

Ministry of Healthcare of Ukraine

Poltava State Medical University

«**Approved**»

at the meeting of the
Chair of Internal medicine №1
Head of the Chair

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(signature)

(PhD, MD., Assoc.Prof.)

**Methodical instruction
for the students self-training
during preparing for practical classes (seminars)**

<i>Subject</i>	Internal medicine
<i>Module №1</i>	FUNDAMENTALS OF INTERNAL MEDICINE
<i>Topic</i>	Anemias
<i>Course</i>	IV
<i>Faculty</i>	Medical

The subject of the lesson: Anemias

Educational goal: 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 B₁₂ 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. 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.

The student must know:

1. Etiology 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.

The student must be able:

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 complete blood count (CBC) 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.

The main problems of the lesson:

1. Anemia, definition, etiology & 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 straight forward 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, 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

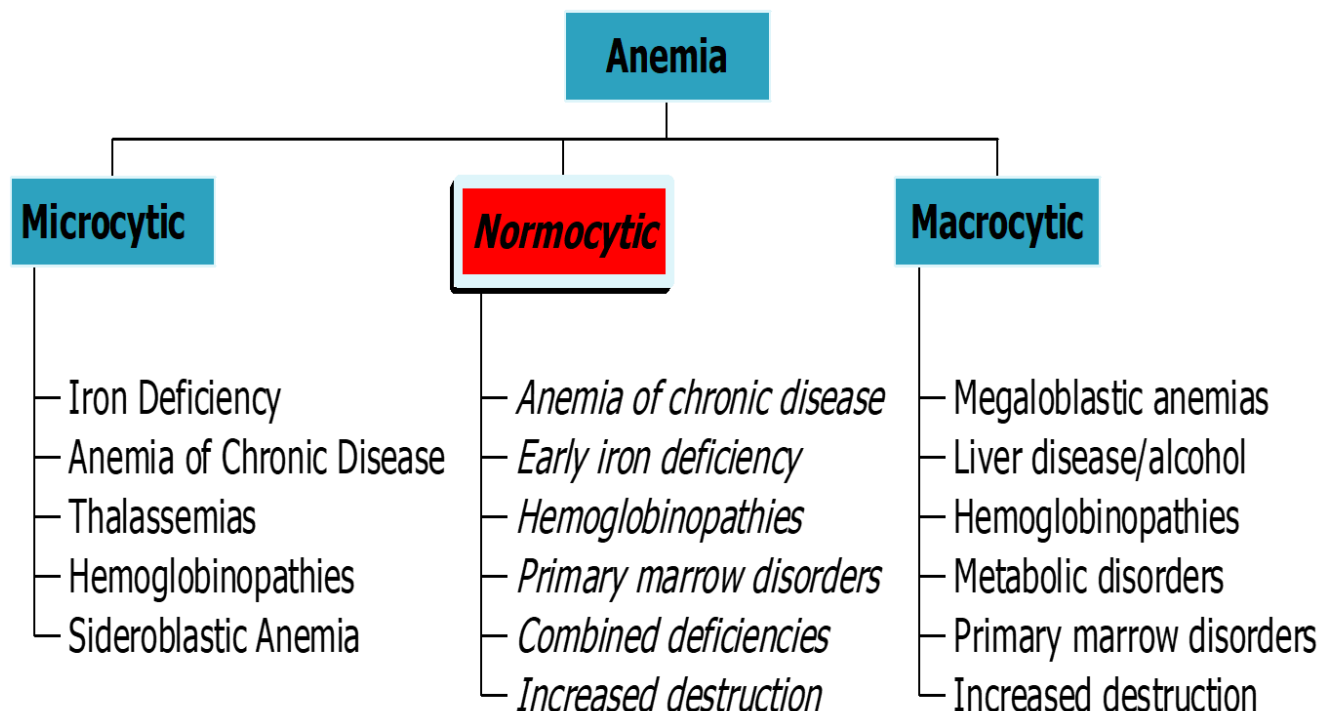
The classifications of anemia by the size of the red cells, hemoglobin content and peculiarities of cell growth and destruction indicate the likely cause. Etiologic classification helps in management of the anemia.

