MINISTRY OF HEALTH CARE OF UKRAINE
ODESA NATIONAL MEDICAL UNIVERSITY

Faculty: International
Department of Pediatrics

APPROVED
Vice-rector for scientific and pedagogical work
_____ Eduard BURIACHKIVSKYI
"__01_" ____09_____ 2024

METHODICAL RECOMMENDATION
FOR THE LECTURE
FROM EDUCATIONAL COMPONENT

Faculty international, course 5

Educational component - "PEDIATRICS"

Topic. "Diseases of the blood system in children"

Approved
Meeting of the Department of Pediatrics
Odesa National Medical University
Protocol No. 1 "29"_08_2024 y.
Head of the department _____ (Mykola ARYAYEV)

2024

Перезатверджено:
Засідання кафедри педіатрії
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Завідувач кафедри_____Микола АРЯЄВ

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(indicate surnames, scientific degrees, scientific titles and positions of developers; everyone who teaches the specified academic discipline must be among the developers)
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Note. In the case of publication of methodological developments as a self-published work, the academic council of the faculty provides a recommendation for publication in the presence of two reviews, one of which is external — from a reviewer of another institution of higher education.

Lecture №4

Topic: “Anemia in children”

Relevance of the topic: The World Health Organization (WHO) reports that 39.8% of children aged 6-59 months suffered from anaemia in 2019, representing an estimated 269 million children worldwide. Defined as low levels of haemoglobin in the blood, anaemia can have serious health impacts, including poor cognitive and motor development. The WHO also reports that 40% of children aged 6-59 months, 37% of pregnant women and 30% of women aged 15-49 years worldwide have anaemia [1]

Purpose:

1. To become familiar with the principles of organizing hematological care for children in Ukraine.
2. To determine the features of providing medical care to children with anemic syndrome.
3. To study the features of the pathogenesis of hemorrhagic syndrome in children.
4. To study the features of the pathogenesis of deficiency and hemolytic anemia in children.
5. To master the knowledge and features of managing children with anemia at the level of family medicine.
5. To study the algorithms for providing preventive and medical care to children with hemorrhagic syndrome and anemia of various origins.
6. To understand and master the meaning and role of bioethical issues in the treatment of blood diseases and hemorrhagic conditions in children.

Basic concepts: Definition, epidemiology, clinical signs of anemia and hemorrhagic diseases in children. Causes and risk factors of anemia and hemorrhagic diseases. Diagnosis of iron deficiency anemia. Prevention of iron deficiency anemia. Cognitive issues with iron deficiency anemia. Thalassemia. Normocytic anemia. Macrocytic anemia. A bleeding disorder. Clinical assays for evaluating primary hemostasis. Von Willebrand disease. Platelet function disorder. Hemophilia. Acquired bleeding disorders. Medical management of hemorrhagic diseases in children.

Plan and organizational structure of the lecture:

1. Background, definition of anemia in children.
2. Epidemiology of anemia.
3. Features of the clinical picture, diagnosis and treatment of iron deficiency anemia.
4. Features of the clinical picture, diagnosis and treatment of thalassemia.
5. Normocytic and macrocytic anemia.

Content of lecture material (lecture text)

1. Background, definition of anemia and hemorrhagic diseases in children.

Background. Worldwide, anemia affects up to one-half of children younger than five years. Anemia is defined as a hemoglobin level that is two standard deviations below the mean for age. After children reach 12 years of age, the hemoglobin norm can be further divided into gender-specific ranges.

Definition. Anemia, defined as a hemoglobin level two standard deviations below the mean for age, is prevalent in infants and children worldwide. The evaluation of a child with anemia should begin with a thorough history and risk assessment. Characterizing the anemia as microcytic, normocytic, or macrocytic based on the mean corpuscular volume will aid in the workup and management. Microcytic anemia due to iron deficiency is the most common type of anemia in children.

