Ministry of Healthcare of Ukraine

Poltava State Medical University

«Approved»
at the meeting of the
Chair of Internal medicine №1
Head of the Chair
_____ G.S. Maslova
(signature) (PhD, MD., Assoc.Prof.)

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

Subject	**Internal medicine**
Module №1	**FUNDAMENTALS OF INTERNAL MEDICINE**
Topic	**Acute leukemias**
Course	**IV**
Faculty	**Medical**

***The subject of the lesson*: Acute Leukaemias**

Educational goal:

The student must know:

1. Etiology and pathogenesis of Acute Leukaemias.
2. Clinical symptoms of Acute Leukaemias.
3. Modern classification of Acute Leukaemias.
4. Methods of diagnostics of Acute Leukaemias.
5. Methods of treatment of Acute Leukaemias.

The student must be able:

1. To choose the symptoms of Acute Leukaemias from the history data.
2. In examination of the patient to choose the symptoms of Acute Leukaemias.
3. To make the scheme of investigation for the determination Acute Leukaemias.
4. To define the cause and the severity of Acute Leukaemias.
5. To assess the haemologic study results.
6. To determinate the treatment of patients with Acute Leukaemias 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 Acute Leukaemias.

The main problems of the lesson:

1. Pathogenesis of Acute Leukaemias.
2. Clinical symptoms of Acute Leukaemias.
3. Modern classification of Acute Leukaemias.
4. Methods of diagnostics of Acute Leukaemias.
5. Differential diagnosis of Myeloid and Lymphoid Acute Leukemias.
1. Treatment of Acute Leukaemias.

The aim: The students must be able to diagnose Acute Leukaemias, determine the types, severity, and prescribe the proper treatment.

Topicality: The incidence of leukaemia of all types in the population is approximately 10/100 000 per annum, of which just under half are acute leukaemia. Males are affected more frequently than females, the ratio being about 3:2 in acute leukaemia, 2:1 in chronic lymphocytic leukaemia and 1.3:1 in chronic myeloid leukaemia.

CONTENTS OF THE TRAINING MATERIALSLeukaemias are malignant disorders of the haematopoietic stem cell compartment, characteristically associated with increased numbers of white cells in the bone marrow and/or peripheral blood.

The cause of the leukaemia is unknown in the majority of patients. Factors, which are associated with the development of leukaemia: Ionising radiation, Cytotoxic drugs, Exposure to benzene in industry, Genetic, Immunological.

Leukemias were originally termed acute or chronic based on life expectancy but now are classified according to cellular maturity.

Acute myeloid leukemia (AML) is a neoplastic disease characterized by infiltration of the blood, bone marrow, and other tissues by proliferative, clonal undifferentiated cells of the hematopoietic system. The main diagnostic criteria is the presence blast cells more than 20% in the bone marrow. To differentiate myeloblasts immunophenotype and cytochemistry are used.

Classification. French-American-British (FAB) classification:

FAB classification of acute myeloblastic leukaemia

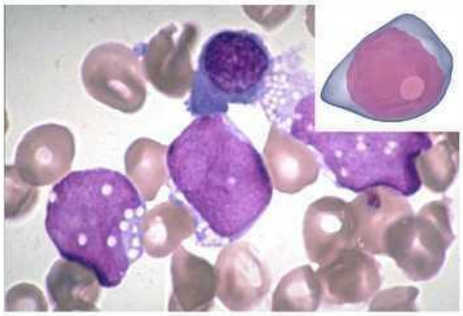


Photo courtesy of: Acute myeloid leukemia pathophysiology, 2012

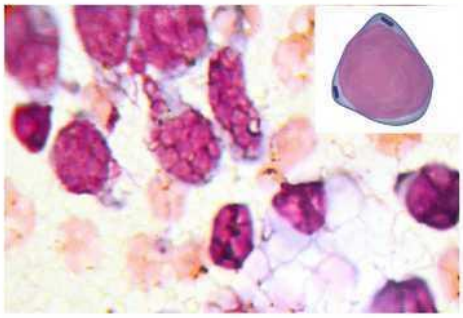
M0 Acute myeloblastic leukaemia with minimal differentiation

Morphology:

Can resemble LLA-L2 blasts. Medium-sized blasts, rounded nucleus, fine chromatin, basophilic non-granular cytoplasm, prominent nucleoli.