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 corpuscular volume (MCV) 80-100 fl)
 - Microcytic (MCV <80 fl)
 - Macrocytic (MCV >100 fl)
3. Classification by hemoglobin content
 - Normochromic (color index 0.8–1.05 or mean corpuscular hemoglobin MCH 26-33 pg)

- Hypochromic (color index <0.8 or MCH <26 pg)
- Hyperchromic (color index >1.05 or MCH >33 pg)

4. Classification by etiology and pathogenesis

- Iron-deficiency anemia
- Anemia of chronic disease
- B₁₂ and folic acid deficiency anemia
- Hemolytic anemias
- Anemia due to acute blood loss
- Aplastic anemia



Iron deficiency anemia (IDA)

Iron deficiency anemia is 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.

Criteria for IDA diagnosis: in CBC – hypochromic and microcytic anemia; decreased **ferritin** level in the blood serum.

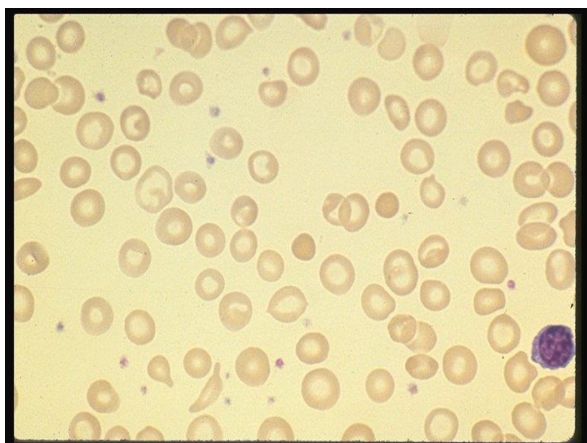


Fig. on the left. Blood smear of patient with hypochromic and microcytic anemia.

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).

Severity 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 less than 120 (f) or 130 (m) – 100 g/l

moderate - Hb of 99 – 80 g/l

severe - Hb less than 80 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, subproducts, 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 can't be carried out only by balanced diet.

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 months, for preterms - 2 years for replenishment of iron reserves in the organism. Iron therapy continues until **ferritin** level normalizes.

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, talassemia, 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. Packed red cells or washed erythrocytes should be used.

Megaloblastic anemias (MA)

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

In the blood smear – anisocytosis, poikilocytosis, hypersegmentation of neutrophils, primary or secondary deficiencies of folic acid and cyanocobalamin (B12).

Folic deficiency anemia (FDA)

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 malabsorption, 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 formiminoglutamine 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)

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: B12-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 atrophy of papillae (the varnished language), pain in the tongue with atrophic changes, nervous system disorders from owing to dorsolateral degenerate changes in the spinal cord (ataxia, paresthesia, hyporeflexion, clonus, pathological reflexes, feeling of wadded feet, hallucinations, dream, signs of heart failure, the diarrhea, hepatolienal syndrome).

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

In urine - increase of methylmalonic acid (a differential-diagnostic sign of FDA).

