticular form, which are characterized by the significant decrease in the number of lymphocytes or their complete lack. In diffuse fibrosis, endless proliferation of fibrous connective

tissue in the form of coarse strands is observed. The cell content is depleted, mostly reticular Berezovsky-Sternberg cells are found. Each variant of Hodgkin's disease is a certain step in the development of cancer.

*Clinical classification of Hodgkin's disease*. There are the following stages of the disease:

The 1st stage (local form) − the lesion of one or two adjacent groups of lymph nodes located on one side of the diaphragm;

The 2nd stage (regional form) − the lesion of two or more non-contiguous groups of lymph nodes located on one side of the diaphragm;

The 3rd stage (generalized form) − the lesion of various groups of lymph nodes located on both sides of the diaphragm;

The 4th stage (disseminated form) − the lesion of extra-nodular organs − liver, pleura, bone, skin, kidneys with the involvement of lymph nodes or without it.

Each stage is divided into two groups depending on the presence or absence of general clinical symptoms: A − no general symptoms of intoxication; B − presence of one or more symptoms of intoxication.

*Symptoms of intoxication* include: 1) body temperature over $38^0$C for 5 days or prolonged low-grade pyrexia; 2) profuse night sweats; 3) generalized itching; 4) reduction of body weight by more than 10% in a short period of time (within the last 6 months).

To diagnose Hodgkin's disease, biological signs of the process activity are very important: ESR more than 30 mm/hr., neutrophilic leukocytosis, hyperfibrinogenemia, reduction of serum iron, increased haptoglobin and ceruloplasmin in serum. In the modern classification of Hodgkin's disease, one should provide information about extra- nodular localization of the process, which is denoted by letter "E".

*Clinical symptoms of Hodgkin's disease* are different. They are due to the stage of the process, the localization of pathological process, reactivity of the body. The first signs of the disease are usually characterized by the increase in isolated groups of lymph nodes. In 70-80% of children, the process is initially localized in the cervical lymph nodes. Their hyperplasia often has one-sided character with the gradual

involvement of neighboring groups in the process. Lymph nodes have different sizes, they are not glomerate to each other and to the surrounding tissues. The skin over them is not changed. If there are multiple lymph nodes, located along each other, they are palpable as A.A. Kissel put it: “like potatoes in a sack”. The nodes are mobile, painless, hard, but can be of soft consistency as well. Regardless of the size of nodes and transition process in the capsule in Hodgkin’s disease, the disintegration of lymph nodes is not observed, except for the rare cases of purulent lesions as a result of secondary infection overlay.

The second place by highest frequency of primary localization of the pathological process is occupied by mediastinal lymph nodes, according to different authors, in 15-20% of cases. Diagnosis of primary mediastinal lesions is difficult due to a long asymptomatic course. The child’s condition is satisfactory for a long time. Later on, symptoms of mediastinal compression, complaints of feeling heaviness in the chest, cough, and breathlessness appear. Pathological effects increase with enlargement of lymph nodes. In the significant enlargement of lymph nodes, auscultation and percussion reveal changes. On X-ray, expansion of the shadow of the mediastinum and significant enlargement of lymph nodes (the pipe symptom) are observed.

Lymph nodes, located in the abdominal cavity, can be affected. This indicates the generalization of the disease. Affected spleen is one of the characteristics of Hodgkin’s disease, in 40% of children spleen is involved in the pathological process.

The feature of Hodgkin’s disease course in children is the late development of the common symptoms of intoxication, the satisfactory general condition is maintained for a long time. Typical symptom of Hodgkin’s disease is fever in which the temperature curve is without any regularity. One may often observe increased sweating, usually of the scalp, especially intense during the night. Parents point out that the child’s scalp and pillow are wet. The profuse night sweats are accompanied by general weakness, disturbing behavior of the child while sleeping. Itchy skin as a manifestation of general intoxication is rarely observed. Among the common symptoms of intoxication in children, one can identify decreased activity, rapid fatigue, appetite loss, progressive loss of body weight.

In disseminated form of Hodgkin's disease, the liver damage is observed in more than half of patients. However, diagnostic capabilities of identifying specific changes in the liver are significantly limited. The nature of the lesions is also varied − from large to small granulomas infiltrate. The development of jaundice worsens the prognosis. In Hodgkin's disease, specific lesions of lung and pleura may be observed. The primary manifestations in the lungs are very rare, the lesions of the lungs are mainly secondary in nature and indicate the generalization process. Lung lesions are the first among extra-nodular manifestations of Hodgkin's disease. The mechanism of destruction has two options: in the first, the invasion in lung tissue occurs from the affected mediastinal lymph nodes, in the second − as a result of metastatic lesions.

Tumor cells can disseminate into the bone tissue, the frequency of skeleton lesions ranges from 3% to 15%. The spine and pelvic bones are the most commonly affected, the process is rarely localized in the long bones and bones of the skull. The dominant symptom is local pain associated with lesions of the periosteum and compression of peripheral nerve trunks.

In Hodgkin's disease, skin lesions of both specific and non-specific nature are possible. In children, non-specific toxic and allergic skin lesions are observed more frequently. Specific skin changes are due to invasion of lymphogranulomatous tissue from the affected lymph nodes or as a result of lymphogenic dissemination. Nodules of different sizes (from millet grains to a walnut) appear on the skin. They are located deep in the dermis, have hard consistency and dark red color. In histological examination, Berezovsky-Sternberg cells are observed in the specimen. Specific skin lesions may have the nature of plaques, ulcers.

The presentation of peripheral blood has no specific changes. Moderate leukocytosis (10000-20000/μl) is observed in leukogram with neutrocytosis with a slight shift to the left, increased ESR. Some patients have eosinophilia, sometimes up to 50%. With the progression of the process, lymphocytopenia develops.

The bone marrow punctate in Hodgkin's disease does not display particular differences from the norm, except for the specific destruction of the bone marrow.

*Diagnosis of Hodgkin's disease*. The essential procedure for diagnosis of the disease is biopsy of the affected lymph node (excisional biopsy of lymph node is preferred since it provides the opportunity to study its architectonics). Percutaneous biopsy is not sufficient for diagnosis of Hodgkin's disease. Affected tissues are studied by cytological, histological, immunohistochemical and molecular genetic methods. The histological confirmation of diagnosis from the reference laboratory is obligatory.

*Differential diagnosis of Hodgkin's disease*. Enlarged lymph nodes in children are very common. The main group is benign lymphadenopathies. Clinical manifestations of lymphadenopathy are different but have a similar presentation with Hodgkin's disease. Late diagnosis of Hodgkin's disease greatly reduces the possibility of treatment and worsens the prognosis.

*Treatment of Hodgkin's disease* includes combination of chemotherapy with radiation of initially affected regions. Schemes OEPA/OPPA and COPP (Protocols DAL-HD-90 and GPOH-HD-95) are the most effective and at the same time the least dangerous in terms of long-term effects. The required amount of schemes is due to the stage of the disease and the degree of destruction of nonlymphoid organs. Depending on the number of polychemotherapy cycles, the cumulative dose of radiation for affected regions is planned in its turn. Irradiation of initially affected lungs and liver is not conducted.

The choice of protocol depends on the stage of the process: the 1st protocol is prescribed for Hodgkin's disease of I, II A stage, taking into account the gender of the child:

• For girls, 2 cycles of OPPA are used (the cycle is named by the first letters of drugs) with a 2-weeks break:

| **Medication** | **Days of intake** | **Dosages** |
|---|---|---|
| Vincristine (onkovin) | 1, 8, 15 | 1.5 mg/m$^2$ (maximum single dose of 2) |
| Procarbazine | 1 to 15 | 100 mg/m$^2$ by mouth in 2-3 intakes |
| Prednisolone | 1 to 15 | 60 mg/m$^2$ by mouth in 3 intakes |
| Doxorubicin (adriamycin) | 1, 15 | 40 mg/m$^2$ i.v. within 2 hr. |

• For boys, 2 cycles of OEPA with a 2-weeks break are used:

| Medication | Days of intake | Dosages |
|---|---|---|
| Vincristine (onkovin) | 1, 8, 15 | 1.5 mg/$m^2$ (maximum single dose of 2 mg) |
| Etoposide | from 3 to 6 | 125 mg/$m^2$ i.v. within 120 min. |
| Prednisolone | 1 to 15 | 60 mg/$m^2$ by mouth in 3 intakes |
| Doxorubicin (adriamycin) | 1, 15 | 40 mg/$m^2$ i.v. within 2 hr. |

At the end of the cycle, girls and boys undergo radiotherapy of affected lymph node at a dose of 30 Gy.

The second protocol is used at II B, III A stage of Hodgkin's disease. There are no differences in the treatment protocol for boys and girls. At first, 2 cycles of OPPA are performed, then 2 cycles of COPP, followed by irradiation of 30 Gy.

COPP cycle:

| Medication | Days of intake | Dosages |
|---|---|---|
| Cyclophosphamide | 1, 8 | 500 mg/$m^2$ i.v. within 30 – 60 min. |
| Vincristine (onkovin) | 1, 8 | 1.5 mg /$m^2$ (maximum single dose of 2 mg) |
| Prednisolone | 1 to 15 | 60 mg /$m^2$ by mouth in 3 intakes |
| Procarbazine | 1 to 15 | 100 mg /$m^2$ by mouth in 2-3 intakes |

The third protocol is used at III-V and IV stages of Hodgkin's disease. There are no differences in the treatment protocol for boys and girls. Two cycles of OPPA and 4 cycles of COPP are prescribed, followed by irradiation with 25 Gy. The sensitivity of Hodgkin's disease to chemotherapy is very high.

For adolescents above the age of 15, it is more effective to apply treatment protocols in accordance with the treatment of adult patients, using ABVD and BEACOPP schemes in various combinations (in accordance with the Protocol GHSG-LP HD and HD 10-12); in this regard, the most effective treatment for severe stages is the use of BEACOPP scheme.

BEACOPP block scheme:

| **Medication** | **Dosage** | **Route of administration** | **Day of intake** |
|---|---|---|---|
| Cyclophosphamide | 650 mg/m$^2$ | i.v. | 1 |
| Uromitexan | 650 mg/m$^2$ | i.v. | 1 |
| Doxorubicin | 25 mg/m$^2$ | i.v. | 1 |
| VP-16 | 100 mg/m$^2$ | i.v. | 1-3 |
| Procarbazine | 100 mg/m$^2$ | by mouth | 1-7 |
| Prednisolone | 40 mg/m$^2$ | by mouth | 1-14 |
| Vincristine | 1.4 mg/m$^2$ (max 2 mg) | i.v. | 8 |
| Bleomycin | 10 mg/m$^2$ | i.v. | 8 |

*Prognosis*. The probability of recovery (remission for more than 5 years) depends primarily on the stage of the disease at the time of diagnosis, and treatment methods. At I-II stages, most patients (100%) recover; at stages III-IV − 85%. Children with Hodgkin's disease are on the dispensary observation with check-ups of hematologist in the first 2 years, once in 3 months (95% relapse cases occur within the first 2 years), further on − once in 6 months.

# UNIT 7. HEMORRHAGIC DIATHESES

This is a group of polyetiological diseases that are united by a common feature − increased bleeding or tendency to hemorrhagic syndrome.

Hemostatic system maintains the blood in liquid state, prevents bleeding and is responsible for the structure of walls of blood vessels. Hemostasis (blood clotting) begins with adhesion and aggregation of platelets with further inclusion of fibrin. In this regard, between the platelets and around them, the “hemostatic plug” is formed − the narrowing of the small blood vessels (capillaries and precapillaries) and platelets aggregation in them. In large vessels, fibrin is formed for constant and reliable hemostasis.

Normal hemostasis depends on: the state of blood vessels, the number and functional activity of platelets, levels of ionized calcium, plasma coagulation factors, fibrinolytic system activity. Each component has a unique role in hemostasis and other components cannot perform its functions. Hemostatic system is a system in the human body, the operation of which, on the one hand, prevents bleeding and stops it by keeping the structural integrity of vessel walls and rapid local thrombosis of the latter in case of injuries, and on the other hand − maintains blood in the liquid form in the bloodstream with constant transcapillary movement of tissue fluid and plasma. Hemostatic system is subject to other systems of the body − the nervous, endocrine, and immune, and depends on their functional status and close interaction between them.

Hemostatic system performs the following functions:

1. Takes an active role in regulating the resistance and penetration (passage) of vascular wall that prevents the ingress of excessive amounts of plasma and blood in the vessels walls and beyond them.

2. Maintains blood in the liquid state, thus ensuring the normal blood circulation and tissue metabolism.

3. Stops spontaneous and traumatic bleedings and hemorrhages into the tissues, maintaining the blood volume.

4. Eliminates the effects of permanent local intra-vascular coagulation, thrombosis and hemorrhage.

5. Participates in the body's defense reactions, which is an important part of the processes of inflammation, regeneration, cellular and humoral immunity.

**Hemostasis in the norm**

The mechanism of bleeding control in a healthy person in the disrupted integrity of the vascular wall can be divided into two phases − primary and secondary. The primary phase is the formation of the hemostatic plug, in which vascular wall and platelets are involved. The main function of the vessel wall in the process of bleeding control is its ability to decrease (spasmodic ability), thus decreasing the amount of blood circulating through the affected vessel.

Platelets also have a significant impact on the strength and duration of spasm. They migrate to the site of injury when there is a threat of injury to blood vessels, stick (adhere) to endothelial myofibrils and basement membrane of damaged vessels and are aggregated together. As a result, they express active humoral factors, namely, serotonin, adenosine diphosphoric acid, thromboxane $A_2$, which contribute to the constriction of vessels.