Immunophenotype

- CD13 +
- CD33 +
- CD11b +
- CD11c +
- CD14 +
- CD15 +



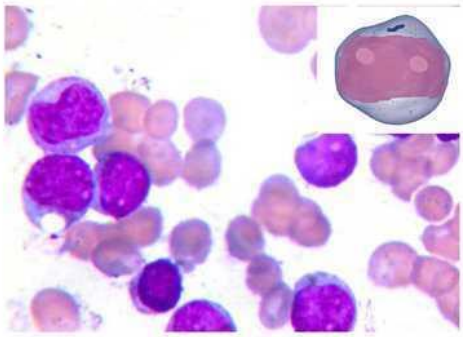
M1 Acute myeloblastic leukaemia without maturation

Morphology:

Medium-sized blasts with high nucleo:cytoplasm (n:c) ratio, rounded nuclei with immature, dispersed chromatin with one or more prominent nucleoli. Blasts can show fine azurophilic granulation or isolated Auer rods in the cytoplasm in 5% to 10% of cases

Immunophenotype

- MPO +
- CD13 +
- CD33 +
- CD117+
- CD34 +/-



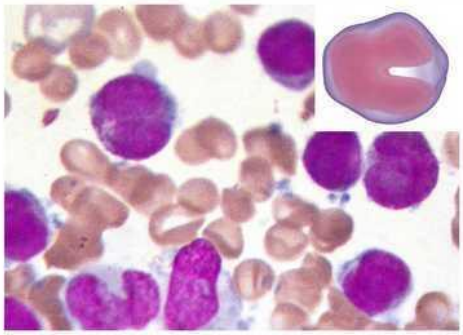
M2 Acute myeloblastic leukaemia with maturation

Morphology:

Small to medium-sized blasts with high nucleo: cytoplasm (n:c) ratio and rounded nuclei sometimes located in a corner of the cytoplasm. The nucleus shows dispersed, immature chromatin with one or more nucleoli. The cytoplasm is basophilic and can contain traces of primary azurophilic granulation or isolated Auer rods.

Immunophenotype

- MPO +
- CD34 +/-
- CD13 +
- CD15 +
- HLA-DR +/-
- Sudan black +
- CD117 +/-



M3 Promyelocytic leukaemia

Morphology:

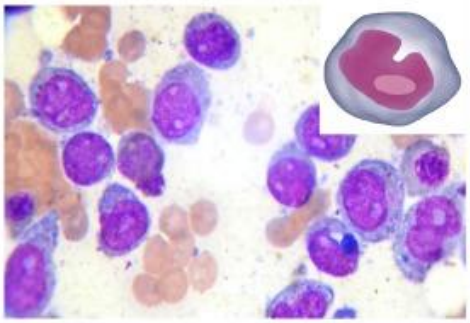
Abundant, intensely azurophilic granulation. The nucleus is usually monocytic in appearance (reniform) and is either irregular or bilobed with a deep cleft. Scarcely basophilic cytoplasm due to the proliferation of azurophilic granulation. Some atypical promyelocytes also contain elongated or splinter-shaped crystalline cytoplasmic inclusions specific to this type of leukaemia.These usually form clumps, but differ from Auer rods in that they show a tubular substructure on electronic microscopy.

Immunophenotype

- CD13 +
- CD33 +
- HLA-DR -
- CD34 -

Rev Med Hosp Gen Mex. 2016;79:107–13

FAB classification of acute myeloblastic leukaemia



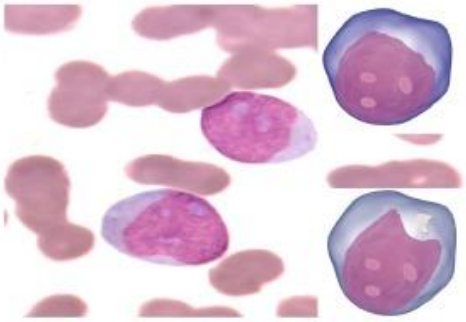
M4 Acute myelomonocytic leukaemia

Morphology:

Large blasts, moderate nucleo:cytoplasm (n:c) ratio and variable basophilia. The nucleus may be rounded, kidney-shaped or irregular. Nucleoli are usually prominent.

