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Extended neonatal screening in the Russian Federation: characteristics of nozological forms

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ABSTRACT. Neonatal screening is aimed at early preclinical detection of hereditary and congenital diseases in order to start treatment early, prevent early death and disability of children. In the Russian Federation since 2023 Newborn babies are examined for 36 hereditary and congenital diseases with an organizational division into two types of care: neonatal screening, including screening for 5 diseases, and extended neonatal screening, including screening for 31 diseases: aminoacidopathy, organic aciduria, disorders of beta-oxidation of fatty acids, primary immunodeficiency, spinal muscular atrophy. All newborns, without exception, are subject to screening. Capillary blood samples are taken from the newborn's heel at the age of 24–48 hours in a full-term baby and on the 7th day (144–168 hours) of life in a premature newborn. The time of screening tests is no more than 72 hours from the time of receipt of test forms in the laboratory. The diagnosis uses enzyme immunoassay, fluorimetric method, tandem mass spectrometry and molecular genetic methods. Diagnostic algorithms have been developed for each disease. If the pathology is confirmed, the child is prescribed pathogenetic therapy. The article contains a list of 36 nosological forms included in the neonatal screening program, and describes the clinical characteristics for each disease. A family in which a child with a hereditary disease is identified is indicated medical genetic counseling.

KEYWORDS: *neonatal screening, congenital hypothyroidism, cystic fibrosis, adrenogenital syndrome, galactosemia, biotinidase deficiency, expanded neonatal screening, aminoacidopathies, organic acidurias, disorders of fatty acid beta-oxidation, primary immunodeficiencies, spinal muscular atrophy*

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Расширенный неонатальный скрининг в Российской Федерации: характеристика нозологических форм

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РЕЗЮМЕ. Неонатальный скрининг нацелен на доклиническое выявление наследственных и врожденных заболеваний с целью раннего начала лечения, профилактики младенческой смерти и инвалидизации детей. В Российской Федерации с 2023 г. проводится обследование новорожденных на 36 наследственных и врожденных заболеваний с организационным разделением на два вида помощи: неонатальный скрининг, в который входит обследование на 5 заболеваний, и расширенный неонатальный скрининг, включающий обследование на 31 заболевание — аминоацидопатии, органические ацидурии, нарушения бета-окисления жирных кислот, первичные иммунодефициты, спинально-мышечную атрофию. Скринингу подлежат все без исключения новорожденные дети. Забор образцов капиллярной крови осуществляется из пятки новорожденного в возрасте 24–48 ч у доношенного и на 7-е сутки (144–168 ч) жизни у недоношенного новорожденного. Время проведения скрининговых исследований составляет не более 72 ч от времени поступления тест-бланков в лабораторию. В диагностике применяются иммуноферментный анализ, флуориметрический метод, тандемная масс-спектрометрия и молекулярно-генетические методы. Для каждого заболевания разработаны алгоритмы диагностики. При подтверждении патологии ребенку назначается патогенетическая терапия. В статье приведен перечень 36 нозологических форм, включенных в программу неонатального скрининга, и описаны клинические характеристики для каждого заболевания. Семье, в которой выявлен ребенок с наследственным заболеванием, показано медико-генетическое консультирование.

КЛЮЧЕВЫЕ СЛОВА: *неонатальный скрининг, врожденный гипотиреоз, муковисцидоз, адреногенитальный синдром, галактоземия, недостаточность биотинидазы, расширенный неонатальный скрининг, аминоацидопатии, органические ацидурии, нарушения бета-окисления жирных кислот, первичные иммунодефициты, спинально-мышечная атрофия*

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INTRODUCTION

Neonatal screening is designed to detect hereditary and congenital disorders before clinical symptoms appear, with the aim of initiating treatment early and preventing infant mortality and childhood disability. Mass screening of newborns for phenylketonuria began in the Russian Federation (RF) in 1985, and for congenital hypothyroidism in 1993. Additionally, since 2006, screening for cystic fibrosis, adrenogenital syndrome, and galactosemia has been implemented in the RF (Order of the Ministry of Health and Social Development of the RF No. 185 dated March 22, 2006, "On Mass Screening of Newborns for Hereditary Diseases"). Since 2023, the Russian Federation has been screening newborns for 36 hereditary and congenital diseases, with the program organized into two types of care: neonatal screening, which includes testing for 5 diseases, and expanded neonatal screening (ENS), which includes testing for 31 diseases: aminoacidopathies, organic acidurias, fatty acid oxidation disorders, primary immunodeficiencies, and spinal muscular atrophy. Currently, tests as part of neonatal screening (for congenital hypothyroidism, cystic fibrosis, adrenogenital syndrome, galactosemia, and biotinidase deficiency) are conducted in neonatal screening laboratories at regional institutions, primarily medical-genetic counseling centers (MGK). In the Russian Federation, 10 centers have been established to diagnose diseases within the framework of ENS. The main regulatory documents governing neonatal screening are Order No. 222n of the Ministry of Health of Russia dated April 17, 2025, "On the Approval of the Procedure for the Provision of Medical Care in the Field of 'Neonatology'," Order of the Ministry of Health of Russia No. 274n dated April 21, 2022, "On the Approval of the Procedure for the Provision of Medical Care to Patients with Congenital and/or Hereditary Diseases," and Order of the Ministry of Health of Russia No. 745n dated December 19, 2025, "On Amending Paragraph 10 of the Procedure for Providing Medical Care to Patients with Congenital and/or Hereditary Diseases, Approved by Order of the Ministry of Health of the Russian Federation No. 274n dated April 21, 2022," Directive of the Government of the Russian Federation No. 1510-r dated June 9, 2022 No. 1510-r "On the procurement by the Federal State Budgetary Institution 'Federal Center for Planning and Medication Provision for Citizens' of the Ministry of Health of Russia of medical equipment for the implementation of expanded neonatal screening" (as amended and supplemented), Order of the Ministry of Health of Russia No. 808n dated December 27, 2022, "On the Approval of Lists of Federal State Medical Organizations under the Jurisdiction of Constituent Entities of the Russian Federation That Conduct Expanded Neonatal Screening, as well as conducting confirmatory biochemical, and/or molecular genetic, and/or molecular cytogenetic diagnostics, and the constituent entities of the Russian Federation attached to them," Methodological Recommendations "Method for Obtaining a Dried Blood Spot on a Test Card for Clinical Laboratory Testing" (2022), developed by the Association of Medical Geneticists and the Russian Society of Neonatologists. The methodological recommendations are available on the website of the Federal State Budgetary Scientific Institution "Academician N.P. Bochkov Medical-Genetic Research Center," Regulations on information exchange between medical organizations during the conduct of neonatal and expanded neonatal screening. Information exchange as part of neonatal and expanded neonatal screening for hereditary diseases is carried out through the Newborn Registry (ENS) of the VIMIS "Akineo" system. This is a specialized, vertically integrated medical information system for "Obstetrics and Gynecology" and "Neonatology" of the Russian Ministry of Health. These regulations are available on the website of the Federal State Budgetary Institution "V.I. Kulakov National Medical Research Center for Obstetrics, Gynecology, and Perinatology" of the Ministry of Health of Russia.

PROCEDURE FOR NEONATAL (EXPANDED NEONATAL) SCREENING FOR CONGENITAL AND/OR HEREDITARY DISEASES

All newborns, without exception, are required to undergo screening. Capillary blood samples are collected from the heel of a newborn at 24–48 hours of age for full-term newborns and on the 7th day (144–168 hours) of life for preterm neonates. Blood samples are collected onto two filter paper test forms: five blood spots are applied to one for neonatal screening, and three spots to the second for expanded neonatal screening. A referral form is filled out electronically, printed, and attached to the

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test form. All test forms with blood samples are delivered to regional neonatal screening laboratories, where testing for five conditions is conducted as part of neonatal screening, and the shipment of test forms to designated centers for expanded neonatal screening is arranged. Screening tests are conducted within 72 hours after the test forms arrive at a laboratory. If a newborn is in a high-risk group, the MGC will call within 24 hours to schedule an appointment for blood sample collection for repeat screening or for biological material collection (blood, urine) for confirmatory diagnosis. A decision is made regarding the need for hospitalization, the prescription of therapy, and referral to a specialist in the relevant field. Confirmatory diagnostics for newborns with suspected hereditary diseases identified through expanded neonatal screening in all regions of the Russian Federation is conducted at the Federal State Budgetary Scientific Institution "Academician N.P. Bochkov Medical-Genetic Research Center" (Moscow), which serves as a reference center. Confirmatory testing takes no more than 10 working days. Diagnostic methods include enzyme-linked immunosorbent assay (ELISA), fluorimetry, tandem mass spectrometry, and molecular genetic methods. Diagnostic algorithms have been developed for each disease. Upon confirmation of a pathology, a child is prescribed pathogenetic therapy [1]. Medications are provided at the expense of regional and federal budgets, as well as through the "Circle of Kindness" State Foundation for Assistance to Children with Severe and Rare Diseases. Federal clinical guidelines have been developed for most nosological forms.

According to the results of the ENS Federal Program for 2024, more than 1,226,000 children were born in all constituent entities of the Russian Federation. Coverage by primary screening was approximately 99%. About 1.6% of those screened were identified as being at risk. During 2024, a diagnosis of a hereditary disease included in the screening was confirmed in 726 children, including 430 newborns with inherited metabolic disorders, 121 newborns with primary immunodeficiencies, and 175 newborns with spinal muscular atrophy[1] [2]. In the Russian Federation, starting in 2026, neonatal screening is planned to be expanded to include two hereditary diseases: aromatic acid decarboxylase deficiency and X-linked adrenoleukodystrophy.

DISORDERS DETECTED THROUGH NEONATAL SCREENING

Congenital hypothyroidism (ICD-10 codes: E03.0 Congenital hypothyroidism with diffuse goiter; E03.1 Congenital hypothyroidism without goiter)

In 80% of cases, the condition results from congenital abnormalities of the thyroid gland. During screening, the level of thyroid-stimulating hormone (TSH) is measured. If the TSH level exceeds the threshold, it is remeasured (retest). If the capillary blood TSH level exceeds 40 mU/L, treatment is initiated immediately, prior to receiving the retest results. The next step is to measure the levels of TSH and free T4 in venous blood. If congenital hypothyroidism is suspected, an endocrinologist performs the differential diagnosis of various forms of hypothyroidism and initiates hormone replacement therapy. In the absence of treatment, the primary clinical manifestations are delayed mental and physical development. The incidence of congenital hypothyroidism in the Russian Federation, based on neonatal screening results, is 1:3,600 [3].

Cystic fibrosis (ICD-10 code — E84.9 Cystic fibrosis, unspecified (cystic fibrosis))

Cystic fibrosis is a hereditary disease with an autosomal recessive pattern of inheritance. During screening, the level of immunoreactive trypsinogen (IRT) is determined. If the threshold value is exceeded, a retest is performed on the 21st–28th day of life, as IRT activity subsequently decreases. Confirmatory diagnostic methods include a sweat test and molecular genetic testing, which involves searching for pathogenic variants (mutations) in the *CFTR* gene. Main clinical manifestations include chronic diseases of the respiratory tract and gastrointestinal tract. In some cases, a child with cystic fibrosis may have an IRT level within the reference range at birth; therefore, if a characteristic clinical picture develops, cystic fibrosis must be ruled out by performing a sweat test and/or molecular genetic testing. Modern treatment may include the use of targeted therapy that affects the function of the mutant CFTR protein. The prevalence of cystic fibrosis in the Russian Federation is 1:7,400 [4].

