MINISTRY OF HEALTH OF UKRAINE

O.O. BOGOMOLETS NATIONAL MEDICAL UNIVERSITY

Unified guidelines (for Internal medicine departments 1-4)

to Hematology practical classes

for 4th course foreign students

**Educational discipline**

“Internal medicine, including endocrinology”

**Educational level** second (master's)

**Fields of knowledge** 22 Health care

**Specialty** 222 Medicine

in English

KYIV – 2022

Unified GUIDELINES (for internal medicine departments 1-4) to hematology practical classes for 4th course foreign students by educational discipline “Internal medicine, including endocrinology” in English

Kyiv - 2022

У60

УДК 61:612.43]-054.62(076+072)=111

Composed by internal medicine department # 4.

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ISBN

Unified GUIDELINES (for internal medicine departments 1-4) to hematology practical classes for 4th course foreign students by educational discipline “Internal medicine, including endocrinology” in English. – Kyiv, 2022. – 84 p.

УДК 61:612.43]-054.62(076+072)=111

Approved by O.O. Bogomolets National Medical University Academic Council

(Protocol 4 from 01.12.2022 )

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Publishing house

Kyiv 2022

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***Fundamentals of diagnosis, treatment and prevention of major hematological diseases.***

GUIDELINES for the topic:

ANEMIA

1. **The purpose of the lesson:**

To teach students to collect complaints and anamnesis, to conduct a physical examination of patients with anemia.

To acquaint students with the specific examination methods used to diagnose anemia, to acquaint them with the indications for their use, the method of their implementation, and the diagnostic value of each of these methods.

To teach students to interpret examination results, correctly formulate a diagnosis, conduct and analyze differential diagnosis.

To teach students to draw up a treatment protocol for a patient with anemia, considering the clinical features of the course of the disease and the presence of concomitant pathology.

1. **Competences (formation of competencies):**

1. Be able to find out and analyze the complaints of patients with anemia.

2. To teach students to recognize the main symptoms and syndromes in patients with anemia.

3. To improve the method of physical examination of patients with anemia.

4. To be able to determine the stage of anemia of a particular patient and to formulate a diagnosis.

5. To be able to prescribe the optimal diagnostic algorithm for patients with anemia.

6. To teach students to independently interpret the data of instrumental and laboratory research methods used in the diagnosis of anemia.

7. To interpret blood test data for different variants of anemia.

8. To prescribe a scheme of treatment and maintenance therapy for anemia.

1. **Plan and structure of the lesson.**

|  |  |  |  |
| --- | --- | --- | --- |
| **The name of the stage** | **Stage description** | **Levels of assimilation** | **Time** |
| **Preparatory stage** | | | |
| Organizational arrangements  Checking workbooks  Setting learning goals and motivation  Control of the initial level of knowledge:  1. Etiology and pathogenesis  2. Clinic  3. Diagnosis  4. Differential diagnosis  5. Treatment | Methods of control theoretical knowledge:  -individual theoretical survey;  - test control;  -solving typical problems. | Questions  Typical tasks  Tests  Written theoretical tasks  Tables  Pictures  Structural and logical schemes  Audio and video materials. | 45-60 min. |
| **The main stage** | | | |
| Formation of practical skills  1. Collection of anamnesis and physical examination of patients with various forms of anemia.  2. Interpretation of blood tests for anemia.  Formation of professional skills  1. Supervise the patient  2. Plan for examining the patient.  3. Make a treatment plan for a patient with anemia. | Method of forming practical skills:  Practical training  Method of formation of professional skills:  training in solving typical and atypical situational problems (real clinical, simulated, textual) | Algorithm for the formation of practical skills.  Professional algorithms for the formation of professional skills;  patients, medical histories, situational tasks | 100-150 min. |
| **The final stage** | | | |
| Control and correction of the level of practical skills and professional abilities | Methods of control of practical skills:  Individual control of practical skills and their results  Methods of control of professional skills: analysis and evaluation of the results students’ clinical work | The results of working with the patient, with a medical history.  Atypical situational tasks. | 45-60 min. |
| Summarizing the lesson: theoretical, practical, organizational |  |  | 5-10 min. |
| Hometask | Approximate map for independent work with literature. Recommended reading (basic, additional) |  | 5 min. |

1. **Content of the lesson topic**

Anemia is a pathological process characterized by a decrease in the number of erythrocytes and the concentration of hemoglobin per unit volume of blood and the development of hypoxia in body tissues. The normal level of hemoglobin in men is (130 - 164) g/l, in women - (120 - 145) g/l; the number of erythrocytes in men - (4 - 5) × 1012/l, in women - (3.7 - 4.7) × 1012/l.

**Epidemiology**

The prevalence of anemia in population-based studies of healthy nonpregnant people in the United States is approximately 4% of men and 8% of women.

International distribution

According to research, the prevalence of anemia in Canada and Northern Europe is the same as in the United States. In poor countries, studies show that the prevalence of anemia is 2 to 5 times higher than in the United States.

Dietary factors with iron deficiency and, to a lesser extent, folic acid deficiency play a key role in increasing the number of anemias. Populations that consume little meat in their diet have a high incidence of iron deficiency anemia because iron in meat is better absorbed from food than inorganic iron.

Sickle cell disease is common in Africa, India, Saudi Arabia and the Mediterranean. Thalassemia is the most common genetic blood disorder found in Southeast Asia.

Chronic anemia is common in populations with a high incidence of chronic infectious diseases (eg, malaria, tuberculosis, acquired immunodeficiency syndrome [AIDS]), and this is exacerbated in part by the socioeconomic status of these populations and their limited access to adequate health care.

The development of anemic conditions is based on various pathological processes, in most cases anemia is secondary and should be considered together with the main disease. Therefore, timely diagnosis of anemia, identification of diseases that caused them, treatment and prevention are important.

**Etiology**

***Classification of anemias by etiology and pathogenesis***

*I. Anemia caused by blood loss.*

1. Acute posthemorrhagic anemia.

2. Chronic posthemorrhagic anemia.

*ІІ. Anemia caused by hematopoietic disorders.*

1. Anemia caused by impaired hemoglobin formation:

a) anemia caused by iron deficiency;

b) anemia caused by redistribution of iron (infections and inflammation);

c) anemia caused by impaired synthesis or utilization of porphyrins;

d) anemia caused by impaired synthesis of heme and globin.

2. Anemia caused by impaired synthesis of DNA or RNA (megaloblastic anemia).

3. Anemia caused by a violation of the division of erythrocytes (dyserythropoietic).

4. Anemia caused by inhibition of bone marrow cell proliferation.

5. Anemia caused by the replacement of hematopoietic bone marrow by a tumor process.

6. Anemia caused by a violation of erythropoietin production or the appearance of inhibitors to it:

a) anemia due to reduced oxygen demand (hypothyroidism, starvation, endocrine pathology);

b) anemia due to increased destruction of erythropoietin (red cell aplasia).

III. Anemia associated with increased erythrocyte destruction.

1. Hereditary hemolytic anemias:

a) caused by a violation of the structure of the erythrocyte membrane;

b) due to impaired activity of erythrocyte enzymes;

c) caused by a violation of the structure or synthesis of hemoglobin (thalassemia, sickle cell anemia).

2. Acquired hemolytic anemia:

a) due to the action of antibodies (immune);

b) caused by a change in the structure of the erythrocyte membrane due to a somatic mutation (Markiafava-Micheli disease);

c) caused by mechanical damage to the membrane of erythrocytes (marching hemoglobinuria, prosthetic heart valves, hemangiomas, DIC syndrome, etc.);

d) caused by chemical damage of erythrocytes;

e) due to deficiency of vitamins (E, B12, folate);

f) caused by the destruction of erythrocytes by parasites (malaria, toxoplasmosis).

**Classification of anemias by color index**

|  |  |
| --- | --- |
| **Color index** | **Types of anemia** |
| Erythrocyte hypochromia (CI <0.86) | IDA, thalassemia |
| Normochromia of erythrocytes (CI in the range of 0.86 - 1.05) | Hemolytic, aplastic, partial red cell aplasia, anemia of chronic diseases |
| Erythrocyte hyperchromia (CI> 1.06) | B12-deficient, folate-deficient, etc. |

**Classification of anemias by erythrocyte size**

|  |  |
| --- | --- |
| **Mean erythrocyte volume** | **Types of anemia** |
| Macrocytic (MCV > 100) | B12-deficient, folate-deficient, etc. |
| Normocytic  (MCV in the range 81 – 94) | Hemolytic, aplastic, partial red cell aplasia, anemia of chronic diseases |
| Microcytic (MCV < 80) | IDA, thalassemia |

1. Posthemorrhagic anemia

Acute posthemorrhagic anemia is anemia caused by internal or external bleeding, characterized by a decrease in the number of red blood cells and the level of hemoglobin in the blood. The minimum bleeding, at which clinical manifestations occur, is (500 - 700) ml.

Etiology

Anemias caused by blood loss are always secondary. They can be caused by destructive lesions of internal organs and tissues (erosions, ulcers, varicose veins, destruction of the vascular wall due to damage or disintegrating tumor tissue), acquired or hereditary hemorrhagic diatheses, overdose of anticoagulants. Blood loss can be visible (bloody vomiting, uterine, nasal, pulmonary bleeding, melena, bleeding from wounds) or hidden (internal) - pleural and pericardial cavities (hemothorax, hemopericardium), in the abdominal cavity (ectopic pregnancy), due to dissection of the aorta, stomach -intestinal bleeding, etc.

Pathogenesis

1. Hypovolemia is the main factor in pathogenesis, which leads to the activation of the sympathoadrenal system. Acute blood loss is accompanied by a rapid decrease in blood volume and the development of hemorrhagic shock. Compensatory activation of the sympathoadrenal system ensures the outflow of blood from the depot to normalize hemodynamics.

2. Redistribution of blood develops, viscosity increases, as a result of which intravascular aggregation of formed elements occurs.

3. Deterioration of capillary blood flow (formation of microthrombi) causes hypoxia of organ tissues.

4. As a result of a decrease in venous blood flow, cardiac output decreases. Compensatory tachycardia develops.

5. Deterioration of microcirculation blocks the opening of blood vessels, contributing to thrombosis.

6. With the formation of aggregates from erythrocytes, the shock becomes irreversible.

Clinic

Clinic of acute posthemorrhagic anemia: syndrome of acute vascular insufficiency (collapse, shock, fainting), increasing hypoxia and symptoms of the underlying disease that caused blood loss.

Patients have pallor of the skin, dizziness, loss of consciousness, aggravation of facial features, cold sweat, nausea, vomiting, convulsions. Decreased blood pressure, thread-like accelerated pulse and tachypnea are observed.

Diagnosis

When diagnosing acute posthemorrhagic anemia, it is necessary to determine its phase, especially in the case of occult bleeding. During the first day, the recognition of such anemia is difficult due to the entry into the bloodstream of deposited blood and reflex narrowing of blood vessels, which reduces the area of ​​the microcirculatory tract. This period is defined as the reflex phase of compensation. After 1-2 days, the lost blood is replaced by tissue fluid, the volume of the vascular bed is restored, hemodilution (blood dilution) occurs. This period corresponds to the hydremic phase of compensation, it lasts for 2 - 3 days. It is characterized by an equal decrease in hematocrit, erythrocyte count and hemoglobin level. Anemia is normochromic normocytic. After 4 - 5 days the bone marrow phase of compensation starts. There is a significant increase in the number of reticulocytes and leukocytes with a shift of the leukocyte formula to the left to metamyelocytes. In the punctate of the bone marrow increased content of erythroid elements up to (30 - 40)% with accelerated maturation of normocytes can be found. The ratio of leukocytes and erythrocytes becomes equal (1: 1). These changes are a natural consequence of increasing the concentration of erythropoietin in the patient's serum after acute blood loss, which causes an increase in the proliferative activity of cells - precursors of erythropoiesis class III maturity (erythropoietin-sensitive).

Acute posthemorrhagic anemia requires timely diagnosis and assessment of blood loss.

**Treatment**

Ways to stop bleeding depend on the etiological factors of bleeding and localization. Hemostatic sponge, fibrin film with thrombin, bioglue, 5% aminocaproic acid solution are used to stop bleeding locally. Filling the lost volume of blood and treating acute vascular insufficiency is carried out by the combined use of blood substitutes and donor blood. First of all, salt crystalloid solutions are introduced: isotonic sodium chloride, Ringer's. Since the electrolyte solutions are quickly moved from the vascular bed to the tissues, the blood plasma volume increases by only 25% of the total volume of the injected solution. Therefore, when eliminating blood loss, the volume of infusion of isotonic solutions should exceed the volume of blood loss by 3-4 times.

Solutions of crystalloids are used as an initial and main remedy for loss of (500 - 700) ml of blood. In case of loss (750 - 1000) ml of blood, in addition to crystalloids, colloid plasma substitutes are administered, and in case of blood loss of more than 1 l (20% of the RBC) - blood preparations and colloid solutions.

With a sharp drop in blood pressure, (1 - 2) ml of a 0.2% solution of norepinephrine hydrotartrate, hydrocortisone or prednisone is added to crystalloid solutions once. Transfusion of fresh erythrocyte mass is used for blood loss of more than 1 - 1.5 l and hemoglobin values less than 80 - 70 g / l.

The optimal ratio of crystalloid and colloid solutions (reopolyglukin and albumin) is 2:1.

After stopping the bleeding and stabilizing the hemodynamics, the treatment is the same as for iron deficiency anemia.

Vitamin B12, folic acid and other hematopoietic stimulants are not indicated for acute post-hemorrhagic anemia.

**2. Iron deficiency anemia**

Iron-deficiency anemia is a disease in which the content of iron in blood serum, bone marrow, and depot decreases. As a result, the formation of hemoglobin and, subsequently, erythrocytes is disturbed. Hypochromic anemia and trophic disorders in tissues occur.

**Etiology and pathogenesis**

**The main etiological factors for the development of iron deficiency anemia**

|  |
| --- |
| **I.** Diseases of the digestive tract, accompanied by chronic blood loss: peptic ulcer disease, cancer of various localizations, hemorrhoids and fissures of the rectum, erosive gastropathy, duodenitis, nonspecific ulcerative colitis, worm infestations, etc. |
| **II.** Diseases of the digestive tract with impaired iron absorption: anenteral conditions (resection), intestinal amyloidosis, chronic enteritis, malabsorption syndrome. |
| **ІІІ** Diseases of the genitourinary system complicated by micro- and macrohematuria: renal form of hemorrhagic vasculitis, chronic glomerulonephritis and pyelonephritis, bladder polyposis, renal tuberculosis, Berge's disease, urolithiasis, leiomyofibroma, urinary tract cancer, cervical cancer, meno- and metrorrhagia in ovarian dysfunction, prolonged and heavy menstruation, etc. |
| **IV.** Diseases of the endocrine system: myxedema, chronic adrenal insufficiency, pituitary hypofunction, etc. |
| **V.** Diseases of the cardiovascular system: hypertension with frequent nosebleeds, extrahepatic portal hypertension, aortic dissection, atherosclerosis of mesenteric vessels |
| **VI.** Respiratory diseases: pulmonary hemosiderosis, lung and bronchial cancer, bronchiectasis, tuberculosis, purulent lung diseases. |
| **VII**. Diseases of the blood system: hemoblastosis, hypoplastic and aplastic anemias complicated by bleeding, Marciafava-Micheli disease, thrombocytopenia, hemorrhagic diathesis, hemophilia, coagulopathy. |
| **VIII**. Diseases accompanied by redistribution of iron: septic conditions, tuberculosis, acute infections, sarcoidosis, chronic osteomyelitis, chronic mycoses, apostematous nephritis, acute pyelonephritis, renal carbuncle, purulent diseases, rheumatoid arthritis. |
| **IX.** Pregnancy, lactation, regular uncontrolled blood donation. |

**Clinic**

With a significant decrease in hemoglobin, symptoms associated with insufficient supply of tissues with oxygen: weakness, palpitations, dizziness, shortness of breath, fainting.

**Symptoms of anemic hypoxia:** tachycardia, arterial hypotension, shortness of breath during physical exertion, dizziness and vertigo, pain in the heart, paresthesias of the limbs, pallor of the skin, swelling of the limbs.

**Symptoms of sideropenic syndrome:** fatigue, memory loss, headache, taste distortion, muscle weakness, hair loss, brittle nails, distortion of smell, "blueing" of the sclera, hypoanacid gastritis, dry skin, nocturnal enuresis, urinary incontinence, difficulty swallowing, tingling of the tongue.

**Symptoms of metabolic intoxication syndrome:** low-grade fever, tachycardia, fatigue, memory loss, headache.

**Diagnosis**

Criteria for laboratory diagnosis of iron deficiency anemia

1. Decreased level of hemoglobin

2. Color index less than 0.86 (hypochromia)

3. Morphological changes of erythrocytes - microcytosis in combination with anisocytosis, poikilocytosis.

4. MСN - less than 27 pg

5. MСNС - less than 33%

6. MCV - less than 80 fl

7. The average diameter of erythrocytes is less than 7.55 ± 0.009 μm.

8. Number of reticulocytes unchanged (2-10:1000)

9. Serum iron is reduced (in women - less than 12 μmol/l; in men - less than 13 μmol/l)

10. The total iron-binding capacity of blood serum is increased (above 85 μmol/l)

11. Iron saturation of transferrin is reduced (less than 16%).

12. Decreased ferritin level (less than 15 μg/l)

**Differential diagnosis**

Differential diagnosis is primarily carried out with other types of hypochromic anemia - conditions in which hemoglobin synthesis disorders are not caused by iron deficiency, but by other factors. This group includes hereditary and acquired anemias associated with impaired synthesis of porphyrins and heme.

**A typical blood test for IDА**

|  |  |
| --- | --- |
| *Нb* | 80 g/l; |
| The number of erythrocytes | 3,5/l; |
| Color index | 0,7; |
| Platelets | 250/l; |
| Leukocytes | 4,7/l; |
| Eosinophils | 2,5%; |
| Basophils | 0,5%; |
| rod-shaped | 2%; |
| Segmented | 65%; |
| Lymphocytes | 24%; |
| Monocytes | 6%; |
| ESR | 22 mm/h. |
| Features of red blood: anisocytes, hypochromia and erythrocyte microcytosis. | |

**Treatment**

1. Eliminating the cause of iron deficiency

2. Appointment of oral iron preparations (daily dose - 2-3 mg of elemental iron per 1 kg of body weight):

• Sorbifer - 1 tablet 2 times a day

• Ranferon - 1 tablet 2 times a day

• Tardiferon - 1 tablet 2 times a day

The course of oral therapy should be long (at least 1-1.5 months). Usually, treatment with iron tablets lasts 2-3 months.

3. The nutrition of patients should be complete with the inclusion of meat products, vegetables and fruits, diverse.

4. Hemotransfusions should not be used without vital indications.

5. For parenteral administration, drugs are prescribed only for special indications.

6. Preventive prescribing of iron preparations is carried out:

- to all women whose menstruation lasts more than 5 days for many years;

- pregnant women with obvious or latent iron deficiency should take iron preparations throughout pregnancy, as well as after childbirth and lactation;

- regular donors should be prescribed iron preparations within 2 weeks after donating blood.