Immunophenotype

- CD13 +
- CD15 +
- CD33 +
- CD11b +
- CD11c +
- CD14 +
- CD64 +
- CD4 +

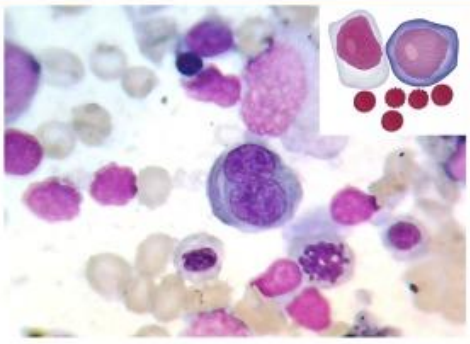


M5 Acute monocytic leukaemia

M5a acute monoblastic leukaemia:
Large blasts with rounded nucleus and dispersed, immature chromatin (1-3 nucleoli) and moderately large and intensely basophilic cytoplasm. The cytoplasm may show some Auer rods and/or prolongations and granulations.
M5b acute monocytic leukaemia
Promonocytes have a rounded or kidney-shaped nucleus with a less basophilic cytoplasm that is more highly granulated than monoblasts and contains some vacuoles. A findings of erythrophagocytosis together with monocytic blasts suggests a t(8;16) translocation.

Immunophenotype

- CD14 +
- CD68 +
- CD4 +
- CD11c +
- HLA-DR +
- CD64 +

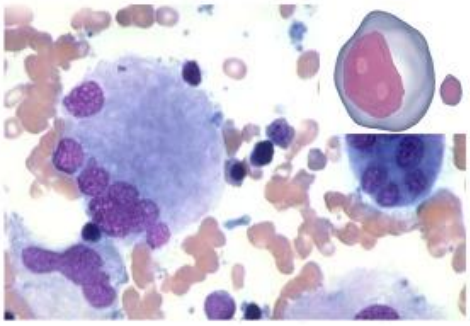


M6 Acute erythroid leukaemia

M6a erythroid leukaemia with proliferation of mixed blasts:
Over 50% erythroid precursors and around 30% myeloblasts. Morphology of erythrocytes in peripheral blood is greatly changed, with schistocytes, "pincered" or mushroom-shaped cells, and spiculated echinocyte and acanthocyte cells.
M6b pure erythroid leukaemia:
Erythroids make up 80% of bone marrow cells, with less than 3% myeloid cells. Erythrocytes in peripheral blood consist of macrocytes, basophilic stippling, Howell-Jolly bodies or Cabot rings.

Immunophenotype

- CD13 +
- CD33 +
- CD15 +
- Glycophorin A +
- Glycophorin C +



M7 Acute megakaryocytic leukaemia

Morphology:

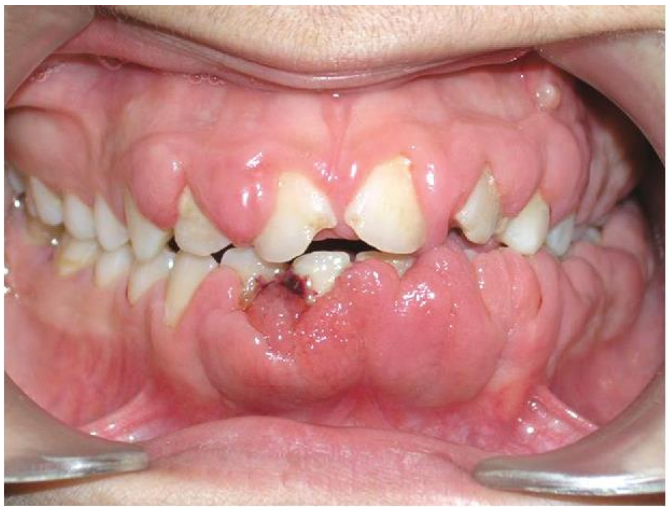
Highly immature, polymorphic blasts. The nucleus is eccentric with dispersed, reticulated chromatin and 1-3 prominent nucleoli. The cytoplasm is non-granular, basophilic, and very similar in appearance to platelets, with pseudopods or granulations. Micromegakaryocytes and fragments of megakarioblasts are seen in peripheral blood (giant platelets, some highly degranulated).

