**MINISTRY OF HEALTHCARE OF UKRAINE**
**HSEEU "Ukrainian Medical Stomatological Academy"**

**GUIDELINES**
**FOR STUDENTS**
**INDEPENDENT WORK**
**IN THE PRACTICAL CLASSES PREPARING**

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|---|---|
| *Academic discipline* | Internal medicine |
| *Module* | Current practice of internal medicine |
| *Content module* | Management of the patients with main symptoms and syndromes in hematology clinic |
| *Study subject* | **Management of the patients with anemia** |
| *Course* | VI |
| *Faculty* | of foreign students training |

<p style="text-align:center"><u>*The subject of the lesson*</u>**: Anemias**</p>

<u>*Educational goal:*</u>  to develop skills and to acquire experience relevant to management of patients with different types of anemia.

**Professional orientation of students:** Anemia is a prevalent condition with a variety of underlying causes. Once the etiology has been established, many forms of anemia can be easily managed by the family physician. Iron deficiency, the most common form of anemia, may be treated orally or, rarely, parenterally. Vitamin $B_{12}$ deficiency has traditionally been treated with intramuscular injections, although oral and intranasal preparations are also available. The treatment of folate deficiency is straightforward, relying on oral supplements. Folic acid supplementation is also recommended for women of child-bearing age to reduce their risk of neural tube defects. Current research focuses on folate's role in reducing the risk of premature cardiovascular disease.

Finding out the anemia in time prevents the difficult changes of blood system and all organism, diminishes temporal disabled of population. The general physician of polyclinic is responsible for dyspancerisation of the patients with anemia. Anemia is very often met in 20% women of the developed countries and in 50% women of the non-developed countries. More than 50% patients with chronic diseases and tumors. Considerably worsens quality of life and capacity.

### *The student must know:*
1. Aetiology and pathogenesis of Anemias.
2. Clinical symptoms of Anemias.
3. Modern classification of Anemias.
4. Methods of diagnostics of Anemias.
5. Methods of treatment of Anemias.

### <u>*The student must be able:*</u>
1.  To choose the symptoms of Anemias from the history data.
2.  In examination of the patient to choose the symptoms of Anemias.
3.  To make the scheme of investigation for the determination Anemias.
4.  To define the cause and the severity of Anemias.
5.  To assess the haemologic study results.
6.  To determinate the treatment of patients with Anemias depending on the types and degree of the disease. To estimate the efficacy of the therapy.
8. To prescribe the proper treatment for the patient with Anemias.

### <u>*The main problems of the lesson:*</u>
1.  Anemia, definition, aetiology & pathogenesis.
2.  Classification of anemia: pathogenetic classification, morphogenetic classification, international classification.
3.  Clinical manifestations of anemia: anemic syndrome, sideropenic syndrome, neurologic manifestations, gastrointestinal manifestations, cytopenic syndrome, hemolytic syndrome.
4.  Clinical manifestations of iron- deficiency anemia, clinical and laboratory and instrumental signs and treatment of iron- deficiency anemia.
5.  Clinical manifestations of vitamin B12- deficiency anemia, clinical and laboratory and instrumental signs and treatment of folic acid - deficiency anemia.
6.  Clinical manifestations of folic acid deficiency anemia, clinical and laboratory and instrumental signs and treatment of folic acid - deficiency anemia.
7.  Clinical manifestations of aplastic anemia, clinical and laboratory and instrumental signs and

treatment of aplastic anemia.

8. Classification, clinical manifestations of hemolytic anemia, clinical and laboratory and instrumental signs and treatment of hemolytic anemia.

**Contents of the training materials**Evaluation for anemia is one of the most common problems seen in clinical practice. While the evaluation may be straightforward in an otherwise healthy individual with a single cause of anemia, in many cases the cause is not readily apparent and multiple conditions may be contributing.

Anemia is a reduction below normal in the concentration of hemoglobin and/or erythrocytes in the body that results in a reduction of the oxygen-carrying capacity of the blood.

Common signs and symptoms of anemia include fatigue, lethargy, dizziness, shortness of breath, headache, edema, and tachycardia. A standard initial laboratory evaluation for anemia includes a complete blood count (evaluation of the serum hemoglobin and hematocrit concentration, red blood cell count, white blood cell count, platelets), measurement of the red blood cell size and shape.