**3. B12 (folate) -deficiency anemia**

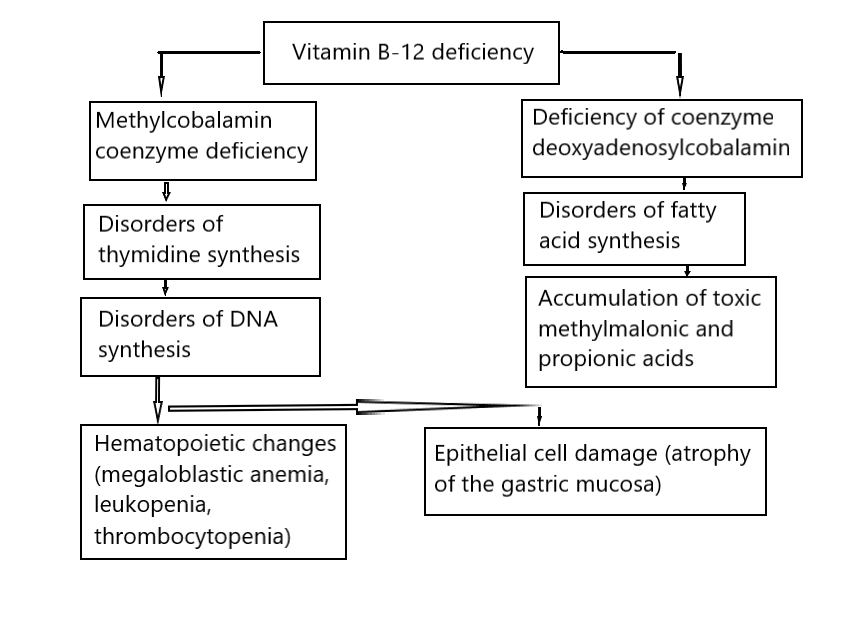
B12 (folate deficiency) anemia is a group of anemias in which the synthesis of DNA and RNA is impaired, which leads to hematopoietic disorders, the appearance of megaloblasts and the destruction of erythrokaryocytes in the bone marrow, a decrease in erythrocytes and hemoglobin, leukopenia, as well as changes in some organs and systems (nervous system, digestive system).

**Etiology and pathogenesis**

Causes of B12 (folate deficiency) anemia: long-term insufficient supply of vitamin B12 with food; total gastric resection, gastric cancer, polyps of the stomach and intestine, regional enteritis, resection of the small intestine, chronic alcoholism, diverticula of the gastrointestinal tract, helminthic infestations, sprue, autoimmune processes, pregnancy, congenital deficiency of intrinsic factor or transcobalamin transporter protein.

Vitamin B12 is found only in products of animal origin, primarily in liver, meat, eggs and fish. An adult's daily need for vitamin B12 is 3-4 μg. Part of vitamin B12 is synthesized by intestinal microflora.

**Pathogenesis of B12-deficiency anemia**



**Clinical picture:**

1. Anemic syndrome: pallor of the skin and mucous membranes, subicterity of the skin and sclera; low-grade fever; shortness of breath, palpitations, weakness, dizziness, tinnitus.

2. Damage to the digestive tract: discomfort in the epigastrium, loss of appetite, heartburn, nausea, vomiting; Genter's glossitis; diarrhea caused by atrophic changes in the digestive tract and secondary malabsorption syndrome; enlargement of the liver and spleen.

3. Neurological syndrome (funicular myelosis): tingling and numbness of the fingertips, tongue, distortion of taste and smell. Gait becomes uncoordinated, ataxia develops, vibrational and positional sensitivity decreases. Progressive general weakness, spastic gait, is determined by a positive sign of Babinsky. Hyperreflexia and clonus of the feet are observed; ophthalmoplegia, bladder atony, retrobulbar neuritis; mental changes in patients: hallucinations, irritability, aggressiveness, manic outbursts, paranoid and schizophrenic states, emotional imbalance.

**Diagnosis**

Laboratory diagnostics

Violation of hematopoiesis in B12-deficient anemia is accompanied by specific changes in the composition of peripheral blood:

• macroovalocytosis of erythrocytes;

• aniso- and poikilocytosis of erythrocytes;

• basophilic puncture of erythrocytes, Jolly bodies, Cabot rings, diffuse polychromatophilia of cells.

• Leukocytopenia up to 1.5×109 / l. The presence of giant segmented neutrophils, the nuclei of which have 8-10 segments, is characteristic.

• thrombocytopenia in peripheral blood, which sometimes reaches (20-30)×109/l.

• an increase in the free bilirubin fraction in blood serum, an increase in the spleen, hypersiderinemia is often observed.

Bone marrow is hyperplastic.

***Diagnostic criteria for B12 (folate) deficiency anemia:***

1. Changes in blood analysis: high color index, macrocytosis of erythrocytes, reticulocytopenia, hypersegmentation of neutrophils, moderate leukopenia and thrombocytopenia.

2. In the bone marrow - megaloblastic hematopoiesis.

3. Determination of vitamin B12 in blood serum.

4. Determination of methylmalonic acid in the urine of patients (with vitamin B12 deficiency, its level increases).

5. Signs of funicular myelosis.

6. Decreased secretion of hydrochloric acid or histamine-resistantachlorhydria.

**A typical blood test for *B12*-deficient anemia**

|  |  |
| --- | --- |
| *Нb* | 60 g/l; |
| The number of erythrocytes | 1,2/l; |
| Color index | 1,5; |
| There is macrocytosis of erythrocytes, there are megalocytes, erythrocytes with Jolie’s bodies and Kebot’s rings. | |
| Platelets | 80/l; |
| Leukocytes | 2,4/l; |
| rod-shaped | 5%; |
| segmental | 45%; |
| eosinophils | 1%; |
| lymphocytes | 25%; |
| monocytes | 2%; |
| Hypersegmentation of neutrophil nuclei is observed. | |

**Treatment**

Treatment of B12-deficiency anemia is started only after aspiration biopsy of the bone marrow.

After confirmation of the diagnosis, treatment is carried out by intramuscular administration of vitamin B12 (cyanocobalamin). Cyanocobalamin is prescribed (500-1000) mcg intramuscularly once a day for 7-10 days, then the dose is halved and the treatment is continued for another 7-10 days. From the 14th to the 20th day, they switch to taking the drug every other day at a dose of 200 mcg for 4 - 6 weeks. An increase in the number of reticulocytes in the peripheral blood is observed on the 3-4th day after the start of pathogenetically justified treatment, and on the 7-10th day a reticulocyte crisis occurs (the number of reticulocytes reaches (20-60%).

For funicular myelosis, large doses of vitamin B12 (1000 mcg per day) are prescribed in combination with the coenzyme of vitamin B12-cobamide (500 mcg 1 time per day intramuscularly), which participates in the metabolism of fatty acids and improves the functioning of spinal cord structures and nerve fibers.

Transfusion of erythrocyte mass in the treatment of B12-deficient anemia should be carried out only for vital indications. Preventive treatment of B12-deficiency anemia is carried out twice a year, using 500μg of cyanocobalamin daily for 10-15 days.

In case of folic acid deficiency, it is prescribed in a dose of (5-15) mg/day.

The forecast is generally favorable.

**4. Aplastic anemia**

Aplastic anemia is a disease caused by a large number of exogenous and endogenous factors, characterized by qualitative and quantitative changes in hematopoietic cells and their microenvironment, manifested by pancytopenia of peripheral blood and fatty infiltration of the bone marrow.

**Etiology and pathogenesis**

Most authors tend to consider AA a polyetiological disease. Possible etiological factors include some drugs (antibiotics, sulfonamides, gold preparations, nonsteroidal anti-inflammatory drugs, sedatives, tranquilizers, cytostatics, etc.), physical factors (ionizing radiation, microwave radiation), chemical substances (mercury vapors, acids, dyes , varnishes, paints, household chemicals, gasoline, benzene etc.), infectious agents (hepatitis B, C, G, F, TT viruses, retroviruses, tuberculosis, etc.), autoimmune processes and diseases (systemic lupus erythematosus, Sjogren's).

Currently, three main concepts of possible mechanisms of bone marrow hematopoiesis in AA are discussed. These include: damage to stem hematopoietic cells, violation of immunological control over hematopoietic processes (cellular and humoral), defects of the hematopoietic microenvironment. However, it should be noted that many issues of the etiology and pathogenesis of AA remain unsolved and require further research.

**Clinical picture:**

A patient with AA may have increasing weakness, lethargy, pallor, shortness of breath and palpitations when walking, the presence of heart pain, as a manifestation of anemic hypoxia.

Clinical manifestations of AA are associated with changes in peripheral blood (anemia, leukopenia, thrombocytopenia) and include, respectively, anemic, hemorrhagic syndromes and the syndrome of infectious complications. Symptoms such as splenomegaly, hepatomegaly, and enlarged lymph nodes are not characteristic of AA. An increase in the size of the liver can be observed in people who have suffered hepatitis, and the spleen - in patients who have received a large number of blood transfusions.

AA often develops over a long period of time (months and years) and may be accompanied initially by a reduction in one of the hematopoietic lineages with gradual changes in all lineages.

**Diagnosis**

The diagnosis of aplastic anemia is confirmed by the results of the peripheral blood and bone marrow examination.

*Examination of the peripheral blood of AA patients reveals:*

• normochromic anemia of varying severity, fluctuations in hemoglobin concentration;

• leukopenia with granulocytopenia and relative lymphocytosis;

• thrombocytopenia;

• significant increase in ESR;

• decrease in the number of reticulocytes.

• iron content is normal or slightly increased.

*Bone marrow aspiration biopsy reveals:*

• decrease in the total number of myelokaryocytes;

• suppression of all lines of hematopoiesis;

• bone marrow punctate is usually poor in nuclear elements;

• a decrease in the total percentage of cellular elements of granulopoiesis both due to a decrease in the content of young forms of cells of the neutrophilic series and mature granulocytes;

• increase in the relative content of lymphocytes and plasma cells;

• a significant number of fat cells and elements of stromal origin are visible.

Biochemical studies are not essential for verifying the diagnosis of AA, but are important for assessing liver and kidney function, as a number of drugs.

**Diagnostic criteria for aplastic anemia:**

- hemoglobin concentration is less than 100 g / l, or hematocrit is less than 30%;

- the number of peripheral blood leukocytes is less than 3.5x109/l, or granulocytes less than 1.5x109/l;

- the number of platelets in peripheral blood is less than 50.0×109/l.

The diagnosis of aplastic anemia is considered reliable in the presence of two of the three criteria in combination with bone marrow hypocellularity in the absence of blast forms in peripheral blood and bone marrow.

**Differential diagnosis**

Differential diagnosis of aplastic anemia is carried out with diseases accompanied by pancytopenia.

**A typical blood test for aplastic anemia**

|  |  |
| --- | --- |
| *Нb* | 40 g/l; |
| The number of erythrocytes | 1,2/l; |
| Color index | 1,0; |
| Reticulocytes | 1,0; |
| Plateletes | 40/l; |
| Leukocytes | 1,4/l; |
| rod-shaped | 1%; |
| Segmented | 30,5%; |
| Lymphocytes | 62%; |
| Monocytes | 6,5%; |
| ESR | 35 mm/h. |

**Treatment**

Bone marrow transplantation is the only radical treatment method for aplastic anemia in patients under 40 years of age who have an HLA-compatible donor.

For patients without a donor and all patients over 40 years of age on immunosuppressive therapy:

• Anti-lymphocyte globulin is prescribed at a dose of 15 mg/kg per day as a result of long-term (8-12)-year intravenous infusion for 8-10 days.

• Cyclosporine A in a dose of 5 to 10 mg/kg per day in two doses. The duration of the course is on average 3 - 10 months.

• Antiplatelet globulin is prescribed at a dose of 0.75 mg/kg per day as a long (4-5)-hour intravenous infusion every day for 8-10 days.

• High doses of methylprednisolone (0.5 - 1 g per day intravenously for 5 days) can be recommended as an alternative form of immunosuppressive therapy in patients with a severe course.

Substitute therapy with blood components is carried out according to justified indications before its appointment.

Patients with fever are prescribed empiric antibacterial therapy with antibiotics, which primarily suppress gram-negative microflora.

Treatment lasts an average of 1-3 months.

Splenectomy, as a method of treatment of aplastic anemia, has not been used in recent years.

**5. Hemolytic anemia**

Hemolytic anemias are a large group of diseases that differ in etiology, pathogenesis, clinical picture, and treatment methods, the main feature of which is the breakdown and shortening of the lifespan of erythrocytes.

Pathological hemolysis can be extravascular and intravascular. Hemolytic anemias can be hereditary or acquired.

**Classification of hemolytic anemias**

**I. Hereditary hemolytic anemias.**

1. Hereditary HA due to violation of the erythrocyte membrane.

a) Hereditary microspherocytosis.

b) Hereditary ellipsocytosis.

c) Hereditary stomatocytosis.

d) Hereditary pyropoikilocytosis.

e) HA, due to the hereditary absence of Rh antigens.

e) HA, due to a violation of the structure of lipids

- hereditary abetalipoproteinemia;

- hereditary deficiency of lecithin-cholesterol-acetyltransferase activity;

- hereditary HA with intravascular hemolysis, due to a violation of the composition of fatty acids and signs of complement sensitivity of erythrocytes.

2. Hereditary HA due to impaired activity of erythrocyte enzymes

a) Hereditary HA due to deficiency of glucose-6-phosphate dehydrogenesis activity of erythrocytes.

b) Hereditary HA due to deficiency of erythrocyte pyruvate kinase activity.

3. Thalassemia.

4. Anemia caused by a violation of the structure of globin chains.

a) Anemia in carriers of hemoglobin, which changes the structure under conditions of hypoxia.

b) Sickle cell anemia.

c) Anemia in carriers of abnormal stable hemoglobin.

d) Anemia in carriers of abnormal unstable hemoglobin.

**ІІ. Acquired HA.**

1. HA due to the action of antibodies (immune).

a) Autoimmune HA against peripheral erythrocyte antigens:

- with incomplete thermal agglutinins;

- with thermal hemolysins;

- with complete cold agglutinins;

- paroxysmal cold hemoglobinuria.

b) Partial red cell aplasia.

2. Markiafava-Micheli disease (paroxysmal nocturnal hemoglobinuria).

3. HA due to mechanical damage of erythrocytes.

a) Mechanical hemolysis in prosthetics of blood vessels and heart valves.

b) March hemoglobinuria.

c) Hemolytic-uremic syndrome.

4. Hemolytic anemia caused by vitamin E deficiency.

**Differential diagnostic signs of congenital and acquired hemolytic anemia**

|  |  |  |
| --- | --- | --- |
| **Clinical syndromes of the disease** | **Hemolytic anemia** | |
| **Congenital** | **Acquired** |
| The onset of the disease | In early childhood | At a more mature age |
| Familial nature of the disease | Often | Absent |
| Duration of the disease | Decades | From a few weeks to several years |
| The course of the disease | Chronic with prolonged remissions | Cyclic - with severe hemolytic crises |
| Jaundice | Significantly pronounced | Insignificant |
| Developmental anomalies ("tower" skull, saddle-shaped nose, high standing of the hard palate) | Often observed | Absent |
| Trophic calf ulcers | Often observed | Absent |
| Anemia | Moderately expressed | Usually severe |
| Osmotic resistance of erythrocytes | Sharply reduced (0,6 – 0,7) | Slightly reduced (0,52 – 0,56) |
| The size of erythrocytes | Microcytosis | Norm or macrocytosis |
| Coombs' test | Negative | Positive |

**The main differential diagnostic signs of hereditary microspherocytosis and some diseases**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Hereditary microspherocytosis | Present | Moderately increased | For the whole time | Constantly | Reduced | Enlarged | Moderately enlarged |
| Chronic hepatitis | Absent | Increased direct | Always | Not constantly | Norm | Norm | Norm |
| Benign iron deficiency anemia | Present | Moderatly increased direct | Sometimes  Moderately | Absent | Norm | Norm | Norm |
| Posthemorrhagic and iron deficiency anemia | Absent | Norm | Absent | Absent | Norm | Norm | Reduced |

***Notes: ORE -*** *osmotic resistance of erythrocytes.*

**The main differential diagnostic signs of autoimmune and**

**other hemolytic anemias**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Anemia** | **Provocative factors** | **Heredity** | **Morphology of erythrocyte** | **Coombs test** | **Hemosiderinuria** |
| Autoimmune hemolytic anemia | Viral infections, cold | Absent | Microspherocytosis, sometimes macrocytosis | Positive | May be |
| Hereditary microspherocytosis | Infections | Present | Constant microspherocytosis | Negative | Absent |
| Glucose-6-phosphate dehydrogenase deficiency | Some medications | Present | Macroplanocytosis, heinz's body | Negative | Often |
| Markiafa-Micheli disease | Infections, blood transfusions, iron supplements | Absent | Without features | Negative | All time |
| Thalassemia | Absent | Present | Target-like | Negative | Absent |

**Laboratory research methods**

|  |  |  |
| --- | --- | --- |
| № | **Laboratory methods** | **The method is the most**  **informative at:** |
| 1 | General blood test with reticulocyte count | All forms |
| 2 | Morphological examination of erythrocytes | All forms |
| 3 | Serum bilirubin | All forms |
| 4 | Hemoglobin and hemosiderin in urine | All forms |
| 5 | Serum hemoglobin level | All forms |
| 6 | Osmotic stability of erythrocytes | Minkowski-Schoffar diseases |
| 7 | Study of enzymes in erythrocytes | Enzymopathy |
| 8 | Hemoglobin electrophoresis | Hemoglobinopathies |
| 9 | Hartmann's sucrose disease, Hem's acid test | Markiafava-Micheli disease |
| 10 | Coombs' test | AIHA |

**Treatment**

|  |  |
| --- | --- |
| **Disease** | **Treatment** |
| Hereditary microspherocytosis (Minkowski-Schoffar disease). | Splenectomy is a radical method of treatment |
| Anemia due to deficiency of glucose-6-phosphate dehydrogenase activity. | Symptomatic therapy, transfusion of erythromass, isotonic sodium chloride solution, 5% glucose solution, eryvit, riboflavin etc. |
| Autoimmune hemolytic anemia | Corticosteroid hormones (prednisolone 40 - 60 mg / day, in the absence of effect increases to 100 mg / day, splenectomy, immunosuppressants: 6-mercaptopurine, imuran, chlorbutin, methotrexate, cyclophosphamide, antilymphocytic globulin, transfusion of erythrois mass, fitted up with Coomb’s reaction |
| Paroxysmal nocturnal hemoglobinuria (Markiafava-Micheli disease) | Transfusions of washed erythrocytes, nerobol 30 - 50 mg for 2 - 3 months, tocopherol (vitamin E), anticoagulants in the presence of thrombotic complications, bone marrow transplantation. |

1. **Questions for self-preparation of the student for practical training:**

1. What is anemia.

2. Prevalence of anemia.

3. Etiological factors of anemia.

4. Pathogenesis of different types of anemia.

5. The main criteria for laboratory diagnosis of iron deficiency anemia.

6. What is aplastic anemia and criteria for its diagnosis.

7. What are the anemias associated with increased destruction of erythrocytes.

8. Treatment of autoimmune hemolytic anemia.

9. Laboratory methods for the study of anemia.

10. Differential diagnostic criteria for anemia.

1. **Literature**

***Basic:***

1. Guidelines for the Management of Iron Deficiency Anaemia in Adults. Editors: Jonathon Snook, Neeraj Bhala, Ian L P Beales, David Cannings, Chris Kightley, Robert PH Logan, D Mark Pritchard, Reena Sidhu, Sue Surgenor, Wayne Thomas, Ajay M Verma, Andrew F Goddard, 2021, рages 1–22.