As a result of this aggregation and subsequent irreversible changes, the primary unstable platelet plug is produced; it is sufficient for hemostasis in vessels of small caliber. In large vessels, such a "plug" can be washed off by blood flow before it will consolidate the fibrin strands if the vessel dilates again. The whole process of the formation of the primary hemostatic plug typically runs for 1-2 minutes. In a healthy person, primary platelet plug is stabilized by fibrin in a few minutes, which is included in the formation of the clotting process involving plasma coagulation factors.

According to international nomenclature, plasma coagulation factors (procoagulants) are denoted by Roman numerals. Currently, there are 13 clotting factors (Table 7). A number of factors (XIII, XII, XI, X, IX, VII, II) are proenzymic, other (VII, V) are cofactors. Each proenzyme is converted into an active form and, in turn, activates the next factor. Conventionally, the clotting process can be divided into three phases: phase I − formation of active factor Xa, phase II − formation of thrombin, phase III −

formation of fibrin. Phase I is the most complex in blood clotting. Conventionally, there are 2 ways of the formation of active factor X − external and internal. This division is purely practical for proper evaluation of the results of tests used to study the blood coagulation system.

The process of blood clotting can be represented as three groups of reactions:

1. The internal system of reactions involves the interaction of factors XII, XI, IX, VIII, V, X and phospholipid of platelets, which is completed with activation of factor X. To characterize the internal system, one uses the following tests: venous blood clotting time, plasma recalcification time, activated partial thromboplastin time (APTT). Determination of capillary blood clotting time can be used to characterize the internal system, because the technology of study does not involve the entry of tissue thromboplastin into the blood test samples.

2. The external system of reactions − interaction of factors VII, X, V and tissue thromboplastin (it is called external because “external” blood component − tissue thromboplastin − is necessary). External system is assessed by prothrombin index.

3. The third group of reactions is characterized by the fact that active factor X, formed as a result of the activation of factors of internal and external systems, converts prothrombin (factor II) into thrombin and further on thrombin triggers the transition of fibrinogen into a dense clot. The transformation of fibrinogen into fibrin is determined by thrombin time, fibrinogen concentration and fibrin clot solubility in urea. After the formation of fibrin under the influence of thrombosthenin − contractile actomyosin-like protein, found in platelets − a blood clot retraction occurs. The energy source for thrombosthenin contraction is ATP. Therefore, any inhibition of energy metabolism, such as glycolysis, impairs blood clot retraction. The physiological significance of retraction for bleeding control consists in the fact that dense clot is better fixed in place of damaged blood vessels and thus facilitates the reliable arrest of bleeding.

Under physiological conditions, the formed fibrin clot is subject to aseptic dissolution (fibrinolysis) for recanalization of the vessel. The active enzyme of fibrinolytic system is plasmin, which is formed from the inactive precursor − plasminogen. In the process of fibrinolysis, the fibrin molecules are split into fragments

− fibrin degradation products. Thus, the fibrinolytic system has the effect, which is opposite to the process of blood clotting and helps to maintain the blood in liquid state and prevents intra-vascular thrombosis. Along with coagulation and fibrinolytic systems, an important role belongs to natural anticoagulants: heparin, $\alpha_2$-macroglobulin, antithrombin-I, antithrombin-IV.

Thus, one can conclude that any damage to the integrity of the vessel wall is an incentive for activation of blood clotting. However, thanks to the adaptive response of the body, the equilibrium is reached under normal conditions, which helps stop bleeding, without developing the hypercoagulable state. In the impairment of this balance, hypercoagulation or hypocoagulation may occur. It is important to remember that the hemostatic system, as one of the physiological systems of the body, forms and matures during embryogenesis and early ontogenesis, and has certain age features during the life. The hemostatic system in newborns is particularly labile. Normal indicators of hemostasis in children above the age of 1 year are presented in Table 8.

In the clinical presentation of hemostasis disorders, one can distinguish: hemorrhages (bleedings), thromboses and thromboembolism, thrombohemorrhagic syndrome due to DIC.

*Diagnostics of hemorrhagic diatheses*

When collecting history in children with hemorrhagic syndrome, physician should address the following questions:

- Whether the result of bleeding in the patient results from the disturbances in the hemostatic system, whether it is associated with local tissue and vascular changes;

- If there are disturbances in the hemostatic system, whether they are congenital or acquired;

- How severe are the hemorrhagic disorders;

- What is the type of bleeding − capillary or coagulatory (Table 9).

In patients with the defect of vascular-platelet link, bleeding starts immediately after injury because the primary hemostatic plug formation is disrupted, but the final hemostasis is also impaired due to the difficulty of fibrin clot formation because of insufficient coagulation function of platelets.

Late bleeding is characteristic for coagulopathy due to defects in plasma factors of blood coagulation. There may be a considerable period of time between the moment of injury and bleeding (from several hours to several days). The lack of bleeding immediately after the injury is caused by the fact that vascular spasm and platelet plug formation in patients with the plasma defect are not disrupted. However, hemostatic plug in them is unstable due to insufficient formation of dense fibrin clot that can withstand the pressure of blood. As a result, the bleeding occurs in the area of injury after 1-2 hours from restoration of normal levels of blood pressure.

The required volume of laboratory studies for patients with hemorrhagic diathesis is presented in Table 10.

*Tests that characterize the "internal" mechanism of blood clotting*

Time of venous blood clotting estimates the coagulation activity of whole blood by the rate of clot formation in it. Counting time starts from the moment of getting blood to a glass tube till its complete coagulation. The test is of low-sensitivity because its results are within the normal range when the level of factor VIII is more than 5%.

Time of plasma recalcification is the clotting time of citrate plasma in thermostatic conditions ($37^0$C) after adding calcium chloride to it. Unlike venous blood clotting time, this figure more subtly reveals the disorders in the "internal" coagulation system due to the fact that plasma is free of formed elements (erythrocytes, leukocytes) which have thromboplastic activity.

Activated partial thromboplastin time (APTT) defines "internal" coagulation activity of plasma. Due to the addition of partial thromboplastin (platelet factor 3 substitute) and kaolin that promote maximum activation of plasma factors, APTT test is sensitive enough to detect disorders at the stage of the internal activation of blood coagulation. APTT indicator is disturbed in reduced factor VIII activity by 25% and below.

*Tests that characterize the "external" system of blood clotting*

Prothrombin time (prothrombin index). The test is based on the timing of recalcification of citrate plasma in the presence of excess tissue thromboplastin, in other words, the external coagulation way is represented, which excludes the impact of factors

XII, XI, IX, VIII on the speed of the fibrin clot formation in the experimental system. This test characterizes the total activity of factors II, V, VII and X and to a lesser extent − fibrinogen. Prothrombin time is prolonged in the treatment with heparin.

*Tests, describing the general way of clotting*

Thrombin time. This test is based on the definition of citrate plasma clotting time after adding thereto the solution of low concentration of thrombin. Thrombin time allows to evaluate the final phase of blood clotting. The results of the test are affected by two factors: the concentration of fibrin and plasma inhibitory activity. Thrombin time of blood anticlotting activity is extended in decreased levels of fibrinogen, and in disfibrinogenemias.

Determination of fibrin level. Increased fibrinogen level is determined in various conditions involving hypercoagulable state. Reduced fibrinogen displays the complex hemostatic disorder.

*Methods for study of the hemostatic function of platelets*

Determining the amount of platelets. The normal platelets count is $180\text{-}320 \cdot 10^9$/l.

Initial duration of bleeding. The method is based on the timing of the bleeding from a wound of standard size inflicted on the skin surface. This time depends on the ability of vascular-platelet mechanisms for stopping bleeding from damaged small blood vessels and capillaries. Therefore, the duration of bleeding is a common screening test for the detection of disorders of processes in primary hemostasis due to vessel wall defects, significant thrombocytopenia, inadequate functional properties of platelets or deficiency of factors of thrombocytic responses (fibrinogen, von Willebrand factor). In thrombocytopenia (platelets count $<100 \cdot 10^9$/l), there is a direct relationship between the degree of thrombocytopenia and prolongation of bleeding time. Currently, Duke's method is used to determine the duration of bleeding.

Duke's test. In conducting classical tests, one should pierce the bottom cushion of ear lobe to a depth of 3.5-4 mm after mild warming. Bleeding time does not exceed 4 minutes and drops of blood on the filtering paper must be relatively small and quickly begin to decrease in size, starting from 1-1.5 min. In deep thrombocytopenia (less than $20 \cdot 10^9$/l) and severe platelets dysfunction, the bleeding time increases up to 20-40 min,

the size of blood stains is much greater and is not reduced or changes in waves for a long time − now it decreases, then it increases.

The test of resistance (fragility) of the vascular wall. The most accessible for practical implementation and informative enough is Konchalovsky-Rumpel-Leede test. Assessment is made by the number and size of hemorrhage formed on top of the palmar surface of the forearm (a circle with a diameter of 5 cm) after the 5-minute compression of arm with a cuff at the pressure of 90-100 mm Hg.mm. The calculation of hemorrhage is performed in 5 minutes, after removing the cuff. The number of petechiae in the circle of more than 10, indicates the increased fragility of microvessels, often associated with thrombocytopenia or thrombocytopathy. The occurrence of hemorrhages under the cuff is also important.

Classification of hemorrhagic diatheses

The pathology of blood coagulation is presented by hemorrhagic diatheses and hemorrhagic diseases. All primary hemorrhagic diatheses and hemorrhagic diseases are divided into 3 groups: coagulopathies, thrombocytopenias and thrombocytopathies, angiopathies.

*Classification of blood coagulation pathologies*

I. Hemorrhagic hemostasiopathies:

A. Thrombocytopenias:

1) hereditary and congenital;

2) acquired.

B. Thrombocytopathies:

1) hereditary and congenital:

a) forms with the primary disorder of aggregation function of platelets (disaggregation);

b) forms with the primary disorder of platelets adhesion to collagen;

c) forms with the deficiency and reduction in the availability of factor III;

d) forms with complex abnormalities and dysfunction of platelets, which are combined with other genetic defects;

e) forms which are not sufficiently identified.

2) acquired, secondary (in other diseases).

C. Coagulopathies:

1) hereditary and congenital:

a) forms with disrupted prothrombin formation;

b) disrupted thrombin formation;

c) disrupted fibrin formation;

d) disrupted formation of hemostatically adequate thrombus.

2) acquired (symptomatic):

a) comprehensive deficiency of vitamin K-dependent factors;

b) immunocoagulopathies;

c) paraproteinemic and dysglycemic immunocoagulopathies;

d) isolated hyperheparinemia anticoagulant effect and direct action;

e) in artificial activation of fibrinolysis and fibrination therapy;

f) isolated acquired deficiency of certain clotting factors;

g) combined coagulopathy.

D. Angiopathies:

1) hereditary and congenital:

a) hemorrhagic telangiectasias;

b) hemangiomas with thrombocytopenia;

c) hereditary thrombocytopenic microangiomatosis;

d) ataxia-telangiectasias (Louis-Bar syndrome);

e) encephalotrigeminal angiomatosis (Sturge-Weber syndrome);

f) angiomatosis of retina;

2) acquired:

a) hemorrhagic vasculitis;

b) neurovegetative and endocrine angiopathies.

E. Polycomponent hemorrhagic hemostasiopathies:

1) hereditary and congenital − Willebrand disease;

2) acquired:

a) stage III of DIC (hypocoagulation):

b) polycomponent hemorrhagic hemostasiopathies in terminal diseases.

II. Thrombophilic hemostasiopathies:

1) hereditary and congenital − Willebrand disease;

2) acquired.

III. Acquired thrombohemorrhagic hemostasiopathies: DIC syndrome.

## Hereditary coagulopathies

### Hemophilia (hereditary deficiency of factor VIII and IX)

ICD-10: D66, D67. Hemophilia is an inherited disease caused by the deficiency or molecular abnormalities of one of factors participating in the activation of blood coagulation.

There are:

- hemophilia A (HA) − lack of factor VIII (87-94% of cases);
- hemophilia B (HB) − factor IX deficiency (6-13% of the total number of patients with hemophilia);
- hemophilia C − factor XI deficiency.

Hemophilias A and B are inherited by recessively coupled with X-chromosome type, therefore only men suffer from this disease. Women inheriting the X chromosome from the hemophiliac father, and one X chromosome from a healthy mother are hemophilia conductors. Hemophilia conventionally also includes genetically caused deficiency of factor XI, allocating it as hemophilia C or Rosenthal disease which affects both men and women. It is manifested exclusively in boys who inherit a changed X chromosome from the mother. The prevalence of hemophilia in most countries amounts to 10-14 patients per 100.000 men. The ratio of HA and HB is on average 4:1. There are isolated cases of hemophilia in women with gene inheritance from the father with hemophilia and the gene carrying mother, or in women with mutation of a gene on a chromosome where a gene on another one is not active (Shereshevsky disease and others.). There are few descriptions of combined initial decrease in the activity of factor VIII and IX. This condition is referred to as combined hemophilia. Approximately 70-

75% of patients have a family history of the disease, other new cases are caused by spontaneous mutations. The severity of the hemorrhagic syndrome is caused by the level of antihemophilic factor.

There are the following options for hemophilia course:

• severe form − at the level of factor <2%

• moderate form − factor VIII level at 2-5%

• mild − at the level of factor> 5%

• latent form − factor level of 15-50%.

The condition is characterized by periods of increased bleeding, alternating with periods of relative clinical remission.

*Clinical course*. Manifestations of HA and HB are identical. The first clinical manifestations are observed in young children, but rarely in the neonatal period. Sometimes in newborns one can observe bleeding from the umbilical cord, melena, intracranial hemorrhage. Most often in the first 6-9 months, there are no clinical manifestations, due to the positive influence of mother's milk. Once the child begins to walk, the likelihood of trauma increases and bleedings begin to appear. Approximately 50% of patients with hemophilia are revealed in the first year of life, 25% − in the second year of life, 13% − in the 3rd, 5% − above the age of 7 years. Among school-age children, the incidence of hemorrhage is decreased, but frequency of recurrent bleeding, especially into joints, increases.