The American Academy of Pediatrics and the World Health Organization recommend routine screening for anemia at 12 months of age; the U.S. Preventive Services Task Force found insufficient evidence to assess the benefits vs. harms of screening. Iron deficiency anemia, which can be associated with cognitive issues, is prevented and treated with iron supplements or increased intake of dietary iron. The U.S. Preventive Services Task Force found insufficient evidence to recommend screening or treating pregnant women for iron deficiency anemia to improve maternal or neonatal outcomes. Delayed cord clamping can improve iron status in infancy, especially for at-risk populations, such as those who are preterm or small for gestational age. Normocytic anemia may be caused by congenital membranopathies, hemoglobinopathies, enzymopathies, metabolic defects, and immune-mediated destruction. An initial reticulocyte count is needed to determine bone marrow function. Macrocytic anemia, which is uncommon in children, warrants subsequent evaluation for vitamin B_{12} and folate deficiencies, hypothyroidism, hepatic disease, and bone marrow disorders.

2. Epidemiology of anemia.

Epidemiology. The World Health Organization (WHO) reports that 39.8% of children aged 6-59 months suffered from anaemia in 2019, representing an estimated 269 million children worldwide. Defined as low levels of haemoglobin in the blood, anaemia can have serious health impacts, including poor cognitive and motor development. The WHO also reports that 40% of children aged 6-59 months, 37% of pregnant women and 30% of women aged 15-49 years worldwide have anaemia. It is recommended to read the WHO information for more information.

3. Features of the clinical picture, diagnosis and treatment

of iron deficiency anemia.

Clinical signs of anemia and hemorrhagic diseases in children. The American Academy of Pediatrics (AAP) and the World Health Organization recommend universal screening for anemia at one year of age. However, the U.S. Preventive Services Task Force (USPSTF) found insufficient evidence to assess the benefits vs. harms of screening. The AAP also recommends selective screening at any age in children with risk factors for anemia, such as feeding problems, poor growth, and inadequate dietary iron intake. When screening is positive for anemia, follow-up is essential. One study showed that 25% of patients who screened positive for anemia had no documented follow-up testing.

Initial Evaluation. Most infants and children with mild anemia do not exhibit overt clinical signs and symptoms. Initial evaluation should include a thorough history, such as questions to determine prematurity, low birth weight, diet, chronic diseases, family history of anemia, and ethnic background. A complete blood count is the most common initial diagnostic test used to evaluate for anemia, and it allows for differentiating microcytic, normocytic, and macrocytic anemia based on the mean corpuscular volume. Figure 1 is an algorithm for the evaluation of children with low hemoglobin levels.