2. Guideline for the laboratory diagnosis of iron deficiency in adults (excluding pregnancy) and children. Editors: Andrew Fletcher, Adam Forbes, Nicola Svenson, D. Wayne Thomas. British Journal of Haematology, 196 (3), 2021, рages 523-529.

3. Autoimmune hemolytic anemia. Editors: Anita Hill, Quentin A. Hill. Hematology, 2018 (1), 2018, рages 382–389.

4. Aplastic Anemia. Editor: Christine A. Moore, 2021.

5. Randomized controlled trial of twice-daily versus alternate-day oral iron therapy in the treatment of iron-deficiency anemia. Editors: Kaundal R, Bhatia P, Jain A. Haematology, 2020, рages 57–63.

***Additional:***

1. Disorders of iron metabolism: new diagnostic and treatment approaches to iron deficiency / Powers JM et al. // Hematol Oncol Clin North Am. 2019 Jun;33(3), р. 393–408.

2. Anemia epidemiology, pathophysiology, and etiology in low- and middle-income countries. Editors: Camila M. Chaparro, Parminder S. Suchdev. New York Academy of Sciences, 2019, 1450 (1), рages 15-31.

3. Australian Aplastic Anaemia Registry Steering Committee. Revisiting acquired aplastic anaemia: current concepts in diagnosis and management. Editors: Clucas DB, 2019, 49(2), рages 2–9.

4. Approach to the diagnosis of aplastic anemia. Editors: Amy E. DeZern1 and Jane E. Churpek, 2021, 5 (12), рages 2660-2676.

GUIDELINES for the topic:

ACUTE LEUKEMIA

1. **The purpose of the lesson:**

To teach students the ability to collect complaints, history and physical examination in patients with acute leukemia (AL).

To acquaint students with the methods of examinations used for the diagnosis of AL, indications for their use, methods of implementation, the diagnostic value of each of them.

To teach students to independently interpret the results of examinations, to formulate a diagnosis and to be able to conduct and analyze a differential diagnosis.

To teach students to make an algorithm for the treatment of a particular patient with AL, taking into account the clinical features of the course and the presence of concomitant pathology.

1. **Competences (formation of competencies):**

1. Be able to find out and analyze the complaints of patients with AL.

2. To teach students to recognize the main symptoms and syndromes in patients with GL.

3. To improve the method of physical examination of patients with AL.

4. Be able to determine the stage of AL of a particular patient and formulate a diagnosis.

5. Be able to assign the optimal algorithm for diagnosis in patients with AL.

6. To teach students to independently interpret the data of instrumental and laboratory research methods used in the diagnosis of AL.

7. To interpret the data of blood analysis and analysis of sternal punctate in patients with GL.

8. Prescribe treatment depending on the option of AL.

9. To acquaint students with the tactics of treatment of complications in AL.

1. **Plan and structure of the lesson**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **The name of the stage** | **Stage description** | **Levels of assimilation** | | **Time** |
| **Preparatory stage** | | | | |
| Organizational arrangements  Checking workbooks  Setting learning goals and motivation  Control of the initial level of knowledge:  1. Etiology and pathogenesis  2. Clinic  3. Diagnosis  4. Differential diagnosis  5. Treatment | Methods of control of theoretical knowledge:  - individual theoretical survey;  - test control;  - solving typical problems. | Question  Typical tasks  Tests  Written theoretical tasks  Tables  Pictures  Structural and logical schemes  Audio and video materials. | | 45-60 min. |
| **The main stage** | | | | |
| Formation of practical skills  1. Diagnostic value of clinical analysis of blood and myelogram in AL;  2. Diagnostic value of results of cytomorphological, cytochemical, cytogenetic analyzes;  3. Diagnostic value of sterile puncture in acute leukemias, indications, contraindications;  4. Diagnostic value of tre-panobiopsy of the iliac bone in AL;  5. List of additional instrumental studies used to detect splenomegaly, hepatomegaly, enlargement of internal lymph nodes, leukemic infiltrates in various organs and tissues;  6. Complications of AL;  7. Features of management of patients with AL;  8. Features of AL treatment (treatment regimen, chemotherapy, radiation therapy, bone marrow transplantation) | Method of forming practical skills:  Practical training  Method of formation of professional skills:  training in solving typical and atypical situational problems (real clinical, simulated, textual | Algorithm for the formation of practical skills.  Professional algorithms for the formation of professional skills;  patients, case histories, situational tasks | | 100-150 min. |
| **The final stage** | | | | |
| Control and correction of the level of practical skills and professional skills | Methods of control of practical skills:  Individual control of practical skills and their results  Methods of control of professional skills: analysis and evaluation of the results of clinical work of students | | The results of work with the patient, with a history of the disease.  Atypical situational problems. | 45-60 min. |
| Summarizing the lesson: theoretical, practical, organizational |  | |  | 5-10 min. |
| Homework | Approximate map for independent work with literature. Recommended literature (basic, additional) | |  | 5 min. |

1. **Content of the lesson topic**

Acute leukemia is a malignant disease of hematopoietic stem cells characterized by an increase in the number of blast cells (clonal) in the bone marrow and / or peripheral blood.

Epidemiology and etiology.

The incidence of leukemia of all types in the population is approximately 10 / 100,000 per year, of which slightly less than half are cases of acute leukemia. Men suffer more often than women, the ratio of which is approximately 3: 2 in acute leukemia.

Acute leukemia occurs at any age. Acute lymphoblastic leukemia shows a peak incidence in children aged 1 to 5 years. All types of acute myeloid leukemia have the lowest incidence in young adults and increase markedly after the age of 50.

The cause of leukemia in most patients is unknown. However, several risk factors have been identified

Risk factors for leukemia:

**Ionizing radiation**

• After the atomic bombing of Japanese cities (myeloid leu-goats)

• Radiation therapy for ankylosing spondylitis

• Diagnostic X-ray manifestations of the fetus during pregnancy

**Cytotoxic drugs**

• Particularly alkylating agents (myeloid leukemia, usually after a latent period of several years)

• Industrial effects of benzene

**Retroviruses**

• One rare form of T-cell leukemia / lymphoma appears to be associated with a retrovirus similar to the viruses that cause leukemia in cats and cattle.

**Genetic**

• Identical twin of patients with leukemia

• Down syndrome and some other genetic disorders

**Immunological**

• Immunodeficiency (eg, hypogammaglobulinemia).

In acute leukemia, the spread of immature hundred-stem cells occurs, which leads to the accumulation of blast cells, mainly in the bone marrow, which leads to dysfunction of the bone marrow.

The diagnosis of leukemia is usually suspected when pathological changes are detected in the analysis of peripheral blood, in which blast cells are often detected, and this is confirmed by bone marrow examination. Diagnosis of AL includes morphology of abnormal (blast) cells, analysis of markers expressed on the cell surface (immunopheno-typing), clonal chromosomal abnormalities and molecular changes.

Morphological changes, immunophenotyping results, chromosomal and cytogenetic changes are included in the classification of tumors of hematopoiesis and lymphoid tissues of the World Health Organization (WHO), which not only provide an accurate diagnosis but also determine the prognosis.

**ACUTE LEUKEMIA**

Acute leukemias are divided into lymphoblastic and non-lymphoblastic (myeloblastic).

The etiology, pathogenesis and main clinical manifestations of lymphoblastic and myeloblastic leukemias do not differ significantly. Therefore, these issues will be covered together.

The main differences are the data of cytomorphological, cytochemical and cytoimmune analysis and different approaches to the treatment of these types of acute leukemias.

**Etiology of acute leukemia.**

a. Ionizing radiation:

• Radiation therapy;

• Man-made disasters at nuclear power plants.

b. Chemical substances:

• Benzene, pesticides, insecticides, tobacco smoke;

• Paints, solvents containing chlorine;

• Medicines (chlorambucil, cyclophosphamide, etc.).

c. Viral infection:

• Epstein-Barr virus;

• HTLV retrovirus.

d. Genetic defects and chromosomal abnormalities.

**Pathogenesis of acute leukemia**

Under the influence of etiological factors, somatic mutations of progenitor cells of hematopoietic and lymphoid tissues occur. This is facilitated by the processes of violation of the body's immune defenses and violation of apoptosis (programmed cell death). The first stage of leukemia formation begins with a mutation in the stem cell, which acquires the ability to proliferate rapidly. Cells formed as a result of such proliferation are considered clones.

At the stage of formation of the first clone, tumor cells retain the ability to differentiate (benign tumor growth). However, over time, numerous mutations occur in the cells of the primary leukemic clone. As a result, the cells of the secondary leukemic clone not only actively proliferate, but also lose the ability to differentiate (malignant tumor growth).

Proliferation of leukemic cells in the bone marrow, leukemic infiltration of organs and tissues, autoimmune and infectious-inflammatory complications form the clinical picture of acute anemia.

**Stages of acute leukemia**

1. The initial period.

2. The period of full development of the disease (expanded).

3. Period of remission (disappearance of clinical symptoms, normalization of peripheral blood and myelogram).

4. Period of exacerbation (relapse).

5. Terminal period.

Clinical presentation of acute leukemia

Clinical symptoms of AL can be grouped into 5 main syndromes:

• hyperplastic;

• hemorrhagic;

• anemic;

• intoxication;

• immunodeficient.

Hyperplastic syndrome is caused by leukemic tissue infiltration. It is characterized by painless enlargement of lymph nodes, liver and spleen, tonsils (they are significantly enlarged, become loose, can make breathing difficult). Enlargement of lymph nodes in the mediastinum can compress the superior vena cava, cause disruption of blood flow to the right atrium and as a result - shortness of breath, cyanosis, swelling of the neck. Hyperplastic syndrome is characterized by hyperplasia of the gums and the development of severe ulcerative necrotic stomatitis, ulcers and necrosis can be observed on the tonsils, mucous membranes of the oral cavity, pharynx and esophagus. There is a sharp pain when tapping the sternum due to leukemic subperiosteal infiltrates. Leukemic infiltrates appear on the skin in the form of leukemias - reddish-bluish papule-like plaques. A severe manifestation of the hyperplastic syndrome is painful infiltration of the testicles and lesions of the nervous system - neuroleukemia.

Hemorrhagic syndrome - is observed in 50-60% of patients with AL. It is caused by thrombocytopenia, increased permeability and decreased blood coagulation activity due to a deficiency of coagulation factors V, VII, protrobin, fibrinogen, increased fibrinolytic activity. Hemorrhagic syndrome is manifested by massive intradermal hemorrhage, nasal, gastric, intestinal, renal, pulmonary, uterine, cerebral hemorrhage. Bleeding can be massive and cause death in 15-20% of patients.

Anemic syndrome - develops in all patients with AL, due to a sharp reduction of the red hematopoietic sprout in the bone marrow (due to progressive infiltration of malignant leukemic bone marrow tissue), intoxication and bleeding. The degree of anemia clearly correlates with the degree of proliferation of leukemic cells in the bone marrow and, thus, anemia can be considered a kind of barometer of leukemia.

Intoxication syndrome accompanies the stage of advanced clinical and hematological manifestations of AL, is characterized by severe general weakness, fever, sweating (especially at night, when sweating may be profuse), headaches, loss of appetite, weight loss, muscle atrophy, osalgia, nausea, vomiting.

Immunodeficiency syndrome. At AL the immunodeficiency state which is characterized by disturbance of cellular and humoral immunity, phagocytic function of leukocytes, decrease in activity of a complement develops. This contributes to the development of various infectious and inflammatory processes, which are characterized by severe course, may develop a septic condition. Infectious and inflammatory diseases, in particular, severe pneumonia, can cause death.

Diagnosis and determination of AL risk group.

The National Comprehensive Cancer Network (NCCN) guidelines state that the diagnosis of GLL generally requires the following:

• The diagnosis of acute leukemia is established if the number of ballast cells is more than 20% in the bone marrow (counting by 500 cells)

• Morphological evaluation of bone marrow aspirate smears (Wright / Giemsa)

• Histological examination of bone marrow (Hematoxylin and eosin)

• Conducting flow cytometry (immunophenotyping).

To optimally identify risk groups and plan treatment in patients with AL, NCCN recommends identifying specific genetic abnormalities of bone marrow or peripheral blood lymphoblasts as follows:

• Cytogenetics - Karyotyping of metaphase chromosomes

• Interphase fluorescence hybridization in situ (FISH)

• Polymerase chain reaction (RT-PCR) for fusion genes (eg BCR-ABL)

The recommendations of the European Society for Medical Oncology (ESMO) are consistent with the recommendations of the NCCN, noting that the initial diagnostic work should be completed quickly and before the introduction of any chemotherapy to:

• confirm the diagnosis and reduce the time to treatment

• distinguish B-cell lymphoblastic leukemia B-GLL from T-cell GLL (T-GLL

• distinguish Burkitt (B-ALL) from B-GLL

• determine Philadelphia (Ph) chromosomes-positive (Ph +) GLL from Ph-negative (Ph-) GLL

**Diagnosis of AL**

Both NCCN and ESMO guidelines recommend that follow-up tests be included in the diagnostic test for AL:

• Complete general blood test with manual differential and routine biochemical tests (including tests for liver function, serum creatinine, lactate dehydrogenase [LDH] and uric acid)

• Coagulation profile - Prothrombin time (PT), time of partial thromboplastin (PTT), fibrinogen).

• Bone marrow aspiration and biopsy, including classical cytogenetics, immunophenotyping and molecular testing for c-KIT, FLT3-ITD, NPM1 and CEBPA

• HLA-typing of the patient and family

The ESMO guidelines include the following additional diagnostic tests for all patients:

• Imaging, including dental examinations and computed tomography (CT) scans, chest and abdomen scans,

• Preservation of sperm in men (at the request of the patient)

• Pregnancy test in women

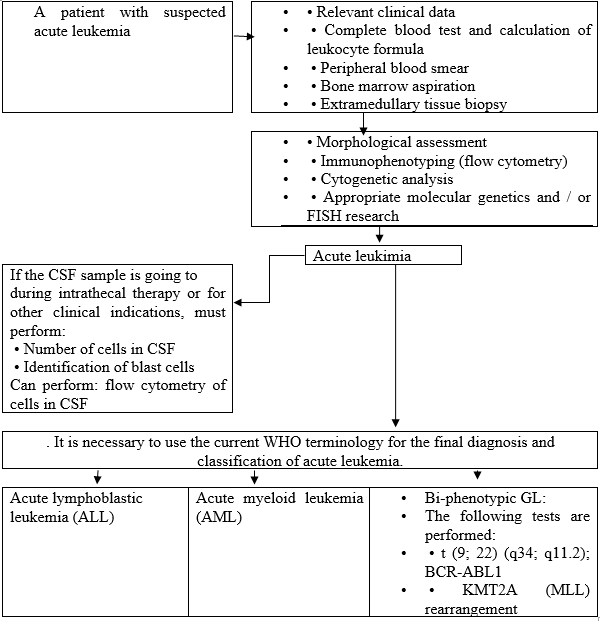
Although not specifically stated in the NCCN guidelines, sperm storage and pregnancy testing are standard practice in the United States.

NCCN further recommends the following tests if neurological symptoms are present:

• CT or magnetic resonance imaging (MRI)

• Lumbar puncture

**Algorithm for diagnosing acute leukemia**



**Differential diagnosis of acute leukemia**

1. Leukemoid reactions.

2. Hypoplastic anemia.

3. Agranulocytosis.

4. Megaloblastic anemia (diff. Diagnosis with acute erythromyelosis).

5. Metastases of malignant tumors in the bone marrow.

**ACUTE MYELOID LEUKIMIA**

**DEFINITION, ETIOLOGY, PATHOGENESIS**

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy that is characterized by the presence of a clone of transformed myeloid cells originating at early stages of myelopoiesis. The cells predominate in bone marrow and peripheral blood and infiltrate various organs, affecting their function.

Risk factors include exposure to ionizing radiation, benzene, and cytotoxic agents (alkylating drugs, topoisomerase inhibitors).

Classification had been based on morphology until some recurrent cytogenetic abnormalities were identified, which helped with better understanding of disease biology and choice of therapy. AML can be classified into de novo AML or secondary AML with antecedent blood cancer. There is also a subset that is therapy-related where prior radiation therapy or chemotherapy cause the emergence of a malignant clone.

AML with myelodysplasia-related changes (AML-MRC) is known to be of poor prognosis due to the higher incidence of cytogenetic abnormalities associated with poor risk, commonly in older patients with comorbidities, transfusion dependence, risk of catastrophic bleeding, and/or iron overload.

**CLINICAL FEATURES AND NATURAL HISTORY**

1. General symptoms: Constitutional symptoms including fevers, weight loss, and drenching sweats in addition to fatigue and bone and joint pain.

2. Manifestations of anemia; thrombocytopenia with associated mucocutaneous bleeding, petechial rash, urogenital and/or gastrointestinal bleeding. Other features involve those of immunodeficiency with recurrent infection symptoms, including bacterial sepsis and fungal infections.

3. Manifestations of leukostasis associated with white blood cell (WBC) count >100×109/L: Altered mental status, headache, visual disturbances, angina, features of hypoxemia caused by impaired pulmonary perfusion, and priapism.

4. Manifestations of leukemic infiltrates in various tissues and organs, more commonly seen in patients with monocytic leukemia: Leukemia cutis, gingival infiltrates, pulmonary infiltrates, splenomegaly and/or hepatomegaly, and/or lymphadenopathy. Central nervous system (CNS) leukemia is common in patients with higher WBC count who present with various symptoms including headaches, visual changes, and nausea or vomiting.

**DIAGNOSIS**

Diagnostic Tests

1. Complete blood count (CBC): Any degree of pancytopenia with leukopenia, anemia and thrombocytopenia. Leukocytosis with accompanying left shift and pathognomonic circulating blasts is also possible.

2. Bone marrow aspiration and biopsy: Assessment by morphology, cytochemistry, immunophenotyping, cytogenetic analysis, and molecular studies to detect mutations using the myeloid next-generation sequencing panel. Such mutations could carry a prognostic significance or would indicate targeted therapy (see Treatment, below). Bone marrow biopsy gives an idea on cellularity, stromal abnormalities, or antecedent myeloid malignancy. The presence of Auer rods on bone marrow examination is pathognomonic of AML.

3. Other laboratory studies: Coagulation parameters, serum lactate dehydrogenase, uric acid, electrolytes, calcium, magnesium, and phosphate levels. Tumor lysis (hyperuricemia, hyperkalemia, hypocalcemia, and hyperphosphatemia) is common in patients with high WBC counts at presentation. Acute kidney injury can be seen due to tumor lysis or leukostasis. Patients with high WBC counts may develop artifactual hyperkalemia, hypoxemia, and hypoglycemia due to the effects of leukemic cells after the samples are drawn.