Hemarthrosis is the most characteristic hemorrhagic manifestation of hemophilia. Most often, knee joints, elbow, ankle, shoulder, and hip joints are affected. In severe disease, they begin to occur in children above the age of 3 years. Hemarthrosis leads to the progression of arthropathy. In the later stages of arthropathy, contractures occur, cartilage is replaced by fibrous tissue. The muscles that support the joint become weakened, atrophied, contributing to even greater atrophy of the joints. The consequence of these changes is ankylosing arthropathy and disability.

Hemarthroses occur not immediately after the injury, but after 6-12 hours or more depending on the severity of the injury and hemophilia. After another hemorrhage, the child wakes up at night from acute joint pain. The affected joint is increased in size. The

skin over it becomes tense, hyperemic, and hot to the touch. General condition of the child is deteriorating; there is fever, decreased appetite, other signs of aseptic inflammation. Mild forms of acute hemarthrosis terminate with resorption of blood in 7-12 days and restoration of joint function. A more severe form can last for 3-4 weeks. In repeated bleeding, the blood does not dissolve completely.

There are 3 forms of joint damage: acute hemarthrosis − primary and recurrent, chronic destructive osteoarthrosis, secondary rheumatoid syndrome. In addition to intra-articular hemorrhages, children can develop the bone damage in the form of exostosis-like bony bodies, periosteal ossifications of hematomas, cysts and pseudotumors. There may be pathological fractures, compression of nerve trunks, vessels, resulting in gangrene of the limbs.

Hemorrhages in the soft tissues, or hematomas, occupy the second place by frequency in patients with hemophilia. Small subcutaneous hematomas on the limbs and trunk do not cause unpleasant subjective sensations in the child. They may be the result of trauma or medical procedures (injections). Hematoma is characterized by the fact that the blood remains liquid for a long time, penetrates the tissue and along the fascia. Intratissual hematomas are accompanied by a number of complications: compression of blood vessels, muscles, nerves, causing ischemia, paralysis, contractures, pain. Hemorrhages in the muscle disrupt the general condition of the child, causing fever, jaundice.

One of the first manifestations of hemophilia may be bleeding from the mucous membrane of the mouth. They occur with injuries by toys, objects that children often take to the mouth. During the period of tooth eruption, there may be bleeding from the gums. Bleedings from the mucous membrane of the larynx are dangerous. They may occur due to minor causes − when straining the vocal cords with weeping, coughing, shouting. They may threaten with asphyxia, accumulation of blood in the airways.

In disrupted integrity of the skin, bleedings occur and last for hours and even for days. In hemophilia, there may be spontaneous bleeding. Major hemorrhages cause anemia.

Hematuria is one of the main hemorrhagic manifestations of hemophilia in children above the age of 5 years. Pathogenesis immunocomplex of hematuria is associated with glomerular lesions due to repeated episodes of hematuria and the use of substitution therapy, where medications are protein components, injury of lumbar region, damage to blood vessels due to increased excretion of calcium, frequent intake of analgesics, high activity of urokinase. Hematuria often begins spontaneously, there are no symptoms of intoxication, extrarenal manifestations. Urine is dark red or brown. Dysuria with difficulty in urinating may occur; pain in the lumbar region, along the ureters, may appear. After several painful urinates, the blood clot is excreted and the pain subsides.

Neurological complications depend on the location of the hemorrhage, rate of occurrence, the effectiveness of substitution therapy. Intracranial hemorrhage is one of the causes of death of patients with hemophilia. Their frequency is 3-13%.

In the absence of the history of head injury, any signs that indicate intracranial pressure are the indication for urgent substitution therapy.

In children with hemophilia, excitation processes predominate over the processes of inhibition that is reflected in their behavior. They are of asthenic stature and low nutrition. Without hemorrhages, the internal organs are without pathological changes. With lengthening of life expectancy, the number of complications is increased, especially in the immune nature. Patients have allergic reactions to transfusion drugs − forming inhibitory form of hemophilia, the frequency of which is up to 20% of hemophilia cases.

*Diagnostic program*

Collecting anamnestic data and complaints in diseases of the blood and hematopoietic system:

One should find out: hereditary history of hemophilia; treatment with antihemophilic drugs, their dosage, effectiveness; in hemarthrosis and hemorrhage − when they occurred, under which circumstances, the presence and intensity of pain at present.

Visual studies in diseases of the blood and blood system: one should examine the skin and visible mucous membranes, pay attention to the presence of hematomas, hemarthroses; examine the joints symmetry, their size, possible deformation, volume of motion in the joints. In hematomas and hemarthroses, palpation is performed.

*Laboratory diagnostics*. Coagulation test is done by stages:

The first stage. Coagulation screening in suspected hemorrhagic states: activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (PT), the amount of fibrinogen (by Klaus), the bleeding time by standardized method or instrumental assessment of platelets function.

The second stage is performed in the isolated APTT prolongation or in the absence of changes in screening and the presence of clinical signs of mild hemophilia: correction test (correction of APTT by mixing patient's plasma with normal plasma), activity of factor VIII, factor IX activity, the activity of von Willebrand factor, factor XI activity.

The third stage is performed in case of detected reduction in the activity of factor VIII or IX: identification of specific inhibitor to reduced factor(s).

An important laboratory test for the diagnosis of hemophilia is determination of activated partial thromboplastin time (APTT). It displays the deficiency of factors XII, XI, IX (at the level of factor 20% and below) or VIII (30% or below, and the presence of inhibitors in the blood). In these cases, APTT is prolonged. If APTT is prolonged, then one should define the activity of factors VIII and IX.

*Basic principles for management of patients*.

• The comprehensive approach that includes observation by all relevant specialists, psychological and social counseling, rehabilitation activities; adequate specific substitution therapy;

• The principle of home treatment; clinical, laboratory and instrumental control.

*Hemostatic therapy* is prescribed for hemophilia patients after diagnosis and in hemorrhagic manifestations (excluding prophylactic treatment). The basic principle of treatment for hemophilia patients is a timely and adequate substitution therapy with coagulation factors VIII or IX (plasma and recombinant), which will increase its

concentration in blood plasma to the level that will provide effective hemostasis. For the treatment of patients with hemophilia, only purified, virus-inactivated medications must be used. Using the raw drugs (fresh frozen plasma or cryoprecipitate) may be allowed exceptionally and must not become a constant practice.

As the frequent change of drugs with factors VIII and IX leads to increased risk of inhibitory forms, it is desirable to create conditions for patient to use one medication for a long period of time. The preference is given to the drug which is best tolerated by the patient, has better pharmacokinetic parameters and is the most convenient to use under specific conditions.

The formula for calculating the single dose for hemophilia A is:

in severe forms: $X = M \bullet L \bullet 0.5$

in medium and mild forms: $X = M \bullet (L - P) \bullet 0.5$

The formula for calculating the single dose for hemophilia B:

in severe forms: $X = M \bullet L \bullet 1.2$

in medium and mild forms: $X = M \bullet (L - P) \bullet 1.2$,

where X − is the dose of clotting factor for a single injection (IU); M − body weight of the patient, kg; L − percentage of the desired required factor level in the blood plasma of the patient; P − initial level of plasma factor in patient before administration of the drug. It should be taken into account that 1 IU of factor VIII, administered per 1 kg of patient's weight increases the content of factor VIII by 1.5-2% and 1 IU of factor IX − increases the content of factor IX by 0.8-1%.

Fresh frozen plasma contains virtually all clotting factors and can be used to treat all forms of hemophilia. Content of factor VIII in fresh plasma is 0.6 IU/ml. But plasma can be used only for the treatment of mild bleeding when it is enough to raise the AHG level by 15-20% of the norm, it may be allowed exceptionally and must not become a constant practice.

The use of cryoprecipitate is limited due to insignificant concentration of VIII in the preparation that makes it impossible to achieve the desired level of hemostasis, unreliable viral inactivation and possible incompatible blood transfusion reaction, and

therefore is possible only in transfusiology office at healthcare facility. Cryoprecipitate should not be used for prevention and home treatment.

Concentrates of clotting factors are administered intravenously. Bolus infusion is the most commonly used at the rate recommended by the manufacturer. Since the diluted drug can maintain activity in the solution for a long time, one may use continuous bolus infusion. The latter allows to reduce the consumption and avoid significant fluctuations of activity levels in the blood. Preparations with clotting factors are packaged by discrete doses. Because of their high cost, after receiving the estimated doses, one should administer a dose close to the result of calculation, divisible by the content in the vial.

*Therapy with the bypass drugs*. Currently, there are 2 groups of bypass agents: activated concentrate of prothrombin complex factors (coagulation prothrombin complex) and activated recombinant factor VII (Eptacog alfa). Doses of prothrombin coagulation complex are: 50-100 IU/kg every 12 hours. The maximum daily dose is 200 IU/kg. Doses of Eptacog alfa: 90-120 mg/kg every 2-4 hours to stop bleeding, or 270 mg/kg once.

*Concomitant therapy*

Desmopressin. The use of desmopressin can raise the factor VIII activity in patients with mild HA. It is recommended to administer desmopressin by intravenous or subcutaneous injections in children above the age of 4 years, in a single dose of 0.3 mg/kg. The use of special nasal spray is also possible. A single dose is 300 mg. The drug is administered once, repeated administration can cause tachyphylaxis.

Fibrinolysis inhibitors are used in addition to the specific substitution therapy. They are the most effective in hemorrhages from the wounds of mucous membranes. They must not be used in renal bleeding.

*Topical hemostatic medications*. When conducting surgeries, especially in parenchymal organs, in the extraction of teeth, treatment of wounds, it is indicated to use topical hemostatic agents: fibrin adhesive, hemostatic sponge and others. These drugs are used together with substitution therapy to optimize local hemostatic effect.

*Treatment of acute bleeding* requires maximum early implementation of substitution therapy. Optimal timing of the specific drugs administering is the first 2 hours after the start of bleeding. Therefore, the basis for the initiation of therapy may be patient's subjective feelings or the fact of injury.

*Home treatment:* patients with severe and moderate with inhibitory forms of hemophilia after training and instruction by the hematologist learn to recognize the early signs of bleeding and administer the required amount of clotting factor concentrates or anti-inhibitor drugs to stop bleeding at home. Both preventive treatment and treatment of actual bleeding can be carried out.

Home treatment is most effective because it significantly reduces the time between the occurrence of bleeding and the beginning of treatment, which is crucial for patients with hemophilia. Home treatment can reduce both the duration of treatment and the amount of antihemophilic administered drug. It significantly improves the quality of life of patients.

*Prophylactic treatment* consists in the intravenous administration of clotting factor concentrates to prevent bleedings and hemorrhages. The aim of prevention is: to transfer the severe form of hemophilia into the moderate one, reaching the minimum level of deficiency factor> 1%, and in some cases into the mild form (> 5.0%), which prevents the development of hemophilic arthropathy, reduces the frequency of exacerbations and the risk of serious complications.

*Types of prevention*: primary, secondary. Primary prevention is the long-term treatment, which is used in patients with severe HA and HB. It can be started at the age of 1 to 2 years before the manifestation of clinical symptoms of the disease (primary prevention, determined by age), regardless of age of the patient who has no more than one joint hemorrhage (primary prevention, determined by the first bleeding).

In the secondary prevention, the long-term treatment is carried out when the conditions of the primary prevention are adequately followed.

Ensuring hemostasis in the inhibitory form of hemophilia is implemented with anti-inhibitor drugs regardless of inhibitor's titer: blood clotting factors II, VII, IX, X in combination (anti-inhibitor coagulation complex), activated Eptacog alfa.

The simultaneous use of these drugs is unacceptable because of likelihood of thrombotic complications. It is allowed to use coagulation factors II, VII, IX, X in combination no earlier than 4 hours after administering activated Eptacog alfa. Prescription of activated Eptacog alfa should only be within 48 hours after application of clotting factors II, VII, IX, X in combination.

For local arrest of bleeding, 5% solution of aminocaproic acid is used; the wound surface is treated with thrombin. Patients with hemophilia are absolutely contraindicated against intramuscular injections, which can lead to bruising.

*Treatment of hemarthroses*

In the treatment of hemarthroses, the following measures are used: substitution therapy with drugs by repeated infusions, creating the conditions of temporary resting in the new hemorrhage, prescription of pain medications, prevention of disrupted mobility in the inadequate positions, i.e., the physiological position using splints. For rehabilitation, exercises and physiotherapy are used. Immobilization of the affected joint is not recommended for more than 3 days. Prolonged immobilization leads to disrupted joint mobility in the future. In massive hemarthrosis, it is recommended to conduct joint puncture with aspiration of blood in the early hours after the occurrence of hemarthrosis with administering hydrocortisone solution (10-15 mg/10 kg body weight) into the joint cavity. The dose of cryoprecipitate is chosen so that the level of antihemophilic factor in the patient's blood amounted to 20-15% of normal.

Willebrand disease

The disease was first described in 1926 by von Willebrand, and along with the HA, it is one of common forms of congenital bleeding diatheses. The incidence of this disease is 10 per 100 000 of population. The cause of Willebrand disease is the disorder in the synthesis of factor VIII. However, the clinical and laboratory manifestations of hemophilia and Willebrand disease are different.

Thus, HA is inherited as a recessive, coupled with X-linked trait and is characterized by severe disturbances of plasma-coagulation hemostasis link against the background of normal indicators of primary hemostasis.

Willebrand disease is inherited by the autosomal dominant pattern and is manifested by hemorrhagic diathesis with double defect of vascular-platelet and coagulation link of hemostasis. The difference between these diseases is explained by the disruption in the synthesis of subunits, independent from each other in their biological properties, which make up the complex set of factor's VIII molecule. One of the subunits of low molecular weight, the abnormal synthesis of which causes clinical manifestations of HA, is associated with pro-coagulating activity of factor VIII. It provides the participation of factor VIII in blood clotting, and coagulation methods are used for its evaluation (Table 11). The presence of double hemostatic system defect in Willebrand disease explains its characteristic clinical presentation. The result of disrupted vascular-platelet hemostasis link is the early start of bleeding, immediately after the injury or cuts. In HA, bleeding occurs shortly after a similar impact.