Evaluation of Low Hemoglobin Levels in Children

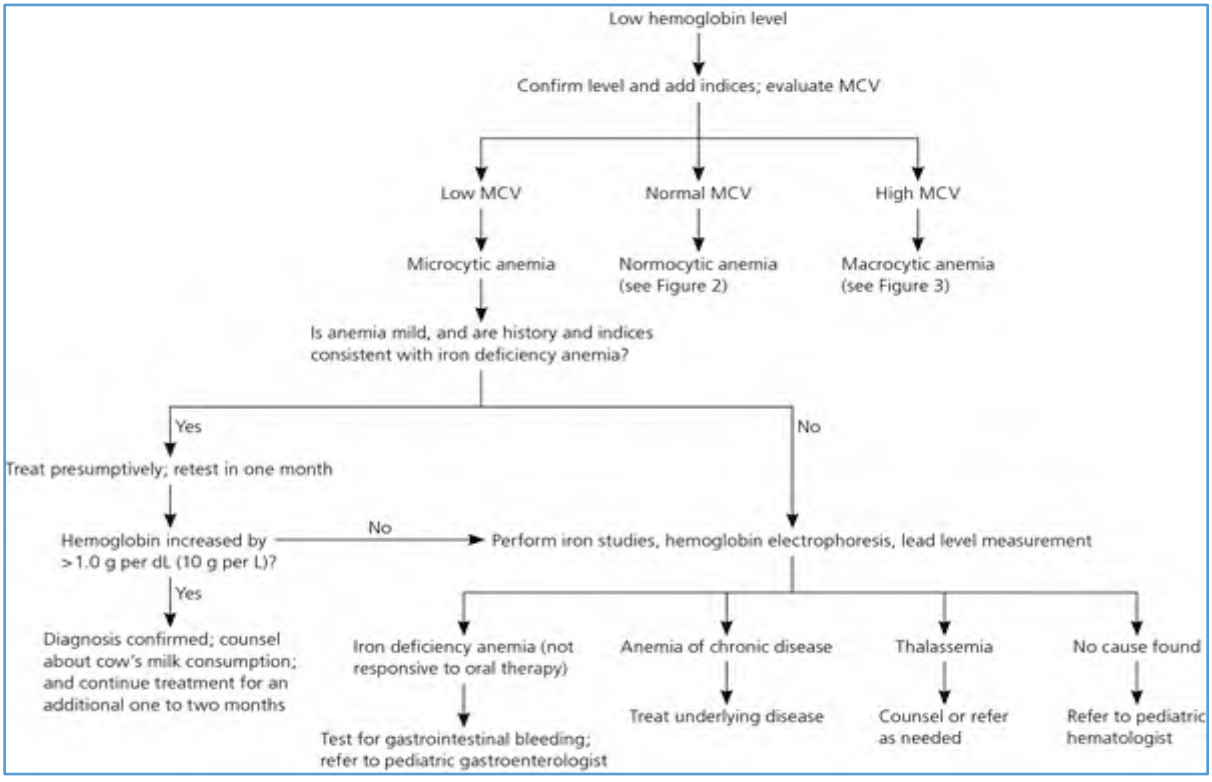

Figure 1. Algorithm for the evaluation of low hemoglobin levels in children. (MCV = mean corpuscular volume.) Adapted with permission from Janus J, Moerschel SK. Evaluation of anemia in children.

Microcytic anemia. Diagnosis of iron deficiency anemia. Microcytic anemia due to iron deficiency is the most common type of anemia in children. The U.S. prevalence of iron deficiency anemia in children one to five years of age is estimated to be 1% to 2%. A child with microcytic anemia and a history of poor dietary iron intake should receive a trial of iron supplementation and dietary counseling. Iron deficiency anemia is likely if the hemoglobin level increases by more than 1.0 g per dL (10 g per L) after one month of presumptive treatment.

Although iron deficiency anemia is usually microcytic, some patients may have normocytic red blood cells. Further testing may also be necessary if suspected iron deficiency anemia does not respond to treatment. Ferritin measurement is the most sensitive test for diagnosing iron deficiency anemia. Ferritin is a good reflection of total iron storage and is also the first laboratory index to decline with iron deficiency.3 It may be less accurate in children with infectious or inflammatory conditions because ferritin is also an acute phase reactant.

An elevated red blood cell distribution width index can also be a sensitive test to differentiate iron deficiency anemia from other types of microcytic anemia if ferritin and iron studies are not available.

Prevention of iron deficiency anemia. During Pregnancy and Delivery. Up to 42% of pregnant women worldwide will have anemia, with a prevalence of 6% in North America. The iron requirement increases with each trimester and should be supported by higher maternal iron intake. Between 60% and 80% of the iron storage in a newborn occurs during the third trimester, but it is unclear whether treatment of maternal anemia prevents anemia in newborns and infants. The USPSTF found insufficient evidence to recommend screening for or treating iron deficiency anemia in pregnant women to improve maternal or neonatal outcomes. Although two Cochrane reviews found that maternal hemoglobin levels improve with antepartum iron supplementation, studies have not demonstrated statistically significant benefits in clinical outcomes (e.g., low birth weight, preterm birth, infection, postpartum hemorrhage) for mothers or newborns.

Delayed umbilical cord clamping (approximately 120 to 180 seconds after delivery) is associated with improved iron status (ferritin levels) at two to six months of age. This benefit may be especially important in those vulnerable to iron deficiency, such as infants who were premature or small for gestational age. A Cochrane review looking at the effects of the timing of cord clamping during preterm births showed a reduction of blood transfusions when clamping was delayed (24% vs. 36%). The effects of delayed cord clamping do not appear to persist beyond the first 12 months.

Iron Supplementation During Infancy. Iron is the most common single-nutrient deficiency. Preterm infants (born at less than 37 weeks' gestation) who are exclusively breastfed should receive 2 mg per kg per day of elemental iron supplementation from one to 12 months of age,2 except for those who have had multiple blood transfusions. In healthy full-term infants, iron storage from in utero is adequate for the first four to six months of life. The AAP recommends that full-term, exclusively breastfed infant’s start 1 mg per kg per day of elemental iron supplementation at four months of age until appropriate iron-containing foods are introduced. Formula-fed infants often receive adequate amounts of iron (average formula contains 10 to 12 mg per L of iron) and thus rarely require further supplementation.