Immunophenotype

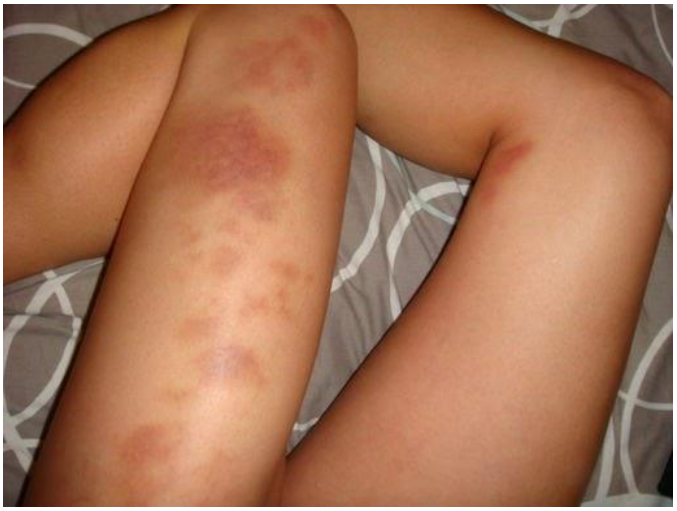
- CD41 +
- CD61 +
- CD42 +
- CD13 +
- CD33 +
- CD34 +

Physical Findings. Fever, splenomegaly, hepatomegaly, lymphadenopathy, sternal tenderness, and evidence of infection and hemorrhage are often found at diagnosis. Significant gastrointestinal bleeding, intrapulmonary hemorrhage, or intracranial hemorrhage occurs most often in APL. Bleeding associated with coagulopathy may also occur in monocytic AML and with extreme degrees of leukocytosis or thrombocytopenia in other morphologic subtypes. Retinal hemorrhages

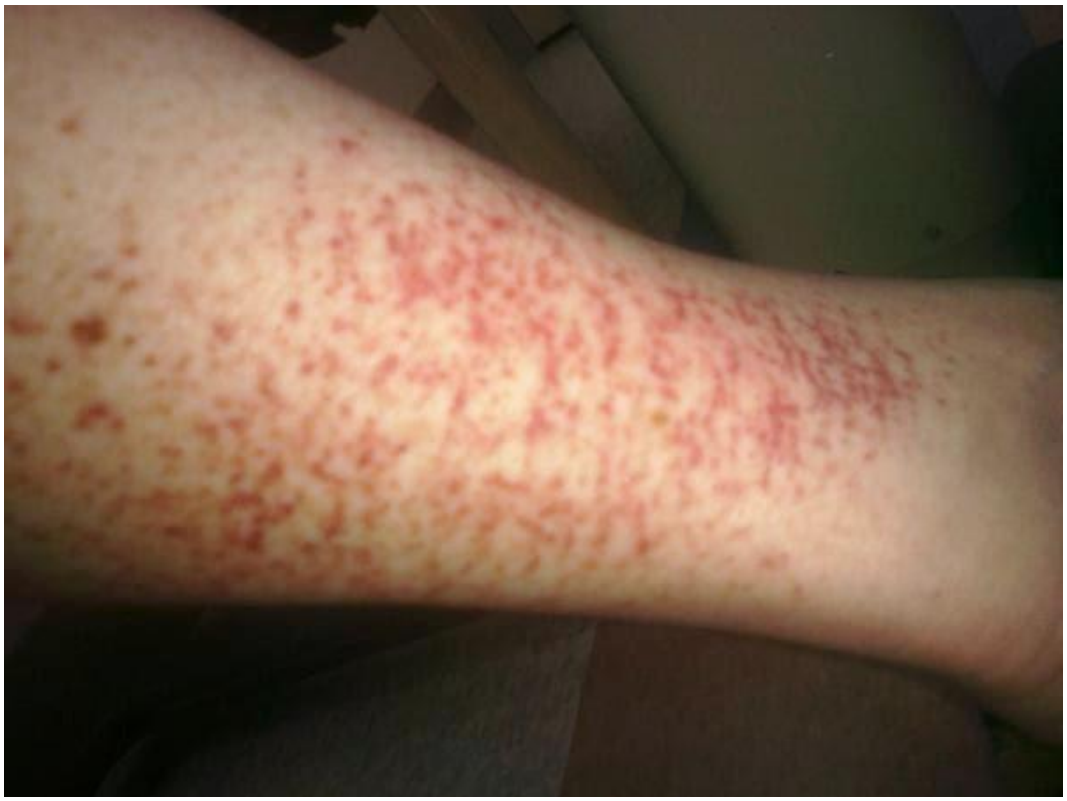
are detected in 15% of patients. Infiltration of the gingivae, skin, soft tissues, or meninges with leukemic blasts at diagnosis is characteristic of the monocytic subtypes and those with 11q23 chromosomal abnormalities.