The clinical presentation of Willebrand disease is dominated by bleeding from mucous membranes (nose, gums, gastrointestinal tract, uterine). The results of the defect in coagulation link of hemostasis are ecchymosis and hematoma. In severe course, the disease appears early in life, and often after the age of 10-12 years.

*Treatment of Willebrand disease.* Patients with Willebrand disease, as a rule, do not require regular treatment, although the risk of bleeding is always increased. Sometimes, patients who will undergo planned surgical operation, need preventive treatment. In this case, drugs are injected, based on the concentrate of factor VIII in the complex with Willebrand factor. If the course of the disease is mild, the prophylaxis can be performed using desmopressin, which increases level of Willebrand factor in the patient's plasma.

Depending on the subtype of Willebrand disease, desmopressin is used in the treatment, concentrates of factor VIII+Willebrand factor (FVIII/FVW-concentrates), and in their absence − cryoprecipitate.

The level of factor VIII, required for hemostasis, is the same as in hemophilia. The effective dose is considered to be such that is able to provide the normal duration of bleeding during 8-13 hours from the moment of transfusion.

## Acquired coagulopathies

**The syndrome of disseminated intravascular coagulation (DIC)**

This circulation system lesion results from excessive activation of thromboplastin formation with subsequent intra-vascular thrombosis formation, hypoxia and degenerative changes of the internal organs with their disrupted functions. This may be caused by factors that are able to activate both external and internal paths of thromboplastin formation.

Pathogenesis of DIC syndrome, starting from the entry of excess portions of thromboplastin into the blood flow, is uniform. Etiological factor is significant only at the initial stage of activation of thromboplastin formation. Ultimately, the occurrence of DIC syndrome is possible in the inconsistency in the rates of accumulation of mediators and products of inflammation, triggers of thromboplastin formation, on the one hand, and the rate in the removal of mononuclear phagocytes from the vascular bed by excretion organs and system cells − on the other.

There are three mechanisms of activation of blood coagulation in DIC syndrome:

1. Activation of coagulation mainly by the external path of thromboplastin formation (prothrombinases). Most often, this mechanism occurs during surgery, trauma, burns, when the vascular bed gets a significant amount of tissue thromboplastin. The interaction of thromboplastin plasma clotting factors (factor V, VII, X, IV) causes the formation of a significant amount of tissue prothrombinases occurs, which determines the development of intra-vascular coagulation.

2. Activation of blood coagulation system is mainly by the internal path of thromboplastin formation. This situation occurs in pathological conditions which are accompanied by damage to the vascular endothelium under various endotoxins, antigen-antibody complexes. Damage to the endothelium leads to activation of the contact factors (factor XII, Hageman factor) and subsequent inclusion of cascade system of blood coagulation involving platelets. Endotoxins, antigen-antibody complexes cause damage to blood vessels and platelets in many sites of the bloodstream which is accompanied by massive widespread intra-vascular clotting with platelet aggregation in different vascular areas, especially in the microcirculation system. A similar situation is observed in children with infections (bacterial or viral), immune complex diseases.

3. Activation of blood coagulation system simultaneously by external and internal ways. This genesis of DIC syndrome is observed in traumatic shock that develops in the extensive tissue damage, in terminal patients with severe metabolic disorders.

Regardless of the way of activation of blood clotting, the body develops the blockage of blood vessels in different regions and microcirculation blockade. In turn, poor circulation and stasis of blood leads to disruption of the integrity of the vascular wall and activation system of blood coagulation. Thus, there is a vicious circle, which simultaneously includes both ways of blood coagulation activation system. Simultaneously, the clotting system of platelets, kallikrein-kinin and fibrinolytic enzymatic systems are activated.

In the development of DIC syndrome, one can distinguish several stages, characterized by certain hemocoagulation disorders and clinical manifestations.

*Stage I of DIC – the hypercoagulation phase.* Its duration varies extensively. It can develop dramatically with rapid and significant activation of blood coagulation system, with massive disseminated intra-vascular coagulation and severe shock. Hypercoagulable period is characterized by activation of plasma coagulation factors, intra-vascular platelet aggregation and other blood cells, disrupted microcirculation in various organs as a result of the blockade of the vascular bed by fibrin masses and cells aggregates. The hypercoagulation phase also can develop gradually with gradual administering of small doses of prothrombinase. However, the slow progress can result in the “explosion” and rapid development of DIC.

*Stage II of DIC − the hypocoagulation phase* that replaces the hypercoagulation phase and is due to consumption of large amount of fibrinogen, factor XIII, V, VIII, other procoagulants and platelets. At the same time, abnormal inhibitors of blood clotting are accumulating in the blood, such as degradation products of fibrin and fibrinogen. This causes an increase in the anticoagulant activity of the blood. The concentration of heparin in the blood does not significantly change, and heparin compounds with fibrin play an important role in hemostasis disorders.

*Stage III − the phase of afibrinogenemia with pathological fibrinolysis* − exhaustion of coagulation potential of the blood and fibrinolytic system, decentralization of circulation, decompensation of DIC.

*Stage IV − renewable* − the return to physiological norms of coagulation potential.

By the nature of DIC course, one can distinguish: acute (from several hours to several weeks), subacute (several weeks), chronic (from several weeks to several months) forms.

*The clinical presentation* depends on the underlying disease and DIC course. Along with the symptoms of the underlying disease, in the course of acute DIC the hypercoagulable phase is clinically characterized by the sudden, as if groundless, appearance of coagulative or mixed shock, collapse, dramatic decrease in arterial and central venous pressure. Because of the blockade of pulmonary capillaries, shortness of breath occurs − "the shock lung". In the most severe cases, death can occur with symptoms of acute pulmonary heart. CNS lesion is characterized by seizures, signs of pulmonary heart encephalopathy, coma. The duration of this phase is different in various diseases.

Further on, the hypercoagulable phase is replaced by the hypocoagulation phase with the development of hemorrhagic syndrome of different severity. Quite often, phase I goes unnoticed and only hemorrhagic syndrome, which has complicated a particular process or a disease, draws the doctor's attention. Hemorrhagic syndrome is characterized by hemorrhages of various sizes, large ecchymosis and hematomas, or bleeding on the sites of palpation. There are also hemorrhages from the mucous membranes (nose, gums, uterine), and in severe cases − generalized massive hemorrhages, renal hemorrhages, bleeding from the digestive tract, hemorrhages in internal organs, central nervous system, profuse bleeding from the genital tract after childbirth, bleeding from incisional wounds and punctures of stitches in the postoperative period. As a result of blood loss, acute posthemorrhagic anemia develops. The signs of hypovolemia and metabolic disorders are manifested; hemocoagulation shock is transformed into the hemorrhagic one.

Afterwards, due to fibrin-embolism, blockade of microcirculation anatomical and functional disturbances in organs and systems develop − acute adrenal insufficiency, parenchymal dystrophy of the liver, hepatorenal failure, fine-foci encephalopathy. Characteristic changes are found in the kidneys, even in the insignificantly manifested DIC, there are oliguria and mild azotemia, and in the massive DIC, cortical necrosis and uremia develop.

In the clinical presentation of subacute form of DIC, the symptoms of the underlying disease are always in the forefront. The variability of clinical manifestations of DIC depends on the underlying disease. In subacute forms of DIC, general condition of the patient is rapidly deteriorating, collapse often occurs, hemorrhages on the skin appear. This course of DIC is observed in the infectious diseases. In patients with other diseases, including malignant tumors, the characteristic clinical symptoms are thrombosis and thrombophlebitis, they may be the only symptoms of DIC for a long time. The development of hypocoagulation phase in such cases is clinically manifested by bleeding of varying intensity.

*Treatment of DIC.* When choosing a method for medical correction of hemostasis disorders in children, preference should be given to etiopathogenetic focus of therapy, that is, complete elimination of the root causes of DIC occurrence. It is necessary to take into account the stage of its development: 1) interrupt the accelerated prothrombinase and thrombin formation; 2) prevent the blockade of microcirculation system of parenchymal organs, due to the consumption of coagulation factors; 3) control the hemorrhagic syndrome.

The nature of DIC determines the need for differentiated treatment of hemostatic disorders at different stages. At stages I and II of DIC, in order to achieve the goal it is enough to use fresh frozen plasma (5 ml/kg/day at stage I and 5-10 ml/kg at stage II), rheologically active drugs, disaggregants, medications and components of blood in the presence of indications. At stage III of DIC, along with the introduction of fresh frozen (10 ml/kg/day) heparin (1 IU heparin per 1 ml of plasma) cryoplasma and contrykal (1000 IU/kg/day), it is necessary to conduct substitution therapy with blood preparations and components. Correction of anemia should be conducted using washed

erythrocytes, or one-group red blood cell mass in the amount necessary to maintain the level of hemoglobin at 90-100 g/l. In hypoalbuminemia and hypoproteinemia it is indicated to administer albumin in a dose that provides blood protein content of at least 60 g/l.

The presence of clinical signs of multiple organ failure (respiratory, hepato-renal failure, circulatory failure and other microcirculatory disorders associated with the progression of DIC) or clinical manifestations of hemorrhagic syndrome and laboratory signs at stages II-III is the indication for heparin prescription. The use of heparin provides the individual selection of daily dose in the mode of controlled hypocoagulation at a given therapeutic level. For hypercoagulation situations, the optimal therapeutic hypocoagulation level is equal to twice the APTT considering the age norm. In expressed hypocoagulation states, the initial APTT often exceeds the value of the indicator in the norm. Therefore, in such cases one should focus on therapeutic hypocoagulation level that exceeds the original value APTT rate by 25-30%.

The recovery period requires the use of symptomatic groups of drugs aimed at restoring the function of affected organs.

## Angiopathies

### Hemorrhagic vasculitis

Schonlein-Henoch disease, hemorrhagic immune thrombovasculitis, belongs to a group of angiopathies of infectious-allergic etiology due to generalized hyperergic inflammation of small blood vessels.

Hemorrhagic vasculitis ranks first among all forms of hemorrhagic diatheses. It often affects children aged 5-14 years (23-25 per 1000). The disease affects equally often boys and girls. The favorable factors include allergies and the presence of foci of chronic infection. Occurrence of hemorrhagic vasculitis may be preceded by infections, vaccinations, administration of immunoglobulin, insect bites, physical and emotional effects, hypothermia, etc.

*Pathogenesis* is associated with immunocomplex lesion of vessels in the microvasculature system. Immune complexes are identified in the form of mixed cryoglobulins as a delayed type allergy: there is aseptic inflammation of blood vessels

with the destruction of the walls and thrombosing. Systematic destruction of capillaries is accompanied by exudation of plasma, red blood cells and perivascular infiltration. Along with the advent of cell and extracapillary swelling, the rheological properties of blood are disrupted, aggregation of platelet and red blood cells increases, which together with the activation of the coagulation system contributes to the development of DIC. Increased vascular permeability and capillary rupture are manifested by hemorrhagic syndrome.

*Classification of hemorrhagic vasculitis*

1. The form of hemorrhagic vasculitis: skin and joints, abdominal, renal, mixed. Distinguishing of these forms is arbitrary, since there is often a combination of manifestations characteristic of several forms.

2. The degree of activity of the process: activity of I, II, III degree on the basis of clinical and laboratory parameters.

3. The course of the process: acute, subacute, protracted, relapsing.

4. Characteristics of complications: intussusception, bleeding from the gastrointestinal tract and others.

In most cases, in hemorrhagic vasculitis one can distinguish the hidden (latent) period of 1-3 weeks − the time between exposure to the etiological factor and the first signs of the disease. The disease often begins acutely. The patient develops fever, symptoms of intoxication that correlate with the severity of hemorrhagic vasculitis. The most typical sign of the disease is hemorrhagic rash, which occurs in all forms. The preferential localization of the rash is on the legs, in the area of knee and ankle joint, lateral thighs, buttocks, on the upper limbs in the area of elbow joints. Hemorrhage can have different sizes: from petechiae to ecchymosis. Typically, the elements have rounded shape, they are not merging. In describing the rash, its symmetrical character is traditionally mentioned. The rash does not disappear when pressed, it is of rich red color. After the “bloom” of the rash, the temporary moderate pigmentation remains. In the severe course, in the center of hemorrhage, the necrosis area may form, which is subsequently covered with crust. Cutaneous hemorrhagic syndrome may be accompanied by itchy skin.

An important feature of the disease is articular syndrome. It has all the signs of inflammation: redness, fever, pain joints. Mainly the large joints are affected. Pain is transient in nature. Articular syndrome passes within 2-5 day without leaving deformities.

More than half of patients have marked abdominal syndrome. Abdominal pain occurs suddenly, it is paroxysmal in nature, imitating the presentation of "acute abdomen", accompanied by dyspeptic disorders. Abdominal form is dangerous due to its complications (intussusception, bleeding).

According to different authors, the incidence of renal syndrome in hemorrhagic vasculitis is 30-60%. Renal symptoms appear 2-4 weeks after the onset of the disease. There is often a moderate urinary syndrome, such as microhematuria, albuminuria. For children of the first 3 years of life, leukocyturia is typical. Urinary syndrome lasts for 2-4 weeks and later disappears. Sometimes there is diffuse glomerulonephritis, hematuria option is observed most often.

Many patients have symptoms of CNS and peripheral nerves lesion − headache, increased irritability, myalgia, paresthesia. Asymmetry of tendon reflexes, cranial nerves lesions can be observed. Many patients with hemorrhagic vasculitis suffer from changes in cardio-vascular system − the weakening of heart tones, tachy- or bradycardia, functional systolic murmur.