**Diagnostic Criteria**

The diagnosis of AML is established in patients with ≥20% blasts (including myeloblasts and their equivalents: monoblasts, promonocytes, and megakaryoblasts). In certain situations the diagnosis of AML can be made regardless of the percentage of blasts: in patients with core-binding factor AML with inv(16) or t(8;21) or those with acute promyelocytic leukemia with t(15;17) as well as patients with granulocytic sarcoma.

Classification of risk groups (according to the European LeukemiaNet) is based on the results of cytogenetic and molecular studies. The adverse-risk group also includes secondary AML in patients after radiotherapy and/or chemotherapy, AML preceded by myelodysplastic syndrome (MDS), and AML with primary treatment resistance.

**Differential Diagnosis**

Infectious mononucleosis, acute lymphoblastic leukemia, large B-cell lymphoma, high-risk MDS, myeloproliferative neoplasms with high blast counts, leukemoid reaction, and recovering marrow (particularly in patients with recently treated vitamin B12 deficiency).

**TREATMENT**

Therapeutic choice is tailored to patient-related and disease-related factors. Scoring systems such as the AML composite model for risk assessment and hematopoietic cell transplant–specific comorbidity index (available at www.hctci.org) are helpful to evaluate the patient’s eligibility for therapy. These decisions should be used in specialized settings.

Individualized therapy is offered based on the patient’s Eastern Cooperative Oncology Group (ECOG) performance status (available at ecog-acrin.org), comorbidities, disease biology, molecular mutations, and cytogenetics. Such tools assist the clinician in decision-making with regard to therapeutic choices and eligibility for allogeneic hematopoietic stem cell transplant (HSCT) after remission induction.

1. Remission induction depends on the patient’s fitness for intensive chemotherapy. All patients receive induction treatment using the 3 + 7 regimen (a combination of daunorubicin and cytarabine). More intensive induction treatment using fludarabine, cytarabine, granulocyte colony-stimulating factor (G-CSF), and idarubicin—the FLAG-IDA regimen—may be offered to patients with secondary AML or therapy-related AML. In elderly patients or those with poor performance status, nonintensive regimens can be used with palliative intent. These include hypomethylating agents (azacitidine or decitabine) or venetoclax combined with a hypomethylating agent or low-dose cytarabine; this line of therapy provides good quality of life and transfusion independence. A specialized hematologist should be making decisions regarding therapy and patients should be cared for in an expert center familiar with the current best practices in treatment.

Outcomes of induction treatment: Complete remission (CR), CR with minimal residual disease (CR-MRD), CR with incomplete hematologic recovery (CR-i), partial remission (PR), or treatment failure in the case of nonresponse or progressive disease.

Criteria for CR: Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count (ANC) ≥1×109/L; platelet count ≥100×109/L.

2. Remission consolidation: Postremission treatment is aimed at eradicating residual disease, including minimal residual disease (MRD) (presence of leukemic cells at a level producing no clinical manifestations and detectable only using sensitive methods [flow cytometry, molecular studies]) in fit, favorable-risk, and some intermediate- or adverse-risk patients. Regimens include high-dose cytarabine administered in 3 cycles.

3. Allogeneic HSCT for patients in the adverse-risk or intermediate-risk group who have good performance status and have both access to a bone marrow transplant center and donor available. This results in 5-year disease-free survival (DFS) rates of 40% to 60%. There is up to 20% transplant-related mortality at 1 year. In patients who are elderly or have poor performance status, allogeneic HSCT with a nonmyeloablative conditioning protocol can be used.

**4. Supportive treatment:**

1) Tumor lysis prophylaxis should be provided to all patients initiating therapy. This includes IV fluids and allopurinol, a xanthine oxidase enzyme inhibitor that is considered to be one of the most effective drugs used to decrease urate levels. In patients with high disease burden and increased urate levels, use rasburicase, a recombinant urate oxidase enzyme that catalyzes uric acid and helps its elimination (see Tumor Lysis Syndrome).

2) Hyperleukocytosis (>100×109/L): Hydroxyurea (INN hydroxycarbamide) 50 to 60 mg/kg/d until WBC counts decrease to <10×109/L.

3) Transfusion support: Packed red blood cells (PRBCs) to maintain hemoglobin (Hb) >70 g/L, platelet concentrates to maintain platelet >10×109/L or in patients with bleeding or coagulopathy.

4) Prevention of infections: Antifungal prophylaxis using posaconazole during the induction phase, antiviral prophylaxis using acyclovir until WBC count recovery. Preemptive antibacterial prophylaxis is not indicated.

5) Treatment of infections: see Febrile Neutropenia.

6) Symptom management: Antiemetic drugs and bowel routine.

7) Multidisciplinary team approach: Involve clinical dietitians for appropriate nutritional management, either enteral or parenteral, social workers for psychological counseling and coping mechanisms, and physiotherapy and occupational therapy for mobilization and prevention of deconditioning.

**COMPLICATIONS**

Severe or life-threatening complications may include neutropenic septicemia, end-organ damage or multiorgan failure, prolonged pancytopenia, and refractory thrombocytopenia with subsequent transfusion dependence. Iron overload, coagulopathy, and risk of intensive care unit (ICU) transfer for mechanical ventilation may all occur.

**ACUTE LYMPHOBLASTIC LEUKIMIA (ALL)**

**DEFINITION, ETIOLOGY, PATHOGENESIS**

Acute lymphoblastic leukemia (ALL)/lymphoblastic lymphoma (LBL) are hematologic malignancies originating from B-lymphocyte or T-lymphocyte precursor cells (lymphoblasts). The lymphoblasts are present mainly in bone marrow and peripheral blood (B-cell ALL, T-cell ALL) or less frequently in lymph nodes and extranodal sites (B-cell LBL, T-cell LBL). In children <15 years ALL/LBL constitute ~25% of all malignancies and ~75% of all leukemias. In adults they usually develop before 30 years of age and account for ~20% of acute leukemias.

The 2016 World Health Organization (WHO) classification is based on cell origin and biology. In B-cell and T-cell subtypes genetically and molecularly distinct clinical entities are defined, while other types are jointly classified as “ALL/LBL, not otherwise specified.”

The immunophenotypic classification is of key importance for clinical practice. It includes:

1) B-cell ALL: Pro-B (pre-pre-B) ALL, common ALL (CD10+, the most frequent type), pre-B ALL.

2) T-cell ALL: Early T-cell precursor (ETP; ≥1 early myeloid marker) pro-T and pre-T ALL (CD1a–, cyCD3+), cortical ALL (CD1a+, relatively good prognosis), medullary T-cell ALL (CD1a–, sCD3+).

**CLINICAL FEATURES AND NATURAL HISTORY**

1. Signs and symptoms are similar to acute myeloid leukemia but lymphadenopathy, splenomegaly, or both are observed in as many as 50% of patients, and manifestations of the involvement of erythropoietic and megakaryopoietic lineages are less severe. Twenty five percent of patients develop bone pain. ALL can present as an oncologic emergency, such as febrile neutropenia, tumor lysis syndrome, or leukostasis. Central nervous system (CNS) involvement is relatively more common than in AML and ranges from 3% in B-cell ALL to 8% in T-cell ALL. In patients with T-cell ALL mediastinal lymph node enlargement as well as high white blood cell (WBC) counts are frequent.

2. Natural history: In patients with early disease the abnormalities may be limited to the complete blood count (CBC). Patients with advanced disease present with bleeding, infection, or with signs of CNS, mediastinal, and other organ involvement, which untreated lead to death within a few weeks.

**DIAGNOSIS**

**Diagnostic Tests**

1. CBC: Leukopenia may be observed in patients with certain subtypes of ALL (particularly in early disease); leukocytosis (very high and rapidly increasing in patients with T-cell ALL subtypes). In ~25% of patients with pro-B ALL, WBC counts are >100×109/L. Anemia, neutropenia, and thrombocytopenia are usually seen. Lymphoblasts may be seen in peripheral blood. Eosinophilia may be also present (in T-cell ALL).

2. Biochemical tests to assess renal function or evidence of tumor lysis (uric acid, phosphate, potassium) in addition to coagulation tests.

3. Bone marrow examination: Bone marrow aspiration with microscopic examination and immunophenotyping.

4. Immunophenotyping using flow cytometry (peripheral blood or bone marrow) is the basis for confirming the diagnosis and the immunophenotypic classification, which facilitates the assessment of prognosis as well as identification of the abnormalities that are used in monitoring minimal residual disease (MRD) during treatment.

5. Cytogenetic and molecular studies: In the majority of patients with ALL, lymphoblasts have an abnormal karyotype, including abnormalities in the chromosome numbers and structure. Translocation t(9;22), also termed the Philadelphia (Ph) chromosome, is found in 20% to 30% of all ALL cases, more frequently in patients with common ALL and in elderly patients (up to 50%), and is associated with the highest risk. Quantitative molecular studies (real-time quantitative polymerase chain reaction) are also used for MRD monitoring (eg, identification of the BCR-ABL1 fusion gene in patients with Ph+ ALL). A number of other genetic abnormalities, beyond the scope of this text, are recognized and tested for in specialized settings to determine prognosis and optimal treatment.

6. Imaging studies: In ~50% of patients with T-cell ALL subtypes, upper mediastinal mass caused by involvement of the thymus and mediastinal lymph nodes is seen. Imaging is useful in assessing the size of the lymph nodes and spleen. A biopsy from extramedullary disease can be obtained for diagnostic purposes.

7. Lumbar puncture: In the case of CNS involvement lumbar puncture may reveal increased cerebrospinal fluid (CSF) cell counts with blasts detected by cytologic examination.

**Diagnostic Criteria**

Bone marrow microscopy and immunophenotyping are essential for diagnosis. The presence of lymphoblasts must be documented and ≥2 B-cell or T-cell markers must be found to confirm the diagnosis. In ~20% of patients, features of LBL are predominant, with infiltrates affecting mainly lymph nodes and <20% to 25% blasts in bone marrow; in such cases examination of a lymph node may be necessary.

**Differential Diagnosis**

Poorly differentiated AML; infectious mononucleosis; other viral infections, particularly causing lymphocytosis, thrombocytopenia, or hemolytic anemia; other conditions causing pancytopenia; non-Hodgkin lymphomas.

**TREATMENT**

Choice of therapy based on patient-related and disease-related factors helps in management decisions. Older patients with comorbidities do not receive the same chemotherapy medications as younger patients with good performance status. In patients with Philadelphia chromosome the use of tyrosine kinase inhibitors (TKIs) is indicated.

1. Initial treatment is aimed at decreasing leukemic cell burden to reduce the risk of tumor lysis syndrome; this may involve the use of prednisone or dexamethasone. Prophylaxis of tumor lysis syndrome should be provided to all patients initiating therapy (see Tumor Lysis Syndrome). This includes IV fluids and allopurinol, a xanthine oxidase enzyme inhibitor that is considered to be one of the most effective drugs used to decrease urate levels. In patients with high disease burden and increased urate levels, rasburicase, a recombinant urate oxidase enzyme that catalyzes uric acid and helps its elimination, should be used.

2. Remission induction is aimed at removing tumor burden; this includes 3-drug to 4-drug combination chemotherapy regimens (eg, vincristine, an anthracycline, glucocorticoids [prednisone or dexamethasone], and pegylated asparaginase; usually for 4 weeks). Assessment for response to therapy at the end of induction determines if further combination chemotherapy is required for refractory or measurable disease.

3. Remission consolidation is aimed at removing MRD; this includes sequential cycles of high-dose or intermediate-dose antineoplastic agents. These usually include vinca alkaloids, glucocorticoids, thiopurines, and asparaginase.

4. Postconsolidation treatment:

1) In standard-risk patients and in patients who are not eligible for hematopoietic stem cell transplant (HSCT), maintenance treatment is continued for 2 years, provided the MRD-negative status is maintained.

2) In high-risk patients (>80% of adult patients; see Prognosis, below), allogeneic HSCT from a human leukocyte antigen (HLA)-compatible sibling or an unrelated donor should be considered.

5. Treatment of Ph+ ALL: Chemotherapy combined with TKIs (imatinib, dasatinib) with the goal of allogeneic HSCT in patients who qualify for this therapy. Because genetic mutations such as T135I may infer resistance to TKI therapy, ponatinib would be the TKI of choice.

6. Prevention and treatment of CNS involvement: All patients receive intrathecal chemotherapy during induction for prophylaxis. Those with CNS disease receive therapeutic intrathecal chemotherapy doses as well as—depending on the risk profile, age, and comorbidities—CNS radiation.

7. Management of patients with no response to the first-line treatment or with relapses: New agents, drugs with no cross-resistance with the first-line agents, other drug combinations, HSCT (all decided in specialized settings only).

8. Supportive treatment as in acute myeloid leukemia.

**9. Complications:**

1) Early complications: Cytopenias and infection, toxicities of CNS-directed therapy, osteonecrosis, deep vein thrombosis, and pancreatitis.

2) Late complications: Obesity and metabolic syndrome, peripheral neuropathy, cardiotoxicity, neurocognitive deficits, and secondary malignant neoplasms.

**PROGNOSIS**

Risk groups:

1) Standard-risk group:

a) Age <35 years.

b) WBC <30×109/L in B-cell ALL or <100×109/L in T-cell ALL.

c) Immunophenotype: Common/pre-B ALL or cortical (CD1a+) T-cell ALL.

d) Complete remission (CR) achieved within <4 weeks.

2) High-risk group: All patients not included in points 1 and 3.

3) Very high-risk group: Karyotype t(9;22) (Ph+, BCR-ABL1+).

The importance of risk groups may change in the course of treatment. Apart from the above cytogenetic abnormalities, the most important adverse prognostic factor that is the basis for the classification of patients into standard-risk and high-risk groups is the MRD status monitored using cytogenetic or molecular studies at subsequent stages of treatment. CR is achieved in >90% of adult patients with ALL. Overall 5-year survival rates in adults: 54% in patients <30 years of age; 35% in patients 30 to 44 years of age; 24% in patients 45 to 60 years of age; and 13% in patients >60 years of age.

Patients with the Ph chromosome historically had a poor prognosis but the use of TKI (imatinib) has improved the rates of event-free survival in this group.

1. **Questions for self-preparation of the student for practical employment:**

1) The main etiological factors and pathogenetic mechanisms of leukemia;

2) The main clinical syndromes in acute leukemia;

3) Complaints and physical examination data in acute leukemia;

4) Methods of physical examination of patients with acute leukemia;

5) Diagnostic value of clinical analysis of blood and myelogram in acute leukemia;

1. **Literature:**

***Basic:***

1. Current Medical Diagnosis &Treatmant 60th Anniversary / M.Hill, M. A.Paradakis, S. J.McPhee, M. W.Rabow., 2021.
2. Davidson’s Principles and Practice of Medicine 23th Edition / S.H Ralston, I. D Penman, M. WJ Strachan, R. P Hobson., 2018
3. 20th Edition Harrison’s Principles of Internal Medicine / J. Fauci, K. Hauser, L. Loscalzo., McGraw-Hill Education 2018.
4. Acute Myeloid Leukemia. McMaster Textbook of Internal Medicine. Kra-ków: Medycyna Praktyczna [Electronic resource] / Khalaf D, Crowther M, Hołowiecki J – Resource access mode: <https://empendium.com/mcmtextbook/chapter/B31.II.15.2>..
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***Additional:***

1. Development and Validation of a Novel Acute Myeloid Leukemia-Composite Model to Estimate Risks of Mortality [Electronic resource] / Mohamed L Sorror, Barry E Storer, Amir T Fathi та ін.] – Resource access mode: JAMA Oncol . 2017 Dec 1;3(12):1675-1682.
2. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia [Electronic resource] / Heidi D. Klepin, Ann M. Geiger, Janet A. Tooze та ін.] – Resource access mode: Blood (2013) 121 (21): 4287–4294.
3. Function, Survival, and Care Utilization Among Older Adults With Hematologic Malignancies [Electronic resource] / Clark DuMontier, Michael A Liu, Anays Murillo та ін.] – Resource access mode: J Am Geriatr Soc . 2019 May;67(5):889-897. doi: 10.1111/jgs.15835. Epub 2019 Apr 4.
4. Prevalence of Cognitive Impairment and Association With Survival Among Older Patients With Hematologic Cancers [Electronic resource] / Tammy T Hshieh, Wooram F Jung, Laura J Grande та ін.] – Resource access mode: JAMA Oncol . 2018 May 1;4(5):686-693. doi: 10.1001/jamaoncol.2017.5674.
5. More Versus Less Therapy for Older Adults With Acute Myeloid Leukemia: New Perspectives on an Old Debate [Electronic resource] / Heidi D Klepin, Elihu Estey, Tapan Kadia – Resource access mode: Am Soc Clin Oncol Educ Book . 2019 Jan;39:421-432. doi: 10.1200/EDBK\_239097. Epub 2019 May 17.

GUIDELINES for the topic:

CHRONIC LEUKEMIA

1. **The purpose of the lesson:**

To teach students the ability to collect complaints, history and physical examination in patients with chronic leukemia (CL).

To acquaint students with the methods of examinations used for the diagnosis of CL, indications for their use, methods of implementation, the diagnostic value of each of them.

To teach students to independently interpret the results of examinations, to formulate a diagnosis and to be able to conduct and analyze a differential diagnosis.

To teach students to make an algorithm for the treatment of a particular patient with CL, taking into account the clinical features of the course and the presence of concomitant pathology.

1. **Competences (formation of competencies):**

1. Be able to find out and analyze the complaints of patients with CL.

2. To teach students to recognize the main symptoms and syndromes in patients with GL.

3. To improve the method of physical examination of patients with CL.

4. Be able to determine the stage of CL of a particular patient and formulate a diagnosis.

5. Be able to assign the optimal algorithm for diagnosis in patients with CL.

6. To teach students to independently interpret the data of instrumental and laboratory research methods used in the diagnosis of CL.