Ideally, the estimated 7-mg daily iron requirement for children one to three years of age should be met through consumption of iron-rich foods. Consumption of large quantities of non–iron-fortified cow's milk increases the risk of iron deficiency. Although iron supplementation may achieve more significant improvements in hemoglobin concentration, children are more likely to tolerate iron-fortified foods. If achieving daily iron supplementation is difficult, intermittent iron supplementation still improves hemoglobin concentration and reduces the risk of iron deficiency.

Cognitive issues with iron deficiency anemia. Iron is important for the neurologic development of infants and children. Iron is required for proper myelinization of neurons, neurogenesis, and differentiation of brain cells that can affect sensory systems, learning, memory, and behavior. Iron is also a cofactor for enzymes that synthesize neurotransmitters.

A landmark study of Costa Rican children concluded that iron deficiency anemia increases the risk of long-lasting developmental disadvantages. However, whether iron supplementation can affect psychomotor development or cognitive function in children is unclear. A Cochrane review concluded that there is no evidence that iron supplementation improves psychomotor or cognitive development in young children with iron deficiency anemia after 30 days of treatment. Furthermore, a systematic review showed that iron supplementation in children who were iron deficient but nonanemic did not positively influence developmental scores at one to five years of age. Thus, screening for iron deficiency in nonanemic infants is not recommended. A recent systematic review for the USPSTF found no studies showing an association between iron supplementation and clinical outcomes in a population relevant to the United States.

4. Features of the clinical picture, diagnosis and treatment of thalassemia.

Thalassemia, a hemoglobinopathy with α-globin or β-globin production defect, should be considered in a child with microcytic anemia if the history or laboratory studies are inconsistent with iron deficiency. α-Thalassemia occurs most often in persons of African and Southeast Asian descent, and β-thalassemia is most common in persons of Mediterranean, African, and Southeast Asian descent. Because of the presence of hemoglobin F at birth, newborns with thalassemia are likely to be asymptomatic until hemoglobin A becomes predominant at six months of age. The Mentzer index (mean corpuscular volume/red blood cell count) uses the complete blood count to differentiate thalassemia from iron deficiency anemia. A Mentzer index of less than 13 suggests thalassemia, and an index of more than 13 suggests iron deficiency.

Thalassemia can be confirmed using hemoglobin electrophoresis. Patients with one or two α-gene deletions (silent carrier or trait) may be asymptomatic with normal hemoglobin electrophoresis, whereas patients with three α-gene deletions (hemoglobin H disease) will have moderate to severe anemia. The presence of four α-gene deletions (hemoglobin Bart's or α-thalassemia major) is usually incompatible with neonatal survival. Infants and children with β-thalassemia trait or β-thalassemia minor may have increased hemoglobin A2 and hemoglobin F on electrophoresis, with asymptomatic, mild anemia. Those with β-thalassemia intermedia or major usually have moderate to severe anemia complications, including hypersplenism, endocrinopathies, cardiac complications, and hypercoagulopathy due to iron overload from repeated transfusions.

5. Normocytic and macrocytic anemia.

Normocytic Anemia. Iron deficiency anemia and acute blood loss are the most common causes of normocytic anemia in infants and children. Evaluation of normocytic anemia (Figure 2) starts with a history, reticulocyte count, and peripheral blood smear.5 A high reticulocyte count indicates increased red blood cell turnover. A high reticulocyte count along with laboratory markers of hemolysis (i.e., increased bilirubin, increased lactate dehydrogenase, and decreased haptoglobin) may help confirm hemolytic anemia. Hemolytic anemia has many causes, including congenital membranopathies, hemoglobinopathies, enzymopathies, metabolic defects, and immune-mediated destruction. Other testing, such as an osmotic fragility test for hereditary spherocytosis and a glucose-6-phosphate dehydrogenase assay to check for a deficiency, may also be useful.