[1] The results of the federal program for expanded neonatal screening for 2024 have been summarized. URL: https://medgen.ru/press-tcentr/novosti/podvedeny-itogi-federal-noi-programmy-rasshirennogo-neonatal-nogo-skrininga-za-2024-god/ (accessed: 11/10/2025).

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Congenital adrenal hyperplasia (adrenogenital syndrome) (ICD-10 codes — E25.0 Adrenogenital disorders associated with enzyme deficiency; E25.9 Adrenogenital disorder, unspecified)

Congenital adrenal hyperplasia is a group of inherited disorders with an autosomal recessive pattern of inheritance associated with impaired steroidogenesis. The most common form (over 90% of cases) is 21-hydroxylase deficiency. During screening, the level of 17-hydroxyprogesterone (17-OHP) is measured. Screening is aimed at detecting the classic forms of congenital adrenal hyperplasia, namely salt-wasting and virilizing ones. In some cases, a non-classic form may be detected. Newborns with 17-OHP levels above the threshold value undergo retesting. Differential diagnosis and hormone replacement therapy are performed by an endocrinologist. Confirmatory diagnosis involves hormonal testing and molecular genetic testing to identify pathogenic variants (mutations) in the *CYP21A2* gene. The incidence of classic forms of adrenogenital syndrome based on neonatal screening results in the Russian Federation is 1:9,638 (ranging from 1:6,749 to 1:14,876 across different regions of the Russian Federation) [5].

Galactosemia (galactose metabolism disorder) (ICD-10 code — E74.2 Galactose metabolism disorder)

Galactosemia is a group of inherited disorders with an autosomal recessive pattern of inheritance. Total galactose levels are measured in the blood of newborns. Mutations in three genes (*GALT, GALK1, GALE*) lead to a deficiency of various enzymes (galactose-1-phosphaturidyltransferase, galactokinase, uridine diphosphate, galactose-4-epimerase) with the biochemical manifestation of galactosemia. The primary condition in the Russian population is type I galactosemia with galactose-1-phosphate uridyltransferase deficiency. If the total galactose level exceeds the threshold, a retest is performed. If a total galactose level above 15 mg/dL is detected in a newborn, immediate dietary intervention and hospitalization are recommended pending the retest results. In the absence of treatment, the classic form of type I galactosemia leads to liver damage progressing to hepatic cell failure and sepsis, which may be fatal. Lifelong treatment is based on an elimination diet that excludes galactose-containing foods (in newborns, this includes breast milk and infant formulas containing galactose or lactose). The confirmatory diagnostic workup includes measurement of galactose-1-phosphate uridyltransferase (*GALT*) enzyme levels and molecular genetic testing to identify pathogenic variants (mutations) in the *GALT* gene and other genes associated with galactosemia. Very often, a slight elevation of galactose in a newborn is associated with polymorphic variants in the *GALT* gene, where enzyme activity may decrease to 25% of normal, the so-called Duarte variant. In the Duarte variant, a decrease in total blood galactose levels is observed over time, with normalization occurring when the infant is fed breast milk or infant formula.In some cases, a diet restricting lactose intake is prescribed for the Duarte variant until blood galactose levels normalize. Patients with galactosemia are monitored by pediatricians, gastroenterologists, and geneticists. Starting in 2023, blood sampling in full-term newborns is performed within the first 24–48 hours, when galactose may not yet have accumulated in the blood to a clinically significant level. If galactosemia is suspected based on the clinical presentation in a child with normal galactose levels according to neonatal screening results, it is recommended to repeat the blood galactose test. In the Russian Federation, based on neonatal screening results, the incidence of galactosemia is 1:20,000 (including the Duarte variant) [6].

Biotinidase deficiency (ICD-10 code — E56.8 Deficiency of other specified B vitamins (biotinidase deficiency))

Biotinidase deficiency (biotin-dependent carboxylase deficiency) is an inherited disorder with an autosomal recessive pattern of inheritance. Biotinidase enzyme activity is measured in newborns. Confirmatory diagnosis involves measuring biotinidase activity in blood serum and molecular genetic testing to identify pathogenic variants (mutations) in the *BTD* gene. The main clinical manifestations are neurological (seizures, muscular hypotonia, psychomotor developmental delay) and cutaneous (seborrhea, atopic dermatitis, hair loss or poor hair growth, conjunctivitis). In the absence of timely treatment, children with very low enzyme activity develop irreversible severe mental retardation. Preclinical administration of biotin (the primary method of lifelong treatment) promotes normal child development. The global incidence is 1:40,000–1:60,000 [7].

DISEASES DETECTED THROUGH EXPANDED NEONATAL SCREENING

Amino acid metabolism disorders (E70 Disorders of aromatic amino acid metabolism)

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A group of inherited disorders with an autosomal recessive pattern of inheritance. Diagnostic method: tandem mass spectrometry (TMS technology, which allows determining the concentrations of various markers for a large number of diseases in a single analysis). Clinically, the disease ranges from mild to severe forms, with classic clinical manifestations in the neonatal and early childhood periods.

Hyperphenylalaninemia (classical phenylketonuria, other types of hyperphenylalaninemia) (ICD-10 codes — E70.0 Disorders of aromatic amino acid metabolism (phenylketonuria); E70.1 Other types of hyperphenylalaninemia (deficiency of biopterin (tetrahydrobiopterin) synthesis, biopterin (tetrahydrobiopterin)

Blood samples from newborns are tested for levels of phenylalanine. If the result is above the threshold, a retest is performed. Confirmatory diagnosis includes determining elevated phenylalanine levels and the phenylalanine/tyrosine ratio prior to dietary therapy, as well as molecular genetic testing to identify pathogenic variants (mutations) in the *PAH* gene and the genes encoding cofactors for the enzyme phenylalanine hydroxylase (*PTS, QDRP, PCBD, GCHI, SPR, DNAJC12*). The most common form is classic phenylketonuria (98% of cases) with mutations in the *PAH* gene. By crossing the blood-brain barrier, phenylalanine breakdown products exert a toxic effect on brain cell metabolism, leading to mental retardation if left untreated.

Treatment for classic phenylketonuria is based on a lifelong diet that restricts phenylalanine intake when its level exceeds 360 μmol/L, along with the use of specialized medical foods that do not contain phenylalanine.

When diagnosing forms of biopterin (tetrahydrobiopterin) synthesis and reactivation deficiency, pathogenetic drug therapy is prescribed using a synthetic analogue of tetrahydrobiopterin (saproterin dihydrochloride) and serotonin precursors (levodopa preparations in combination with carbidopa). Patients with phenylketonuria are primarily monitored by geneticists and pediatricians. The incidence of hyperphenylalaninemia in the Russian Federation, according to neonatal screening data, is 1:7,000 (ranging from 1:4,735 to 1:18,000 across different regions) [8]. New methods of drug treatment for classic phenylketonuria are being developed and implemented worldwide, including in Russia.

Tyrosinemia, type I (tyrosine metabolism disorders) (ICD-10 code — E70.2 Tyrosine metabolism disorders (tyrosinemia)

Concentrations of tyrosine and succinylacetone are measured in blood. If succinylacetone and tyrosine levels exceed the threshold values, a retest is performed. An elevated level of succinylacetone is pathognomonic for type I tyrosinemia. Elevated tyrosine levels are observed in other types of hereditary tyrosinemia and in hepatopathies of other etiologies. The main clinical manifestations include impaired liver and kidney function, neurological symptoms, and rickets-like skeletal changes. Confirmatory diagnosis involves measuring elevated levels of succinylacetone in blood and urine, as well as molecular genetic testing to identify pathogenic variants (mutations) in the *FAH* gene. The mainstay of treatment for type I tyrosinemia is lifelong medication with nitizinone and a diet restricting phenylalanine and tyrosine intake, with the use of specialized medical foods that do not contain phenylalanine or tyrosine. Follow-up is conducted by a pediatrician and a geneticist. The incidence of type I tyrosinemia in various populations ranges from 1:100,000 to 1:120,000. The incidence in the Chechen Republic is 1:16,020 [9].

Leucinemia (maple syrup urine disease) (ICD-10 code — E71.0 Maple syrup urine disease)

The concentration of leucine (Leu/Ile/Pro-OH-leucine/isoleucine/hydroxyproline; amino acids are not separated in the analysis and appear as a single peak) is determined in the blood of a newborn. If leucine levels exceed the threshold, a retest and analysis of organic acids in urine are performed before initiating therapy. If leucine levels exceed 600 μM/L, hospitalization and a low-protein diet are recommended. Mutations in the *BCKDHA, BCKDHB, DBT, DLDA*, and *PPM1K* genes lead to a deficiency of branched-chain ketone acid dehydrogenase (a multi-enzyme complex), which is accompanied by metabolic disturbances and accumulation of the amino acids leucine, isoleucine, valine, and their derivatives. Confirmatory diagnosis involves elevated levels of leucine, isoleucine, and valine in the blood; elevated levels of 2-oxo-isocaproic, 2-hydroxy-isocaproic, 2-oxo-3-methylvaleric, 2-oxo-isovaleric, 2-hydroxyisovaleric, and 2-hydroxy-3-methylvaleric acids in urine; molecular genetic testing to identify pathogenic variants in the *BCKDHA, BCKDHB, DBT, DLDA*, and *PPM1K* genes.

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The main clinical manifestation in the classic course of leucinosis is acute infantile encephalopathy (generalized seizures, hyperexcitability, muscle hypertonia, alternating with lethargy, muscle hypotonia, and impaired consciousness up to coma) with a potentially fatal outcome.

The basis of treatment is a diet restricting foods rich in leucine, isoleucine, and valine, and the use of specialized therapeutic foods that do not contain leucine, isoleucine, or valine. Drug therapy includes the administration of L-carnitine and thiamine. Hospitalization is indicated in case of metabolic crisis. Monitoring is carried out by a pediatrician, a neurologist, and a geneticist. The global incidence is 1 in 185,000 [10].

Homocystinuria (disorders of sulfur-containing amino acid metabolism) (ICD-10 code — E72.1 Disorders of sulfur-containing amino acid metabolism (homocystinuria))

Methionine concentration is measured in blood samples.

1. Screening is primarily aimed at diagnosing the classic form of homocystinuria associated with cystathionine β-synthase deficiency. Inhibition of the enzyme at the level of further homocysteine metabolism leads to its accumulation and, consequently, to the accumulation of methionine as a precursor. If the methionine level exceeds the threshold value, a retest is performed. Confirmatory diagnosis involves the detection of elevated levels of methionine and homocysteine in blood plasma (and homocystine in urine), as well as molecular genetic testing to identify pathogenic variants (mutations) in the *CBS* gene. The main manifestations are mental retardation with clinical signs of connective tissue dysplasia, including tall stature, thrombosis, and cardiovascular pathology. Treatment involves a diet restricting foods rich in methionine and the use of a specialized medical food product that does not contain methionine. A trial treatment with pyridoxine allows for identifying B_6-dependent and B6-resistant forms of homocystinuria, followed by treatment with pyridoxine for the B_6-dependent form of homocystinuria. Elevated blood methionine levels are also observed in liver diseases and other hereditary disorders.