7. To interpret the data of blood analysis and analysis of sternal punctate in patients with CL.

8. Prescribe treatment depending on the option of CL.

9. To acquaint students with the tactics of treatment of complications in CL.

1. **Plan and organizational structure of the lesson.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| The name of the stage | Stage description | | Levels of assimilation | | Time |
| Preparatory stage | | | | | |
| Organizational arrangements  Checking workbooks  Setting learning goals and motivation  Control of the initial level of knowledge:  1. Etiology and pathogenesis  2. Clinic  3. Diagnosis  4. Differential diagnosis  5. Treatment | Methods of control of theoretical knowledge:  - individual theoretical survey;  - test control;  - solving typical problems. | | Question  Typical tasks  Tests  Written theoretical tasks  Tables  Pictures  Structural and logical schemes  Audio and video materials. | | 45-60 min. |
| The main stage | | | | | |
| Formation of practical skills  1. Diagnostic value of clinical analysis of blood and myelogram in CL;  2. Diagnostic value of results of cytomorphological, cytochemical, cytogenetic analyzes;  3. Diagnostic value of sterile puncture in acute leukemias, indications, contraindications;  4. Diagnostic value of tre-panobiopsy of the iliac bone in CL;  5. List of additional instrumental studies used to detect splenomegaly, hepatomegaly, enlargement of internal lymph nodes, leukemic infiltrates in various organs and tissues;  6. Complications of CL;  7. Features of management of patients with CL;  8. Features of CL treatment (treatment regimen, chemotherapy, radiation therapy, bone marrow transplantation) | Method of forming practical skills:  Practical training  Method of formation of professional skills:  training in solving typical and atypical situational problems (real clinical, simulated, textual | | Algorithm for the formation of practical skills.  Professional algorithms for the formation of professional skills;  patients, case histories, situational tasks | | 100-150 min. |
| The final stage | | | | | |
| Control and correction of the level of practical skills and professional skills | | Methods of control of practical skills:  Individual control of practical skills and their results  Methods of control of professional skills: analysis and evaluation of the results of clinical work of students | | The results of work with the patient, with a history of the disease.  Atypical situational problems. | 45-60 min. |
| Summarizing the lesson: theoretical, practical, organizational | |  | |  | 5-10 min. |
| Homework | | Approximate map for independent work with literature. Recommended literature (basic, additional) | |  | 5 min. |

1. **Content of the lesson topic**

Leukemias (leukemias) are malignant tumors of hematopoietic tissue with primary localization in the bone marrow and subsequent dissemination in the peripheral blood, spleen, lymph nodes, other organs and tissues.

Leukemias are divided into acute and chronic.

**Classification of chronic leukemias**

I. Chronic leukemias of myelogenous origin:

Chronic myelogenous leukemia.

Chronic monocytic and myelomonocytic leukemia.

Idiopathic myelofibrosis.

Essential thrombocytosis.

True polycythemia (erythremia).

Myelodysplastic syndrome.

II. Chronic lymphoproliferative diseases:

Chronic lymphocytic leukemia.

Paraproteinemic hemoblastosis (myeloma, Waldenstrom's macroglobulinemia).

Lymphomas and lymphosarcomas.

**CHRONIC MYELOID LEUKIMIA**

DEFINITION, ETIOLOGY, PATHOGENESIS

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm involving clonal proliferation of a malignant multipotential hematopoietic stem cell. As a result of reciprocal translocation of the long arms of chromosomes 9 and 22, the Philadelphia (Ph) chromosome is formed, and the subsequent fusion of the BCR and ABL1 genes leads to the development of a new mutant BCR-ABL1 gene. This gene encodes the BCR-ABL1 fusion protein, which due to its constitutive tyrosine kinase activity causes an increased clonal proliferation of hematopoietic stem cells, inhibition of apoptosis, and impaired adhesion of leukemic cells to the bone marrow matrix.

**CLINICAL FEATURES AND NATURAL HISTORY**

Clinical manifestations include weight loss, constitutional symptoms, and manifestations of splenomegaly (left upper quadrant pain, early satiety). Rarely patients present with leukostasis (leukocytes >200-300×109/L) that alters microcirculation, manifesting as altered mental status, visual disturbances, headache, symptoms of hypoxemia, and priapism. In ~40% of patients CML is an incidental finding in a complete blood count (CBC) performed for other reasons.

The chronic phase of CML always progresses (sometimes rapidly) to blast crisis. The progression usually follows through an intermediate accelerated phase or less often it may be direct. In patients with blast crisis, peripheral blood or bone marrow blast counts increase to >20%, consistent with acute leukemia (in ~50% of patients CML transforms into myeloid leukemia; in ~30%, into lymphoblastic leukemia; in ~10%, into megakaryoblastic leukemia; and in the remaining cases blast crisis has features of myelofibrosis). The accelerated phase and blast crisis in CML are characterized by multiple cytogenetic abnormalities, resistance to treatment, and a poor prognosis.

**DIAGNOSIS**

Diagnostic Tests

1. CBC: White blood cell (WBC) counts are elevated in all patients with CML, with mature and immature granulocytes at all stages of development, thrombocytosis (in a third of patients), basophilia, and eosinophilia. Differential blood count reveals a left shift that may extend to blasts and includes promyelocytes, myelocytes, metamyelocytes, less frequently erythroblasts. Hemoglobin levels at diagnosis are typically normal.

2. Bone marrow examination: Required to confirm the chronic phase. Bone marrow aspiration and trephine biopsy reveal increased bone marrow cellularity with an elevated proportion of cells of neutrophilic (similar to that observed in peripheral blood) and megakaryopoietic lineages.

3. Cytogenetic and molecular studies of bone marrow (Ph chromosome) are performed both to establish diagnosis and exclude additional cytogenetic abnormalities.

4. Molecular studies of peripheral blood: These studies are used to confirm the diagnosis of CML (qualitative) and monitor response to therapy (quantitative).

**Diagnostic Criteria**

At all stages the diagnosis is based on the presence of the Ph chromosome, documented using cytogenetic studies (karyotype or fluorescent in situ hybridization [FISH]), or the BCR-ABL1 gene, documented using molecular studies (reverse transcriptase–polymerase chain reaction [RT-PCR] of peripheral blood or bone marrow cells).

1. The World Health Organization (WHO) diagnostic criteria of accelerated phase (≥1 feature must be present):

1) 10% to 19% blasts in peripheral blood or bone marrow.

2) ≥20% of basophils in peripheral blood.

3) Sustained thrombocytopenia <100×109/L (unrelated to treatment).

4) Clonal cytogenetic evolution (emergent chromosomal aberrations) during treatment.

5) Progressive splenomegaly or leukocytosis not responding to treatment.

2. The WHO diagnostic criteria of blast crisis (≥1 feature must be present):

1) ≥20% blasts in peripheral blood or bone marrow.

2) Extramedullary blastic infiltrates (in organs other than spleen).

3) Large aggregates or clusters of blasts in bone marrow.

**Differential Diagnosis**

1. Conditions associated with elevated neutrophil counts:

1) Other myeloproliferative and myelodysplastic-myeloproliferative neoplasms.

2) Leukemoid reaction: Infection (WBC count ≤100×109/L), particularly in patients with bacterial pneumonia, meningitis, diphtheria, tuberculosis, or fungal infections.

3) Other neoplasms that produce granulocyte growth factors: Small cell lung cancer, ovarian cancer, melanoma, Hodgkin lymphoma.

4) Other conditions (WBC count, 30-40×109/L): Tissue necrosis, myocardial infarction, myositis, acute hemorrhage, glucocorticoid therapy.

5) Exogenous administration of granulocyte colony-stimulating factor or granulocyte and macrophage colony-stimulating factor.

2. Conditions associated with thrombocytosis:

1) Other myeloproliferative neoplasms (eg, essential thrombocythemia).

2) Reactive thrombocytosis: Infection, malignancy, chronic inflammatory disorders, tissue damage.

3) Iron deficiency.

4) Medications: Glucocorticoids, epinephrine, vincristine, tretinoin, methimazole.

**TREATMENT**

1. Long-term treatment with tyrosine kinase inhibitors (TKIs):

1) Imatinib 400 mg orally once daily.

2) Dasatinib 100 mg orally once daily; this is effective in all patients with resistance to imatinib caused by BCR-ABL1 gene mutations except for T315I/A, F317L, and V299L mutations.

3) Nilotinib 300 mg orally bid; this is effective in all patients with resistance to imatinib caused by BCR-ABL1 gene mutations except for T315I, Y253H/F, E255V/K, and F359V mutations.

4) Bosutinib 400 mg orally once daily.

5) Ponatinib 45 mg orally once daily; this is effective in patients with the T315I mutation.

The first-line agents include imatinib, nilotinib, bosutinib, and dasatinib. In the case of imatinib resistance or intolerance, dasatinib, nilotinib (800 mg/d), or bosutinib may be used. Ponatinib is typically reserved for third-line treatment or for patients with the T315I mutation. No significant data in favor of any of these agents are available, except for the BCR-ABL1 mutations causing resistance to any one of them. The choice of the agent should be based on the availability, cost, toxicity profile, as well as the patient’s comorbidities and possible interactions with other administered drugs.

**Criteria for response to treatment:**

1) Complete hematologic response (CHR): WBC <10×109/L, no immature granulocytes on peripheral blood film, basophils <5%, platelet count <450×109/L, nonpalpable spleen. No CHR or presence of >95% Ph+ cells on cytogenetic examination following 3 months of TKI therapy is considered treatment failure.

2) Major hematologic response (MCyR) (≤35% of Ph+ cells on cytogenetic examination) and/or achieving ≤10% of BCR-ABL1 transcript on the International Scale (IS) in real-time quantitative polymerase chain reaction after 3 months of treatment is considered optimal.

3) Complete cytogenetic response (CCyR) (no Ph+ cells on cytogenetic examination) and/or <1% of BCR-ABL1 transcript on the IS after 6 months of treatment is optimal, 1% to 10% requires closer follow-up, and >10% warrants a change in therapy.

4) Major molecular response (MMR) (<0.1% of BCR-ABL1 transcript on the IS) 12 months from treatment initiation or anytime afterwards is optimal. Maintaining this level of response ensures progression-free survival.

2. Allogeneic hematopoietic stem cell transplant (HSCT) should be considered for patients in the chronic phase after failure of ≥2 TKIs and in patients with accelerated phase with a suboptimal response; it should be strongly considered for those with blast crisis.

3. Interferon alpha is used in pregnant women (monotherapy) and in patients with TKI treatment failure who are not eligible for allogeneic HSCT (in combination with cytarabine or another agent).

4. Hydroxyurea (INN hydroxycarbamide) is used as a short-term treatment to reduce WBC counts prior to confirming the diagnosis. It has no disease-modifying effect and no influence on survival.

5. Treatment of accelerated phase and blast crisis requires higher doses of TKIs. In patients with disease progression in the course of treatment, switch to another TKI (see above). Allogeneic HSCT should be considered, optimally after achieving a chronic phase. The only exception is TKI-naive patients with accelerated phase diagnosed de novo in whom the optimal response to TKI treatment has been achieved.

6. Treatment-free remission (TFR) is ongoing molecular remission in the absence of TKI therapy. Patients can only be considered for a trial of TFR if high-quality monitoring can be assured. Following ≥3 years of TKI therapy patients may attempt TFR if they have achieved a deep molecular response (BCR-ABL1 transcript ≤0.01% on the IS or deeper) and maintained it for ≥2 years. Patients attempting TFR must undergo molecular monitoring for relapse (>0.1% of BCR-ABL1 transcript on the IS) every 4 weeks for ≥6 months.

**PROGNOSIS**

The response to TKI treatment is the most important prognostic factor. In patients treated with imatinib, 7-year rates of progression-free survival and survival free of accelerated phase/blast transformation are 81% and 93%, respectively. In patients undergoing allogeneic HSCT (from a related donor), the 3-year survival rate is reported as up to 76%. Various prognostic scores exist. At present the European LeukemiaNet recommends the use of the European Treatment and Outcome Study (EUTOS) long-term survival (ELTS) score at baseline to estimate survival risk.

**CHRONIC LYMPHOCYTIC LEUKIMIA (CLL)**

**DEFINITION, ETIOLOGY, PATHOGENESIS**

Chronic lymphocytic leukemia (CLL) is a neoplasm originating from morphologically mature B cells present in peripheral blood, bone marrow, lymphatic tissue, and other organs. Etiology is unknown. CLL is the most common type of leukemia.

**CLINICAL FEATURES AND NATURAL HISTORY**

The large majority of patients are asymptomatic at diagnosis, as most patients are diagnosed after observing asymptomatic lymphocytosis on complete blood count (CBC).

1. Symptoms: Constitutional symptoms (present in 5%-10% of patients; the first 3 are so-called B symptoms): At least 10% weight loss over the previous 6 months, fever (>38 degrees Celsius) persisting ≥2 weeks (with no infection), drenching night sweating for >2 weeks (with no infection), marked fatigue (≥2 in Eastern Cooperative Oncology Group [ECOG] performance status [available at ecog-acrin.org]), a subjective feeling of abdominal distention and abdominal pain (manifestations of splenomegaly).

2. Signs: Lymphadenopathy; enlargement of the spleen, rarely of the liver or other lymphatic organs (Waldeyer ring, tonsils); very rarely involvement of extralymphatic organs (most frequently skin).

3. Complications: Infections, autoimmune cytopenia (in particular autoimmune hemolytic anemia or immune thrombocytopenia), acquired immunodeficiency states.

4. Natural history: The course of CLL may be predicted on the basis of the Rai staging system (table 9.4-1) or the Binet staging system (table 9.4-2). Other prognostic features include the lymphocyte doubling time; biochemical (including lactate dehydrogenase), cytogenetic, and molecular markers; IGHV mutation status; CD38 and ZAP-70 expression. In <10% of patients, CLL undergoes transformation to a more aggressive lymphoma (Richter syndrome). CLL and small lymphocytic lymphoma fall on a spectrum and may be indistinguishable in some patients.

**DIAGNOSIS**

**Diagnostic Tests**

1. CBC: Lymphocytosis (>5×109/L) with predominant small, morphologically mature lymphocytes as well as anemia and thrombocytopenia (in patients with advanced disease this is due to the suppression of normal hematopoiesis by a leukemic clone; at every stage of the disease cytopenias may also be autoimmune). Peripheral blood smear may show characteristic “smudge cells.”

2. Immunophenotyping (peripheral blood or bone marrow) is used to establish diagnosis and for prognosis evaluation. It reveals clonality (kappa or lambda light chain restriction) and characteristic coexpression of B-cell antigens (CD19, CD22, CD23) and a T-cell antigen (CD5).

3. Cytogenetic (fluorescent in situ hybridization in peripheral blood) and molecular studies: No single cytogenetic abnormality is typical for CLL. The most frequent abnormalities of prognostic value are del(13q), trisomy 12, del(11q), del(17p), and TP53 mutations; del(17p) and TP53 mutations are associated with poor prognosis.

4. Other laboratory studies: Positive direct antiglobulin test results (Coombs test; in 35% of patients), hypogammaglobulinemia.

**Diagnostic Criteria**

1. Peripheral blood lymphocytosis ≥5×109/L with a predominant population of morphologically mature small lymphocytes.

2. Clonal nature of the circulating B cells documented by a characteristic immunophenotype observed by flow cytometry.

**Differential Diagnosis**

Monoclonal B-cell lymphocytosis (this is associated with the presence of a clone of lymphocytes with the phenotype characteristic for CLL, cell counts <5×109/L, and no clinical symptoms or signs; the annual risk of progression to CLL is 1%-2%), prolymphocytic leukemia, hairy cell leukemia, large granular cell leukemia, mantle cell lymphoma, follicular lymphoma, Waldenström macroglobulinemia.

**TREATMENT**

1. Indications to start treatment:

1) Significant constitutional symptoms.

2) Significant anemia or thrombocytopenia caused by bone marrow involvement.

3) Massive, progressive, or symptomatic lymphadenopathy, or massive, progressive, or symptomatic spleen enlargement.

4) Very high lymphocyte counts (usually >500×109/L) causing symptoms of leukostasis, or rapidly progressive lymphocytosis (>50% increase over 2 months, or lymphocyte doubling time <6 months in patients with initial lymphocyte counts >30×109/L).

5) Autoimmune cytopenias refractory to initial treatment with glucocorticoids.

In patients who do not require treatment, follow-up visits are recommended every 3 to 12 months (physical examination, CBC).

2. First-line treatment: CLL is a disease of active research interest with rapid advances being made in therapy. Treatment should be provided in expert clinical centers. There may be significant differences in available therapy between centers, jurisdictions, and countries.

1) The choice of first-line treatment is guided by prognostic features of the disease and the patient’s fitness.

a) For patients with del(17p), first-line therapy with a targeted agent (such as ibrutinib, acalabrutinib, or venetoclax) is preferred.

b) For patients without IGHV mutation, first-line therapy with targeted agents (such as ibrutinib, acalabrutinib, or venetoclax) is prefered.

c) For patients with standard-risk disease, either chemoimmunotherapy (ie, fludarabine, cyclophosphamide, and rituximab) or targeted agents can be considered.

2) Chlorambucil in combination with an anti-CD20 antibody (rituximab, obinutuzumab) or ibrutinib, or acalabrutinib, or venetoclax plus obinutuzumab are recommended in elderly patients or patients with comorbidities.

3) In patients with del(17p) or TP53 mutation: Ibrutinib or acalabrutinib, or venetoclax with or without obinutuzumab, or idelalisib plus rituximab.

3. Management of patients with relapse or failure of the first-line treatment: Use an alternate agent not used in the first line. Allogeneic stem cell transplant may be considered in selected cases following failure of several lines or therapy or earlier in patients with high-risk disease.

4. Patients with purine analogue resistance, del(17p), or Richter transformation: Reduced-intensity allogeneic HSCT for transplant-eligible patients. In patients with Richter transformation, multiagent chemotherapy is required (eg, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] as in diffuse large B-cell lymphoma), and autologous HSCT may be preferred.

5. Prevention of infections: Influenza and pneumococcal vaccination. Oral acyclovir (INN aciclovir) 400 to 800 mg bid and sulfamethoxazole/trimethoprim 800 mg/160 mg daily 3 times a week in patients treated with purine analogues and alemtuzumab. In patients with hypogammaglobulinemia (<500 mg/dL) and recurrent respiratory tract infections requiring intravenous antimicrobial therapy and/or hospitalization, consider intravenous immunoglobulin (IVIG).

6. Treatment of autoimmune cytopenia: Glucocorticoids. Second-line treatments include rituximab, IVIG, and immunosuppressive agents. If there is no response, definitive treatment of the underlying CLL is required.

**PROGNOSIS IN PATIENTS REQUIRING TREATMENT**

Treatment with purine analogues combined with cyclophosphamide and rituximab results in the highest remission rates and longest progression-free survival rates. The most frequent causes of death are infections, and many older patients die “with” the disease rather than “from” it. In younger patients (who are not expected to die of other disease), 10-year survival is >80%. The risk of developing another malignancy (solid tumors or hematologic diseases) is 2-fold to 7-fold higher than in the general population.

**Questions for self-preparation of the student for practical employment:**

1. Schemes of myelocytopoiesis and lymphocytopoiesis.

2. Prevalence of chronic leukemias.

3. Etiological factors of chronic leukemias.

4. Pathogenesis of chronic leukemias.

5. Classification of chronic leukemias.

6. Clinical manifestations and changes in the objective status of chronic leukemias.

7. Methods of diagnosis of chronic leukemias.

8. Indications and contraindications for the appointment of specific therapy for chronic leukemia.

9. Basic schemes of treatment of chronic leukemias and assessment of response to them.

10. Prognosis and prevention of chronic leukemias.

1. **Literature:**

***Basic:***

1. Current Medical Diagnosis &Treatmant 60th Anniversary / M.Hill, M. A.Paradakis, S. J.McPhee, M. W.Rabow., 2021.

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***Additional:***

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2.Jan A Burger. Evolution of CLL treatment - from chemoimmunotherapy to targeted and individualized therapy [Electronic resource] / Jan A Burger, Susan O'Brien. – 2018. – Resource access mode: Nat Rev Clin Oncol . 2018 Aug;15(8):510-527. doi: 10.1038/s41571-018-0037-8.PMID: 29777163..