*Treatment of hemorrhagic vasculitis.* Bed rest should be followed throughout the active period of the disease and for 5-7 days after the last noticed element. The diet consists of excluding allergen products. It is pathogenetically justified to prescribe medications that improve microcirculation and strengthen the blood vessels. Heparin therapy is now widely used. Prescription of anticoagulants is pathogenetically proven as the leading mechanism in hemorrhagic vasculitis is hypercoagulation and micro-clots formation. Heparin has anticoagulant, anti-inflammatory and desensitizing effect, it regulates vascular permeability. Daily dose of heparin is 100-500 IU/kg. The best administering route of heparin is subcutaneous in the anterior abdominal wall every 5-6 hours. The intravenous drop-by-drop introduction with a uniform intake of heparin during the day is also possible. Heparin treatment is performed under the control of the

condition of blood coagulation system. The dose of heparin is considered adequate when extending the clotting time by 2 times. Heparin treatment duration depends on the severity and extent of hemorrhagic vasculitis, recovery of hemocoagulative disorders. On average, it takes 3-4 weeks, with renal syndrome − up to 2 months. Heparin should be withdrawn gradually, by reducing the dose, and not by reducing the number of injections.

*The presence of joint, abdominal syndrome, fever, leukocytosis with neutrocytosis, accelerated ESR is not the indication for antibiotic therapy.*

The prescription of antihistamines is justified.

In renal syndrome, glucocorticoids are used, which prevent the formation of glomerulonephritis and kidney failure. Indications for cytostatics prescription are relapsing course (more than 6 months) of hemorrhagic vasculitis and renal syndrome of chronic or subacute course.

## Thrombocytopenias

Idiopathic thrombocytopenic purpura (ITP) is a primary hemorrhagic diathesis, in which the reduced amount number of platelets in the blood at normal or increased number of megakaryocytes in the bone marrow is observed. The incidence of ITP is maximum in childhood and is 1.5-2 per 100 000 of child population without significant differences among boys and girls. Among older children, ITP affects girls and women by 2 times more often than men.

*The etiology of ITP* has not been established. The states and diseases that can directly precede the emergence of ITP are different: bacterial or viral infections 1-3 weeks prior to the development of ITP, immunizations, administering immunoglobulin, trauma, surgery, intake of drugs (often antibiotics), hypothermia, overheating in the sun. However, in about 50% of patients the onset of the disease occurs without preceding triggering factors.

*Pathogenesis.* Immunopathological process, namely the synthesis of antiplatelet antibodies, is important in the development of thrombocytopenia in most patients. In modern conditions, methods for determining IgG on platelets have been developed. The proof of the immune theory of ITP is detection of lymphocytes, sensitized to

autothrombocytes, in the blood of sick children. The autoimmune process and synthesis of antiplatelet autoantibodies are the causes of drastic reduction in life expectancy of platelets in ITP patients to several hours at their lifetime in healthy children of 7-10 days. Spleen is the location of untimely death of platelets in ITP. In ITP, adhesive and aggregation activity of platelets is reduced.

It has been proved that antiplatelet antibodies can influence megakaryocytes, changing their function. The amount of megakaryocytes in patients with ITP in the bone marrow is increased, but the percentage of active forms is decreased, the number of young forms of megakaryocytes is increased.

Bleeding in patients with ITP is caused by the quantitative (thrombocytopenia) and qualitative (thrombocytopathy) lack of platelets. The endothelium of blood vessels, devoid of angiotrophic function (normally about 10% of circulating platelets “flow” in the endothelium and are absorbed by it), becomes clear, acquires increased permeability. This leads to spontaneous hemorrhage. Disruption of coagulation link in patients with ITP (slowdown of thromboplastin formation, increased fibrinolytic activity) is secondary to platelet deficiency level. Due to thrombocytopenia and thrombocytopathy, plasma of patients with ITP is characterized by reduced serotonin content, which adversely affects hemostasis.

*Classification.* One can distinguish acute (6 months) and chronic forms of ITP. In most children, ITP is acute and only in 10-15% of patients the course becomes chronic. By the period of the disease, the following types are distinguished: exacerbation (crisis), clinical remission (absence of bleeding in the presence of thrombocytopenia), clinical-hematological remission.

*Clinical presentation.* Increased bleeding is the only clinical sign of ITP. Moreover, in 10% of cases of acute course and in 30% of patients with chronic course, increased bleeding was observed more than six months before the expanded clinical presentation and diagnosis: easy bruising, frequent nosebleeds after minor interventions. It is important to point out that acute respiratory infections were observed much more frequently at the hospitalization of patients with acute ITP course. In 60% of patients, acute purpura began after the previous infection or immunization.

The most typical manifestation of ITP is cutaneous hemorrhagic syndrome (it is observed in 100% of patients). The characteristic signs of cutaneous and subcutaneous hemorrhages in patients with ITP are: spontaneous occurrence, mostly at night, polymorphic nature (petechiae and ecchymosis), polychromic character (hemorrhages of different colors, from red to green and yellow), asymmetrical form. The sizes of ecchymoses range from 0.5 to 5 cm or more in diameter. There is no "favorite" location of cutaneous hemorrhagic syndrome. Hemorrhages are not observed on the palms and soles, there is no bleeding into the hair follicles. In severe cases, the number of hemorrhages is quite significant and the skin resembles that of a leopard.

Bleeding is a common sign of ITP. Depending on the presence or absence of bleeding ITP, it is divided into "dry" purpura (without hemorrhages, only skin hemorrhagic syndrome) and "wet" (combination of skin bleeding and hemorrhagic syndrome). The most common are nosebleeds, rarely − gastrointestinal bleeding (melena, bleeding from the gums), hematuria. In the presence of melena, there is no abdominal pain. The most serious and prolonged types of bleeding in girls are meno- and metrorrhagia. Metrorrhagia lasts for 2-4 weeks, it is difficult to manage. In patients with ITP, there can be prolonged bleeding from the socket of the removed tooth or other "minor" surgeries. Moderate splenomegaly occurs in 10% of patients with ITP. Enlarged liver is also atypical.

Hemorrhages in the internal organs are rare. The most difficult complication of ITP is cerebral hemorrhage. Triggers are head injuries, severe viral infections, traumatic procedures (sternal puncture, intravenous injection). The number of platelets does not exceed $10 \cdot 10^9$/l. Common signs of cerebral hemorrhage are headache, dizziness, convulsions, coma or sopor, vomiting, meningeal signs, focal symptoms.

*The diagnosis of ITP*. Peripheral blood analysis: reduced platelet count $<100 \cdot 10^9$/l. In the blood smear, morphological changes of platelets are revealed − the count is dominated by large, small-grained platelets. Other indicators of peripheral blood depend on the presence of bleeding: after the heavy bleeding *acute posthemorrhagic anemia* occurs, in frequent recurrent bleedings − *chronic posthemorrhagic anemia* with characteristic changes in hemogram. Bleeding time is

prolonged (more than 10 min. at the norm of 3-5 min.). Retraction of a blood clot is disrupted. Time of blood clotting is normal. In myelogram − hyperplasia of megakaryocytic lineage, rarely − normal megakaryocytes content. The increase of young forms of megakaryocytes is typical, with dominating megacaryoblasts and promegakaryocytes. After bleeding, there may be irritation of the red marrow lineage.

In 50-70% of ITP, antiplatelet antibodies are observed, that are bound mainly on glycoprotein complexes of platelet membranes. In 20% of cases, there are antiplatelet antibodies in blood serum.

*Treatment*. Diet No.5: food must be mechanically attenuated but with enough minerals and vitamins (fresh fruits, vegetables, berries). The regimen should be moderate, with exclusion of physical activity and procedures that cause mechanical irritation of the skin or mucous membranes.

In the mild forms of ITP, drugs that increase the platelet function, stabilize cell membranes and improve metabolism are used. The positive influence is exerted by the courses of drugs that stimulate adhesion, platelet aggregation function: riboxin, vitamin $B_5$, dicynon, ε-aminocaproic acid. In moderate and severe stages of the disease, corticosteroids are administered at a starting dose of 1-2mh/kg/day for 3-4 weeks.

In patients, who are refractory to hormones, with contraindications for splenectomy, and in case of ineffectiveness of splenectomy, *immunosuppressive therapy* is used: vincristine 0.02 mg/kg (1.2 mg) once a week for 1-2 months; azathioprine 1.4 mg/kg/day for 2 months or cyclophosphamide 1-2 mg/kg/day. These drugs are administered in combination with low doses of steroids. With the aim of immunosuppression, cyclosporine is recently used at a dose of 5 mg/kg/day for several months and monoclonal antibodies − anti-CD20 (rituximab), anti-CD52 (alemtuzumab) and others.

In severe cases, *polyvalent immunoglobulins* are prescribed for intravenous use at a dose of 0.4 g/kg/day for 5 days or at a dose of 1 g/kg/day for 2 days. In 70% of patients with ITP, rapid growth in the number of platelets is observed, but in 2-3 weeks platelet count returns to previous figures. Given the high cost of the drug and its short-

term effect, the administering of antibodies is conducted only in urgent cases, in the threat of brain hemorrhage, in life-threatening hemorrhages.

Splenectomy. All forms of ITP that require repeated courses of hormone therapy, and presence of complications that threaten the patient's life (bleeding in the brain, intense bleeding, leading to severe posthemorrhagic anemia with respiratory failure) involve the indications for splenectomy. In normal situations, splenectomy is performed after 4-6 months after ineffective conservative therapy. Positive outcome after surgery is more than in 90% of patients.

## Appendixes

Table 1

**Circulating blood volume (ml per 1 kg)**

| The period of childhood | Circulating blood volume |
|---|---|
| Neonatal period | 107-195 ml/kg |
| Infancy | 75-110 ml/kg |
| Preschool and primary school | 51-90 ml/kg |
| Senior school age | 50-92 ml/kg |
| Adults | 50 ml/kg |

Table 2

**Basic iron-containing substrates of the body and their functions**

| Iron substrates | Functions |
|---|---|
| **A. Heme** | |
| Hemoglobin (65%) | Oxygen transport |
| Myoglobin (14.8%) | Transport and deposition of oxygen in the muscles |
| Catalase | Decomposition of hydrogen peroxide |
| Cytochrome | Tissue respiration |
| Peroxidase | Oxidation of substances using $H_2O_2$ |
| **B. Non-heme** | |
| Transferrin (0.1-0.2%) | Transport of iron |
| Ferritin (10%) | Tissue iron deposit |
| Hemosiderin (10%) | Tissue iron deposit |
| Xanthine reductasa | Formation of uric acid |
| Dehydrogenase | Catalysis of oxidation and recovery reactions |

Table 3

**Laboratory criteria of IDA and latent iron deficiency**

| Indicator | Norm | Latent iron deficiency | Iron deficiency anemia |
|---|---|---|---|
| Hemoglobin (g/l)<br>under 6 years<br>above the age of 6 years | <br>> 110<br>> 120 | <br>>110<br>> 120 | <br>> 110<br>< 120 |
| CI | 0.86-1.05 | 0.86-1.05 | < 0.86 |
| MCH (pg) | 24-33 | 24-33 | < 24 |
| MCHC (%) | 30-38 | 30-38 | < 30 |
| SI (μmol/l) | 10.6-33.6 | < 14 | < 14 |
| TIBC (μmol/l) | 40.6-62.6 | > 63 | > 63 |
| LIBC (μmol/l) | < 47 | > 47 | > 47 |
| Transferrin saturation rate (%) | > 17 | 17 | < 15-16 |
| Serum ferritin (μg/l) | > 12 | < 12 | < 12 |
| Desferal sideruria (mg/day) | 0.65 + 0.006 | < 0.4 | < 0.4 |

Table 4

**Iron content in food products**

| Name of animal product | Iron content (mg/100 g) | Name of plant product | Iron content (mg/100 g) |
|---|---|---|---|
| Beef liver | 9.0 | Laminaria | 16.0 |
| Pork liver | 8.0 | Oatmeal | 10.7 |
| Beef tongue | 5.0 | Buckwheat | 7.8 |
| Rabbit meat | 4.4 | Porridge | 7.8 |
| Beef (young) | 4.0 | Peaches | 4.1 |
| Turkey meat | 4.0 | Quince | 3.0 |
| Chicken meat | 3.0 | Pears | 2.3 |

| | | | |
|---|---|---|---|
| Sturgeon caviar | 3.0 | Apples | 2.2 |
| Beef (old) | 2.8 | Plums | 2.1 |
| Eggs | 2.7 | Apricots | 2.1 |
| Mackerel | 2.3 | Cherry | 1.4 |
| Carp | 2.2 | Cauliflower | 1.4 |
| Burbot | 1.4 | Currants | 1.3 |
| Cow's milk | 0.4 | Carrots | 1.2 |
| Sour cream 20% fat | 0.3 | Green peas | 0.7 |

Table 5

**The list of medications and herbal products that can cause hemolytic crisis in people with deficiency of glucose 6-phosphate dehydrogenase**

| Group of medications | Medications |
|---|---|
| Antimalarial drugs | Quinine, chinacrin, delagil, resorcine |
| Sulfanilamides | Streptocide, sulfacetamide, sulfazin, sulfacyl sodium, sulfathiazole, bactrim and others. |
| Sulfones | Diaminodiphenylsulfone, solusulfon |
| Nitrofurans | Furacilin, furasolidone, nitrofurantoin, furaginum |
| Antituberculous drugs | PASA sodium, isoniazid, ftivazide, tubasidum |
| Antibiotics | Levomycetin (chloramphenicol) novobiocin, amphotericin B |
| Analgesics and alexipyretics | Acetylsalicylic acid, phenacetin |
| Other drugs and chemicals | Naphthalene, ascorbic acid, phenylhydrazine, colchicine, neosalvarsan, nitroglycerin, nevigramon, methylene blue and others. |
| Plant products | Horse beans (Vicia fava), verbena, field peas, male fern, heathberries, blueberries |