The goal of anemia therapy is to increase hemoglobin, which will improve red cell oxygen-carrying capacity, alleviate symptoms, and prevent anemia complications. The underlying cause of anemia (e.g., blood loss; iron, folic acid, or B12 deficiency; or chronic disease) must be determined and used to guide therapy.

## Classification of anemia

The classifications of anemia by the size of the red cells, hemoglobin content and peculiarities of cell growth and destruction indicate the likely cause. Etiologic classification helps in management of the anemia.

1. Initial classification by peculiarities of cell growth and destruction
   - Marrow production defects "hypoproliferation" (reticulocyte production index <2)
   - Red cell maturation defects "ineffective erythropoiesis" (reticulocyte production index <2)
   - Decreased red cell survival "blood loss/hemolysis" (reticulocyte production index >2.5)

2. Classification by cell size
   - Normocytic (mean cell volume 80-100 fl)
   - Microcytic (mean cell volume <80 fl)
   - Macrocytic (mean cell volume >100 fl)

3. Classification by hemoglobin content
   - Normochromic (color index 0.8–1.05)
   - Hypochromic (color index <0.8)
   - Hyperchromic (color index >1.05)

4. Classification by etiology and pathogenesis
   - Iron-deficiency anemia
   - Anemia of chronic disease
   - $B_{12}$ and folic acid deficiency anemia
   - Hemolytic anemias
   - Anemia due to acute blood loss
   - Aplastic anemia

**Iron deficiency anemia (IDA)**                                    **ICD-X Code: D 50**

Iron deficiency anemia (IDA) - a pathological condition which is characterized by decrease in the content of hemoglobin owing to the deficiency of iron in the organism as the result of the disorders of its income, assimilation or pathological losses.

WHO criteria (1973) - the lower level of hemoglobin of capillary blood at children younger than 6 years - 110 g/l, older than 6 years - 120 g/l.

**Stages of development of IDA (WHO, 1977)**

- prelatent (exhaustion of tissue iron reserves; blood parameters are within normal limits; clinical manifestations are absent).

- latent (deficiency of iron in tissues and reduction of its transport fund; blood parameters are within normal limits; clinical manifestations are caused by trophic disorders which develop owing to

decrease in activity of iron-containing enzymes and are manifested by sideropenic syndrome - epithelial changes of skin, nails, hair, mucous membranes, distortion of the taste, scent, disorders of intestinal absorption and asteno-autonomic functions, decrease in local immunity).

- iron deficiency anemia (more expressed exhaustion of tissue reserves of iron and mechanisms of compensation of its deficiency; changes in blood analysis depending on the severity of the process; clinical manifestations in the form of a sideropeni syndrome and general anemic symptoms which are caused by an anemic hypoxia - tachycardia, a muffled heart tones, systolic murmur, dyspnea on exertion, pallor of skin and mucous membranes, arterial hypotonia, increase of asteno-neurotic disorders).

Severety of an anemic hypoxia depends not only upon hemoglobin level, but also upon the speed of development of anemia and upon compensatory opportunities of an organism. In severe cases the syndrome of metabolic intoxication in the form of decreased memory, subfebrile fever, headache, fatigue, hepatoloenal syndrome, and etc. develops.

Deficiency of iron causes decreased immunity, a delay of psychomotor and physical development of children.

Degrees of severity of IDA by the level of hemoglobin:

light - Hb of 110-91 g/l

moderate - Hb of 90-71 g/l

severe - Hb 70-51 g/l

very severe – Hb less than 50 g/l

**Basic principles of treatment**

- elimination of ethyological factors

- balanced nutrition (for infants – breastfeeding, adapted formulas enriched with iron, timely introduction of solids, meat, especially veal, subptoducts, buckwheat and oat grain, fruits and vegetables, cheese; reduction of phytates, phosphates, tannin, calcium intake which worsen iron absorption).

- pathogenetic treatment by iron preparations mainly in the form of drops, syrups, tablets.

Indications to the parenteral administration of iron preparations: at syndrome of disordered intestinal absorption and after a profound resection of the small intestines, not specific ulcerative colitis, severe chronic enterocolitis andd dysbiosis, intolerance of oral iron preparations, severe degree of anemia.