3. Gottfried von Keudell. The Role of PI3K Inhibition in Lymphoid Malignancies [Electronic resource] / Gottfried von Keudell, Alison J Moskowitz – Resource access mode: Curr Hematol Malig Rep . 2019 Oct;14(5):405-413. doi: 10.1007/s11899-019-00540-w. PMID: 31359259.

GUIDELINES for the topic:

LIMPHOMA. MYELOMA.

1. **The purpose of the lesson:**

To teach students the ability to collect complaints and history, to make physical examination in patients with lymphoma and myeloma.

To acquaint students with the methods of examinations used for the diagnosis of lymphoma and myeloma, indications for their use, methods of implementation, diagnostic value of each of them.

To teach students to independently interpret the results of examinations, to formulate a diagnosis and to be able to conduct and analyze a differential diagnosis.

To teach students to make an algorithm for the treatment of a specific patient with lymphoma and myeloma, taking into account the clinical features of the course and the presence of concomitant pathology.

1. **Competencies (formation of competencies):**

1. Be able to identify and analyze complaints of patients with lymphoma and myeloma.

2. To teach students to recognize the main symptoms and syndromes in patients with lymphoma and myeloma.

3. To improve the method of examination of patients with lymphoma and myeloma.

4. Be able to determine lymphoma and myeloma of a particular patient and formulate a diagnosis.

5. Be able to prescribe the optimal diagnostic algorithm for patients with lymphoma and myeloma.

6. To teach students to independently interpret the data of instrumental and laboratory research methods used in the diagnosis of lymphoma and myeloma.

8. To prescribe treatment of lymphoma and myeloma.

1. **Plan and structure of the lesson.**

|  |  |  |  |
| --- | --- | --- | --- |
| The name of the stage | Stage description | Levels of assimilation | Time |
| Preparatory stage | | | |
| Organizational arrangements  Answering to students’ questions risen during preparing for classes.  Checking workbooks  Setting learning goals and motivation  Control of the initial level of knowledge:  1. Definition of lymphoma and myeloma  2. Etiology and pathogenesis  3. Clinic  4. Diagnosis  5. Differentil diagnosis  6. Complications  7. Treatment  8. Prognosis | Methods of control of theoretical knowledge:  - individual theoretical survey;  - test control;  - solving typical problems | Question  Typical tasks  Tests  Written theoretical tasks  Tables  Pictures  Structural and logical schemes  Audio and video materials. | 45-60 min. |
| The main stage | | | |
| Formation of practical skills  1. Objective examination of the patient  2. Collection of anamnesis  3. Interpretation of laboratory data  Formation of professional skills  1. Supervise the patient  2. Make a plan for examining the patient  3. Make a treatment plan for a patient with lymphoma and myeloma. | Method of forming practical skills:  Practical training  Method formation of professional skills:  training in solving typical and atypical situational problems (real clinical, simulated, textual) | Algorithm for the formation of practical skills.  Professional algorithms for the formation of professional skills:  patients, medical histories, situational tasks | 100-150 min. |
| The final stage | | | |
| Control and correction of the level of practical skills and professional abilities  Theoretical, practical and organizational summarizing the lesson with scoring of students’ studying activity by results of their work during 3 stages of the lesson  Homework: informing of students about next topic, concise tasks for individual outside work including creative and individual | Methods of control of practical skills:  individual control of practical skills and their results  Methods of control of professional skills: analysis and evaluation of the results of clinical work of students  Approximate map for unrestricted work with literature. Recommended reading (basic, additional, information sources) | The results of working with the patient, with a medical history. Defense of the case report. Solution of task grade A (10TT)  Atypical situational tasks. | 45-60 min. |

1. **Content of the lesson topic:**

**Lymphomas**

Hodgkin lymphoma (HL) is a form of lymphoma that derived from a profoundly defective B cell, with the pathobiology, histology, and clinical features being distinct from non-Hodgkin lymphomas.

The etiology of HL is unknown. Despite its relatively low overall incidence, HL represents a significant burden in the young adult population, where it accounts for 15% of diagnosed malignancies. It has a bimodal age distribution, affecting young adults in their 20s and adults older than 60 years of age.

**Clinical picture**

1. Lymphadenopathy: Lymph nodes are painless, typically non-tender and non-mobile or fixed. The most commonly involved nodes are: cervical and mediastinal (60%-80% of patients); as well as axillary nodes (20%-40% of patients). Subdiaphragmatic and retroperitoneal nodes are affected less frequently.

2. General symptoms: Nonspecific symptoms accompanied by “B” symptoms, which are caused by cytokine release, and include a fever, drenching sweats, and an unintentional 10% weight loss within six months in ~30% of patients. Fevers occasionally persist for days to weeks, followed by afebrile periods, with subsequent reoccurrence of the fever (Pel–Ebstein fever). Sometimes patients have pruritus or pain in the lymph nodes after consumption of alcohol.

3. Symptoms related to lymphadenopathy: cough and shortness of breath due to compression of the airways by a lymph node in mediastinum, hoarseness due to compression of the recurrent laryngeal nerve, superior vena cava syndrome, pleural effusion, due to infiltration of the tumor into the pleural space. Retroperitoneal lymph nodes involvement causes abdominal discomfort, urine retention, flatulence, constipation, gastrointestinal obstruction in advanced disease. HL cells also release cytokines that travel through the blood to the kidney where they damage the podocytes, causing minimal change disease, a nephrotic syndrome.

4. Extranodal lesions: extralymphatic lesions in bones kidneys, uterus, ovaries, urinary bladder, skin, central nervous system, and testes. Unlike in NHL, involvement of the Waldeyer ring (pharyngeal lymphoid ring), gastrointestinal tract, liver, and bone marrow is uncommon.

**Diagnostic Tests**

1. Diagnostic Biopsy:

Histologic and immunohistochemical (IHC) examination of an involved lymph node (examination of a excisional complete node is recommended, needle aspiration are not considered appropriate) or other involved tissues.

HL is defined by a characteristic histopathologic picture composed of a minority of disease-defining Reed-Sternberg cells that have a bilobed nucleus and a surrounding clear space like “owe glasses”, associated with large mononuclear version of Reed-Sternberg cells - Hodgkin cells. These abnormal, neoplastic cells are usually surrounded by non-neoplastic inflammatory cells, mostly T cells, and sometimes eosinophils. They can also activate fibroblasts, which secrete collagen.

Classical HL almost always has Reed-Sternberg cells which are positive for the testing for expression of CD (cluster differentiation) cell surface markers CD15 and CD30, and negative for CD20 and CD45. In contrast, non-classical HL contains so-called popcorn cells, rather than Reed-Sternberg cells. And popcorn cells are the opposite of Reed-Sternberg cells - they’re CD15, CD30 negative, and CD20, CD45 positive.

1. Imaging studies:

Contrast-enhanced computed tomography (CT) (of the neck, chest, abdomen, and lesser pelvis), chest radiography, and positron emission tomography (PET)-CT with intravenous bolus of radiolabeled glucose, called fluorodeoxyglucose, or FDG that light up highly metabolically active cells, like lymphoma cells in tissues.

1. Biopsy of the bone marrow:

In addition to the imaging studies, aspiration and biopsy of the bone marrow may be done, especially if a lymph node isn’t easily accessible, like a retroperitoneal lymph node. Immunophenotyping of the neoplastic cells confirms diagnosis and helps to distinguish cHL from nodular lymphocyte predominant HL and non-Hodgkin lymphoma (NHL) subtypes.

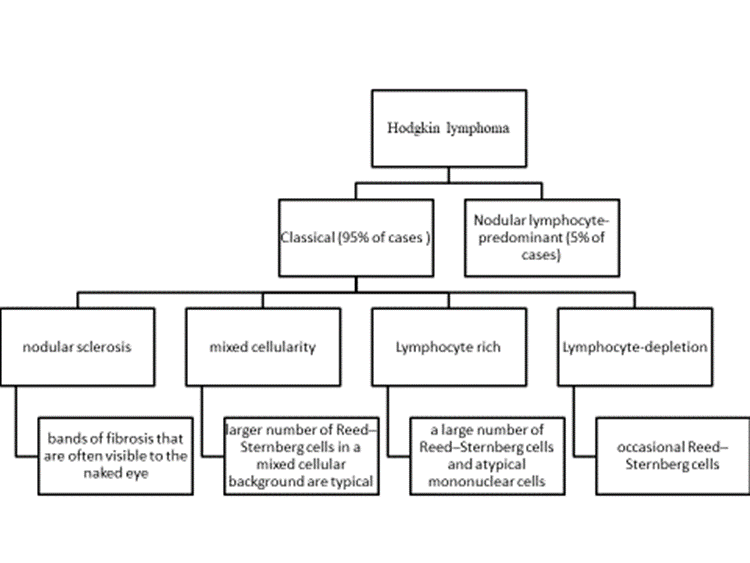
1. Complete blood count (CBC):

Nonspecific abnormalities may include elevated neutrophil and/or eosinophil counts, lymphocytopenia, thrombocytopenia, normocytic anemia (anemia of chronic disease or less frequently autoimmune hemolytic anemia).

**Diagnostic Criteria**

Diagnosis is based on histologic and immunohistochemical examination of an involved lymph node or other involved tissue specimens.

HL can be classified into classical Hodgkin and non-classical HL, which is also called nodular lymphocyte predominant. Classical HL includes four histological subtypes. From most to least common, they are nodular sclerosing (70%-80% of cases), mixed cellularity, lymphocyte-rich, and lymphocyte-depleted. Lymphocyte-rich considered to have the best prognosis, while lymphocyte depleted has the worst prognosis. Nodular lymphocyte-predominant HL is observed in ~5% of patients with HL; it affects peripheral lymph nodes (usually in one lymphatic region only). The development is usually very slow, with no clinical progression over many years. Patients with relapse have better response to treatment.

**Histologic classification of HL** (World Health Organization, 2016):

The next step after imaging results is applying for the modified Ann-Arbor staging system, which has four stages according to the number of lymph node regions involved and the side of the diaphragm the lymph nodes are on.

**The Ann Arbor HL classification with Lugano (2014) modification**

|  |  |
| --- | --- |
| Lugano (2014) staging system for primarily nodal lymphomas | |
| Clinical stage | Definition |
| **I** | One node or a group of adjacent nodes, or single extranodal lesions without nodal involvement |
| **IIa** | ≥2 nodal groups on the same side of the diaphragm, or CS I/II by nodal extent with limited contiguous extranodal involvement |
| **III** | Nodes on both sides of the diaphragm, or nodes above the diaphragm with spleen involvement |
| **IV** | Additional noncontiguous extralymphatic involvement |
| The tonsils, Waldeyer ring, and spleen are considered nodal tissue.  Additionally in Hodgkin lymphoma: **A**, no general symptoms; **B**, general symptoms: unexplained fever (>38°C), drenching night sweats, or weight loss >10% of body weight in the prior 6 months. | |
| aCS II bulky: CS II as above and bulky disease (a single nodal mass of ≥10 cm or >1/3 of the transthoracic diameter at any level of thoracic vertebrae as determined by computed tomography). | |

So stage 1 is one lymph node region, stage II is multiple lymph node regions all on one side of the diaphragm, stage III is multiple lymph node regions on both sides of the diaphragm, and stage IV is metastatic disease beyond the lymph nodes, or involving the bone marrow.

***After process is staged, them subclassified into A, B, X, E, or S.***

“A” means absence of additional symptoms, “B” is presence of B-symptoms, and X is bulky disease meaning that there is a lymph node that is greater than 10 centimeters in diameter. E is for a single contiguous extranodal site, which means involvement of a structure anatomically close to the involved lymph node, such as involvement of the lungs in a patient with mediastinal lymphadenopathy. And S for spleen involvement.

HL usually presents in stage I or II, whereas non-HL - in stages III or IV.

Adverse prognostic factors in clinical stages I and II: Large mediastinal mass (>1/3 of the maximum horizontal chest diameter), ESR >50 mm/h (>30 mm/h if B symptoms are present), age ≥50 years, ≥3 nodal areas, extra nodal disease.

Adverse prognostic factors in clinical stages III and IV: Serum albumin level <4 g/dL, hemoglobin <10.5 g/dL, male sex, age ≥45 years, clinical stage IV, white blood cell count ≥15×109/L, lymphocytopenia <0.6×109/L or <8%.

**TREATMENT**

Treatment of HL depends on the stage and type.

**Treatment of Classical HL**

1. First-line treatment: Chemotherapy (ABVD [doxorubicin, bleomycin, vinblastine, dacarbazine] for I,II stage or BEACOPP [bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone])for III, IV stage, usually in combination with radiotherapy of residual lesions or of the primarily involved field. Additionally, since the popcorn cells in non-classical lymphoma are CD20 positive, rituximab can be used. Patients with refractory or relapsed classical HL can be treated with an anti-CD30 monoclonal antibody like brentuximab vedotin.

2. Progression or relapse: In most cases salvage chemotherapy regimens are used and followed by high-dose chemotherapy and autologous hematopoietic stem cell transplant (HSCT) with or without radiotherapy. In patients not eligible for HSCT or those with late relapses (after 12 months), combination treatment (chemotherapy with radiotherapy) should be considered.

**Treatment of NLPHL:**

Surgery+Chemotherapy ABVD, CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone], CVP [cyclophosphamide, vincristine, prednisone]) ± rituximab ± radiotherapy.

PROGNOSIS

HL is a highly curable disease by current treatment strategies up to 5-years survival of 90% persons. In relapsed or refractory patients undergoing autologous HSCT, cure is possible in ~50% of cases. In untreated patients 5-year survival rates are ~5%. HL generally has a good prognosis, but there are side effects of chemotherapy and radiotherapy. In addition, radiation exposure can lead to cancers of the breast, lung, or thyroid, and can cause Hl cells to mutate and develop into non-HL.

**Non-Hodgkin Lymphoma (NHL)**

Non-Hodgkin lymphomas (NHLs) are a group of neoplasms characterized by the clonal proliferation of lymphoid cells at various stages of B-cell or less commonly T-cell or natural killer (NK)-cell differentiation.

NHL is much more frequent than HL, increased in incidence at a higher rate than almost all other malignancies. Compared to HL, NHL typically causes lymphadenopathy that’s disseminated because it spreads hematogenously rather than through contiguous lymphatic drainage. The specific types of NHL vary in occurrence between countries.

Causal relationship with the development of NHL have environmental factors (exposure to benzene, ionizing radiation), viral infections (human T-lymphotropic virus type I, Epstein-Barr virus [EBV], HIV, human herpesvirus 8, hepatitis C virus), bacterial infections (Helicobacter pylori), autoimmune diseases, immunodeficiencies (including immunosuppressive treatment after transplant), and prior chemotherapy (particularly when combined with radiotherapy).

**The World Health Organization (WHO) histologic classification includes >30 NHL subtypes:**

1. B-lymphoblastic and T-lymphoblastic leukemia/lymphoma (B/T-ALL/LBL)
2. Mature B-cell neoplasms (80%-90%):
3. Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL),
4. hairy cell leukemia (HCL),
5. marginal zone lymphoma (MZL),
6. follicular lymphoma (FL),
7. lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM),
8. mantle cell lymphoma (MCL),
9. diffuse large B-cell lymphoma (DLBCL) and its variants,
10. Burkitt lymphoma (BL), and other types.
11. Mature T-cell and NK-cell neoplasms:
12. Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS),
13. large granular lymphocytic leukemia (LGLL),
14. mycosis fungoides (MF), and other types.

The most common subtype is diffuse large B-cell lymphoma, which is an aggressive type of lymphoma that presents with a rapidly enlarging mass.

Primary CNS lymphoma, which is a type of diffuse large B-cell lymphoma in the brain or spinal cord, can occur in HIV patients, and is an AIDS-defining illness.It usually presents as a ring-enhancing mass on MRI, causing confusion, memory loss, and focal neurological deficits.

The next most common NHL is follicular B-cell lymphoma, and it’s a relatively indolent type of lymphoma that presents with slow-growing lymphadenopathy that comes and goes over the years.

Follicular lymphoma is associated with an 14:18 chromosomal translocation, which alters the anti-apoptotic protein Bcl-2.

Burkitt lymphoma is an aggressive lymphoma that’s classically associated with an 8:14 chromosomal translocation that results in overactivity of the c-myc oncogene.It has three different subtypes; the endemic or African subtype, which is frequently associated with EBV, and presents with a jaw mass in a child, then the sporadic or American subtype which isn’t related to EBV, and usually presents as an ileocecal abdominal mass, and finally there’s an HIV-related subtype, which presents with disseminated disease.

Mantle cell lymphoma is classically associated with the 11:14 chromosomal translocation, which causes an overexpression of cyclin D1.

Marginal zone lymphoma is associated with the 11:18 chromosomal translocation, can present with a salivary or lacrimal gland mass when associated with Sjogrens, and with a gastric mucosa associated lymphatic tissue lymphoma, or MALToma when caused by Helicobacter pylori.

Because it’s still controversial whether natural killer cell lymphoma is its own disease, they’re classified along with the T-cell lymphomas.

Adult natural killer or T-cell lymphoma can present with lytic bone lesions and hypercalcemia, which is a bit like multiple myeloma, but is distinguished by the presence of skin lesions.

Mycosis fungoides, which is a pure cutaneous natural killer or T-cell lymphoma, presenting as skin patches and plaques. A biopsy of the skin lesions would show CD4 positive natural killer or T-cells that are characterized by cerebriform nuclei, which look like they have the gyrations of a real brain.When these cells move from the skin and get into the bloodstream, they’re then seen on peripheral blood smear, so now we call it natural killer or T-cell leukemia, also called Sezary syndrome.

**Clinical picture**

1. Lymphadenopathy: Lymph nodes are usually painles,>1 cm in diameter and tend to form conglomerates. Massive lymphadenopathy may cause superior vena cava syndrome as well as pleural effusions, ascites, and edema of the lower extremities.
2. Manifestations of extranodal tumors as abdominal pain caused by enlargement of the spleen or liver; jaundice caused by liver infiltration; gastrointestinal bleeding, malabsorption or infiltrates in various organs (eg,skin, central nervous system ).
3. General symptoms and Staging are the same as for HL
4. The prognosis and clinical management in NHL are based on the following classification:
   1. Indolent NHLs (about half of cases): these develop mainly in the elderly and present with generalized lymphadenopathy, bone marrow and peripheral blood involvement, and (frequently) splenic and hepatic involvement. General symptoms are rare,usually characterized by slow progression of signs and symptoms, with survival for most types measured in years. The most common indolent NHL is FL (10%-20% of NHLs).
   2. Aggressive NHLs (about half of cases): DLBCL (most common, 30%-35% of NHLs) and MCL, as as the majority of T-cell lymphomas. Live expectancy for months without treatment.
   3. Highly aggressive NHLs: ALL/LBL and BL. Live expectancy for weeks without treatment

**Diagnosis**

Diagnostic Tests:

1. Histologic and immunohistochemical examination of an involved lymph node or organ specimens (excisional biopsy).

2. To identify nodal and extranodal lesions (required for staging): Contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis (in fluorodeoxyglucose [FDG]-avid NHL), Positron emission tomography (PET)-CT , Bone marrow aspiration and biopsy, etc.