Table 6

**Hematological semiotics of some diseases**

| Semiotics | Hematopoiesis | Factors that caused the changes |
|---|---|---|
| Lymphocytosis (in children under the age of 5 years more than 60%; above 5 years − more than 40%) | Stimulation of hematopoietic lineage more often of viral nature | Infectious mononucleosis (combination with monocytosis), rubella, whooping cough, scarlet fever, chicken pox, tuberculosis, viral pneumonia, epidemic hepatitis, influenza, “cat scratch” disease |
| Lymphocytopenia | State of myelopoiesis oppression | Primary immunopathological conditions, kidney failure, AIDS, corticosteroid therapy, pronounced swellings, irradiation |
| Neutrophilia | Leukemoid reaction of bone marrow | Infectious-inflammatory diseases, acute blood loss, malignant formations, ionizing radiation, treatment with corticosteroids, state of shock, fractures, burns |
| Neutropenia | Inhibition of hematopoiesis | Immunodeficiencies, systemic diseases (rheumatoid arthritis, systemic lupus), Hodgkin’s disease, leukemia, agranulocytosis |
| Thrombocytosis | Thrombocytopathy stimulation of hematopoiesis | Primary thrombocytopathy, chronic inflammations, colitis, enteritis, arthritis, tuberculosis; after splenectomy, hemorrhagic states, anemia |
| Thrombocytopenia | Condition of suppressed hematopoietic lineage | Infectious diseases: measles, scarlet fever, diphtheria, infectious mononucleosis, malaria, smallpox, typhoid and typhus; sepsis, inflammatory diseases of the upper respiratory tract, as the post-vaccination reaction due to consumption of medications, in thrombocytopenic purpura, in hypersplenism, congenital heart defects, DIC syndrome |
| Reticulocytosis | Condition of active erythropoiesis | In acute blood loss, hemolytic anemia, effective treatment of anemia |
| Reticulocytopenia | Condition of | In iron anemia, vitamin $B_{12}$- folic acid deficiency |

| | | |
|---|---|---|
| | erythropoiesis suppression | anemia, in the use of cytostatics |

Table 7

**Nomenclature of plasma clotting factors**

| Digital symbol according to the international nomenclature | Plasma factor |
|---|---|
| I | Fibrinogen |
| II | Prothrombin |
| III | Tissue thromboplastin |
| IV | Calcium ions |
| V | Proaccelerin, labile factor |
| VII | Proconvertine |
| VIII | Antihemophilic globulin (AHG) |
| IX | Plasma thromboplastin component, Christmas factor |
| X | Stuar-Prower factor, prothrombinase |
| XI | Plasma thromboplastin precursor |
| XII | Hageman factor, contact factor |
| XIII | Fibrin stabilizing factor, fibrinase |

Table 8

**Indicators of coagulogram in children aged 1-14 years**

| Indicator | Children | Adults |
|---|---|---|
| Clotting time by Lee-White, min. | 3-9 | 5-15 |
| Silicone time, min. | 11-21 | - |
| Recalcification time, sec. | 75-136 | 76-136 |
| Thrombotest, degree | 4-6 | 4-6 |
| Prothrombin index, % | 81-99 | 81-99 |
| Prothrombin intake, % | 92-102 | 92-102 |
| Factor V, % | 78-103 | 78-103 |
| Factor VII, % | 74-114 | 74-114 |
| Factor VIII, % | 86-120 | 86-120 |
| Fibrinogen, g/l | 1.8-3.8 | 1.72-3.82 |

| | | |
|---|---|---|
| Fibrinolytic activity by Kowarzhyk, hr. | 2-5 | 2-4 |
| Tolerance to heparin, min. | 4-9 | 7-11 |
| Free heparin, hr. | 3.5-6 | 5-7 |

Table 9

**Clinical characteristics of different types of bleeding**

| **Clinical manifestations** | **Nature of bleeding** | |
|---|---|---|
| | **Coagulative** | **Capillary** |
| Hematomas | Large sized | Small surfaces |
| Hemarthroses | Often, in severe cases − the main manifestation of the disease | Noncharacteristic |
| Nosebleeds | Rarely | Often (the main type of bleeding) |
| Gastrointestinal bleeding | Rarely (ulcers) | Often (predominant symptom) |
| Hematuria | Characteristic | Noncharacteristic |
| Uterine bleeding | Noncharacteristic (most patients are boys) | Characteristic |
| Bleeding after tooth extraction | Starts a few hours after surgery, does not stop after the applying of pressing bandages | Starts immediately after surgery and is stopped after the applying of pressing bandages |
| Postoperative bleeding | Late bleeding with formation of tissue hematoma | Bleeding mainly during surgery |
| Typical manifestations in moderate forms | Large hematomas after injury and dangerous bleeding after injury | Nasal and uterine bleeding |

Table 10

**The obligatory volume of laboratory studies for patients with hemorrhagic diathesis**

| **Tests for characterization of plasma coagulation hemostasis** | **Tests for characterization of vascular-platelet hemostasis** |
|---|---|
| Time of venous blood coagulation | Vessel wall resistance |
| Plasma recalcification time | The number of platelets |
| Activated partial thromboplastin time | The duration of bleeding |
| Prothrombin index | |
| Concentration of fibrinogen | |
| The activity of factor XIII | |

Table 11

**Structural components of factor VIII**

| Subunit | Functional value | Assessment method |
|---|---|---|
| VIII: C − pro-coagulating, low-molecular subunit | Participation in the internal way of coagulation | Activity of factor VIII |
| VWF – von Willebrand factor, high-molecular subunit | Participation in the reactions of vascular-platelet hemostasis | - the duration of bleeding,<br>- platelet adhesiveness on wound surface (in vivo); on the surface of glass (in vitro),<br>- platelet aggregation under antibiotic ristomycin,<br>- quantitative determination by immunoprecipitation |

Table 12

**Normal parameters of hematology analyzer**

| Parameter | Value | Unit | The norm range |
|---|---|---|---|
| WBC | Number of white blood cells | $*10^9$/l | 4-9 |
| RBC | Number of red blood cells | $*10^{12}$/l | M: 4-5.1<br>W: 3.7-4.7 |
| HGB | Hemoglobin | g/l | M: 132-164<br>W: 115-145 |
| HCT | Hematocrit | % | M: 40-48<br>W: 36-42 |
| PLT | Platelet count | $*10^9$/l | 180-400 |
| MCV | Average volume of red blood cells | fl | 76-95 |
| MPV | Average volume of platelets | fl | 7.5-10.5 |
| MCH | Average content of hemoglobin in 1 erythrocyte | picogram | 23-35 |
| MCHC | Average concentration of hemoglobin in red blood cells | g/l | 322-382 |
| %LYM | Percentage of | % | 18-37 |

| | | | |
|---|---|---|---|
| | lymphocytes | | |
| %MON | Percentage of monocytes | % | 2-11 |
| %GRA | Percentage of granulocytes | % | 52-80 |
| RDW | Erythrocyte distribution width | % | 9.3-19.3 |
| PDW | Platelet distribution width | % | 0.2-0.4 |

## TESTS FOR SELF-CHECK

1. A child, aged 8, after earlier sore throat developed petechial rash of pink color on the skin of the feet, the temperature increased to 38°C. Platelets count in the blood test: 90.0 • $10^9$/l, bleeding time: 15 minutes. What disease can be assumed?

***A*** Iron deficiency anemia

***B*** Idiopathic thrombocytopenic purpura

***C*** Hemorrhagic vasculitis

***D*** Acute lymphoblastic leukemia

***E*** Hemophilia

2. A girl is 4 months old, body weight is 6000 g. From life history: birth weight 2000 g; obtained mixed feeding. On examination: pale skin and mucous membranes, liver protrudes from the edge of the costal arch. In the blood test, hemoglobin − 80 g/l, erythrocytes − 3.6 • $10^{12}$/l, color index − 0.67, leukocytes − 8.9 • $10^9$/l, platelets − 200 • $10^9$/l, reticulocytes − 20 ‰. Hypochromia, poikilocytosis, anisocytosis. What kind of pathology can be suspected?

***A*** Fanconi anemia

***B*** Hypoplastic anemia

***C*** Deficiency anemia

***D*** Hyporegenerative anemia

***E*** Normoregenerative anemia

3. Sasha P., aged 13, was admitted to the department with complaints of weakness, loss of appetite, pale skin and mucous membranes. Parents point out that over the period of 1.5 months, the dark cherry-colored stool was often observed. In the blood count: hemoglobin − 70 g/l, erythrocytes − 2.1 • $10^{12}$/l, color index − 0.7, reticulocytes − 40 ‰, leukocytes − 8.9 • $10^9$/l, platelets − 200 • $10^9$/l. The content of factor VII in the blood is 60% of the norm. What kind of pathology should be considered?

***A*** Deficiency anemia

***B*** Chronic post-hemorrhagic anemia

***C*** Hemophilia A

***D*** Hypoplastic anemia

***E*** Hyporegenerative anemia

4. A child is severely ill, there is weakness, joint pain, increased body temperature. Later on, these symptoms were accompanied with rash on the skin in the form of erythematous patches of 2-5 mm, of itching and hemorrhagic character. One can observe pain and swelling of large joints, cramping pain localized around in the umbilical region and signs of intestinal bleeding. What is the most likely diagnosis?

***A*** Hemorrhagic vasculitis

***B*** Scarlet fever

***C*** Hemorrhagic meningoencephalitis

***D*** Streptoderma

***E*** Rheumatism

5. During the examination of a boy, aged 6, in whom bleeding after tooth extraction did not stop for a long time, the following has been revealed: blood test − red blood cells − $4.2 \cdot 10^{12}$/l, hemoglobin − 120 g/l, platelets − $210 \cdot 10^{9}$/l, duration of bleeding by Duke − 3'20", clotting time by Burker − no clotting occurred in 12', Konchalovsky sign (-). What is the likely diagnosis?

***A*** Aplastic anemia

***B*** Iron deficiency anemia

***C*** Hypoplastic anemia

***D*** Thrombocytopenic purpura

***E*** Hemophilia

6. A boy, aged 11 months, developed petechial rashes and ecchymosis on the skin of the trunk, limbs, mild nosebleeds. Objectively: pale skin and mucous membranes,

skin hemorrhagic syndrome. The heart and lungs are without pathology. Abdomen is soft, the liver and spleen are not enlarged. Complete blood count: erythrocytes − $3.9 \cdot 10^{12}$/l, hemoglobin − 110 g/l, CI − 0.9, leukocytes − $6.8 \cdot 10^{9}$/l, stab − 3% segmented − 38%, lymphocytes − 57 % monocytes − 2%, ESR − 6 mm/hr., platelets − $30 \cdot 10^{9}$/l. Time of blood coagulation by Li-White is 8 minutes. What is the most likely disease?

***A*** Idiopathic thrombocytopenic purpura

***B*** Isoimmune thrombocytopenic purpura

***C*** Transimmune thrombocytopenic purpura

***D*** Hemorrhagic vasculitis

***E*** Thrombocytopathy

7. A boy, aged 12, appealed with complaints of general weakness, dizziness, feeling flickering “butterflies” in the eyes. He considers himself to be sick for 10 days, when the above symptoms appeared. Two years ago, he was treated in the gastroenterology department with the ulcer disease of the antrum. After the breach in the diet, the patient for two weeks felt epigastric pain, occasionally − black stool. In the analysis of blood: erythrocytes − $2.9 \cdot 10^{12}$/l, hemoglobin − 60 g/l, CI − 0.7. How should anemia be interpreted?

***A*** Hemolytic anemia

***B*** Aplastic anemia

***C*** $B_{12}$-deficiency anemia

***D*** Posthemorrhagic anemia

***E*** Folic acid deficiency anemia

8. A girl, aged 2, was directed by the district physician to hematology department with the diagnosis of anemia. From history it is known that the child was on artificial feeding since the neonatal period; milk and semolina porridge still prevail in the diet. The child refuses from meat, liver, vegetable dishes. Objectively: skin is dry, pale, angular stomatitis. In complete blood count: red blood cells − $2.9 \cdot 10^{12}$/l, hemoglobin

− 62 g/l, CI − 0.64, leukocytes − 6.0 • $10^9$/l, segmented − 42%, eosinophils − 2%, lymphocytes − 46%, monocytes − 10%, reticulocytes − 4 ‰, ESR − 10 mm/h. What is the most likely etiology of the disease?

***A*** Selenium deficiency

***B*** Folic acid deficiency

***C*** Zinc deficiency

***D*** Vitamin $B_{12}$ deficiency

***E*** Iron deficiency

9. A child, hospitalized with Hodgkin's disease, developed increased body temperature up to 38.2°C, there is abundant polymorphic rash (spots, papules, vesicles) throughout the body. The additional use of which drug is the most reasonable in this case?

***A*** Ribavarin

***B*** Prednisolone

***C*** Acyclovir

***D*** Ceftriaxone

***E*** Vancomycin

10. A boy, aged 14, has the enlarged anterior cervical lymph nodes on the right, up to 3 cm in diameter, of thick consistency. The child is pale, feverish, has lost weight. On chest X-ray: pulmonary limits without infiltrative focal shadows. Shadow of mediastinum is not extended. On ultrasound of the abdomen: at the hilus of the spleen, there are enlarged lymph nodes. In the biopsy of the cervical lymph node: Berezovsky-Sternberg cells are revealed. Identify the stage of Hodgkin's disease in the child:

***A*** II B stage

***B*** III A stage

***C*** I B stage

***D*** II A stage

***E*** III B stage

11. A child, aged 6, complains of headache, fatigue, weakness, loss of appetite, fever up to 37.4 − 37.8°C, pain in the joints of the left hand, mostly at night, hemorrhages. Complaints appeared 1 month ago. In the blood test: red blood cells − $2.9 \cdot 10^{12}$/l; hemoglobin − 45 g/l; CI − 0.77; ESR − 70 mm/h; platelets − $60 \cdot 10^{9}$/l; leukocytes − $810 \cdot 10^{9}$/l; myeloblasts − 35%; neutrophil promyelocytes − 0.5%; stab neutrophils − 2%; segmented − 21.5%; eosinophils − 6%; lymphocytes − 32%; monocytes − 3%. What diagnosis should be made?