2. A retest is performed if the methionine level in a newborn is below the threshold value. If the methionine level remains below the threshold, hereditary conditions associated with both methylenetetrahydrofolate reductase (*MTHFR*) deficiency and cobalamin metabolism disorders must be ruled out (tandem mass spectrometry shows an increased level of C3 (propionylcarnitine), as well as there is an increase in the level of methylmalonic acid in the urine). Mutations in the *MTHFR* gene lead to a deficiency of methylenetetrahydrofolate reductase, which is involved in converting (remethylation) homocysteine to methionine, resulting in methionine deficiency. Key clinical symptoms include muscle hypotonia, delayed psychomotor development, neurological disorders, microcephaly, and megaloblastic anemia (in certain forms of cobalamin metabolism disorders). Confirmatory diagnosis of homocystinuria with impaired homocysteine remethylation includes measurement of homocysteine levels in blood and urine, analysis of urinary organic acids, and molecular genetic testing of genes associated with non-classical homocystinuria (*MTR, MTRR, MMADHC, PRDX1, LMBRD1, ABCD4*). Medication therapy is based on betaine, which helps lower homocysteine levels by converting it back into methionine and dimethylglycine, followed by breakdown. Betaine is also prescribed for the classic form of homocystinuria. In some cases, children with homocystinuria, whether classic or with methylation defects, have normal methionine levels based on neonatal screening results; therefore, blood homocysteine testing is required when a characteristic clinical picture is present. These children are monitored by a pediatrician, a neurologist, and a geneticist. The global prevalence of classic homocystinuria is 1:100,000–1:200,000 [11].

Citrullinemia, type I (disorders of the urea cycle) (ICD-10 code — E72.2 Disorders of the urea cycle (citrullinemia, type I))

Citrulline levels are measured in blood. If citrulline levels exceed the threshold value, a retest and analysis of urinary organic acids are performed before initiating therapy. If citrulline levels are elevated (>80 μmol/L), a low-protein diet is prescribed and hospitalization is recommended. Lack of the argininosuccinate synthetase, which is involved in the urea cycle, leads to hyperammonemia with a clinical picture of acute encephalopathy following a period of "clear interval," rapid progression of neurological deficits up to neonatal coma and cerebral edema with a potentially fatal outcome. Confirmatory diagnosis includes elevated citrulline levels, ammonia level testing (hyperammonemia), urinary organic acid

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analysis (increased orotic acid excretion), and molecular genetic testing to identify pathogenic variants (mutations) in the *ASS* gene. Treatment includes a low-protein diet, maintaining caloric intake, administration of vitamins and minerals via specialized medical nutrition products, and prescription of L-arginine and medications that lower blood ammonia levels. Extracorporeal detoxification methods and liver transplantation are also used. The global prevalence is 1–9 per 100,000 [1, 12].

Argininosuccinic aciduria (argininosuccinate lyase deficiency) (ICD-10 code — E72.2 Disorders of the urea cycle (argininosuccinate lyase deficiency))

Arginine succinate (Asa) concentrations are measured in blood. If the level exceeds the threshold value, a retest and analysis of urinary organic acids are performed before initiating therapy. If the Asa concentration is >1.5 μmol/L, a low-protein diet and hospitalization are recommended. An acute deficiency of the enzyme argininosuccinate lyase, which is involved in the urea cycle, leads to hyperammonemia with a clinical picture of acute encephalopathy following a "clear interval," rapid progression of neurological disorders up to neonatal coma, cerebral edema with a potentially fatal outcome. Confirmatory diagnosis includes elevated levels of argininosuccinic acid and citrulline in the blood, ammonia level testing (hyperammonemia), urinary organic acid analysis (elevated excretion of argininosuccinic acid), and molecular genetic testing to identify pathogenic variants (mutations) in the *ASL* gene. Treatment is similar to that for type I citrullinemia. The global incidence is 1:70,000–1:91,000 [1, 12].

Argininemia (urea cycle disorders) (ICD-10 code — E72.2 Urea cycle disorders (arginase deficiency))

Arginine concentration is measured in blood. If the arginine level exceeds the threshold value, a retest and analysis of organic acids in the urine are performed before initiating therapy. Deficiency of arginase, which is involved in the urea cycle, leads to hyperammonemia with clinical manifestations of vomiting, anorexia, restlessness, and crying in infants. Acute encephalopathy is less common. Older children may exhibit delayed speech and language development, epilepsy, neurological symptoms. Confirmatory diagnosis includes elevated blood arginine levels, analysis of urinary organic acids (frequently elevated orotic acid excretion), and molecular genetic testing to identify pathogenic variants (mutations) in the *ARG1* gene. Treatment consists of a low-protein diet with minimal arginine content, maintenance of caloric intake, vitamins, and minerals using specialized therapeutic foods, and administration of medications that lower blood ammonia levels in cases of hyperammonemia. The global prevalence is 1 in 353,000 [1, 12].

Organic acidurias

Organic acidurias are a group of inherited disorders with an autosomal recessive pattern of inheritance. The diagnostic method is TMS. To detect organic acidemias (acidurias), acylcarnitine concentrations are measured. Due to gene mutations, an enzyme block occurs, leading to a buildup of organic compounds and their derivatives, which exert a toxic effect on the cell metabolism, central nervous system, liver, and other organs. The biochemical pathway is disrupted, leading to a reduction in subsequent metabolites involved in vital bodily processes, such as gluconeogenesis. These conditions are characterized by varying times of onset, with the most severe course occurring in the neonatal period.

Propionic acidemia (ICD-10 code — E71.1 Other disorders of branched-chain amino acid metabolism (propionic acidemia)) [13]

Methylmalonic acidemia (ICD-10 code — E71.1 Other disorders of branched-chain amino acid metabolism (methylmalonic acidemia/aciduria (methylmalonyl-CoA mutase deficiency)); methylmalonic acidemia (cobalamin A deficiency); methylmalonic acidemia (cobalamin B deficiency); methylmalonic acidemia (methylmalonyl-CoA epimerase deficiency); methylmalonic acidemia (cobalamin D deficiency); methylmalonic acidemia (cobalamin C deficiency).

C3 (propionylcarnitine) concentration and the C3/C2 ratio are measured in blood samples. If their levels exceed the threshold value, a retest is performed. Differential and confirmatory diagnosis of propionic, methylmalonic acidemias, and disorders of cobalamin synthesis (combination of methylmalonic acidemia with non-classical homocystinuria) is performed through the analysis of urinary organic acids (increased excretion of propionic or methylmalonic acids, respectively, as well as 3-hydroxypropionic, 3-hydroxy-n-valeric acids, and methylcitrate), blood and urine homocysteine testing, and molecular genetic diagnosis to identify pathogenic variants (mutations) in the *PCCA, PCCB,*

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MCEE, MMAA, MMAB, MMACHC, MMADHC, PRDX1, LMBRD1, ABCD4, CD320. A slight elevation in C3 may be associated with vitamin B12 deficiency. Clinically, acidemias manifest as feeding difficulties, muscle hypotonia, psychomotor developmental delay, and metabolic crises with a potentially fatal outcome. The mainstay of treatment (except for cobalamin C and D deficiency) is a low-protein diet supplemented with specialized medical foods that do not contain isoleucine, valine, threonine, or methionine. Carnitine, metronidazole, and medications that lower ammonia levels are prescribed; biotin and vitamin B_{12} are prescribed as indicated. In cases of cobalamin deficiency, vitamin B_{12} is prescribed at a dose of 1–5 mg/day (hydroxocobalamin, adenosylcobalamin); betaine and folic acid are also prescribed for cobalamin C and D deficiency. Patients are monitored by a pediatrician, a neurologist, and a geneticist. The global prevalence of methylmalonic acidemia is 1:50,000, and the prevalence of propionic acidemia is 1:350,000 [14].

Isovaleric acidemia (ICD-10 code — E71.1 Other disorders of branched-chain amino acid metabolism (isovaleric acidemia))

The concentration of C5 (isovalerylcarnitine) is measured in blood. If the C5 level exceeds the threshold, a retest and an analysis of urinary organic acids are performed before initiating therapy. Confirmatory diagnosis involves urine organic acid analysis (elevated levels of isovaleric acid, 3-hydroxyisovaleric acid, and isovalerylglycine) and molecular genetic testing to identify pathogenic variants (mutations) in the *IVD* gene. Clinically, the disease ranges from asymptomatic to severe, presenting as acute infantile encephalopathy with severe ketoacidosis and a potentially fatal outcome. An unusual “sweaty feet” odor in the urine is typical. Treatment is based on a low-protein diet supplemented with specialized therapeutic foods that do not contain leucine. L-carnitine, glycine, and medications that lower ammonia levels are prescribed. Metabolic crisis must be managed. These patients are not prescribed medications containing benzoic or salicylic acid due to competition with isovaleryl-CoA for conjugation with glycine. Children are monitored by a pediatrician, a neurologist, and a geneticist. The global incidence is 1:60,000–1:150,000 [15].

3-hydroxy-3-methylglutaric acid deficiency (ICD-10 code — E71.1 Other disorders of branched-chain amino acid metabolism (3-hydroxy-3-methylglutaric acid deficiency))

The concentration of C_5OH (3-hydroxyisovalerylcarnitine) is measured in blood. A C_5OH level above the threshold is also observed in biotinidase deficiency, holocarboxylase synthetase deficiency, and 3-methylcrotonyl-CoA carboxylase deficiency. Differential and confirmatory diagnosis includes determination of biotinidase activity, analysis of urinary organic acids (elevated levels of 3-hydroxy-3-methylglutaric, 3-methylglutaric, 3-methylglutaconic, 3-hydroxyisovaleric, 3-methylglutarylglycine, methyl-crotonylglycine), and molecular genetic testing to identify pathogenic variants (mutations) in the *HMGCL* gene. Clinically, the condition is characterized by neurological symptoms, metabolic crises (metabolic acidosis, hypoketotic hypoglycemia), and a Reye-like syndrome. Treatment is based on a low-protein diet and therapeutic foods that do not contain leucine. Fat intake is restricted. Carnitine is prescribed. Metabolic crises are managed. Patients are monitored by a pediatrician, a neurologist, and a geneticist. The global incidence is 1 in 1,000,000 [16].