- preventive measures to prevent its recurrence

Correction of iron deficiency at light anemia is carried out mainly by balanced diet, sufficient stay of the child in the open air. Iron preparations should not be administered at the level of hemoglobin of 100 g/l and above.

Control of efficiency of the prescribed dose is performed by the definition of the increase of the reticulocyte level at 10-14 days of treatment. Iron therapy is carried out until the level of hemoglobin normalizes with further reduction of a dose. Treatment duration - 6 month, for preterms - 2 years for replenishment of iron reserves in the organism.

Parenteral iron preparations have to be used only by special indications, owing to the risk of development of local and system adverse reactions.

Contraindications to iron-therapy: aplastic and haemolytic anemia, hemochromatoses, hemosiderosis, sideroachrestic anemia, talassemiya, other types of anemias which aren't caused by the deficiency of iron in the organism.

*Hemotransfusions* are carried out only on vital indicators when there is acute massive blood loss. Packet red cells or washed erythrocytes should be used.

**Megaloblastic anemias (MA).**

The group of anemias with inefficient erithropoesis that is characterized by disorder of maturing and change of morphology of erythrocytes.

In the blood swab - anysocytosis, poikilocytosis, hypersegmentation of neutrophils, primary or secondary deficiencies of folic acid and cyanocobalamine (B12).

**Folic deficiency anemia (FDA). ICD-X D52 code**

More often is observed at preterms. FDA develops at children who eat exclusively goat milk. Causes of FDA: congenital disorders of adsorption and exchange of folates, acquired malabsorbtion, increased requirements in folates at severe preterm infants, at haemolytic anemias and others.

In 2-3 weeks after folic deficiency its level in serum decreases, in 3 months – megaloblastic changes in marrow and peripheral blood, in urine increase of forminin-glutamine acid (a sign of folate and B12 deficiency at MA).

Clinical manifestations: deeply prematurely born children in case of folate deficiency at the age of 3-6 months have MA, weakness, anorexia, glossitis, chronic diarrhea, increased bleeding and bacterial infections.

Treatment: folic acid is administered orally in a dose –5 mg/day, duration – not less than 3 weeks. In the absence of effect at MA it is necessary to think of deficiency of vitamin B12, at malabsorption – parenteral administration.

### B12 - deficiency anemia (B12 – DA). ICD-X D51 code

Can be a consequence of deficiency of vitamin in food (strict vegetarianism), hereditary disorders (congenital deficiencies of sorption – Kastl's internal factor, transport and metabolism of vitamin B12), acquired defects of absorption, etc.

Clinical manifestations: V12-DA signs (pallor, icterous sclera and skin, dryness of skin, fragility of hair and nails, weakness, decreased appetite with special disgust for meat, etc.), glossitis with an atrophy of papillas (the varnished language), pain in the tongue with aphtous changes, nervous system disorders from owing to dorsolateral degenerate changes in the spinal cord (ataxy, paresteziya, hyporeflection, clonuses, pathological reflexes, feeling of wadded feet, hallucinations, dream, signs of heart failure, the diarrhea, hepatolienal syndrome).

In peripheral blood - MA (erythrocytes with Zholli's bodies, Cabot`s rings, megalocytes, megaloblasts), neutropenia, thrombocytopenia.

In urine - increase of metilmalone acid (a differintial-diagnostic sign of FDA).

Treatment: parenteral administration of vitamin B12 in a dose of 200-500 mcg every day, at neurologic manifestations a dose increase to 1 mg. At hereditary forms of V12-DA after resolution of acute clinical manifestations it is recommended to administer cyanocobalamine 1 mg into 3 months.

### Treatment general

The main principle is to initiate treatment of mild to moderate anemia only when a specific diagnosis is made. Rarely, in acute setting, anemia may be so severe that red cell transfusions are required before a specific diagnosis is available. Whether the anemia is of acute or gradual onset, the selection of the appropriate treatment is determined by the documented cause of the anemia. Often, the cause of the anemia is multifactorial (for example, a combination of anemia of chronic disease with iron-deficiency anemia). In every circumstance, it is important to evaluate the patient's iron status fully before and during the treatment of any anemia. Red cell transfusions can be used for treatment of any severe anemia irrespective to cause. The indication for red cell transfusion for anemia is decreasing of hemoglobin level less than 70 g/l.