3. Laboratory studies:

Complete blood count (CBC), other: renal and liver function tests and lactate dehydrogenase levels, beta2-microglobulin; serum protein electrophoresis and immunoglobulins concentration, direct antiglobulin (Coombs) tests; HIV, hepatitis B or C virus, EBV.

Cytogenetic studies and molecular studies are performed for those lymphomas that have identifiable abnormalities.

**Diagnostic Criteria**

Diagnosis is made on the basis of histologic and immunohistochemical examination of an entire lymph node or a specimen of an involved organ.

**Treatment**

Treatment strategies depends on the histologic type and stage of NHL

Treatment of Indolent NHL

Currently available treatment cannot achieve a radical cure in this group of patients, except as localized lymphomas (clinical stage I or II), which sometimes may regress spontaneously or may be successfully treated by eradicating the etiologic factor using antimicrobial agents (eg, H pylori in patients with gastric mucosa-associated lymphoid tissue lymphoma) and/or surgical resection of the primary lesion (eg, spleen in patients with splenic MZL) combined with adjuvant radiotherapy and/or chemotherapy. Localized FL can sometimes be cured with radiation alone. Blood and marrow transplant can be used with curative intent in a subset of patients.

Treatment of Aggressive Lymphomas

1. First-line treatment: multiagent chemotherapy in combination with rituximab (in B-cell NHL) and involved field radiotherapy (if necessary).

2. In patients with refractoriness or relapse, use alternative chemotherapy regimens with or without radiotherapy followed by autologous hematopoietic stem cell transplant (HSCT) in transplant-eligible patients. Chimeric antigen receptor (CAR) T cells have perspective.

Treatment of Highly Aggressive Lymphomas-supportive palliative treatment

**Prognosis**

Indolent lymphomas: Remissions are frequent (>75%) but short-lasting (although up to several years), and cure is very rare. In general, curable rates are higher with the aggressive forms of B-cell lymphomas and lower in the elderly and in patients with comorbid conditions that restrict the use of intensive chemotherapy regimens. NHL are typically treated using the R-CHOP chemotherapy , radiation therapy can be added for localized disease.

**Summary:**

Lymphoma is a tumor of lymphocytes presenting as a non-tender lymphadenopathy.

First, an excisional biopsy is done, to assess whether it’s a Hodgkin or non-Hodgkin lymphoma, based on the presence or absence of the Reed-Sternberg cell.

Second, staging is done with the modified Ann-Arbor staging system. HL patients usually present in stages 1 and II, with contiguously spreading lymphadenopathy, while non-Hodgkin patients present in stages III and IV, with disseminated lymphadenopathy.

Finally, HL is typically starts treatment with the ABVD chemotherapy regimen, while non-Hodgkin is treated with the R-CHOP regimen. Radiation therapy may be use in combination.

**Multiple myeloma**

Multiple myeloma (MM) or plasma cell myeloma (PCM) is a hematologic malignancy as the proliferation and accumulation of monoclonal plasma cells, which produce monoclonal immunoglobulin or its fragments (M protein). MM is a cancer of plasma cells, which are normally responsible for producing antibodies and collections of abnormal plasma cells accumulate in the bone marrow, where they interfere with the production of normal blood cells. Etiology is unknown. It accounts for 1%-1.8% of all cancers and is the second most common haematological malignancy with an estimated incidence in Europe of 4.5-6.0/100 000/year. Despite the improvement in treatment over the past 20 years, only 10%-15% of patients achieve or exceed expected survival compared with the matched general population.

MM is the most common primary bone tumor in people older than 40 to 50 years of age, most cases are diagnosed in men at around the age of 70, is about twice as common in black populations than white and Asian populations; people with a family history of condition called monoclonal gammopathy of unknown significance (MGUS).

In MM, the most common M-protein produced is IgG, followed by IgA, and these immunoglobulins have both a heavy and light chain. Responsible for the hyperviscosity syndrome which interferes with fibrin aggregation and platelet function. More rarely, the myeloma cells can only make the kappa or lambda light chain of the immunoglobulin, and in that situation, the resulting protein is called the Bence-Jones protein, that may precipitate and deposit, producing organ damage (kidney) while secreted in the urine. A bone marrow-based plasma cell neoplasm usually characterised by a serum monoclonal protein and/or urinary light chains.

***Clinical picture:***

The pathological and clinical features are due to:

1. Tissue infiltration

2. Production of large amount of paraprotein

3. Impairment of immunity

In the early stages, MM may not cause any symptoms. Then observation include:

1)Persistent bone pain (the most common symptom, present at some stage in a majority of patients) in the lumbar spine, pelvis, ribs, or less commonly in the skull and long bones. This is caused by osteolytic lesions and pathologic fractures (eg, vertebral compression fractures), precipitated by movement (unlike the pain of metastatic carcinoma, which often is worse at night), break (fracture) easily – if this affects the spine, it might cause symptoms such as pins and needles, numbness and weakness in the legs and feet, and problems controlling bladder and bowels, which requires emergency investigation

2) Features of hypercalcemia and its complications: symptoms including extreme thirst, stomach pain, needing to pee frequently, constipation or confusion

3) Features of renal failure ( control level of creatinine)

4) Symptoms of anemia (tiredness, weakness and shortness of breath)

5) Neurologic signs and symptoms: limb paresis or paralysis (due to spinal cord or nerve compression caused by vertebral body fracture or extramedullary plasma cell tumor [plasmacytoma]) and rarely features of peripheral neuropathy.

6) Recurrent respiratory and urinary tract infections, susceptibility to infection

7) Features of hyperviscosity syndrome : somnolence, headache, hearing impairment, altered mental status, blurred vision, dizziness. Clotting abnormalities: bruising and unusual nosebleeds, bleeding gums and heavy periods

8) Rarely extramedullary plasmacytoma and enlargement of the liver, peripheral lymph nodes, and spleen.

In ~10% to 15% of patients the disease is indolent and requires no treatment (so-called smoldering MM). However, in the majority of patients the disease is progressive or relapses nevertheless treatment.

Clinical presentation of MM can be summarized with the mnemonic CRAB :

“**C**” is for hypercalcemia, which results due to osteoclast activating factor from the malignant plasma cells, which resorbs the bone and releases free calcium into the blood ( abdominal pain, psychiatric changes, constipation).

“**R**” is for renal disease, which can be caused by multiple mechanisms. Light chains can deposit in and obstruct the renal tubules - nephropathy. Renal disease can also be due to type two renal tubular acidosis, or even hypercalcemia that may cause the formation of calcium phosphate kidney stones. MM can also lead to primary amyloidosis, where the immunoglobulin light chains leave the circulation and abnormally aggregate in various tissues, resulting in clinical manifestations (restrictive cardiomyopathy, macroglossia, and nephrotic syndrome).

“**A**” is for anemia, with fatigue and shortness of breath. The anemia occurs because the malignant cells infiltrate the bone marrow, and disrupt the normal production of red blood cells.

Finally, “**B**” is for bone pain, which is due to increased osteoclast activity causing pathologic fractures and lytic bone lesions.

Other manifestations include spinal cord compression if the tumor infiltrates from the vertebrae, and frequent infections, because although the tumor is making lots of inappropriate immunoglobulins.

**Classification:**

ICD-11 classification ( WHO,2021)

2A83.1 Plasma cell myeloma

2A83.Y Other specified multiple myeloma and plasma cell neoplasms

**Diagnostic Tests**

1. Complete blood count (CBC) in the majority of patients reveals normocytic normochromic anemia, with the formation of red blood cells in the form of rouleaux in 50% of patients. Leukopenia or thrombocytopenia less common.

2. Bone marrow examination: More than 10% of clonal plasma cells.

3. Other laboratory tests: Hypergammaglobulinemia; decreased levels of normal immunoglobulins; monoclonal protein identified in blood and urine electrophoresis and immunofixation; presence of abnormal light chains in blood and/or urine (monoclonal urinary light chains are referred to as Bence Jones proteinuria); hypercalcemia; increased serum uric acid, creatinine, beta2-microglobulin, C-reactive protein, and lactate dehydrogenase levels; rarely cryoglobulinemia. Hyperproteinemia and ESR(this may be markedly elevated) are nonspecific tests.

4. Skeletal imaging studies (radiography, computed tomography [CT] and/or magnetic resonance imaging [MRI], or positron emission tomography [PET]-CT) reveal focal osteolytic lesions, most commonly in the flat and long bones, as well as osteoporosis and pathologic fractures. Radiographs should include the skull, brachial and femoral bones, pelvis, spine, and all painful locations.

**Diagnostic Criteria**

The classic triad of MM :

Marrow plasmacytosis (>10%) or biopsy-proven bony or extramedullary plasmacytoma

Lytic bone lesions “punched out”

Serum and/or urine M component, Urine beta 2 mircoglobulin level - best test for prognosis of MM

Serum and urine protein electrophoresis, or SPEP(es-pep) and UPEP(you-pep), respectively, are important to see which M protein is predominantly being produced, and is seen as an M-spike. SPEP detects most MM patients that predominantly make IgG, followed by IgA, while UPEP is used to detect the minority of patients, who only make the Bence-Jones protein. UPEP is needed because these light chains are rapidly filtered from the blood, so they may not be seen on SPEP

**Differential Diagnosis**

”CRAB” criteria (hypercalcaemia, renal failure, anaemia, bone pain ) separate symptomatic MM form asymptomatic (smoldering) myeloma and other types of monoclonal gammopathy (diseases characterized by the proliferation of a single clone of plasma cells producing the M protein) or other plasma cell dyscrasias like amyloidosis, leukemia, bone metastases of cancer (eg, renal cancer, breast cancer, non–small cell lung cancer, prostate cancer).

**Treatment**

Treatment for MM usually includes: anti-myeloma medicines to destroy the myeloma cells or control the cancer when it comes back (relapses) and medicines and procedures to prevent and treat problems caused by disorder – such as bone pain, fractures and anaemia

1. Patients with asymptomatic (smoldering) myeloma require monitoring .
2. Patients aged <70 years and patients ≥70 years with no comorbidities are candidates for high-dose chemotherapy (myeloablative dose of melphalan) followed by autologous peripheral blood stem cell transplant (PBSCT) after achieving a response to induction chemotherapy (usually 4 cycles of multiagent therapy such as VTd [bortezomib, thalidomide, dexamethasone], CyBorD [cyclophosphamide, bortezomib, dexamethasone], or VRd [bortezomib, lenalidomide, dexamethasone]). Maintenance therapy (eg, lenalidomide) is used.
3. Patients with treatment resistance or relapse: Immunomodulators (thalidomide, lenalidomide, pomalidomide), proteasome inhibitors (bortezomib, carfilzomib), bendamustine, monoclonal antibodies (daratumumab). In selected patients a second autologous transplant or allogeneic PBSCT may be performed.
4. Solitary plasmacytoma: Surgery or radiation and close monitoring for progression to systemic myeloma.
5. Supportive treatment: kidney failure (appropriate hydration), hyperuricemia, prevention of osteolysis is based on bisphosphonates ( pamidronic or zoledronic acid), erythropoiesis, plasmapheresis, prevention of infections

**Prognosis**

Prognosis in MM vary depending on staging and risk stratification. Overall 5-year survival rates are >45%.

1. **Questions for self-preparation of the student for practical training:**

1. L/M definition.

2. L/M epidemiology

3. L/M etiology.

4. L/M pathogenesis.

5. L/M classification.

6. L/M clinical symptoms and signs.

7. L/M diagnosis.

8. L/M differential diagnosis

9. L/M treatment strategies.

10. L/M complications and prognosis.

1. **Literature:**

***Basic:***

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GUIDELINES for the topic:

HEMOPHILIA AND THROMBOCYTOPENIA

1. **The purpose of the lesson:**

To teach students the ability to collect complaints and history, to make physical examination in patients with hemophilia and thrombocytopenic purpura.

To acquaint students with the methods of examinations used for the diagnosis of hemophilia and thrombocytopenic purpura, indications for their use, methods of implementation, diagnostic value of each of them.

To teach students to independently interpret the results of examinations, to formulate a diagnosis and to be able to conduct and analyze a differential diagnosis.

To teach students to make an algorithm for the treatment of a specific patient with hemophilia, thrombocytopenic purpura, taking into account the clinical features of the course and the presence of concomitant pathology.

1. **Competencies (formation of competencies):**

1. Be able to identify and analyze complaints of patients with hemophilia and thrombocytopenic purpura.

2. To teach students to recognize the main symptoms and syndromes in patients with hemophilia and thrombocytopenic purpura.

3. To improve the method of examination of patients with hemophilia and thrombocytopenic purpura.

4. Be able to determine the type of hemophilia of a particular patient and formulate a diagnosis.

5. Be able to prescribe the optimal diagnostic algorithm for patients with hemophilia and thrombocytopenic purpura.

6. To teach students to independently interpret the data of instrumental and laboratory research methods used in the diagnosis of hemophilia and thrombocytopenic purpura.

7. To interpret coagulogram data in patients with hemophilia and thrombocytopenic purpura.

8. To prescribe treatment depending on the type of hemophilia and thrombocytopenic purpura.

1. **Plan and organizational structure of the lesson.**

|  |  |  |  |
| --- | --- | --- | --- |
| The name of the stage | Stage description | Levels of assimilation | Time |
| Preparatory stage | | | |
| Organizational arrangements  Answering to students’ questions risen during preparing for classes.  Checking workbooks  Setting learning goals and motivation  Control of the initial level of knowledge:  1. Definition of hemophilia and thrombocytopenia  2. Etiology and pathogenesis  3. Clinic  4. Diagnosis  5. Differentil diagnosis  6. Complications  7. Treatment  8. Prognosis | Methods of control of theoretical knowledge:  - individual theoretical survey;  - test control;  - solving typical problems | Question  Typical tasks  Tests  Written theoretical tasks  Tables  Pictures  Structural and logical schemes  Audio and video materials. | 45-60 min. |
| The main stage | | | |
| Formation of practical skills  1. Objective examination of the patient  2. Collection of anamnesis  3. Interpretation of laboratory data  Formation of professional skills  1. Supervise the patient  2. Make a plan for examining the patient  3. Make a treatment plan for a patient with hemophilia and thrombocytopenic purpura. | Method of forming practical skills:  Practical training  Method of formation of professional skills:  training in solving typical and atypical situational problems (real clinical, simulated, textual) | Algorithm for the formation of practical skills.  Professional algorithms for the formation of professional skills:  patients, medical histories, situational tasks | 100-150 min. |
| The final stage | | | |
| Control and correction of the level of practical skills and professional abilities  Theoretical, practical and organizational summarizing the lesson with scoring of students’ studying activity by results of their work during 3 stages of the lesson  Homework: informing of students about next topic, concise tasks for individual outside work including creative and individual | Methods of control of practical skills:  individual control of practical skills and their results  Methods of control of professional skills: analysis and evaluation of the results of clinical work of students  Approximate map for unrestricted work with literature. Recommended reading (basic, additional, information sources) | The results of working with the patient, with a medical history. Defense of the case report. Solution of task grade A (10TT)  Atypical situational tasks. | 45-60 min. |

1. **Contents of the lesson topic**

Hemophilia is a hereditary disease, characterized by impaired synthesis of clotting factors VIII (hemophilia A), IX (hemophilia B) or XI (hemophilia C). Hemophilia is inherited on a recessive trait linked to the sex X chromosome. On average, 30-40% of cases are sporadic caused by a gene mutation, without family history. The disease leads to disability of most patients, mostly in childhood.

The prevalence of hemophilia A in the world is 1: 10000, hemophilia B - 1: 30000-50000 males. The prevalence of hemophilia C varies within countries and ethnic groups. A significant number of people with factor XI deficiency are not detected, as the disease is asymptomatic or proceeds with minimal hemorrhage.

**Etiology**

The genes responsible for the synthesis of factors VIII and IX are located on the X chromosome. As men have only one X chromosome, in disorders of the corresponding gene, the synthesis will be absent, much lower, and in some cases the protein will be functionally incapable. In contrast, in women with two X chromosomes, disruption in one of them does not lead to such consequences due to the fact that the gene located on the second X chromosome partially compensates the synthesis of clotting factors.

There may be four inheritance options for a female’s-carrier children: a non-carrier daughter, a carrier daughter, a healthy boy, and a boy with hemophilia. The birth of girls with hemophilia by the classic type of inheritance of this classic trait is extremely rare and is possible if the father has hemophilia and the mother is a carrier of a pathological gene.

**Pathogenesis**

In hemophilia, one of the blood clotting factors is absent or its level is insufficient, therefore the bleeding continues for a long time.

**Clinical picture**

The most characteristic symptom is hemorrhage to large joints - hemarthrosis. Intramuscular and retroperitoneal hematomas, prolonged bleeding after injuries, tooth extraction and surgery. There are rarely hemorrhages to the abdominal cavity, gastrointestinal bleeding, hematuria, intracranial hemorrhage.

Of the total number of hemorrhages:

- hemarthrosis are 70-80%,

- hematomas - 10-20%,

- intracranial hemorrhage - less than 5%,

- hematuria - 14-20%,

- gastrointestinal hemorrhage - about 8%.

Hemarthrosis is a hemorrhage into the joint capsule. Most often, the first hemarthrosis occurs at the age of 1-8 years as a consequence of injury. Acute hemarthrosis is accompanied with pain caused by increased intra-articular pressure. The joint is enlarged, the skin is hyperemic and hot, fluctuation can be found.

The course of hemophilic arthropathy includes three phases:

• acute hemorrhage into joint cavity;

• synovitis;

• development of deforming osteoarthritis and contractures.

In virtue of clinical and radiological data hemorrhagic-destructive osteoarthritis is categorized for 5 stages:

Stage I (early) - is characterized by enlargement of the joint, the expansion of the joint space due to hemorrhage. X-rays may show thickening of the joint capsule, moderate osteoporosis. The function of the joint is preserved;

Stage II - is characterized by a moderate narrowing of the joint space without violating the congruence of the joint surfaces. There are more expressed signs of osteoporosis. Subchondral sclerosis, further periarticular tissue compaction occurs;

Stage III - is characterized by marginal erosions, destruction of cartilage with the cysts formation. Osteoporosis is more pronounced. The joint space is narrowed with broken congruence of articular surfaces. Joint function is moderately affected, movements are slightly limited, muscle atrophy is present;

Stage IV - joints are sharply deformed, the joint space is narrowed. Intra-articular cartilage is destroyed, muscle atrophy is pronounced. The function of the joint is significantly impaired;

Stage V - is characterized by complete loss of joint function. The joint space is poorly contoured on the radiograph, it is often filled with connective tissue. There is severe sclerosis of the subchondral parts of the bone, significant erosion and cystosis of the epiphysis with formation of bone ankylosis.

Deforming osteoarthritis affects the entire musculoskeletal system with curvatures of the spine and pelvis, muscle wasting and osteoporosis, valgus deformity of the knee joint and formation of permanent contracture in the ankle joint by type "horse's foot".

Secondary rheumatoid syndrome is characterized by destructive inflammatory processes in the small joints followed by their deformation. In most patients it  manifests over the age of 14 years.