Evaluation of Normocytic Anemia in Children

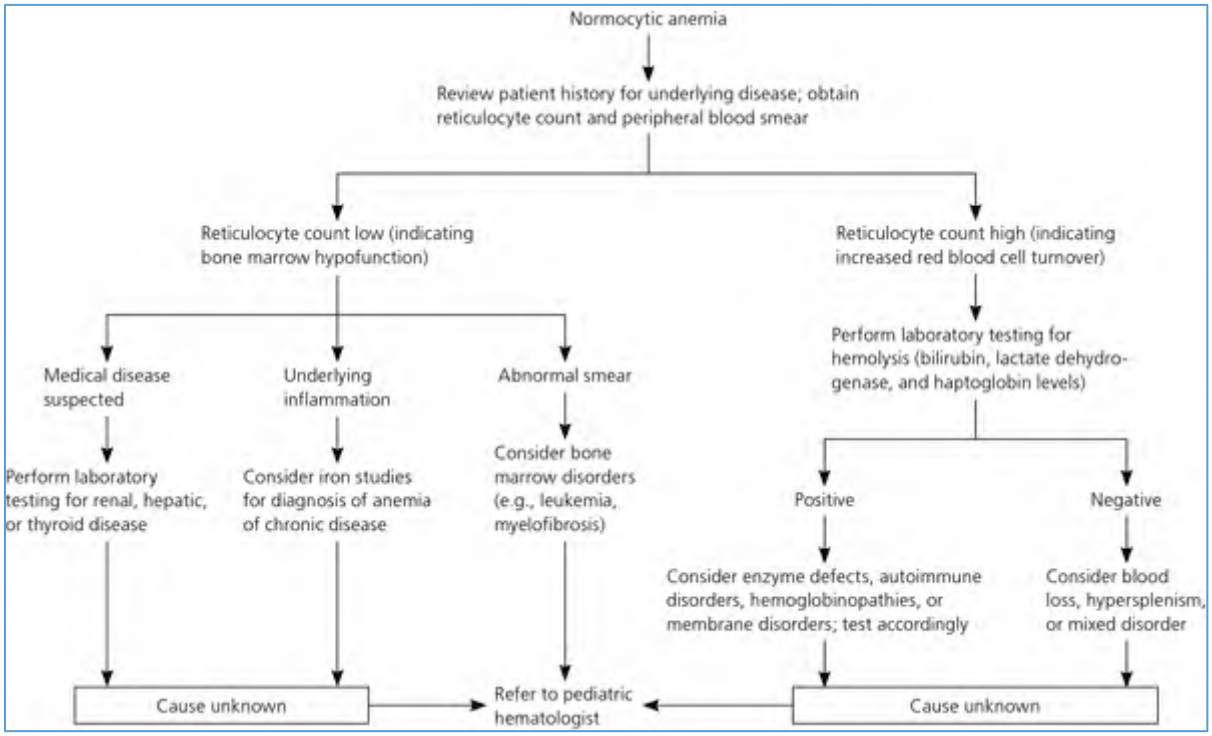

Figure 2. Algorithm for the evaluation of normocytic anemia in children. Adapted with permission from Janus J, Moerschel SK. Evaluation of anemia in children.

Sickle cell disease, caused by a genetic defect in the β-globin, is a hemoglobinopathy that results in normocytic anemia. In the United States, it is typically diagnosed through newborn screening. A review of the management of sickle cell anemia was recently published in American Family Physician. A low reticulocyte count with normocytic anemia in infants and children suggests impaired bone marrow function. This can be due to anemia of chronic inflammation; acquired red blood cell aplasias; and bone marrow disorders, such as leukemia. Acquired aplasias can have an infectious cause, such as parvovirus B19 or transient erythroblastopenia of childhood. Transient erythroblastopenia of childhood usually resolves spontaneously within four to eight weeks with no recurrence or subsequent hematologic disorders at 15 years of follow-up. If bone marrow disorders

are suspected, peripheral blood smear and bone marrow aspiration are indicated with a referral to a pediatric hematologist.