**Test evaluation and situational tasks.**

Choose the correct answer/statement:

1. The most common cause of aplastic anemia is:

     A. Idiopathic

     B. Chloramphenicol

     C. Phenylbutazone

     D. Petroleum products

     E. Prednisolone

2. Treatment of choice for aplastic anemia is:

A. Methotrexat

B. ampicillini

C. chloramphenicol

D. Bone marrow transplantation

E. plasmaphoresis

3. Most sensitive and specific test for diagnosis of iron deficiency is:

A. Serum ferritin levels

B. Serum iron levels

C. Serum transferrin receptor population

D. Transferrin saturation

E. Hb, Ht

4. Laboratory finding in autoimmune haemolytic anemia is

A. Positive Coombe's test

B. Serum iron decreased

C. Ferritin decreased

D. Hypoalbulinemia

E. Macrocytic anemia

5. Reduced serum iron and ferritin level is seen in:

A. Sideroblastic anemia

B. Thalassemia

C. Anemia of chronic disease

D. Iron deficiency anemia

E. Hemolytic anemia

6. Following features may be present in patients of paroxysmal nocturnal haemoglobinuria except

A. Raised lactate dehydrogenase

B. Reticulocytjsis

C. High leucocyte alkaline phosphatase

D. Hemosiderinuria

E. Decreased RBC

7. Mucosal transfer of iron in GIT by

A. Transferrin

B. Apoferritin

C. Apotransferrin

D. Ferritin

E. Haptoglobin

8. Pernicious anemia is due to:

A. Iron deficiency

B. Chronic liver disease

C. Bleeding

D. Atrophic gastritis

E. Hemolysis

9. Spherocytosis is best diagnosed by:

A. Splenic puncture

B. BM aspiration

C. Plasma

D. Peripheral blood smear

E. Phenotyping

**10.** Coomb's positive hemolytic anaemia is seen in:

A. Lymphprolipherative diseases

B. Thrombotic thrombocytopenic purpura

C. Scleroderma

D. Polyarteritis nodosa

E. Idiopathic thrombocytopenic purpura

**Real-life situations to be solved:**

1. Patient M, 52 year old, complains of weakness, dyspnea, numbness in extremities, subfebrile temperature and diarrhea. Objective: pale skin she has lemon-yellow hue, legs edema. Sternum is painful on percussion. Pulse – 100 per min, BP - 130/80 mmHg. Heart sounds weakened, systolic murmur at the apex. Smooth tongue. Liver + 2 cm, spleen + 1 cm. RBC - $2,0 \times 10^{12}$/l, Hb – 60g/l, Leucocytes - $2,5 \times 10^{9}$/l, Eosinophils - 1%, band neutrophils -5%, segmented neutrophils - 57%, lymphocytes - 37%, ESR – 62 mm/h, megaloblasts, Howell-Jolly bodies, hyperchromasia. What is the most likely diagnosis?

2. Patient O., 35 year-old, mother of many children, complains of tiredness, palpitation, fragile nails, losing of hair. RBC- $2,3 \times 10^{12}$/L, Hb -65g/L, CI - 0,7, reticulocytes - 0,5 %, Pletelets – 400 $\times 10^{9}$/L, WBC – $6,6 \times 10^{9}$/L, band neutrophils--2%, Segmented neutrophils – 56 %, basophils - 2%, lymphocytes - 29%, m - 10%, anisocytosis, poikilocytosis, ESR – 5 mm/h. What is the most likely diagnosis?

**Recommended literature:**

*A. Main:*

1. Davidson's Principles and practice of medicine (21$^{st}$ revised ed.) / by Colledge N.R., Walker B.R., and Ralston S.H., eds. – Churchill Livingstone, 2010. – 1376 p.

2. Harrison's Principles of Internal Medicine, 19th Edition / by Longo D.L., Kasper D.L., Jameson J.L. et al. (eds.). – McGraw-Hill Professional, 2015. – 4012 p.

3. The Merck Manual of Diagnosis and Therapy (nineteenth Edition) / Robert Berkow, Andrew J. Fletcher and others. – published by Merck Research Laboratories, 2011.

*B. Additional:*

1. H.Loffler, J.Rastetter, T.Haferlach. 6th edition. Atlas of clinical hematology. Springer Berlin Heidelberg New York, 2006, - 429 p.

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