Beta-ketothiolase deficiency (ICD-10 code — E71.1 Other disorders of branched-chain amino acid metabolism (beta-ketothiolase deficiency))

Concentrations of C5:1 (tiglilcarnitine) and C_5OH (3-hydroxyisovalerylcarnitine) are measured in blood. If the C5:1 level exceeds the threshold, a retest is performed. Confirmatory diagnosis includes: elevated C5:1 and C_5OH levels in the blood, analysis of urinary organic acids (elevated tiglylglycine, 2-methyl-3-hydroxybutyrate, and 2-methylacetoacetate), and molecular genetic testing, namely searching for mutations in the *ACAT1* gene. Episodes of ketoacidosis, triggered by fasting, stress, or intercurrent illnesses, are common. Clinically, symptoms include vomiting, muscle hypotonia, shortness of breath, seizures, impaired consciousness, delayed motor and mental development, and motor disorders. The basis of treatment is a low-protein diet, restriction of fat intake; frequent meals; increased carbohydrate intake; and administration of carnitine in cases of free carnitine (C0) deficiency. Children are monitored by a pediatrician, a neurologist, and a geneticist. The global prevalence is 1 in 1,000,000 [1, 14].

Glutaric acidemia, type I (ICD-10 code — E72.3 Disorders of lysine and hydroxylysine metabolism (glutaric acidemia, type I))

The concentration of C5DC (glutaric acid) is measured in blood. If the C5DC level is above the threshold, a retest and an analysis of urinary

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organic acids are performed before starting therapy. Confirmatory diagnosis involves testing for organic acids in urine (elevated levels of glutamic and 3-hydroxyglutamic acids) and molecular genetic testing to identify pathogenic variants (mutations) in the *GCDH* gene. Clinically, the condition is characterized by macrocephaly, encephalitis-like seizures, neurological symptoms, and a spastic-hyperkinetic pattern of cerebral palsy. The basis of treatment is a diet restricting foods rich in lysine and tryptophan, along with specialized therapeutic foods that do not contain lysine or tryptophan. Levocarnitine is prescribed. Patients are monitored by a pediatrician, a neurologist, and a geneticist. In 5% of cases, when a child has type I glutaric aciduria, the C5DC concentration is within normal limits according to neonatal screening results; therefore, if the disease is clinically suspected, urine organic acid analysis and molecular genetic testing are performed. Elevated C5DC levels are observed in type II glutaric aciduria and kidney diseases. The prevalence in Western European countries is 1:30,000–1:100,000. In the Russian Federation, the prevalence of the disease has not been determined [17] and will be clarified upon implementation of the newborn screening program.

Holocarboxylase synthetase deficiency (biotin-sensitive multiple carboxylase deficiency) (ICD-10 code — E56.8 Deficiency of other specified B vitamins (holocarboxylase synthetase deficiency))

C_5OH (3-hydroxyisovalerylcarnitine) concentration is measured in blood. Elevated C_5OH levels are also observed in biotinidase deficiency and other metabolic disorders. Differential and confirmatory diagnosis includes: determination of biotinidase activity, analysis of urinary organic acids (elevated levels of β-hydroxyisovaleric, β-hydroxypropionic, fumaric, and 2-ketoglutaric acids, 3-methylcrotonylglycine, methylcitrate, and tiglylglycine), and molecular genetic diagnosis to identify pathogenic variants (mutations) in the *HLCS* gene. Clinically, the condition is characterized by neurological manifestations (seizures, muscle hypotonia, impaired consciousness), mental retardation, motor delay, dermatitis, and metabolic acidosis. Primary treatment involves the administration of biotin and L-carnitine, as well as correction of metabolic acidosis. The global prevalence is 1:200,000. The prevalence in the Russian Federation has not yet been established [1, 7, 18].

Fatty acid beta-oxidation disorders (ICD-10 code — E71.3 Fatty acid metabolism disorder)

Fatty acid beta-oxidation disorders are hereditary diseases with an autosomal recessive pattern of inheritance. Diagnostic method: TMS. To diagnose organic acidurias, acylcarnitine concentrations are measured. If there is an initial deviation from the acylcarnitine threshold level, a retest is performed. Confirmatory diagnosis includes characteristic TMS acylcarnitine spectrum profiles, urinary organic acids, and molecular genetic testing. The main clinical manifestations are muscle hypotonia and weakness, ketotic hypoglycemia, metabolic crises, dicarboxylic aciduria, Reye-like syndrome. Treatment is lifelong. Patients are monitored by a pediatrician, a neurologist, and a geneticist [19]. The prevalence of nosological forms of fatty acid β-oxidation disorders in the Russian Federation will be clarified based on the results of the ENS Program.

Primary carnitine deficiency (ICD-10 code — E71.3 Fatty acid metabolism disorder (primary carnitine deficiency))

A decrease in C0 (free carnitine) concentration is observed. The disease is caused by mutations in the *SLC22A5* gene. Primary treatment consists of levocarnitine at an average dose of 100 mg/kg per day (50–400 mg/kg), with correction during a metabolic crisis. The global incidence is 1:20,000–1:70,000.

Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) (ICD-10 code — E71.3 Fatty acid metabolism disorder (medium-chain acyl-CoA dehydrogenase deficiency))

Elevated concentrations of medium-chain acylcarnitines are detected: C8 (octanoylcarnitine), C6 (hexanoylcarnitine), C10 (decanoylcarnitine), and C10:1 (decenylcarnitine), as well as the C8/C10 and C8/C2 ratios. The disorder is caused by mutations in the *ACADM* gene. Primary treatment involves avoiding fasting to prevent hypoglycemic episodes, eating every 3–6 hours for children over 1 year of age. Infants under 1 year old should eat more frequently. If C0 is low, carnitine should be prescribed. Metabolic crisis requires immediate intervention. The incidence in Europe and the U.S. is 1:8,300–1:15,000.

Long-chain acetyl-CoA dehydrogenase deficiency (mitochondrial trifunctional protein (TFP) deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHADD) deficiency) (ICD-10 code — E71.3 Fatty acid metabolism disorder (long-chain acyl-CoA dehydrogenase deficiency))

Elevated concentrations of acylcarnitines are detected, including C18OH (3-hydroxy-octadecanoylcarnitine), C18:1OH (3-hydroxy-octadecenoic acid carnitine), C16OH (3-hydroxy-hexadecanoic

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acid carnitine), C16:1OH (3-hydroxy-hexadecenoic acid carnitine). Levels of C0 (free carnitine) are decreased. the disorder is caused by mutations in the *HADHA* gene. Primary treatment includes frequent meals. Breaks should not exceed 3–6 hours during the day and 3–8 hours at night, depending on age. A diet should limit foods rich in long-chain fatty acids and include specialized medical foods containing medium-chain fatty acids. Valproic acid is not recommended in cases of concomitant conditions. The global prevalence is 1 in 300,000.

Very-long-chain acetyl-CoA dehydrogenase deficiency (VLCADD) (ICD-10 code — E71.3 Fatty acid metabolism disorder (very-long-chain acetyl-CoA dehydrogenase deficiency))

Elevated concentrations of acylcarnitines C14:1 (tetradecenoic acid carnitine), C14 (tetradecanoic acid carnitine), C14:2 (tetradecadienoic acid carnitine), C16:1 (hexadecenoic carnitine), and the C14:1/C16 ratio are identified. The disorder is caused by mutations in the *ACADVL* gene. Elevated levels of these metabolites are observed in heterozygous carriers of the ACADV gene in clinically healthy individuals. The main treatment is similar to long-chain acetyl-CoA dehydrogenase deficiency. The global prevalence is 1:30,000–1:100,000.

Carnitine palmitoyltransferase deficiency, type I (ICD-10 code — E71.3 Fatty acid metabolism disorder (carnitine palmitoyltransferase deficiency, type I))

Elevated concentrations of C0 (free carnitine) and the C0/(C16+C18) ratio, as well as decreased concentrations of C16 (hexadecanoylcarnitine) and C18 (stearoylcarnitine), are observed. The disorder is caused by mutations in the *CPT1A* gene. The primary treatment corresponds to therapy for fatty acid beta-oxidation disorders. The global prevalence is less than 1 in 1,000,000.

Carnitine/palmitoyltransferase deficiency, type II (ICD-10 code — E71.3 Fatty acid metabolism disorder (carnitine/palmitoyltransferase deficiency, type II))

Elevated (C16+C18:1)/C2 ratios and decreased C0 (free carnitine) levels are observed. This condition is caused by mutations in the *CPT2* gene. Primary treatment corresponds to therapy for Type I. Carnitine is prescribed when free carnitine levels are low until C0 normalizes. The global prevalence is 1–9 per 100,000.

Carnitine/acylcarnitine translocase deficiency (ICD-10 code — E71.3 Fatty acid metabolism disorder (carnitine/acylcarnitine translocase deficiency))

The disorder is characterized by elevated (C16+C18:1)/C2 ratios and decreased C0 (free carnitine) levels, and caused by mutations in the *SLC25A20* gene. Primary therapy involves avoiding fasting (see above), a low-fat diet (30% fat in the diet: 20% medium-chain fatty acids with low caprylic acid (C10) content, 10% long-chain fatty acids), and administration of carnitine when free carnitine levels are low until C0 normalizes, followed by discontinuation. The estimated global prevalence is 1:1,000,000.

Glutaric acidemia, type II (ICD-10 code — E71.3 Fatty acid metabolism disorder (glutaric acidemia, type II (multiple acyl-CoA dehydrogenase deficiency); glutaric acidemia, type II (riboflavin-sensitive form))

Elevated concentrations of C4 (isobutyrylcarnitine), C5 (isovalerylcarnitine), C5-DC (glutaric acid carnitine), C6 (hexanoylcarnitine), C8 (octanoic acid-carnitine), C10 (decanoic acid-carnitine), C12 (dodecanoic acid-carnitine), C14:1 (tetradecenoic acid-carnitine), C16 (hexadecanoic acid-carnitine), C18:1 (octadecenoic acid-carnitine) are observed. The disorder is caused by mutations in the *ETFA, ETFB*, and *ETFDH* genes. Elevated levels of these metabolites are also observed in other riboflavin metabolism disorders and in cases of maternal riboflavin deficiency. Elevated levels of the following organic acids are detected in urine: glutamic acid, 2-hydroxyglutamic acid, isovaleric acid, 2-methylbutyrate, isobutyrate, isovalerylglycine, isobutyrylglycine, and others. The main treatment consists of a low-protein, low-fat diet, administration of riboflavin and carnitine, and management of metabolic crises. The global incidence is 1:300,000. The incidence of the disease in the Russian Federation, according to the Russian National Registry (RNS), is 1:205,233 live births [22].

Proximal spinal muscular atrophy 5q

(ICD-10 code — G12.0 Infantile spinal muscular atrophy, type I (Werding–Hoffmann); G12.1 Other hereditary spinal muscular atrophies)

This is an autosomal recessive disorder. Mutations in the *SMN1* gene lead to a reduction in SMN protein levels, resulting in damage to the spinal cord's α-motor neurons. Clinically, it manifests as progressive muscle atrophy, muscle weakness, and hypotonia. Based on clinical course and age of onset, four types of spinal muscular atrophy (SMA) are distinguished. During newborn screening using molecular genetic methods, a common mutation (95–98% of cases) in the *SMN1* gene is identified, that is a homozygous deletion of exon 7. Upon detection of a homozygous deletion, verification is performed at a reference center, and

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the number of copies of the *SMN2* gene, a gene 99% structurally similar to *SMN1*, is determined. As the number of *SMN2* gene copies increases, the severity of SMA's clinical presentation decreases. The number of *SMN2* copies determines the choice of targeted therapy. Etiopathogenic treatment has been developed to prevent the development of severe symptoms. Patients with SMA are monitored and treated by neurologists. In the presence of a clinical picture of SMA and the absence of pathology based on screening results, sequencing of the *SMN1* gene is required to rule out point mutations in this gene. The prevalence of the disease in the Russian Federation, based on the results of expanded neonatal screening for 2023–2024, is 1:8,439 [20].