***A*** Chronic leukemia

***B*** Acute leukemia

***C*** Rheumatoid arthritis

***D*** Thrombocytopenic purpura

***E*** Deficiency anemia

12. On examination of a boy, aged 11, the following was revealed: enlarged cervical lymph nodes, freely movable from each other and surrounding tissues, of tight elastic consistency. In the biopsy of lymph node: Berezovsky-Sternberg cells are revealed. What is the likely diagnosis in this case?

***A*** Lymphogranulomatosis

***B*** Toxoplasmosis

***C*** Infectious mononucleosis

***D*** Benign lymphoreticulosis

***E*** Tuberculous lymphadenitis

13. A girl, aged 14, developed anemic syndrome due to metrorrhagia during 3 months: hemoglobin − 86 g/l, erythrocytes − $2.9 \cdot 10^{12}$/l, CI − 0.7, anisocytosis, poikilocytosis, serum iron − 7.6 μmol/l. What means to treat this type of anemia will you apply?

***A*** Vitamin $B_6$

***B*** Vitamins $B_{12}$

***C*** Transfusion of packed red blood cells

***D*** Folic acid

***E*** Iron preparations

14. A child is 2 months old. She was born full-term weighing 3300 g, now she weighs 4800 g. The mother is healthy. The infant obtains mixed feeding using "Detolakt" mixture. What corrective supplements should be prescribed to prevent iron deficiency anemia?

***A*** Apple juice

***B*** Corrective supplement should not be prescribed

***C*** Carrot juice

***D*** Boiled egg yolk

***E*** Pomegranate juice

15. On examination of a child aged 1 year, the following has been detected: erythrocytes − $3.6 \cdot 10^{12}$/l, hemoglobin − 68 g/l, CI − 0.6, reticulocytes − 1 ‰, platelets − $230.0 \cdot 10^{9}$/l. From the history of life: the child was bottle-fed with cow's milk and semolina porridge. On examination: the child's condition is of medium severity, skin is pale and clean. Lymph nodes are not enlarged. The liver and spleen are of normal size. What underlies the pathogenesis of anemia in this case?

***A*** Suppression of the bone marrow function

***B*** Vitamin $B_{12}$ deficiency

***C*** Iron deficiency

***D*** Accelerated erythrocyte hemolysis

***E*** Folic acid deficiency

16. In a child with hemorrhages on the skin of the trunk and limbs, the bleeding from the sore on the tongue has developed. What additional study will help to exclude hemophilia?

***A*** Blood clot retraction

***B*** Blood count with platelet definition

***C*** Duration of bleeding y Duke

***D*** Duration of clotting by Duke

***E*** Prothrombin time

17. A girl, aged 10, after sustained ARVI, developed hemorrhages on the skin; a day before the nasal hemorrhage joined, which has not stopped since that time. On examination: severe condition. Manifested pallor. On the skin of the trunk and limbs: hemorrhages of different color and size, placed asymmetrically. What is your preliminary diagnosis?

***A*** Hemolytic anemia

***B*** Hemorrhagic vasculitis

***C*** Hemophilia

***D*** DIC

***E*** Thrombocytopenic purpura

18. In the history of a 6-month infant who is bottle-fed, there is recurrent diarrhea over a month, which is not accompanied by disruption of general condition. After several unsuccessful attempts to correct nutrition, the pediatrician prescribed goat's milk. At the age of 11 months, the infant developed pale skin and lethargy. What is the most likely diagnosis?

***A*** Crohn's disease

***B*** Iron deficiency anemia

***C*** Food deficiency of copper

***D*** Deficiency anemia due to folic acid

***E*** Malabsorption syndrome

19. An infant is aged 7 months. Mother complains of child's pallor, loss of appetite. Since the age of 2 months, the infant is fed with cow's milk, from 6 months the diet includes semolina porridge. Vegetables, fruit, cheese, egg yolk are included to the

dies irregularly. On objective examination: pale skin and mucous membranes, functional systolic murmur at the apex of the heart. In the blood test: RBCs − 3.1 • $10^{12/}$l, hemoglobin − 82 g/l, CI − 0.7. What disease can be suspected?

***A*** Protein-deficiency anemia

***B*** $B_{12}$-folic deficiency anemia

***C*** Iron deficiency anemia

***D*** Minkowski-Chauffard anemia

***E*** Hemolytic anemia

20. An infant aged 5 months was admitted with complaints from the mother about jaundice and pallor of the skin, poor appetite, increase in temperature to 37.3°C. The infant is from the Ist pregnancy and birth, the mother's blood group B (III), Rh (+), child's − O (I), Rh (+). The mother is healthy, the father has reticulocytosis. Objectively: severe condition, jaundice, pallor, anxiety. Enlarged abdomen, liver − by 3 cm, spleen − by 4 cm, protruding from under the costal arch. Urine is saturated, urinary bladder emptying is not changed. What is the most probable diagnosis?

***A*** Hepatitis

***B*** Hemolytic disease of the newborns

***C*** Congenital hemolytic anemia

***D*** Acute leukemia

***E*** Lucius Jaundice

21. An infant of 3 days of life is being treated in the specialized department with the diagnosis of birth trauma, affected CNS, subarachnoid hemorrhage. Cephalhematoma of the occipital bone. In the blood test: red blood cells − 3.4 • $10^{12}$/l, Hb − 118 g/l, CI − 1.0. What caused the identified changes?

***A*** Hemolytic anemia

***B*** Posthemorrhagic anemia

***C*** Deficiency of erythropoetin

***D*** Impaired hemapoiesis

***E*** Iron deficiency

22. A girl is 3 years old. The parents appealed to the doctor with complaints about child's weakness, pale skin, dizziness. A few days ago the child injured the nose, there was significant nosebleed. On examination: pallor of the skin and mucous membranes. In the blood test: red blood cells − $2.0 \cdot 10^{12}$/l, Hb − 49 g/l, CI − 1.0, leukocytes − $6.4 \cdot 10^{9}$/l, eosinophils − 2%, stab − 4%; segmented − 55%; lymphocytes − 38%; monocytes − 1%, ESR − 10 mm/h. Posthemorrhagic anemia was diagnosed. What treatment is it advisable to prescribe to the child?

***A*** Aktiferrin

***B*** Hemofer

***C*** Hemotransfusions

***D*** Ferroplex

***E*** Ferrum-Lek

23. A 5-year old child after ARVI developed yellowness of the skin and sclera against the background of progressive pale skin, fever, lethargy. Liver +1.5 cm, spleen +4 cm. In the blood test: red blood cells − $2.7 \cdot 10^{12}$/l, hemoglobin − 88 g/l, total bilirubin − 80 μmol/l, indirect − 75 μmol/l. Coombs reaction (direct) − positive. Price-Jones curve: 7-7.2 μm − 79%. What disease can be suspected in the child?

***A*** Cirrhosis

***B*** Viral hepatitis

***C*** Acquired hemolytic anemia

***D*** Hereditary microspherocytic hemolytic anemia

***E*** Hemolytic uremic syndrome

24. In a boy, aged 4, diagnosed with delayed physical development, during the examination the following was detected: dark color of the upper body, pale mucous membranes, bleeding gums, hemorrhagic skin rash, manifestations of

dysembryogenesis, additional sixth fingers, rough systolic murmur at the apex of the heart. On hemogram: pancytopenia. What is the most likely diagnosis?

***A*** Klinefelter syndrome

***B*** Fanconi anemia

***C*** Acquired aplastic anemia

***D*** Blackfan-Diamond syndrome

***E*** Down Syndrome

25. A patient during the last 2 months suffers from increasing pain, weakness, bleeding (skin hemorrhages, bleeding nose) and fever. Lymph nodes, liver and spleen are not enlarged. On hemogram: hemoglobin − 50 g/l, erythrocytes − $1.5 \cdot 10^{12}$/l, CI − 1.0, leukocytes − $1.8 \cdot 10^{9}$/l, stab neutrophils − 1%, segmented neutrophils − 28% eosinophils − 1%, lymphocytes − 6%, monocytes − 5%, ESR − 60 mm/hr., platelets − $30 \cdot 10^{9}$/l. What is the diagnosis?

***A*** Aplastic anemia

***B*** Iron deficiency anemia

***C*** Hemolytic anemia

***D*** Acute leukemia

***E*** $B_{12}$-deficiency anemia

26. A child aged 10 months was admitted for examination with complaints from the mother about significantly pale skin of the child, loss of appetite, enlarged belly. In the neonatal age, the child was treated at the hospital for jaundice and anemia. Objectively: pale skin with icteric shade, no teeth, enlarged abdomen, palpable spleen. Hb 90 g/l, erythrocyte $3.0 \cdot 10^{12}$/l, CI 0.9, microspherocytosis, reticulocytosis 20 ‰, total serum bilirubin 37 μmol/l, indirect 28 μmol/l. What type of anemia has occurred?

***A*** Hereditary elliptocytosis

***B*** Iron deficiency anemia

***C*** Protein deficiency anemia

***D*** $B_{12}$-deficiency anemia

***E*** Hemolytic anemia

27. The in-patient department admitted a child aged 6 months with clinical and laboratory presentation of iron deficiency anemia, II severity degree. The child was prematurely born weighing 1800 g; bottle-fed during 2 months. Over the past 2 weeks, the child became significantly pale. What medication is advisable to use for pathogenetic therapy?

***A*** Ferrum-Lek

***B*** Vitamin $B_{12}$

***C*** Folic acid

***D*** Packed red blood cells

***E*** Prednisolone

28. An 8-years-old girl developed pain in the lower extremities, fever, hemorrhages on the skin, weakness. On examination: pale skin, pronounced hemorrhagic rash all over the body. On palpation: cervical, axillary and inguinal lymph nodes are enlarged. Liver size: +3.5 cm, spleen +2.5 cm. Blood analysis: red blood cells − $1.8 \cdot 10^{12}$/l, Hb − 60 g/l, platelets − $25 \cdot 10^{9}$/l, white blood cells − $32 \cdot 10^{9}$/l, stab − 1%, segmented − 9%, lymphocytes − 88%, monocytes − 2%, ESR − 48 mm/hr., bleeding duration − 10 min. What study should be conducted in the first place for further diagnosis?

***A*** Sternal puncture

***B*** Biopsy of the affected lymph node

***C*** Study of adhesive-aggregation function of platelets

***D*** Coagulogram

***E*** Ultrasound of the liver and spleen

**Answers keys:**

1-***B***, 2 − ***C***, 3 − ***B***, 4 − ***A***, 5 − ***E***, 6 − ***A***, 7 − ***D***, 8 − ***E***, 9 − ***C***, 10 − ***E***, 11 − ***B***, 12 − ***A***, 13 − ***E***, 14 − ***B***, 15 − ***C***, 16 − ***D***, 17 − ***E***, 18 − ***D***, 19 − ***C***, 20 − ***C***, 21- ***B***, 22 − ***C***, 23 − ***C***, 24 − ***B***, 25 − ***A***, 26 − ***E***, 27 − ***A***, 28 − ***A***,

## THE LIST OF REFERENCES CITED IN THE TEXT


1. Абдулкадыров К.М. Гематология: Новейший справочник. – М.: Эксмо; СПб.: Сова – 2004. – С. 928.
2. Алексеєв Н.А. «Анемии» /Алексеєв Н.А. //СПб.: Гиппократ, 2004.- С. 512.
3. Алексеєв Н.А. «Гематология и иммунология детского возраста». – СПб.: Гиппократ. – 2009. – С. 1040.
4. Алексеєв Н.А. « Геморрагические диатезы и тромбофилии: Руководство для врачей» /Алексеєв Н.А. //СПб.: Гиппократ. – 2004. – С. 608.
5. Алиева М.Д., В.Г. Полякова, Г.Л. Менткевич, С.А. Маяковой Детская онкология. Национальное руководство /Под ред. М.Д. Алиева, В.Г. Полякова, Г.Л. Менткевич, С.А. Маяковой //М.: Издательская группа РОНЦ. – 2012.
6. Анічков М.М. «Биология опухолевого роста: (молекулярно-медицинские аспекты)» /Анічков М.М., Квєтной І.М., Коновалов С.С. //Прайм-Еврознак. – 2004. – С. 224.
7. Балашова В.А. «Стволовые клетки. Перспективы клеточной терапии» /Балашова В.А. //Вестник гематологи. – 2005. – №3. – С. 57-62.
8. Баркаган З.С. Геморрагические заболевания и синдромы /Баркаган З.С. //М: Медицина. – 1988. – С. 437.
9. Баркаган З.С. Основы диагностики нарушений гемостаза /Баркаган З.С., Момот А.П. //М. – 1999. – С. 217.
10. Баркаган З.С. «Диагностика и контролирующая терапія нарушений гемостаза» /Баркаган З.С., Момот А.П. //Нью-диамед. – 2001. – С. 296.
11. Белогуровой М.Б. Детская онкология /Под редакцией М.Б. Белогуровой. // СПб.: СпецЛит. – 2002. – С. 353.
12. Василевский И.В. Наследственные болезни обмена веществ /И.В. Василевский //Справочник по госпитальной педиатрии. – 2002. – С. 829 – 891.
13. Витебский Е.М. Принципы и практика современной терапии абдоминальной формы геморрагического васкулита у детей /Витебский Е.М., Прохоров Е.В // Рос. вест. перинатологии и педиатрии. – 2003. – № 2. – С. 31-33.