Macrocytic Anemia. Macrocytic anemia refers to macrocytosis (mean corpuscular volume (MCV) greater than 100 fL) in the setting of anemia (hemoglobin less than 12 g/dL or hematocrit (Hct) less than 36% in nonpregnant females, hemoglobin less than 11 g/dL in pregnant females, or hemoglobin less than 13 g/dL or Hct less than 41% in males). It is divided into two forms, megaloblastic (hypersegmented neutrophils) and non-megaloblastic. The megaloblastic form is due to impaired DNA synthesis from folate and/or vitamin B12 deficiencies, while the non-megaloblastic moiety occurs from multiple mechanisms.

The evaluation of macrocytic anemia in children (Figure 3) begins with examination of a peripheral blood smear for hypersegmented neutrophils, which indicate megaloblastic anemia. If megaloblastic anemia is shown, folate and vitamin B_{12} measurements are indicated. Low vitamin B_{12} levels may be nutrition/absorption related or congenital and have neurologic consequences, ranging from growth retardation to seizure disorders. Clinicians should have a low threshold to refer these patients to a pediatric hematologist. Nonmegaloblastic causes of macrocytic anemia in children include hemolysis, hemorrhage, bone marrow disorders, hypothyroidism, and hepatic disease.

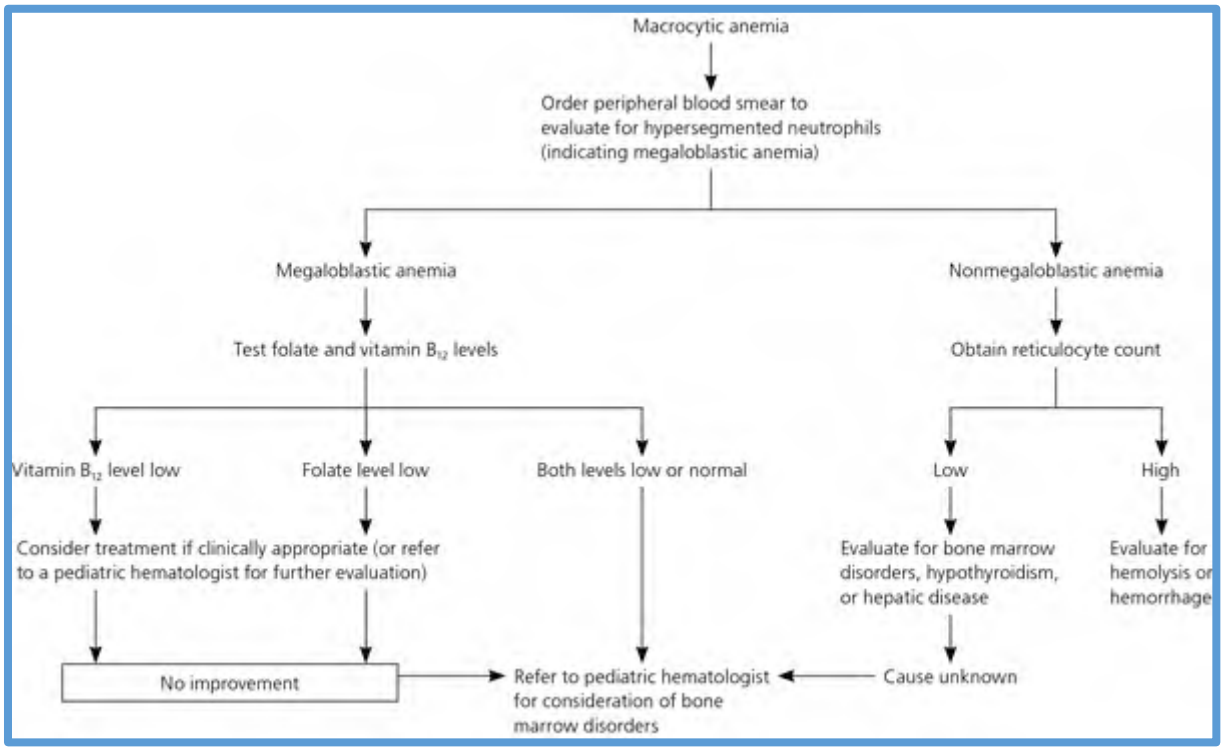

Figure 3. Evaluation of Macrocytic Anemia in Children

Epidemiology. Macrocytosis affects 2% to 4% of the population, 60% of whom have anemia. Mild macrocytic anemia (MCV 100 fL to 110 fL) is more likely to be caused by benign conditions compared to marked macrocytic anemia (MCV more than 110 fL), the latter of which is due to primary bone marrow disease or megaloblastic anemia from folate or vitamin B12 deficiencies.