Primary immunodeficiencies

(ICD-10 code — D80 Immunodeficiencies with predominant antibody deficiency; D81 Combined immunodeficiencies; D82 Immunodeficiencies associated with other significant defects; D83 Common variable immunodeficiency; D84 Other immunodeficiencies)

Congenital immune disorders are a diverse group of genetically determined diseases characterized by defects in components of the immune system. Primary immunodeficiencies are caused by genomic, chromosomal, and gene mutations. Screening for primary immunodeficiencies is performed using a molecular genetic method. Extrachromosomal circular structures formed during the differentiation of T-cell (TREC — T-receptor excision circle) and B-cell (KREC — kappa-deletion recombination excision circle) lymphocyte receptors are identified. The number of TREC/KREC copies reflects how many T and B cells have left the thymus and bone marrow and entered the bloodstream. A decrease in TREC/KREC levels below the threshold indicates a possible defect in the T- and B-cell components of immunodeficiency. Retesting and confirmatory diagnosis are performed using lymphocyte immunophenotyping by flow cytometry, as well as molecular cytogenetic and molecular genetic testing methods. The most common conditions identified by neonatal screening results are: severe combined immunodeficiency, Di George syndrome, Nijmegen syndrome, and agammaglobulinemia with B-cell deficiency. Patients are monitored by an immunologist. It should be noted that TREC/KREC screening does not detect all forms of primary immunodeficiencies [21].

CONCLUSION

Neonatal screening allows for early detection of the targeted diseases and the initiation of timely treatment. It is important to remember that despite normal levels of tested markers, a newborn should be re-examined and/or referred for consultation with an appropriate specialist if there is clinical suspicion of a disease that can be diagnosed through neonatal screening. Identifying a hereditary disease in a family makes it possible to provide medical-genetic counseling and assist parents in having a healthy child, including the use of assisted reproductive technologies.

ADDITIONAL INFORMATION

Author contribution. D.O. Ivanov — significant contribution to the concept and design of the article, data collection and analysis; L.V. Lyazina — collection of information on nosological forms of diseases included in the diagnosis of neonatal screening, data on the frequency of occurrence, description of the clinical picture, and preparation of the article; L.A. Fedorova — collection of data and description of the clinical picture in the neonatal period for nosological forms, and final approval.

All authors read and approved the final version before publication.

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REFERENCES

1. Neonatal screening: national guidelines. S.I. Kutsev, ed. Moscow: GEOTAR-Media; 2023. 360 p.
2. Dokshukina A.A., Shubina E., Pavlova N.S. et al. Pilot regional project using selective exome screening of newborns: first results. *Neonatology: News, Opinions, Training*. 2025;13(2):33–44. (In Russ.). https://doi.org/10.33029/2308-2402-2025-13-2-33-44.
3. Clinical guidelines. Congenital hypothyroidism in children. URL: https://cr.minzdrav.gov.ru/preview-cr/712_2 (accessed: 12.11.2025).
4. Clinical guidelines. Cystic fibrosis (mucoviscidosis). URL: https://cr.minzdrav.gov.ru/preview-cr/372_3 (accessed: 12.11.2025).
5. Clinical guidelines. Congenital dysfunction of the adrenal cortex (Adrenogenital syndrome). Available at: https://cr.minzdrav.gov.ru/preview-cr/914_1 (accessed: 12.11.2025).
6. Clinical guidelines. Galactose metabolism disorders (Galactosemia). URL: https://cr.minzdrav.gov.ru/preview-cr/375_3 (accessed: 12.11.2025).
7. Clinical guidelines. Multiple carboxylase deficiencies (biotinidase and holocarboxylase synthetase deficiency). URL: https://cr.minzdrav.gov.ru/preview-cr/937_1 (accessed: 12.11.2025).
8. Clinical guidelines. Classical phenylketonuria and other types of hyperphenylalaninemia). URL: https://cr.minzdrav.gov.ru/preview-cr/482_2 (accessed: 12.11.2025).
9. Clinical guidelines. Hereditary tyrosinemia type 1. URL: https://cr.minzdrav.gov.ru/preview-cr/409_3 (accessed: 12.11.2025).
10. Clinical guidelines. Maple syrup urine disease. URL: https://cr.minzdrav.gov.ru/preview-cr/385_3 (accessed: 12.11.2025).
11. Clinical guidelines. Disorder of sulfur-containing amino acid metabolism (homocystinuria). URL: https://cr.minzdrav.gov.ru/preview-cr/483_3 (accessed: 12.11.2025).
12. Baydakova G.V., Avakyan M.M., Kekeeva T.N., Degtyareva A.V., Sokolova E.V., Abrukova A.V. et al. Urea cycle disorders: clinical and genetic characteristics of the cases identified in the Russian Federation during the expanded neonatal screening. *Medical Genetics*. 2024;23(11):18–33. (In Russ.). https://doi.org/10.25557/2073-7998.2024.11.18-33.
13. Clinical guidelines. Propionic acidemia/aciduria. URL: https://cr.minzdrav.gov.ru/preview-cr/681_2 (accessed: 12.11.2025).
14. Clinical guidelines. Other branched-chain amino acid metabolism disorders (Methylmalonic acidemia/aciduria). URL: https://cr.minzdrav.gov.ru/preview-cr/387_3 (accessed: 12.11.2025).
15. Clinical guidelines. Isovaleric acidemia/aciduria. URL: https://cr.minzdrav.gov.ru/preview-cr/405_3 (accessed: 12.11.2025).
16. Clinical guidelines. 3-hydroxy-3-methylglutaryl-CoA lyase deficiency. URL: https://cr.minzdrav.gov.ru/preview-cr/790_1 (accessed: 12.11.2025).
17. Clinical guidelines. Glutaric aciduria type 1. URL: https://cr.minzdrav.gov.ru/preview-cr/406_3 (accessed: 12.11.2025).
18. Clinical guidelines. 3-Methylcrotonyl-CoA carboxylase deficiency (3-methylcrotonylglycinuria, methylcrotonyl CoA carboxylase deficiency). URL: https://cr.minzdrav.gov.ru/preview-cr/788_1 (accessed: 12.11.2025).
19. Clinical guidelines. Mitochondrial beta oxidation of fatty acids. URL: https://cr.minzdrav.gov.ru/preview-cr/694_2 (accessed: 12.11.2025).
20. Clinical guidelines. Proximal spinal muscular atrophy 5q. URL: https://cr.minzdrav.gov.ru/preview-cr/593_3 (accessed: 12.11.2025).
21. Clinical guidelines. Primary immunodeficiencies with predominant deficiency of antibody synthesis. URL: https://cr.minzdrav.gov.ru/preview-cr/735_1 (accessed: 12.11.2025).

ЛИТЕРАТУРА

1. Неонатальный скрининг: национальное руководство. С.И. Куцев, ред. М.: ГЭОТАР-Медиа; 2023. 360 с.
2. Докшукина А.А., Шубина Е., Павлова Н.С. и др. Пилотный региональный проект по селективному экзомному скринингу новорожденных: первые результаты. *Неонатология: новости, мнения, обучение*. 2025;13(2):33–44. https://doi.org/10.33029/2308-2402-2025-13-2-33-44.
3. Клинические рекомендации. Врожденный гипотиреоз у детей. URL: https://cr.minzdrav.gov.ru/preview-cr/712_2 (дата обращения: 12.11.2025).
4. Клинические рекомендации. Кистозный фиброз (муковисцидоз). URL: https://cr.minzdrav.gov.ru/preview-cr/372_3 (дата обращения: 12.11.2025).
5. Клинические рекомендации. Врожденная дисфункция коры надпочечников (Адреногенитальный синдром). URL: https://cr.minzdrav.gov.ru/preview-cr/914_1 (дата обращения: 12.11.2025).
6. Клинические рекомендации. Нарушения обмена галактозы (Галактоземия). URL: https://cr.minzdrav.gov.ru/preview-cr/375_3 (дата обращения: 12.11.2025).
7. Клинические рекомендации. Множественная недостаточность карбоксилаз (недостаточность биотинидазы и синтетазы голокарбоксилаз). URL: https://cr.minzdrav.gov.ru/preview-cr/937_1 (дата обращения: 12.11.2025).
8. Клинические рекомендации. Классическая фенилкетонурия и другие виды гиперфенилаланинемии. URL: https://cr.minzdrav.gov.ru/preview-cr/482_2 (дата обращения: 12.11.2025).

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

9. Клинические рекомендации. Наследственная тирозинемия 1 типа. URL: https://cr.minzdrav.gov.ru/preview-cr/409_3 (дата обращения: 12.11.2025).
10. Клинические рекомендации. Болезнь «кленового сиропа». URL: https://cr.minzdrav.gov.ru/preview-cr/385_3 (дата обращения: 12.11.2025).
11. Клинические рекомендации. Нарушение обмена серосодержащих аминокислот (гомоцистинурия). URL: https://cr.minzdrav.gov.ru/preview-cr/483_3 (дата обращения: 12.11.2025).
12. Байдакова Г.В., Авакян М.М., Кекеева Т.Н., Дегтярева А.В., Соколова Е.В., Абрукова А.В. и др. Нарушения цикла мочевины: клинико-генетические характеристики случаев, выявленных в Российской Федерации в рамках программы расширенного неонатального скрининга. *Медицинская генетика*. 2024;23(11):18–33. https://doi.org/10.25557/2073-7998.2024.11.18-33.
13. Клинические рекомендации. Пропионовая ацидемия/ацидурия. URL: https://cr.minzdrav.gov.ru/preview-cr/681_2 (дата обращения: 12.11.2025).
14. Клинические рекомендации. Другие виды нарушения обмена аминокислот с разветвленной цепью (Метилмалоновая ацидемия/ацидурия). URL: https://cr.minzdrav.gov.ru/preview-cr/387_3 (дата обращения: 12.11.2025).
15. Клинические рекомендации. Изовалериановая ацидемия/ацидурия. URL: https://cr.minzdrav.gov.ru/preview-cr/405_3 (дата обращения: 12.11.2025).
16. Клинические рекомендации. Дефицит 3-гидрокси-3-метилглутарил-КоА лиазы. URL: https://cr.minzdrav.gov.ru/preview-cr/790_1 (дата обращения: 12.11.2025).
17. Клинические рекомендации. Глутаровая ацидурия тип 1. URL: https://cr.minzdrav.gov.ru/preview-cr/406_3 (дата обращения: 12.11.2025).
18. Клинические рекомендации. Недостаточность 3-метилкротонил-КоА карбоксилазы (3-метилкротонилглицинурия, метилкротонил КоА карбоксилазная недостаточность). URL: https://cr.minzdrav.gov.ru/preview-cr/788_1 (дата обращения: 12.11.2025).
19. Клинические рекомендации. Нарушения митохондриального бета окисления жирных кислот. URL: https://cr.minzdrav.gov.ru/preview-cr/694_2 (дата обращения: 12.11.2025).
20. Клинические рекомендации. Проксимальная спинальная мышечная атрофия 5q. URL: https://cr.minzdrav.gov.ru/preview-cr/593_3 (дата обращения: 12.11.2025).
21. Клинические рекомендации. Первичные иммунодефициты с преимущественной недостаточностью синтеза антител. URL: https://cr.minzdrav.gov.ru/preview-cr/735_1 (дата обращения: 12.11.2025).