Hematomas are hemorrhages into soft tissues, mostly in the large muscles such as lumbosacral, quadriceps femoris, triceps. Extensive hematomas can reach significant sizes, causing anemia and compression of the surrounding tissues. Hematomas by pressing on nerve trunks or muscles cause sensory disturbances, muscle atrophy and contractures. Hemorrhages to the soft tissues of the neck pose a risk of upper respiratory stenosis and asphyxia. With adequate treatment, hematomas are completely resorbed, or can transform into "hemophilic pseudotumors."

Hematuria can occur spontaneously or due to lumbar injuries and may be accompanied by dysuric manifestations, attacks of renal colic, caused by the formation of blood clots in the urinary tract.

Hemorrhages to the mesentery and omentum can mimic acute surgical disease of the abdominal cavity (acute appendicitis, intestinal obstruction, etc.).

Hemorrhages to the brain and spinal cord and their membranes in hemophilia occur as a result of injury or due to hypertensive crisis. Apperance of focal symptoms requires urgent administration of antihemophilic drugs and hospitalisation.

**Classification of hemophilia (ICD-11):**

- Code 3B10 Hereditary factor VIII deficiency (Hemophilia A).

- Code 3B11 Hereditary factor IX deficiency (Hemophilia B).

- Code 3B13 Hemophilia C

Severity of hemophilia depends on lasting quantity of affected clotting factor. The level of factor VIII or IX in blood usually stays the same throughout the life. Normal values of FVIII, IX, XI are 50-150%.

Severe (factor levels < 1% of normal) represent app. 60% cases of patients with hemophilia A. Spontaneous bleedings into joints or muscles, predominantly in the absence of identifiable hemostatic challenge are seen.

Moderate (factor levels of 1-5% of normal) represent app. 15% cases of patients with hemophilia A. There are occasional spontaneous bleedings with minor trauma or surgery.

Mild (factor levels of 6%-40%) represent app. 25% cases of patients with hemophilia A. There are severe bleedings with major trauma or surgery. Spontaneous bleeding is rare.

**Diagnosis**

It is based on family history, clinical manifestations and laboratory results. The level of factor VIII in the blood, as well as other clotting factors, is measured as a percentage. The basis is the average amount of factor in the population, expressed in "units per 1 ml" or "100 units per deciliter (100 U / dl)".

**Laboratory tests:**

• Common blood test with platelets and leukocyte formula;

• Coagulogram data screening (prothrombin time [PT], activated partial thromboplastin time [APTT];

• Analysis of FVIII, IX, XI;

• Analysis of immune inhibitor FVIII, IX, XI.

**Interpretation of screening tests**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Possible diagnosis | PT | APTT | Bleeding time | Pletelet count |
| Normal | Normal | Normal | Normal | Normal |
| Hemophilia A or B | Normal | Prolonged | Normal | Normal |
| VWD | Normal | Normal or prolonged | Normal or prolonged | Normal or reduced |
| Platelet defect | Normal | Normal | Normal or prolonged | Normal or reduced |

Testing for FVIII inhibitors is indicated when bleeding is not controlled after administration of a sufficient amount of factor during bleeding. The absence of correction of the clotting time of a 1:1 mixture with normal plasma is indicated by the presence of inhibitors. The inhibitor concentration is titrated using the Bethesda method:

• Positive result: ≥ 0.6 Bethesda units (BU);

• Low temperature inhibitor: ≤5 BU;

• High titer inhibitor: > 5 BU.

Genetic testing to define disease biology, establish diagnosis in difficult cases, predict risk of inhibitor development, identify female carriers and to provid prenatal diagnosis.

**Differential diagnosis**

***1. Von Willebrand's disease (vWD)***

This is the most common (0.6–1.3% of the population) congenital hemorrhagic diathesis caused by deficiency or dysfunction of von Willebrand factor (vWF). The disease is more commonly diagnosed in women due to heavy menstrual bleeding. There is autosomal dominant type of inheritance with variable expressiveness and penetrance, except for type 2N and 3 (autosomal recessive). In these types, there are disorders of both primary and secondary hemostasis (vWF is a mediator of platelet adhesion to the damaged vascular wall and protects FVIII from inactivation).

Symptoms: hemorrhage on the skin and mucous membranes - persistent bleeding from the nose and gums, intradermal hemorrhage, heavy and prolonged menstrual bleeding, bleeding after teeth extraction and after surgery, gastrointestinal bleeding, intra-articular and intramuscular bleeding.

Diagnosis

Ancillary research

- Screening studies of hemostasis: PT, thrombin time (TT) and fibrinogen levels - within normal limits; APTT may be prolonged, bleeding time and clotting time (CT - clotting time), always extended in type 3, may be normal in types 1 and 2; platelet count within normal limits (except for subtype 2B, which may occur with recurrent thrombocytopenia).

- Confirmatory studies: decreased level and activity of vWF, reduced or normal activity of FVIII.

- Qualifying studies: analysis of vWF multimers, platelet aggregation with ristocetin, test for FVIII binding by vWF, collagen-binding activity of vWF (vWF:CB), sequencing DNA - in the diagnosis of types 2 and 3, vWF propeptide.

***2. Acquired hemophilia*** caused by autoantibodies to a single clotting factor;

***3. Violation of coagulation hemostasis in liver disease*** as result of vitamin K deficiency;

***4. Disseminated intravascular coagulation syndrome (DIC)*** with increased consumption of clotting factors.

**Treatment**

***General recommendations***

• Teaching the patient about the diagnosis, plan of action in emergencies, as well as contact details of the attending physician.

• Avoid medicines, impairing platelet function, such as acetylsalicylic acid. For the treatment of pain paracetamol, selective COX-2 inhibitors and opioids are preferred. In exceptional situations, the use of antiplatelet drugs is allowed, provided that the activity of the deficient clotting factor in the patient's plasma remains above a certain set level;

• Prophylactic therapy is recommended for all patients with severe hemophilia by using corresponding clotting factor (2-3 times weekly) or emilizumab (in hemophilia A) -  an engineered bispecific antibody, that binds both human FIX/FIXa and FX/FXa and which is not regulated by the mechanisms that regulate FVIII, but which acts as a FVIII mimetic. It mimics the cofactor activity of FVIII.

• After intra-articular bleeding unload the joint, put ice, use a compression bandage with elevation of the limb. A patient with life-threatening bleeding such as into head and neck, chest, or abdomen, requires hospitalization;

• Surgery and treatment of life-threatening bleeding should be performed in centers that have the ability to conduct daily laboratory monitoring of the treatment (determination of FVIII, FIX activity and FVIII, FIX inhibitor titer).

In severe hemophilia A, episodes of bleeding should be treated by increasing factor VIII levels, usually by intravenous administration of a concentrate of this clotting factor. Doses of FVIII concentrate are calculated depending on the severity and location of bleeding. Typically, FVIII 1 U / kg increases plasma FVIII levels by 2%. Target levels for the degree of bleeding are as follows:

• Mild hemorrhages (early hemarthrosis, epiphytic edema, purulent bleeding) - FVIII level 30%;

• Major hemorrhages (hemarthrosis or muscle bleeding, prevention after head injury with negative tests’ results) - FVIII level by 50%;

• Life-threatening episodes (massive trauma or surgery, exacerbated or recurrent hemarthrosis) - FVIII level 80-90%; after stabilization it is necessary to maintain FVIII levels above 40-50% for at least 7-10 days.

Synthetic version of vasopressin (antidiuretic hormone) desmopressin acetate (DDAVP) increases the level of vWF and factor VIII by 3-4 times, may be used to stop bleeding in patients with mild or moderate hemophilia A. It is ineffective in cases of severe hemophilia. It is administered intravenously at a dose of 0.3 μg / kg body weight. The peak effect is observed in 30-60 minutes.

It does not affect factor IX levels, is of no value in hemophilia B.

Concentrated intranasal DDAVP spray is available for outpatient use. Its effectiveness is similar to IV drug, but the peak effect is observed in 60-90 minutes after administration.

Hyponatremia is a serious side effect of DDAVP due to water retention. Patients should be advised to limit water intake approximately 12-18 hours after DDAVP administration until the antidiuretic effect has resolved.

Tranexamic acid and Epsilon aminocaproic acid are antifibrinolytic agents. They copmetitively inhibit the activation of plasminogen to plasmin and promote clot stability. They are valuable in controlling bleeding from skin and mucosa. May be given alone or together with standard doses of clotting factor concentrates. Tranexamic acid should not be given to patients with factor IX deficiency receiving Prothrombin complex concentrate, as this exacerbates the risk of thromboembolism.

Bypassing agents: sed for the treatment and prevention of bleedings in hemophilia A or B with alloantibodies (inhibitors) that typically neutralize the function of infused clotting factor concentrates. Based on different mechanisms to achieve hemostasis.

Recombinant activated factor VIIa (rFVIIa) promotes coagulation through tissue factor-dependent and independent pathways - binds to tissue factor to activate FX and FIX and allows the coagulation cascade to resume (is used for Hemophilia A and B).

Activated prothrombin complex concentrate (aPCC) is used to treat hemophilia A with inhibitors, it contains mainly non-activated FII (prothrombin), FIX, FX, and mainly activated FVII (for Hemophilia A only).

Hemostatic rebalancing agents: Fitusiran - RNA interference therapy, specifically targets antithrombin messenger RNA to suppress the production of antithrombin in the liver. Advantage - S/C administration, prolonged action, used in hemophilia A and B patients with/without inhibitors.

Anti-tissue factor pathway inhibitor (Anti-TFPI) antibodies are in development, all of which bind to the K2 domain or to both the K1 and K2 domains of TFPI, rescuing FXa and FVIIa from inhibition. May be used S/C, in hemophilia A and B, with/without inhibitors, but duration of action is limited by target-mediated drug disposition.

Intramuscular administration of drugs to patients with hemophilia is contraindicated. At insignificant bleedings from a wound the hemostatic sponge with thrombin is applied locally. Tooth extraction is performed in a hematological hospital under the protection of antihemophilic drugs.

***Treatment of patients with inhibitors***

Inhibitors are IgG alloantibodies to exogenous FVIII or FIX that neutralize the function of infused clotting factor concentrates (CFCs).

They should be suspected in patient who fails to respond to CFC replacement therapy, particularly in previously responsive. More frequently encountered in patients with severe disease and in hemophilia A. Their presense is associated with a higher disease burden, such as risk of musculoskeletal complications, pain, physical limitations, and treatment challenges. Detected by the Nijmegen-modified Bethesda assay. Positive is Bethesda titer of >0.6 Bethesda units (BU) for FVIII and ≥0.3 BU for FIX.

Approaches for the treatment of acute bleeds in hemophilia A with inhibitors.

• FVIII, which has a low cross-reaction with human antibodies to FVIII;

• Activated prothrombin complex concentrate (aPCC);

• Activated recombinant FVII (rFVIIa);

• Immune tolerance induction therapy;

• Monoclonal antibodies that overlap FIXa and FX (eg, emicizumab).

Approaches for the treatment of acute bleeds in hemophilia B with inhibitors.

* Clotting factor IX
* Activated recombinant FVII (rFVIIa)
* Activated prothrombin complex concentrate (aPCC)

***Gene therapy***

Possible approaches to gene therapy for hemophilia A include the following:

• Gene therapy ex vivo: cells are obtained from the patient and grown in culture. The cell culture is infected with a genetically modified virus, and later the modified cells are returned to the patient. The therapeutic gene begins to work in liver cells producing clotting factor VIII.

• Gene therapy in vivo: the therapeutic gene is inserted into viral DNA, injected into the patient's tissues. The therapeutic gene begins to work in liver cells, producing clotting factor VIII. To date, stem cell implantation is also being considered.

For the treatment of hemophilia B recombinant (preffered) or human-derived clotting factor IX are used. In the absence of the factor  prothrombin complex concentrate (PCC) can be used. It contains clotting factors II, VII, IX, X, as well as standard amounts of protein C and S. In the absence of these drugs, corrective therapy for hemophilia B can be performed with fresh frozen plasma (FFP). After administration of 1 U factor IX / kg of mass, its activity in the plasma of the recipient increases by 1 U / dl.

In the treatment of hemophilia C, a concentrated factor XI drug or fresh-frozen plasma is administered at a dose of 10–15 ml / kg body weight. The half-life of factor XI in the circulation of the recipient is 60-80 hours, due to that "maintenance" transfusions can be performed after 48-72 hours.

**Thrombocytopenia**

Thrombocytopenia is characterized by a decrease in the number of platelets (less than 100x109 / l) in the peripheral blood.

Thrombocytopenia may be hereditary or aquired.

**Hereditary thrombocytopenia**

|  |  |
| --- | --- |
| Fanconi's anemia | hemorrhagic syndrome, it manifests at the age 5-8 years, combines pancytopenia, skeletal and renal malformations. |
| May-Heglin anomaly | triad of symptoms: thrombocytopenia, giant platelets, basophilic spindle-shaped inclusions in leukocytes (Deleh's bodies). Inherited by autosomal dominant type. |
| Wiscott-Aldrich syndrome | immunodeficiency disease, inherited by a recessive, X-linked type, manifests during first months of life. There is triad of symptoms: thrombocytopenia, eczematous skin rash and susceptibility to infections. Splenomegaly, lymphadenopathy are characteristic. The forecast is unfavorable. |

In most cases, thrombocytopenia is acquired and may be the result of decreased platelet production, increased destruction of platelets or their redistribution.

**Etiological factors of thrombocytopenia**

|  |  |
| --- | --- |
| Pathogenetic mechanisms | Etiological factors |
| 1. Decreased production of plateletes | Medicines |
| Chemical substances |
| Radiation exposure |
| Aplastic anemia |
| Bone marrow infiltration by tumor cells (leukemias, metastases of solid tumors) |
| Myelofibrosis |
| В12-deficiency anemia |
| Tuberculosis |
| Viral infection (cytomegalovirus, hepatitis viruses, immunodeficiency virus, Epstein-Barr virus) |
| Immunization due to vaccination |
| 1. Increased platelet destruction | Hypersplenism |
| Medicines and chemicals |
| Autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, idiopathic thrombocytopenic purpura) |
| Disseminated intravascular coagulation (DIC) |
| Sepsis |
| Acute respiratory distress syndrome |
| Artificial heart valves |
| 1. Due to impaired platelet distribution | Massive blood transfusions |
| Cardiopulmonary operations |
| Thrombosis and DIC syndrome |

**Groups of medicines that cause thrombocytopenia**

|  |  |
| --- | --- |
| Antibiotics | penicillin, streptomycin, cephalosporins, erythromycin, rifampicin, sulfonamides |
| Nonsteroidal anti-inflammatory drugs | aspirin, indomethacin, butadione |
| Diuretics | furosemide, diacarb, spironolactone, thiazide diuretics |
| Anticonvulsants | carbamazepine, metuxemide, diphenine |
| Psychotropic drugs | diazepam, aminazine, barbiturates |
| Anticoagulants | Heparin |

**Clinical picture:** spontaneous petechiae, small bruises, bleeding from the mucous membranes (nose, gums), in women - heavy and prolonged menstruation. With severe thrombocytopenia - hemorrhage into the sclera or retina, renal hemorrhage, hemorrhage into the brain. Petechiae are more often localized on the anterior surface of the torso, upper and lower extremities, in places where friction and compression of clothing is possible and in places of injection. Large hematomas usually do not occur.

To date, only 10% of patients with thrombocytopenia can perform a laboratory test to identify the cause of platelet depletion, so most cases of thrombocytopenia are classified as a separate disease - idiopathic thrombocytopenic purpura (ITP).

**Pathogenesis of ITP:** immune disorders, when the T-cells contribute to the production of cytokines that are involved in the activation and differentiation of B-lymphocytes into antibody-producing cells (plasma cells). Plasma cells lead to hyperproduction of various antibodies, form circulating immune complexes (CIC), which are deposited on the basement membranes of platelets and cause their damage and destruction.

The incidence of ITP ranges from 7 to 13 cases per 100 000 population. Among patients with ITP women dominate with ratio of 3.9:1, and in reproductive age this ratio increases to 8:1.

The clinical course of idiopathic thrombocytopenic purpura (also called immune thrombocytopenia, ITP) in children and adults differs. In children, as a rule, there is an acute course with a tendency to spontaneous recovery. In adults, almost 90% of the disease cases have a chronic recurrent course.

At laboratory study in peripheral blood the number of plateletes is below 100х109/l. There are possible morphological changes of plateletes (poikilocytosis, anisocytosis), the appearance of fine-grained "blue" platelets, prolongation of bleeding time (according to Duke - up to 15 minutes or more), a positive symptom of the constrictor. Blood clotting time is normal. Prothrombin time, activated partial thromboplastin time, thrombin and fibrinogen also are normal. During investigation of bone marrow the number of megakaryocytes is within normal limits or slightly increased, which helps to differentiate ITP from other conditions accompanied by thrombocytopenia.

Patients with ITP and platelet count less than 20x109/l with bleeding require immediate hospitalization. If the platelet level is above 20x109/l and there is no bleeding, patients are under the supervision of a hematologist on outpatient settings. Treatment is not required for patients whose platelet count is kept at a "safe level" (more than 30x109/l).

First-line drugs are corticosteroids (dexamethasone, prednisolone, methylprednisolone).

**The main medicines for immune thrombocytopenia**

|  |  |  |
| --- | --- | --- |
| Therapy | Dose | Initial response rate and speed of response |
| First-line therapy | | |
| Corticosteroids:  Prednisone  Dexamethasone | 1 mg/kg (range 0.5-2 mg/kg) given until pletelets rise above 30-50×109 /litre  40 mg/kg for 4 days every 2-4 weeks for 1-4 cycles | 70-80% respond within a few weeks,  90% respond within a few weeks |
| Intravenous anti-D | 50-75 mcg/kg | 80% respond within 4-5 days |
| Intravenous Ig | 0.4 g/kg per day for 5 days or  1 g/kg per day for 1-2 days | 80% respond within 2-4  days (occasionally by 24h) |
| Second-line therapy | | |
| Rituximab | 375 mg/m2 IV every week for 4 weeks | 60% respond within median time to response 5.5 weeks |
| TPO receptor agonists:  Romiplostim  Eltrombopag | 1-10 μg/kg SC weekly  25-75 mg/day orally | 80-90% respond within 1-4 weeks,  70-80% respond within 2-3 weeks |
| Splenectomy | - | 80% respond within 3 weeks |

Thrombomass (thromboconcentrate) is prescribed to patients with intracranial hemorrhage. In confirmed by CT intracranial bleeding intravenous immunoglobulin and platelet mass (platelet concentrate) should be prescribed to maintain a platelet count greater than 50x109/l.

Nonspecific drugs are also used to stop bleeding in thrombocytopenia: aminocaproic acid, tranexamin acid.

1. **Questions for self-preparation of the student for a practical lesson:**

1. Definitions and types of hemophilia.

2. Etiological and pathogenesis of hemophilia.

3. The main clinical manifestations of hemophilia.

4. Clinical course of hemophilia.

5. Differential diagnosis of hemophilia.

6. The range of basic laboratory tests for suspected hemophilia.

7. Basic principles of treatment of different types of hemophilia.

8. Clinical picture of idiopathic thrombocytopenic purpura.

9. Changes in laboratory studies in idiopathic thrombocytopenic purpura.

10. Approaches to the treatment of idiopathic thrombocytopenic purpura.

1. **Literature:**

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