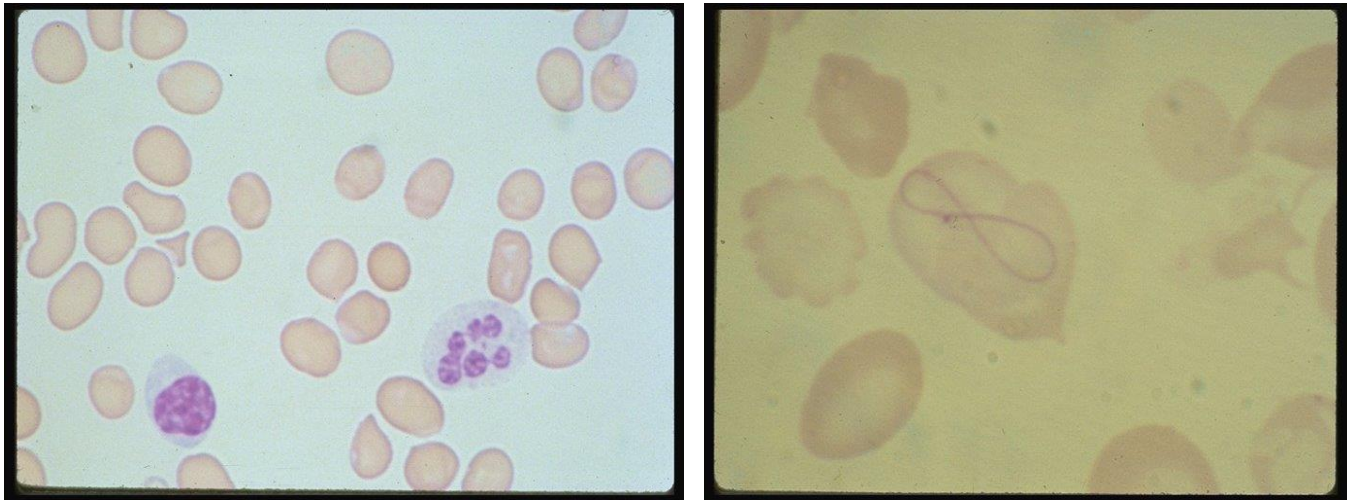


Fig. on the left. Blood smear of patient with cobalamin deficiency.

Fig. on the right. Cabot ring.

Treatment: parenteral administration of vitamin B₁₂ in a dose of 500 mcg every day, at neurologic manifestations a dose increase to 1 mg. After resolution of acute clinical manifestations it is recommended to administer cyanocobalamine 1 mg intramuscle every month.

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.

Aplastic anemia

Aplastic anemia is pancytopenia with bone marrow hypocellularity. Bone marrow failure results from severe damage to the hematopoietic cell compartment. In aplastic anemia, replacement of the bone marrow *by fat* is apparent in the morphology of the biopsy specimen and magnetic resonance imaging (MRI) of the spine.

Aplastic anemia can appear abruptly or insidiously. Bleeding is the most common early symptom; a complaint of days to weeks of easy bruising, oozing from the gums, nose bleeds, heavy menstrual flow, and sometimes petechiae will have been noticed. With thrombocytopenia, massive hemorrhage is unusual, but small amounts of bleeding in the central nervous system can result in catastrophic intracranial or retinal hemorrhage. Symptoms of anemia are also frequent, including lassitude, weakness, shortness of breath, and a pounding sensation in the ears.

Treatment. Severe acquired aplastic anemia can be cured by replacement of the absent hematopoietic cells (and the immune system) by stem cell transplant. This is the best therapy for the younger patient with a fully histocompatible sibling donor. If the donor can't be found the suppression of the immune system is used to allow recovery of the patient's residual bone marrow function. Antithymocyte globulin (ATG) in combination with cyclosporine shows the best results of primary treatment. Horse ATG is administered as intravenous infusions during 5 days at a daily dose 15 mg/kg. Cyclosporine is administered orally at an initial high dose 10-15 mg/kg/day, with subsequent adjustment to 5 mg/kg/day during 10-12 months.

Hemolytic anemia

Classification of Hemolytic Anemias

Hereditary	1. Abnormalities of RBC interior a. Enzyme defects: G-6-PD def, PK def b. Hemoglobinopathies 2. RBC membrane abnormalities a. Hereditary spherocytosis etc. b. PNH
Acquired	c. Spur cell anemia 3. Extrinsic factors a. Hypersplenism b. Antibody: immune hemolysis c. Mechanical trauma: MAHA d. Infections, toxins, etc

Ref : Harrison's

Acquired autoimmune hemolytic anemia (AIHA)

Once a red cell is coated by an autoantibody, it will be destroyed by one or more mechanisms. The onset of AIHA is often abrupt and can be dramatic. The hemoglobin level can drop, within days, to as low as 4 g/dL; the massive red cell removal will produce jaundice; and sometimes the spleen is enlarged. The diagnostic test for AIHA is the direct antiglobulin test developed in 1945 by R. R. A. Coombs and known since by this name. The beauty of this test is that it detects directly the pathogenetic mediator of the disease, i.e., the presence of antibody on the red cells themselves. When the test is positive, it clinches the diagnosis; when it is negative, the diagnosis is unlikely.

Treatment. Medical treatment should be started immediately with prednisone (1 mg/kg per day), which will produce a remission promptly in at least one-half of patients. Rituximab (anti-CD20) was regarded as second-line treatment, but it is increasingly likely that a relatively low dose (100 mg/wk × 4) of rituximab together with prednisone will become a first-line standard. For patients who do relapse or are refractory to medical treatment, one may have to consider splenectomy.