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Review

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Gut microbiota of full-term and preterm newborns: role in the development of infectious diseases and possibilities for correction (literature review)

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ABSTRACT. ***Introduction.*** The study of the gut microbiota in newborns is an important area of modern medicine, as its development affects immunity, metabolism, and overall child health. This issue is particularly relevant for preterm infants, whose microbiota maturation is delayed, increasing the risk of infections and chronic diseases. The composition and functional state of the microbiota are significantly influenced by the mode of delivery, antibiotic therapy, and type of feeding, although these factors require further investigation. ***Aim*** – to systematize current data on the factors affecting the intestinal microbiota of full-term and premature newborns, and methods of its correction. ***Materials and methods.*** This article presents a review of scientific literature, including clinical studies and systematic reviews. Data were analyzed regarding methods of microbiota assessment, and the influence of delivery mode, antibiotic therapy, breastfeeding, formula feeding, and treatment with prebiotics and probiotics on gut microbiota composition. ***Results.*** A healthy gut microbiota in newborns plays a crucial role in preventing infectious diseases. Disturbances of the intestinal microbiota caused by cesarean section, antibiotic therapy, and formula feeding are associated with reduced colonization resistance and the proliferation of opportunistic bacteria (*Klebsiella* spp., *Enterococcus* spp., *Pseudomonas* spp.), increasing the risk of sepsis and necrotizing enterocolitis. The use of probiotics and prebiotics helps reduce infectious morbidity by restoring microbial balance and strengthening the intestinal barrier, making microbiota correction an important direction in the prevention and treatment of neonatal infections. ***Conclusion.*** The formation of a healthy gut microbiota in newborns is critical for their long-term health. Current evidence highlights the importance of vaginal delivery, breastfeeding, and rational antibiotic use in the care of preterm infants. Probiotics represent a promising approach for correcting microbiota disturbances in newborns; however, further studies are needed to optimize their use.

KEYWORDS: *intestinal microbiota, newborns, preterm infants, infectious diseases, probiotics*

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Обзор
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Микробиота кишечника доношенных и недоношенных новорожденных: роль в развитии инфекционных заболеваний и возможности коррекции (обзор литературы)

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РЕЗЮМЕ. ***Введение***. Изучение микробиоты кишечника новорожденных является важным направлением современной медицины, так как ее становление влияет на иммунитет, метаболизм и здоровье детей. Особенно актуальна эта проблема для недоношенных детей, у которых замедлено развитие микробиоты, что повышает риск инфекций и хронических заболеваний. На состав и функциональное состояние микробиоты существенно влияют способ родоразрешения, антибиотикотерапия и тип вскармливания, хотя это и требует дальнейшего изучения. ***Цель*** — систематизировать современные данные о факторах, влияющих на микробиоту кишечника доношенных и недоношенных новорожденных, и методах ее коррекции. ***Материалы и методы.*** В статье проведен обзор научной литературы, включая клинические исследования и систематические обзоры. Использованы данные о методах изучения микробиоты, влиянии на микробиоту способа родоразрешения, антибиотикотерапии, грудного вскармливания и искусственных питательных смесей, лечения пребиотиками и пробиотиками. ***Результаты.*** Здоровая кишечная микробиота новорожденных играет значительную роль в профилактике инфекционных заболеваний. Нарушение микробиоты кишечника, вызванное кесаревым сечением, антибиотикотерапией и искусственным вскармливанием, сопровождается снижением колонизационной резистентности и ростом условно-патогенных бактерий (*Klebsiella* spp., *Enterococcus* spp., *Pseudomonas* spp.), что повышает риск развития сепсиса и некротизирующего энтероколита. Применение пробиотиков и пребиотиков способствует снижению инфекционной заболеваемости за счет восстановления микробного баланса, укрепления барьерной функции кишечника, что делает коррекцию микробиоты важным направлением профилактики и терапии инфекций у новорожденных. ***Заключение***. Формирование здоровой микробиоты у новорожденных критически важно для их долгосрочного здоровья. Современные данные подтверждают значимость естественных родов, грудного вскармливания и рационального использования антибиотиков при выхаживании недоношенных детей. Пробиотики представляют перспективное направление для коррекции нарушений микробиоты новорожденных, однако необходимы дополнительные исследования для оптимизации их применения.

КЛЮЧЕВЫЕ СЛОВА: *микробиота кишечника, новорожденные, недоношенные дети, инфекционные заболевания, пробиотики*

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INTRODUCTION

The development of gut microbiota in newborns is one of the most promising yet under-researched areas of modern medicine. Although recent studies by scientists such as Y. Chen et al. (2021) have significantly advanced our understanding of the microbiota's impact on human health, many aspects of its impact on newborns remain unclear [1, 2].

The book by V.P. Novikova et al., "The Gut Microbiota as a Regulator of Human Organs and Systems" (2025), demonstrates that gut microbial communities participate in shaping the immune response, regulating inflammatory processes, metabolism, and neurohumoral interactions. Disruptions in their composition are associated with infectious, inflammatory, and metabolic diseases. During the neonatal period, particularly in preterm infants, microbial immaturity and its high sensitivity to external factors determine an increased risk of infectious complications. Therefore, the establishment and regulation of a healthy gut microbiota represent a priority in modern medicine [3].

There are a number of gaps in our understanding of mechanisms influencing delivery methods, dietary characteristics, and the effects of antibiotic therapy on microbiota development during the neonatal period. Furthermore, long-term consequences of impaired intestinal microbiota development, including autoimmune and metabolic diseases, remain poorly understood [4].

Current approaches to restoring and maintaining a healthy microbiota in preterm infants involve the use of probiotics and prebiotics. However, methods for their administration are not yet fully developed, although the results of studies examining their effect on the gut microbiota in infants are encouraging [5–7].

Thus, this topic is important due to its role in preserving children's health, as well as the need to develop effective approaches in order to prevent and treat diseases caused by an imbalance in the microbiota of newborns, which should help reduce morbidity and improve the quality of life for infants.

METHODS FOR ANALYZING THE GUT MICROBIOTA ARE RESEARCH TECHNIQUES, STANDARDIZATION OF SAMPLE COLLECTION AND STORAGE CONDITIONS

Gut microbiota profiling provides an assessment of the qualitative and quantitative composition of the microbial community, as well as its functional capabilities [8]. Traditionally, intestinal microbiota is studied by isolating and culturing bacteria. However, there are difficulties in culturing anaerobic microorganisms, which significantly reduce reliability of the results. Metagenomic sequencing analyzes the DNA of both cultivable and uncultivable microorganisms based on 16S rRNA gene sequencing. The application of next-generation sequencing (NGS) technologies for microbiome research is particularly interesting. The real-time polymerase chain reaction (PCR) allows for determining representation of bacteria of a single species or closely related species using taxon-specific primers. DNA fingerprinting provides a semi-quantitative assessment of the overall diversity of the bacterial community of gut microorganisms. Functional metagenomic profiling provides quantitative information on the relative abundance of individual genes, gene clusters, and metabolic pathways. Microbiome profiling results are used to assess the pathogenic burden of dysbiosis, predict its consequences, and develop targeted measures to correct microbiome imbalances.

Fecal samples are most commonly used in studies of the gut microbiota composition. However, it is important to note that the microbial community in the mucosa of different sections of the colon and in feces differs [9].

Since fresh fecal samples are not always analyzed immediately, there is a need to store them. Freezing at –80 °C without preservatives preserves the microbial composition and is considered the "gold standard" for microbiome studies [10]. Large-scale population studies typically employ optimal sample collection methods; however, maintaining a temperature of –80 °C is not always feasible. This necessitates the search for alternative methods that minimize analytical errors. Swallowed capsules for sample collection are considered one of the most promising options, as they ensure high accuracy and sensitivity of the research data [11].

In addition to freezing, there are other sample storage methods (with or without preservatives) that allow the microbiota to be preserved in a state close to fresh samples. These are fecal occult blood test cards, FTA (Fast Technology for Analysis of Nucleic Acids) cards, Whatman® FTA® cards), and the Genotek DNA kit, which enables the development of microbiome-based clinical

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applications using OMNIgene™ GUT Dx—the first and only FDA-approved (Food and Drug Administration, U.S. Department of Health and Human Services) device for self-collection of stool samples. These methods have now proven effective for storing samples for several days at room temperature [12]. For stable storage of stool samples, 95% ethanol or RNAlater sample preservation solution is recommended as a preservative [13].

G.M. Williams et al. (2019) recommend to collect the first samples within the first 24 hours of life (the first stool, meconium), and then to repeat the collection on days 1, 3, 7, 14, and 30. Collecting meconium allows for assessing initial sterility or early intestinal colonization. However, the bacterial load in meconium is very low, and it is not always possible to obtain a sufficient amount of DNA for sequencing. On the 1st–3rd day of life, after contact with a mother and environment, active intestinal colonization begins. Microbiome studies on days 7, 14, and 30 allow for tracking the dynamics of microbiome formation and the influence of external factors (mode of delivery, feeding methods, etc.) [14].

FORMATION OF THE PRIMARY GUT MICROBIOTA IMMEDIATELY AFTER BIRTH AND ITS CHANGES IN NEWBORNS AND INFANTS

The development of the gut microbiota during the neonatal period is characterized by significant changes in taxonomic composition and biodiversity. This process is determined by a complex of factors: the gestational age at birth, mode of delivery, characteristics of the mother's diet and health, type of feeding, use of antibiotics in premature infants, as well as social and environmental conditions (family members, presence of siblings and pets).

The existence of microbial colonization of the human gut before birth remains a controversial topic. For a long time, the scientific community held the view that the amniotic cavity was "sterile." However, recent years have seen the detection of protein markers of microbial colonization in amniotic fluid from women with preterm rupture of membranes using an antibody microarray via enzyme-linked immunosorbent assay (ELISA) and protein and antibody microchip technology, which supports the possibility of fetal intestinal colonization by maternal microorganisms [15].

The results of microbiological studies of the human placenta are contradictory. Data from K.M. Kennedy et al. (2023) and I. Sterpu et al. (2021) did not confirm the presence of placental microbiota. The authors believe that their findings are most likely the result of "contamination of the material under study", when obtaining samples of fetal tissue during clinical procedures or during DNA extraction and sequencing [16, 17]. At the same time, data from A. Stupak et al. (2024), based on studies of placental proteins obtained during childbirth using liquid chromatography coupled with mass spectrometry, indicated the possible presence of a number of proteins specific to bacteriophages and viruses, whose role as early markers of fetal infection has not been definitively established [18].