Pathophysiology. Folate and vitamin B12 are necessary for RBC nucleic acid synthesis. Without DNA or RNA, erythropoiesis is ineffective with nuclear/cytoplasmic asynchrony, resulting in larger erythrogenic precursors with abnormal nuclei (ex. hypersegmentation) but normal cytoplasms. Anemia occurring in the presence of macrocytosis and hypersegmented neutrophils is known as megaloblastic anemia. The absence of hypersegmented neutrophils characterizes non-megaloblastic anemia. This occurs from mechanisms discussed earlier: abnormalities involving the RBC membrane, excess erythrocytic precursors, increased cell volume, or RBC toxicity.

Symptoms of macrocytic anemia

The symptoms of macrocytic anemia can depend on the underlying cause. For example, those macrocytic anemia caused by a vitamin B12 deficiency:

- uncontrollable muscle movements
- vision problems
- pain or tingling sensations
- confusion
- forgetfulness or memory loss
- slower thinking
- mood changes
- unexplained weight loss
- diarrhea
- changes in smell or taste
- glossitis, which refers to a painful, smooth, red tongue

Macrocytic anemia is only one type of anemia. All anemia types have similar symptoms, so a doctor uses blood tests to diagnose a person's specific anemia. However, different types of anemia also have unique symptoms, so sometimes, a doctor may be able to identify the type based on symptoms alone.

Differential diagnosis:

- Folate deficiency anemia
- Anemia due to liver disease
- Hypothyroidism
- Myelodysplastic syndrome
- Alcoholism

Treating macrocytic anemia

When a person shows signs of macrocytic anemia, a doctor orders several blood tests to find the underlying cause. They may also ask questions about a person's diet, lifestyle, and other symptoms. In most cases, oral folic acid taken at 1–5 milligrams (mg) daily resolves a folic acid deficiency. Alternatively, a doctor may recommend vitamin injections. Injecting vitamins ensures the body can absorb them even if an underlying condition, such as celiac disease, prevents vitamin absorption.

Eating more foods containing vitamin B12 may improve symptoms if a person is deficient in this vitamin because of their diet.
Other treatment options include:

- changing medications when a drug interferes with vitamin absorption
- taking medication for certain autoimmune or liver diseases
- taking medication for thyroid disorders
- making lifestyle changes, such as avoiding alcohol
- having blood transfusions or bone marrow transplants for bone marrow disorders

Evaluation of children with macrocytosis. Macrocytosis is a significant symptom in the diagnosis of bone marrow diseases and acute leukemia in childhood. Although, given the present conditions of our country, vitamin B12 deficiency is the first suspect in patients with cytopenia and macrocytosis, yet haematological malignancies, bone marrow deficiencies (congenital or acquired), myelodysplasia, and myeloproliferative diseases should be borne in mind especially in the individuals with Down syndrome, as well.
Prognosis. With early identification and treatment of underlying cause, the prognosis for macrocytic anemia is excellent. Specialist referral is rarely needed unless anemia is resistant to therapy or there is evidence of underlying myelodysplasia or leukemia.

8. Materials on the activation of higher education applicants during the lecture: questions, situational tasks, etc. (if necessary).

9.General material and educational and methodological support of the lecture: computer equipment, multimedia presentation, mannequins.

10. Questions for self-control

1. Concepts: anemia, hemorrhagic syndrome.
2. Classification of anemias.
3. Causes and risk factors of iron deficiency anemia.
4. Methods for assessing iron content in the body.
6. Principles of medical tactics for managing children with anemia.
7. Emergency care for hemorrhagic conditions in children.
8. Prevention of deficiency anemia in children.
9. Genetic counseling and bioethics issues in blood diseases in children.

11. Basic literature:

1. Nelson Textbook of Pediatrics, 2-Volume Set, 22nd Edition, 2024. Robert M. Kliegman, Joseph W. St. Geme III, Nathan J. Blum, et al.