Gingivitis in patient with AML M5.



Unexplained bruising



Hemorrhagic syndrome: petechias

Hematologic Findings Anemia is usually present at diagnosis and can be severe. The degree varies considerably, irrespective of other hematologic findings, splenomegaly, or duration of symptoms. The anemia is usually normocytic normochromic. Decreased erythropoiesis often results in a reduced reticulocyte count, and red blood cell (RBC) survival is decreased by accelerated destruction.

The median presenting leukocyte count is about 15,000/μL. Between 25 and 40% of patients have counts <5000/μL, and 20% have counts >100,000/μL. Fewer than 5% have no detectable leukemic cells in the blood. The morphology of the malignant cell varies in different subsets. In AML, the cytoplasm often contains primary (nonspecific) granules, and the nucleus shows fine, lacy chromatin with one or more nucleoli characteristic of immature cells. Abnormal rod-shaped granules called Auer rods are not uniformly present, but when they are, myeloid lineage is virtually certain. Poor neutrophil function may be noted functionally by impaired phagocytosis and migration and morphologically by abnormal lobulation and deficient granulation.

Platelet counts <100,000/μL are found at diagnosis in ~75% of patients, and about 25% have counts <25,000/μL. Both morphologic and functional platelet abnormalities can be observed, including large and bizarre shapes with abnormal granulation and inability of platelets to aggregate or adhere normally to one another.

Treatment of the newly diagnosed patient with AML is usually divided into two phases,The initial goal is to induce complete remissin.

Specific therapy (chemotherapy) – is generally aggressive, has a number of side effects, and may not be appropriate for the very elderly or patients with other serious disorders. The most commonly used remission induction regimens consist of combination chemotherapy with cytarabine and an anthracycline (e.g., daunorubicin, idarubicin, mitoxantrone). **"7+3" regimen**: cytarabine standard dose (100–200 mg/m^2) administered as a continuous intravenous infusion for 7 days and daunorubicin (60–90mg/m^2) or idarubicin (12 mg/m^2) intravenously on days 1, 2, and 3.

Anaemia is treated with packed RBC transfusions (red cell concentrate infusions) to maintain Hb above 100 g/l. Bleeding – transfusions of platelets are administered.

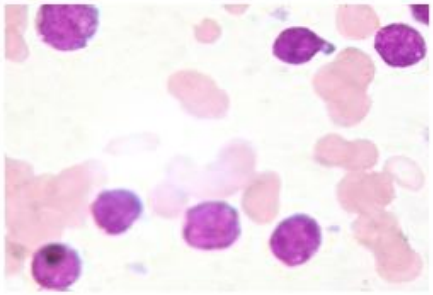
Infection – fever (> 38°C) lasting over 1 hour in a neutropenic patient (absolute neutrophil count < 1.0×10^9/l) indicates febrile neutropenia. Parenteral broad-spectrum antibiotic therapy is essential.

Psychological support.

Acute lymphoid leukemias (ALLs) are predominantly cancers of children and young adults. The L3 or Burkitt's leukemia occurring in children in developing countries seems to be associated with infection by the Epstein-Barr virus (EBV) in infancy. However, the explanation for the etiology of more common subtypes of ALL is much less certain. Childhood ALL occurs more often in higher socioeconomic subgroups. Children with trisomy 21 (Down's syndrome) have an increased risk for childhood ALL. The main diagnostic criteria is the presence blast cells more than 20% in the bone marrow. To differentiate lymphoblasts immunophenotype and cytochemistry are used.