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. Hypoalbuminemia
 - 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. Lymphoproliferative 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:

I. Main:

1. Internal Medicine: in 2 books. Book 1. Diseases of the Cardiovascular and Respiratory Systems: textbook / N.M. Seredyuk, I.P. Vakaliuk, R.I. Yatsyshyn et al. Київ, Медицина., 2019. - 664 + 48 кольор. вкл.).
2. Internal medicine: Part 1 (cardiology, rheumatology, haematology): textbook for English-speaking students of higher medical schools / edited by Professor M.A. Stanislavchuk and Professor V.A. Serkova. - Vinnytsia: Nova Knyha, 2019. - 392 p.

3. Медицина за Девідсоном: принципи і практика / Навчальний посібник: пер. 23-го англ. вид.: у 3 т. Т.3 С. Ралстона, Я. Пенмана, М. Стрекена, Р. Гобсона; К.: ВСВ «Медицина», 2021. – 642 с.
4. CURRENT Medical Diagnosis and Treatment 2012, Fifty-First Edition (LANGE CURRENT Series) by Stephen McPhee, Maxine Papadakis and Michael W. Rabow (Paperback - Sep 12, 2011)/
5. Побічна дія ліків – Side Effects of Medications: навчальний посібник у 2 т. / за заг. ред. В.М. Бобирьова, М.М. Потяженка. – Вінниця:
6. Cardiovascular diseases. Classification, standards of diagnosis and treatment / Edited by Academician Kovalenko V.M., Prof. Lutaia M.I., Prof. Sirenko Yu.M., Prof. Sychova O.S. – Kyiv. – 2020.
7. Perederii V.H., Tkach S.M. Principles of internal medicine. – Vol.2 / Textbook for students of higher educational institutions. – Vinnytsia: Nova knyha. – 2018.
8. Internal diseases. The textbook based on the principles of evidentiary medicine, 2018.

II. Additional literature:

1. Recommendations of the Association of Cardiologists of Ukraine for the diagnosis and treatment of chronic heart failure / Voronkov L.H. – moderator, working group of the Ukrainian Association of Heart Failure Specialists. – 2017.
2. Respiratory diseases / Ghanei M. - In Tech, 2012. - 242 p.
3. Clinical respiratory medicine / Spiro S., Silvestri G., Agusti A. - Saunders, 2012. - 1000 p.
4. Principles and practice of interventional pulmonology / Ernst A., Herth F. - Springer, 2012. - 757 p.
5. Clinical respiratory medicine / Spiro S., Silvestri G., Agusti A. - Saunders, 2012. - 1000 p.
6. Petrov Y. The chief symptoms and syndromes in patients with cardiovascular pathology : The practical handbook for medical students / Ye.

Petrov, Yu. Goldenberg, N. Chekalina; UMSA. - Poltava : TexcepBic, 2010. - 143

7. Gastroenterology and Hepatology Board Review: Pearls of Wisdom, Third Edition (Pearls of Wisdom Medicine) by John K. DiBaise (May 11, 2012)
8. Clinical Pulmonology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Oct 30, 2011) - Kindle eBook
9. Clinical Nephrology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2011) - Kindle eBook
10. Clinical Nephrology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2011) - Kindle eBook
11. Hematology: Clinical Principles and Applications, 4e by Bernadette F. Rodak MS MLS (Feb 18, 2017)
12. Rheumatology, 2-Volume Set: EXPERT CONSULT - ENHANCED ONLINE FEATURES AND PRINT, 5e by Marc C. Hochberg MD MPH, Alan J. Silman MD, Josef S. Smolen MD and Michael E. Weinblatt MD (Oct 19, 2019)
13. Endocrine Pathology: Differential Diagnosis and Molecular Advances by Ricardo V. Lloyd (Nov 5, 2018)
14. Clinical Endocrinology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2017) - Kindle eBook
15. Williams Textbook of Endocrinology: Expert Consult-Online and Print, 12e by Shlomo Melmed, Kenneth S. Polonsky MD, P. Reed MD Larsen and Henry M. Kronenberg MD (May 27, 2016)
16. Electrocardiography, 3e with Student CD (Booth, Electrocardiography for Health Care Personnel) by Kathryn A. Booth (Jan 27, 2017)
17. Echocardiography Review Guide: Companion to the Textbook of Clinical Echocardiography: Expert Consult: Online and Print, 2e (Expert Consult Title: Online + Print) by Catherine M. Otto (Mar 7, 2017).

Composed by

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