2. Nelson Textbook of Pediatrics / R. M. Kliegman [et al.]; ed. R. E. Behrman. - 21th ed. - Edinburgh [etc.]: Elsevier, 2020. - Vol. 1. – LXXV.Nelson textbook of pediatrics, 2 volume set. Edition: 21st, 2019. PDF format. http://pediacalls.com/e-books/nelson-textbook-of-pediatrics-21st-edition/
3. Nelson Textbook of Pediatrics. Expert Consult Premium Edition. Enhanced Online Features and Print 19th Edition ISBN-13: 978-1437707557 https://www.amazon.com/s?i=stripbooks&rh=p_27%3ARobert+M.+Kliegman+MD&s=relevancerank&text=Robert+M.+Kliegman+MD&ref=dp_byline_sr_book_1
4. "Nelson textbook of Pediatrics, 2 volume set, 21th edition, 2019. Part XI, Chapter 97: https://www.us.elsevierhealth.com/nelson-textbook-of-pediatrics-2-volume-set-9780323529501.html

12. Additional literature

1. 2. Anaemia in women and children. WHO Global Anaemia estimates, 2021 Edition
2. Global anaemia estimates in women of reproductive age, by pregnancy status, and in children aged 6-59 months https://www.who.int/data/gho/data/themes/topics/anaemia_in_women_and_children

3. Aliyo A, Jibril A. Assessment of anemia and associated risk factors among children under-five years old in the West Guji Zone, southern Ethiopia: Hospital-based cross-sectional study. PLoS One. 2022 Jul 5;17(7):e0270853. doi: 10.1371/journal.pone.0270853. PMID: 35789228; PMCID: PMC9255756. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9255756/

4. Tesfa Alamneh, Alemakef Melesse, Kassahun Gelaye. Determinants of anemia severity levels among children aged 6–59 months in Ethiopia: Multilevel Bayesian statistical approach*Scientific Reports*Published: 13 March 2023 https://www.nature.com/articles/s41598-022-20381-7
5. Pawani Kher. Hemorrhagic Disease of Newborn // StatPearls [Internet].- June 26, 2023. https://www.ncbi.nlm.nih.gov/books/NBK558994/
6. Jayson Stoffman Bleeding Disorders in Children: von Willebrand Disease and Hemophilia https://www.healthychildren.org/English/health-issues/conditions/chronic/Pages/bleeding-disorders-in-children-von-

willebrand-disease-and-hemophilia.aspx

7. Jacquelyn Powers, Claudio Sandoval. Approach to the child with anemia. UpToDate/ This topic last updated: Jan 12, 2023. https://www.uptodate.com/contents/approach-to-the-child-with-anemia#H366934981

13. Electronic information resources

1. http://moz.gov.ua– Міністерство охорони здоров'я України
2. www.ama-assn.org – Американська медична асоціація / American Medical Association
3. www.oapn.od.ua- ГО "Одеська Асоціація лікарів-педіатрів та неонатологів"
4. www.who.int – Всесвітня організація охорони здоров'я
5. www.dec.gov.ua/mtd/home/ - Державний експертний центр МОЗ України
6. http://bma.org.uk– Британська медична асоціація
7. www.gmc-uk.org- *General Medical Council* (*GMC*)
8. www.bundesaerztekammer.de – Німецька медична асоціація
9. https://www.who.int/workforcealliance/members_partners/member_list/ipa/en/ - Міжнародна асоціація педіатрів / International Pediatric Association (IPA).
10. https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Strategy-Report-24_05_22_WMS.pdf GINA Global Initiative For Asthma. 2024
11. https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2021-Glomerular-Diseases-Guideline_English_LN-2024-Update.pdf KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases
12. https://aamsmedacademy.com/ American Academy of Medical Sciences (AAMS)
13. https://nam.edu/ The **National Academy of Medicine (NAM)**
14. https://cutt.ly/utqqtt7I Підручник Нельсона з педіатрії - електронна книга Elsevier на VitalSource, 21-ше видання
15. https://www.amazon.com/Averys-Neonatology-Pathophysiology-Management-Pathophusiology/dp/1451192681