Classification. French-American-British (FAB) classification (see the next page):

FAB classification of lymphoblastic leukaemia



L1 Lymphoblastic leukaemia with homogeneous structure

Frequency:

Between 25% and 30% of cases in adults, and 85% of cases in children.

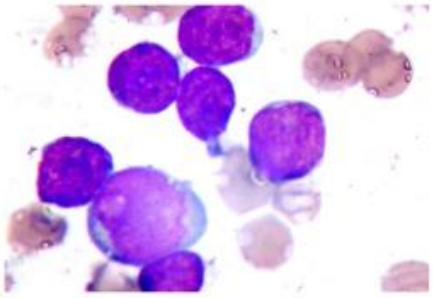
Morphology:

Blasts are homogeneous, nucleus is regular, chromatin is homogeneous, small or no nucleoli, scanty cytoplasm, and mild to moderate basophilia.

Immunophenotype

B:	T:
• CD19	•CD3
•CD22	•CD7
•CD79a	•CD5
•CD10	•CD2
•CD20	•CD4

•Cytoplasmic or superficial immunoglobulin



L2 Lymphoblastic leukaemia with varied structure

Frequency:

Accounts for 70% of cases in adults, and 14% in children.

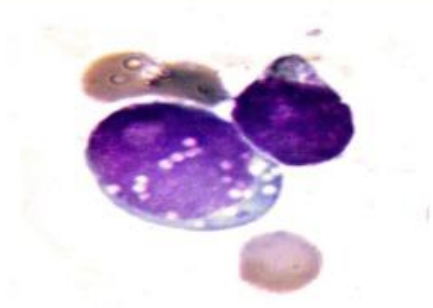
Morphology:

Nucleus is irregular, heterogeneous chromatin structure, large nucleoli.

Immunophenotype

B:	T:
•CD19	•CD3
•CD22	•CD7
•CD79a	•CD5
•CD10	•CD2
•CD20	•CD4

•Cytoplasmic or superficial immunoglobulin



L3 Burkitt's leukaemia

Frequency:

Rare subtype, accounting for less than 1% to 2% of cases.

Morphology:

Large blasts, prominent nucleoli, stippled homogeneous chromatin structure, abundant cytoplasm, abundant cytoplasmic vacuolation (bubble type) covering the nucleus.

Immunophenotype

B:	T:
•CD19	•CD3
•CD22	•CD7
•CD79a	•CD5
•CD10	•CD2
•CD20	•CD4

•Cytoplasmic or superficial immunoglobulin

Clinically cannot be differentiated from AML.

Treatment also consists of induction and postremission management (remission consolidation and maintenance). Hoelzer-based protocols are used. Induction of remission: prednisolone 60 mg/m^2 orally during 28 days, vincristine 2 mg/day IV on the 1, 8, 15, 22 days, daunorubicine 45 mg/m^2/day IV infusion on the 1, 8, 15, 22 days, L-asparaginase 5000 U/m^2/day IV infusion every other day since 15th till 28th days. Additionally, for CNS (central nervous system) injury prophylaxis methotrexate 15 mg intrathecal on the 1st day.

Tests for the determining of basis knowledge

1. The most common symptoms of acute leukemias are:

A. fever, malaise, weight loss
B. petechiae, easy bruising, epistaxis,
C. pallor, fatigue, tachycardia
D. all of above

2. Symptoms of bone marrow failure in patients with acute leukemias include all, except:

A. bone pain
B. multiple ecchymoses
C. fatigue
D. fever

3. “7+3” chemotherapy regimen for treatment of AML consists of:

A. cytarabine + idarubicine
B. imatinib
C. vincristine + prednisolone
D. cyanocobalamin + folic acid

Recommended literature for students:

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.: у3 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. Побічнадіяліків – SideEffectsofMedications: навчальнийпосібнику 2 т. / зазаг.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 fur 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 **Lymanets T.V.**