14. Воробйова Н.А. «К вопросу об оптимизации интенсивной терапии острого ДВС-синдрома» /Воробйова Н.А., Недашковський Е.В. //Анестезиология и реаниматология. – 2003. – №4. – С. 50-54.
15. Воробьева А.И. Руководство по гематологии /Под ред. академика А.И. Воробьева //Т. 3. – М.: Ньюдиамед. – 2005. – С. 361.
16. Головко О. К. Клинические аспекты иммунных тромбоцитопений в неонатологии /Головко О. К., Линчевский Г. Л., Воробьева О. В. // Здоровье ребенка. – 2006. – № 2. – С. 115-122.
17. Глузман Д.Ф. Диагностика лейкозов. Атлас и практическое руководство. / Глузман Д.Ф. //К.: МОРИОН. – 2000. – С. 224.
18. Глузман Д.Ф. Иммуноцитохимическая диагностика опухолей кроветворной и лимфоидной тканей у детей /Глузман Д.Ф. //К.:ДИА. – 2005. – С. 216 .
19. Дурнов Л.А. Руководство по детской онкологии /Под ред. академика РАМН Л.А. Дурнова /М.: Миклош. – 2003. – С. 301-316.
20. Дурнов Л.А. Злокачественные новообразования кроветворной и лимфоидной ткани у детей. Руководство для врачей /Дурнов Л.А. //М.: Медицина. – 2001. – С. 272.
21. Ермолин А.Э. Дифференциальная диагностика и лечение острых и хронических лейкозов / Ермолин А.Э. //М.: БИНОМ. – 2008. – С. 200.
22. Коколина Е.Ф. Практическое руководство по детским болезням / Под общей ред. Е.Ф. Коколиной, А.Г. Румянцева. Гематология/онкология детского возраста / Под ред. А.Г. Румянцева, Е.В. Самочатовой. // М: Медпрактика. – 2004. – Т. 4. – С. 518-555.
23. Колигин Б.А. «Лимфогранулематозы у детей и подростков» /Колигин Б.А., Кобиков С.Х. //Гиппократ. – 2008. – 280 с.
24. Кузьмина Л.А. Гематология детского возраста. – М.: МЕДпресс-информ – 2001. – С. 365-381.
25. Кузник Б.І. «Клиническая гематология детского возраста» /Кузнік Б.І., Максимова О.Г. //Вузовская книга. – 2010. – С. 316.

26. Лыскина Г.А. Программа лечения болезни Шонлейн-Геноха у детей / Лыскина Г.А., Зиновьева Г.А., Кякинская Е.Г., Донов Г.И. // Междунар. журн. мед. практики. – 2000. – № 4. – С. 13-15.
27. Мазурин А.В. Сосков Г.И. Гематурия как проявление геморрагических болезней у детей /Мазурин А.В., Петров В.Ю., Плахута Т.Г., Якунина Л.Н., Сосков Г.И. //Гематология и трансфузиология. – 2001. – Т. 46, №1. – С. 29-31.
28. Масчан А.А. Иммунно-опосредованные тромбоцитопении новорожден-ных: дифференциальный диагноз и принципы терапии / Масчан А. А., Румянцев А. Г. //Вопросы гематологии/онкологии и иммунопатологии в педиатрии. – 2010, т. 9, № 3. – С. 13-18.
29. Меткевич Г.Л. Лейкозы у детей /Г.Л. Меткевич, С.А. Маякова //М.: Практическая медицина. – 2009. – С. 384.
30. Папаян А.В. «Анемии у детей – руководство для врачей» /Папаян А.В., Жукова Л.Ю. – 2001р. – 384 с.
31. Петрушина А.Д. Неотложные состояния у детей /Петрушина А.Д., Мальченко Л.А., Кретинина Л.Н. и др. //М.: Мед. книга: Изд. центр «Академия»: Изд-во НГМА – 2002. – С. 176.
32. Романова А. Справочник по гематологии /Под ред. Романовой. А. //Ростов-на-Дону: Феникс. – 2000. — С. 270-341.
33. Румянцева А.Г. «Анемии у детей: диагностика, диференциальная диагностика, лечение» /А.Г. Румянцева, Ю.Н. Токарева //МАКС Пресс. – 2004. – С. 215.
34. Семочкин С.В. Лечение лимфомы Ходжкина у подростков и молодых взрослых /С.В. Семочкин, С.С. Лория, А.Г. Румянцев, В.М. Сотников //Онкогематология. – 2008. – № 1-2. – С. 18-21.
35. Сисла Б. Руководство по лабораторной гематологии: Пер с англ. /Под общей ред. А.И. Воробьева //М.: Практическая медицина. – 2011. – С. 37-3, 174-190.
36. Титов Л.П. Иммунология. Терминологический словарь. – 2004.- С. 351.
37. Третьякова О. Алгоритм диагностики и лечения тромбоцитопений у детей и подростков /Третьякова О. //Ліки України.- 2004 – №11 (88).- С. 44-48.

38. Федорова А.В. Роль нарушений системы гемостаза в патогенезе геморрагического васкулита у детей и возможности медикаментозной коррекции /Под ред. А.В.Федорова //Барнаул. – 1997. – С. 19.
39. Цымбал И.Н. Идиопатическая тромбоцитопеническая пурпура у детей /Цымбал И.Н. //Лечащий Врач. – 2000. – № 2.
40. Algarin C. Iron deficiency anemia in infancy: long-lasting effects on auditory and visual system functioning /Algarin C.,Peirano P., Garrido M. //Pediatr. Res. – 2003. – Vol. 53, №2/ – P. 217-223.
41. Alving B. How I treat heparin-induced thrombocytopenia and thrombosis /Alving B. //Blood. – 2003. – Vol. 101, №1 – P. 31-37.
42. Arbuthnot C., Wilde J. Haemostatic problems in acute promyelocytic leukaemia /Arbuthnot C. //Blood Rev. – 2006. – Vol. 20, №6 – P. 289-297.
43. Beris P. Role of intravenous iron terapy in anemia management: state of the art /Beris P., Maniatis A. //Semin.Hematol. – 2006. – Vol. 43, №4 – P. 1-20.
44. Blaustein M. Cellular physiology / Blaustein M., Kao J., Matteson D. //Elsevier Inc. – 2004.
45. Bussel J. Novel approaches to refractory thrombocytopenic purpura /Bussel J. //Blood Rev. – 2002. – Vol. 16, №1 – P. 31-36.
46. Carrol l W. Childhool acute lumphoblastic leukemia in the age of genomics /Carrol l W., Bhojwany D., Min D. //Pediaatr. Blood Cancer. – 2006.- Vol. 46. – P. 570
47. Wong W.Approach to the newborn who has thrombocytopenia /Wong W., Glader B. //NeoRewievs. – 2004. – Vol. 5. – №10.
48. Vandendries E.R. Drug-Associated Disease: Hematologic Dysfunction /Vandendries E.R., Drews R.E. //Critical Care Clinics,. – 2006.- V. 22.- P. 347-355.
49. Takechi T. et al. Idiopathic thrombocytopenic purpura associated with Helicobacter pylori infection /Takechi T. et al. //Pediatrics International. – 2006. – V. 48. – P. 76-78.
50. Stowe J. et al. Idiopathic thrombocytopenic purpura and the second dose of MMR /Stowe J. et al. //Archives of Disease in Childhood. – 2008. – V. 93. – P. 182-183.

51. Rehman A. Acute immune thrombocytopenic purpura in children /Rehman A. //Turk J Hematol. – 2007. – V. 24. – P. 41 –51.
52. Lada P. Heparin-Induced Thtombocytopenia /Lada P. //Current Topics from the Drug Information Center, University of Kentucky. – 2003. – № 3. 24 p.
53. Kojouri K. et al. Occult quinine-induced thrombocytopea /Kojouri K. et al //J Ocla State Med Assoc. – 2000. – V. 93. – P. 519 – 521.
54. Howell M.D. Utility of thrombocytopenia as a marker for heparin allergy in adult ED patients /Howell M.D., Powers R.D. //The American Journal of Emergency Medicine. – 2006. – V. 24. – № 3. – P. 268-270.
55. Gruchalla R.S. Approach to the patient with multiple antibiotic sensitivities. Allergy-Asthma-Proc. – 2000. – V. 21(1). – P. 39-44.
56. Dracopoulos S. et al. Heparin-Induced Thrombocytopenia Type 2: a serious hazard in preemptive renal transplantation /Dracopoulos S. et al. //Transplantation Proceedings. – 2007. – V. 39. – P. 3481-3484
57. Christensen R.D. Hematologic problems of the neonate //W.B. Saunders Company. – 2000. – P. 282-301.
58. Baroletti S.A., Heparin-Induced Thrombocytopenia /Baroletti S.A., Goldhaber S.Z. //Circulation. – 2006. – V.114. – P. 355-356.
59. Miller D. R. Blood Diseases of Infancy and Childhood. – 2005. – P. 877-893.
60. Roberts I.A.G., Review. Management of thrombocytopenia in neonates / Roberts I.A.G., Murray N.A. //Br J Haematol. – 2009. – V. 105. – P. 864 – 870.
61. Carbone A. HIV-associated Hodgkin lymphoma /A. Carbone, A. Gloghini, D. Serraino, M. Spina //Curr. Opin. HIV AIDS. – 2009 Jan. – 4(1). – 3-10.
62. Amato M. et al. Treatment of neonatal thrombocytopenia /Amato M. et al. // J. Pediatr. – 1985. – V.107. – P. 650.
63. Berkowitz R. L. Parralel randomized trials of risk-based therapy for fetal alloimmune thrombocytopenia /Berkowitz R. L., Kolb E. A., McFarland J. G. et al. //Am. J. Obstet Gynecol. – 2006. № 107 (1). – C. 91-96.

64. Richard E. Behrman, Nelson textbook of pediatrics / Richard E. Behrman, Robert M. Kliegman, Hal B. Jenson. // 16th ed. – Philadelphia: W.B. Saunders. – 2000. – 2414 p.
65. Carbone A. HIV-associated Hodgkin lymphoma / A. Carbone, A. Gloghini, D. Serraino, M. Spina // Curr. Opin. HIV AIDS. – 2009 Jan. – 4(1). – C. 3-10.

## RECOMMENDED LITERATURE FOR FOREIGN STUDENTS

1. Brady P.G. Iron deficiency anemia: a call for / P.G. Brady // South. Med. J. – 2007. – 100 (10). – P. 966-967.
2. Caudill J.S. Congenital sideroblastic anemia associated with germline polymorphisms reducing expression of FECH / J.S. Caudill, H. Imran, J.C. Porcher, D.P. Steensma // Haematologica. – 2008. – 93 (10). – P. 1582-1584.
3. Cherif-Zahar B. Structure and expression of the RH locus in the Rh-deficiency syndrome / B. Cherif-Zahar, V. Raynal, C. Le Van Kim, A.M. D'Ambrosio, P. Bailly, J.P. Cartron, Y. Colin // Blood Journal. – 2011. – P. 656-662.
4. Gräsbeck R. Imerslund-Gräsbeck syndrome (selective vitamin B(12) malabsorption with proteinuria) / R.Gräsbeck // Orphanet J Rare Dis. National Center for Biotechnology Information, U.S. National Library of Medicine, 2006. – (1). – P. 17.
5. Hastings C.A. Handbook of Pediatric Hematology and Oncology: Children's Hospital & Research Center Oakland / C.A. Hastings, J. C. Torkildson, Agrawal A.K. [Published Online: 19 Apr 2012]. – DOI: 10.1002/9781118358139.ch4.
6. Hillman R.S. Hematology in Clinical Practice (5th ed.) / R.S. Hillman, K.A. Ault, M. Leporrier, H.M. Rinder. – New York : McGraw-Hill, 2011. – 356 p.
7. Longo D. Harrison's Principles of Internal Medicine (18th ed.) / D. Longo, A.S. Fauci, D.L. Kasper, S.L. Hauser, J.L. Jameson, J. Loscalzo. – New York : McGraw-Hill, 2012. – 408 p.
8. Mackey A.C. Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease / A.C. Mackey, L. Green,

L.C. Liang, P. Dinndorf // J. Pediatr. Gastroenterol. Nutr. – 2007. – 44 (2). – P. 265-267.

9. Nathan and Oski's Hematology and Oncology of Infancy and Childhood / Stuart H. Orkin, David G. Nathan, David Ginsburg, A. Thomas Look, David E. Fisher, and Samuel Lux. – 2015. – 2752 p.
10. Nelson textbook 18th Edition / Robert M. Kliegman, MD, Richard E. Behrman, MD, Hal B. Jenson, MD and Bonita F. Stanton, MD. – Elsevier Health Sciences, 2007. – 3200 p.
11. Nelson Texbook of Pediatrics. – London, Toronto : W.B. Saunders Company Philadelphia, 1995. – 1589 p.
12. Pernicious anemia / National Center for Biotechnology Information (NCBI). U.S. National Library of Medicine. November 23, 2008. Retrieved 1 March 2011.
13. Rivella S. Ineffective erythropoiesis and thalassemias / S. Rivella // Curr. Opin. Hematol. National Center for Biotechnology Information, U.S. National Library of Medicine, 2009. – 16 (3). – P. 187-194.
14. Tiazhka O. Pediatry Guidance Aid / O. Tiazhka. – Київ : Медицина, 2007. – 158 с.
15. Turgeon M. Clinical Hematology: Theory and Procedures (4th ed.) / M. Turgeon. Philadelphia : Lippincott Williams & Wilkins, 2005. – 517 p.

NOTES

**Похилько Валерій Іванович**

**Цвіренко Світлана Миколаївна**

**Лисанець Юлія Валеріївна**

# ВІКОВІ ОСОБЛИВОСТІ ТА ПАТОЛОГІЯ КРОВІ У ДІТЕЙ

**Навчальний посібник**

*(англ. мовою)*