Research by Q. He (2020) detected the presence of bacteria in the meconium of newborns, indicating that the intestine is not sterile prior to birth. In the first days and months of life, the number and diversity of bacteria in children's feces were low, but shortly after complementary feeding began and against the backdrop of active physical development, a rapid increase in the number of bacteria and an expansion of their diversity were observed [19].

Composition and functions of the mother's gut microbiota directly influence fetal and newborn microbiota development. Experimental studies in germ-free animals and clinical observations in humans have confirmed that the mother's microbial profile during pregnancy determines the development of the fetus's immune system and its resistance to infections after birth. Disruptions in the mother's microbiota are associated with an increased risk of intrauterine inflammatory reactions and infectious complications in newborns. It has been shown that the intestinal microbiota participates in shaping the fetal "gut-brain axis," mediating the maturation of immune and neuroregulatory mechanisms that provide anti-infectious protection in the early postnatal period [20].

Initially, the gut is colonized by microbes acquired from the mother and the environment. Children born naturally are dominated by bacteria from the mother's birth canal, such as *Lactobacillus spp., Prevotella* spp., and *Sneathia* spp., whereas children born via cesarean section are predominantly colonized by "skin" microorganisms, including *Staphylococcus* spp. and *Propionibacterium*

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spp. During the first week of life, bacteria that are adapted to the intestinal environment predominate, including *Bifidobacterium* spp., *Bacteroides* spp., and *Escherichia coli* spp. [21].

A single-study analysis of the gut microbiota in 11 healthy infants in their first year of life, conducted by N.V. Gonchar et al. (2017) using sequencing of amplified *16S* rRNA gene regions, revealed a predominance of Gram-positive anaerobic bacteria (71±23%). The quantitative distribution of phyla decreased in the following order: the phylum *Firmicutes* – 43±15% (represented by *Clostridium* spp., *Blautia* spp., *Lactobacillus* spp., *Enterococcus* spp., and *Veillonella* spp.), the phylum Actinobacteria – 38±10% (more than 90% of OTUs represented by *Bifidobacterium* spp.), and the phylum *Proteobacteria* – 15±8% (represented by the family *Enterobacteriaceae*). Representatives of the phylum Bacteroidetes were identified (7–15%) in three samples only. All samples were characterized by low species diversity; the Shannon index and α-diversity criterion ranged from 1.5 to 4.2 and 3 to 20, respectively. Breastfed infants had a higher abundance of *Proteobacteria* compared to formula-fed infants. The influence of adverse factors during the mothers' pregnancies (antibiotic use, respiratory infection) on infants' gut microbiota composition was noted [22].

According to data from A.V. Kaplina et al. (2023), intestinal dysbiosis may serve as a predisposing factor for necrotizing enterocolitis. Antibiotic therapy leads to a predominance of facultative anaerobes, such as *Enterococcus* spp. and *Enterobacteriaceae*, as well as a decrease in *Bifidobacteriaceae* in the gut microbiome of preterm newborns. Antimicrobial therapy disrupts the physiological process of colonization, and the formation of normal microbiota (its "maturation") may be delayed. However, they note that dysbiosis is not the primary cause of necrotizing enterocolitis, and the mother's health status, as well as the characteristics of fetal development and the early postnatal period, play a significant role [23].

S. Graspeuntner et al. (2024) investigated the gut microbiota in infants under 90 days of age with late-onset sepsis using 16S rRNA sequencing of stool samples. They found a decrease in the number of *B. longum* and an increase in the number of *Bacteroidia* spp. in patients with lactic acidosis upon hospital admission. Authors suggested that previously healthy infants developing sepsis exhibited gut microbiota dysbiosis combined with undefined specific immunological patterns. The study demonstrated that the healthy gut microbiota of infants is characterized by the absence of overgrowth of opportunistic microorganisms (OM). Furthermore, it plays a crucial role in the development and stable functioning of the immune and digestive systems [24].

A dissertation study by G.N. Chistyakov (2024) identified informative immunological markers such as absolute white blood cell count, relative counts of CD14+HLA-DR+ and CD14+CD11b+ monocytes in umbilical cord blood. These markers make it possible to predict the risk of intestinal colonization by *K. pneumoniae*, an opportunistic pathogen from ESKAPE group in premature infants during the neonatal period [25].

A systematic literature review by C. Alcazar et al. (2022) attempted to confirm the association between the gut microbiota in infants aged 0 to 12 months, assessed using genomic sequencing, and respiratory diseases of infectious and allergic nature in children under 18 years of age. The authors suggest that low α-diversity of the microbiota and the relative abundance of certain genera of commensal gut bacteria (*Bifidobacterium, Faecalibacterium, Ruminococcus*, and *Roseburia*) are associated with respiratory diseases in children. However, the study results were contradictory, as there were significant limitations, including insufficient characterization of bacterial taxa at the species level, inconsistent interpretation of the data, residual confounding factors, and a small sample [26].

A study by Y. Gao et al. (2021) provides evidence that the maternal gut microbiome influences the risk of allergic diseases and asthma in children. Similarly, a study by X. Yuan et al. (2022) demonstrates a link between gut microbiota dysbiosis in early childhood and an increased risk of developing metabolic diseases, such as obesity and type 1 diabetes [27, 28]. These findings have served as the basis for developing therapeutic strategies aimed at early correction of gut dysbiosis using probiotics and prebiotics [29].

As shown in the study by Q. Jia et al. (2022), preterm newborns exhibit slower gut microbiota establishment compared to term infants, accompanied by higher species diversity of the gut microbiota. These findings provide new insights

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into the need for individualized interventions to modulate the microbiota composition regarding varying gestational ages at different periods after birth [30].

Y. Chen et al. (2023) analyzed changes in microbial composition in fecal samples from 92 preterm infants treated in the intensive care unit, starting at birth and continuing at 1, 3, 7, 14, 21, 28, and 60 days of life using 16S rRNA sequencing. The results showed that the main types of gut bacteria in preterm infants were *Proteobacteria, Firmicutes, Actinobacteria, Tenericutes*, and *Bacteroidetes*, collectively accounting for 99.7% of the microbial community. *Pseudomonas* spp., *Staphylococcus* spp., and *Klebsiella* spp. predominated at the genus level, along with unclassified members of the *Enterobacteriaceae* family and the *Clostridium-sensu-stricto-1* group, which together accounted for 90.9% of the total microbiota. The abundance of *Proteobacteria*, including the genus *Pseudomonas*, initially decreased, reaching a minimum on the 14th day of life, after which it increased again. Concurrently, there was a decrease in the number of *Firmicutes*. At the same time, in formula-fed infants, the proportion of *Proteobacteria* (at the phylum level) and *Streptococcus* spp. (at the genus level) was significantly higher compared to breastfed infants [31].

The study by C. Chi et al. (2019) aimed to compare gut microbiome composition in infants with very low birth weight (VLBW) and normal birth weight (NBW) during the first three months of life using 16S rRNA gene sequencing. Fecal samples were collected at 0 and 3 days, 2 and 6 weeks, and 3 months of age (defined as microbiota development stages 1–5). The authors found that α-diversity decreased over time in both groups. The Shannon index revealed significant differences between the groups at stages 1–3. The structure of the gut microbiota in LBW infants differed significantly from that in NBW infants throughout the entire observation period. In children with LBW, an increase in Firmicutes and a decrease in *Proteobacteria* were observed; at birth, *Enterococcus* spp., *Klebsiella* spp., and *Streptococcus* spp. predominated, whereas *Haemophilus* spp. were underrepresented [32].

E.W. Blakstad et al. (2019) investigated the effect of feeding practices on the development of healthy gut microbiota in infants with very low birth weight (VLBW) and extremely low birth weight (ELBW). Fifty preterm newborns were divided into an experimental group receiving enhanced nutrition and a control group. Fecal samples from 45 infants were analyzed using 16S rRNA sequencing. The group receiving enhanced nutrition showed a more significant increase in gut microbiota diversity and a decrease of staphylococci, while no increase in the number of pathogenic microorganisms was observed. The relative abundance of bifidobacteria increased more in the control group, where better weight gain was also observed. In preterm newborns, the establishment of the *Bifidobacterium* spp. population was characterized by delayed colonization and low abundance, requiring more time to achieve an optimal composition [33].

DELIVERY METHOD AND ITS IMPACT ON GUT MICROBIOTA IN NEWBORNS

A systematic review by L. Princisval et al. (2021) showed that neonates born vaginally acquire a gut microbiota in the first weeks of life that is similar in composition to their mother's. At the same time, newborns delivered via cesarean section have a gut microbiota composition that more closely corresponds to the environment. During the first 90 days of life, infants born via vaginal delivery exhibit increased bacterial diversity in the *Actinobacteria* and *Bacteroidetes phyla*, including *Bifidobacterium* spp. and *Bacteroides*, compared to those born via cesarean section [34].

According to a study by Y. Chen et al. (2021), infants born via cesarean section exhibited a decrease in α-diversity of the microbiota. A particularly notable decrease was observed in the abundance of *Bifidobacterium* spp. during the first three months of life, whereas representatives of the genera *Enterococcus* spp., *Klebsiella* spp., *Streptococcus* spp., *Haemophilus* spp., and *Veillonella* spp. demonstrated active colonization from the first week of life up to one month. Among bacterial families, *Veillonellaceae* and *Enterobacteriaceae* were dominant [35].

The lack of contact with the maternal vaginal microbiota in children born via cesarean section is considered one of the reasons for the increased prevalence of bacteria from the *Firmicutes* phylum and reduced colonization by mem-

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bers of *Bifidobacterium* spp. and *Bacteroidetes*. All of these are crucial for carbohydrate digestion and the development of the immune system. This change is associated with a reduced ability of the microbiota to metabolize carbohydrates, including oligosaccharides found in breast milk [36].

The work of L. Li et al. (2021) shows that elective cesarean section is considered the most important factor that can delay the onset of breastfeeding and shorten its duration [37]. Research by L.M. Mallick et al. (2024) also shows that women who underwent both elective and emergency cesarean sections are generally more likely to discontinue breastfeeding than women who gave birth vaginally [38]. This negatively affects the diversity and structure of infant gut microbiota, reducing the colonization of *Lactobacilli* spp. and *Bifidobacterium* spp., and increases the risk of developing autoimmune diseases (inflammatory bowel disease, rheumatoid arthritis, celiac disease) and metabolic disorders due to a feedback mechanism between systemic inflammation and dysregulation of the gut microbiota [36].

FEEDING OF NEWBORNS IN RELATION TO THE INTESTINAL MICROBIOTA

Active research continues, focusing on how microbial populations develop in the intestines of infants depending on their age and feeding method. N. Chin et al. (2021) found that adding formula to breast milk affects the gut microbiota and the immune system of infants. The study included 24 infants who, by one month of age, were either exclusively breastfed or formula-fed. The analysis involved 16S rRNA gene sequencing of stool samples and flow cytometry of blood samples from birth to six months of age, as well as classification of *Bifidobacterium* spp. strains. The results showed that the addition of formula caused temporary changes in microbial composition, which disappeared by six months of age. At the same time, *B. longum*, a species associated with breastfeeding, decreased significantly upon formula introduction during the first month of life. No significant immunological differences, including the development of T- and B-cell subpopulations or monocytes, were identified [39].

L. Beller et al. (2021) conducted a study of changes in microbiota composition during the first year of life in 8 infants, analyzing 303 samples. In order to assess the transition from infant to adult microbiota, the authors compared the obtained data with samples from participants in the "Flemish Gut Microbiota" project (1,106 samples). Formula feeding reduced the likelihood of *Bifidobacterium* spp. presence compared to breastfeeding. In some infants, *Bifidobacterium* spp. appeared only after the introduction of solid foods, whereas in their absence, *Bacteroides, Clostridia*, and *E. coli* typically dominated [40].

A study by I. Cuxart et al. (2022) provides additional data on the enzymatic processing of oligosaccharides by the gut microbiota in the first months of life. Breast milk oligosaccharides (BMOs), such as galacto-oligosaccharides, play a leading role in microbiota development; these are partially digested in the small intestine and fermented in the large intestine, promoting the growth of *Bifidobacterium* spp. It has been established that lacto-N-biosidase (LnbB), produced by *B. bifidum*, plays a crucial role in the breakdown of human milk oligosaccharides in the intestines of breastfed infants [41]. This process leads to the formation of short-chain fatty acids; the latter inhibit opportunistic pathogens, including members of the *Clostridiaceae, Enterobacteriaceae*, and *Staphylococcaceae* families. Breastfed infants show an increase in *Bifidobacterium* spp., a decrease in BMO in stool, and elevated levels of acetic and lactic acids. These findings confirm the prebiotic effect of breast milk, which promotes the selective enrichment of the microbiota with *Bifidobacterium* spp. [42].

Breast milk is referred to as a complex food matrix with numerous components that can potentially influence the composition of an infant's microbiota, promoting the growth of indigenous bacteria and limiting the growth of opportunistic pathogens. It has also been shown that *Bifidobacterium* spp., particularly *B. infantis*, correlate with increased levels of secretory immunoglobulin A (sIgA), ensuring adequate local immunity in the gut. The synergistic effects of BMO and *Bifidobacterium* spp. on infants promote the diversity and maintenance of gut microbiota balance, as well as the strengthening of the immune system [43].

Research by G. Boudry et al. (2021) indicates that breastfeeding in early life opens a "window

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of opportunity" for health development through microbial modulation. The authors described the composition of breast milk and established the role of its components in shaping the gut microbiota. Among the most frequently mentioned genera, *Staphylococcus* spp. and *Streptococcus* spp. were identified as universally predominant in breast milk. Other bacterial genera are also frequently mentioned, including *Corynebacterium* spp., *Bifidobacterium* spp., *Propionibacterium* spp., *Bacteroides* spp., *Enterococcus* spp., *Faecalibacterium* spp., *Lactobacillus* spp., *Veillonella* spp., *Serratia* spp., *Ralstonia* spp., *Acinetobacter* spp., *Rothia* spp., and several representatives of the families *Lachnospiraceae* and *Ruminococcaceae* [44]. Studies by J.M. Vélez-Ixta et al. (2024) show that breast milk-mediated colonization is a specialized pathway through which bacteria selectively migrate into the newborn's gut, playing a crucial role in its development, as breast milk contains a wide range of microorganisms, including "skin" and "non-skin" Gram-positive bacteria [45].

Studies by V. Notarbartolo et al. (2022) have established that breast milk contains not only bacterial but also viral, fungal, and archaea components. The composition of breast milk can be influenced by various factors, such as the mother's body mass index and diet, antibiotic use, the timing and method of delivery, as well as the method of breastfeeding. At the same time, indigenous microorganisms such as streptococci (*S. mitis* and *S. salivarius*) and coagulase-negative staphylococci, which predominate in breast milk, compete for space and resources with opportunistic microorganisms, such as *S. aureus* [46].

K. Ingram et al. (2024) analyzed 46 breast milk samples from 15 women, collected 1, 4, 7, and 10 months postpartum. The authors used a metagenomic approach to assess the bacterial microbiota and found that microbiota composition in breast milk changes at different stages of lactation. They believe that data on breast milk bacteria can be used to predict and reduce health risks for infants [47]. The results of a study by Y. Komatsu et al. (2022) established that oligosaccharides disappear from infants' feces at the beginning of the fourth month of breastfeeding, when a shift in the species of Bifidobacterium occurs (from *B. breve* to *B. longum* subsp. *infantis*). This process is accompanied by fluctuations in the levels of several metabolites in infant feces, including acetate and butyrate. Consequently, breast milk components modulate gut microbiota composition and metabolite production (e.g., short-chain fatty acids) and may indirectly influence the immune and metabolic responses of infants [48].

Although breastfeeding is the gold standard for infant nutrition, there is a growing need to devote more effort to the production of infant formula, which must closely resemble the composition of breast milk and act similarly. One way to achieve these goals is to add various bioactive ingredients to formula, including probiotics, prebiotics, vitamins, and trace elements. Scientific data on beneficial effects of infant formula indicate its overall positive impact on the gut microbiota and its metabolic activity [49].

ANTIBIOTIC THERAPY AND GUT MICROBIOTA OF NEWBORNS

Antibiotics remain a key method for treating infectious diseases. However, irrational use of such drugs, particularly during pregnancy and in the first months of a child's life, can lead to adverse long-term consequences. These include developing resistance to antibiotics, as well as persistent disruptions in the structure and activity of gut microbiome, which may negatively affect health in future [50].

T.H. Dierikx et al. (2020) found that antibiotic therapy in mothers before or during childbirth negatively affects intestinal microbiota establishment in newborns, reducing microbial diversity, lowering the proportion of *Actinobacteria* and *Bacteroidetes*, and increasing *Proteobacteria*. It has been shown that these changes in the gut microbiota are distinctly pronounced in children born vaginally and may persist for up to 12 months of life [1].

According to data from C. Argentini et al. (2022), as well as C. Ozkul et al. (2020), antibiotic therapy in newborns, particularly the combination of amoxicillin and clavulanic acid, significantly disrupts gut microbiota, reducing its species diversity and triggering metabolic disorders and dyspeptic symptoms [51, 52]. At the same time, since resistance to amoxicillin among *Bifidobacterium* spp. is rarely observed (and this is considered a species-independent trait), its use reduces the potential influence of bifidobacteria [53].

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Intrapartum antibiotic therapy has become a common practice in obstetrics and is used in 40% of assisted deliveries. A systematic review by P. Zimmermann and N. Curtis (2020) demonstrated how ampicillin, prescribed to pregnant women with a positive GBS status (*group B Streptococcus*), negatively affects the gut microbiota of infants. The authors identified six studies involving 272 infants. A total of 502 stool samples were analyzed from children under 3 months of age. Infants exposed to intrapartum antibiotic therapy for group B streptococcal infection had fewer bacteria in their gut microbiota, fewer actinobacteria, particularly bifidobacteria, and more proteobacteria compared to infants who did not receive intrapartum antibiotic treatment [54]

Understanding the impact of widely used antibiotic therapy on the gut microbiota and butyrate-producing microorganisms in infants can aid in making therapeutic decisions in neonatal intensive care units. According to data from J. Qiu et al. (2025), antibiotic therapy in newborns negatively affects the initial development of the gut microbiota: it leads to a decrease in diversity, a reduction in the relative abundance of butyrate-producing bacteria (especially *Clostridiaceae*), and an increase in *Enterococcidae* [55].

According to R. Ventin-Holmberg et al. (2022), even a single course of antibiotics during the period of gut microbiota formation in infants caused a shift in the fungal composition of the gut. The shift was characterized by an increased relative abundance of *Candida* as well as diversity and abundance of fungal species, which may be one of undesirable long-term health effects of antibiotics [56].

EFFECTS OF PROBIOTICS IN NEWBORNS, INCLUDING PRETERM NEONATES

There is ongoing discussion regarding differences in gut microbiota between breastfed and formula-fed infants. It is hypothesized that these differences partly explain why breastfeeding is associated with a reduced risk of numerous infectious and non-infectious diseases in early life. Recent studies by T.K. Das et al. (2022) and A. Blanchetière et al. (2023) focus on the effects of probiotic microorganisms, including members of the genera *Lactobacillus* spp., *Bifidobacterium* spp., and *Saccharomyces* spp. *Lactobacillus* spp. is the most studied and widely used bacteria in neonatology. The beneficial effects of *Lactobacillus* are associated with their ability to enhance colonization resistance, inhibit the growth of opportunistic bacteria by producing organic acids and bacteriocins, and modulate the innate and adaptive immune response. Thus, it reduces the risk of infectious diseases and necrotizing enterocolitis in preterm newborns. At the same time, the literature describes potential negative effects, which are most often associated with transfer of genetic determinants of antimicrobial resistance from *Lactobacillus* to Gram-negative microbiota. Furthermore, heterogeneity of *Lactobacillus* strains and the lack of a unified classification complicate clinical data interpretation, underscoring the need for rigorous strain selection and an individualized approach to their use in neonatal practice [6, 7, 57].

Studies by E.C. Davis et al. (2022) and Q.S. Damaceno et al. (2023) explore opportunities for using probiotic bacteria isolated from breast milk to develop new infant formulas [58, 59]. Based on the results of these studies, the strains *Lacticaseibacillus rhamnosus* and *Leuconostoc mesenteroides* have been proposed as potential probiotics in a formula mimicking breast milk [59].

Studies by M. Nguyen et al. (2023) provide a strong rationale for using probiotics in neonatal intensive care units. They found that premature infants who received the activated strain *B. infantis* EVC001 at a dose of 8×10^9 CFU per day rapidly developed a high degree of *Bifidobacteriaceae* colonization, the majority of which consisted of *B. infantis*. There was also a decrease in the number of antibiotic resistance genes and a reduction in the number of taxa containing them, such as *Enterobacteriaceae* representatives like *E. coli* and *K. pneumoniae*. Children receiving *B. infantis* EVC001 demonstrated reduced levels of enteritis inflammation markers, including calprotectin, IL-8, IL-17A, and TNFα [60].

Experience of using probiotic Enterococcus strains in long-term nutritional support for preterm infants also appeared to be successful. N.V. Gonchar et al. (2021) confirmed the efficacy and safety of long-term use of the domestic strain *E. faecium* L3 with a titer of at least 10^8 CFU/mL, which was administered orally to infants at a dose of 1 mL twice daily during meals.

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Probiotic nutritional therapy for infants with the *E. faecium* L3 strain, as part of a rehabilitation program for preterm newborns whose inpatient care had already concluded, demonstrated the potential to improve the nutritional status and neurocognitive development of preterm infants [61].

According to data from G.C. Deshpande et al. (2011), the greatest efficacy of probiotics is observed in the first week of life, provided the infant is ready for enteral feeding. Early administration of probiotics significantly reduces all-cause mortality and the incidence of necrotizing enterocolitis in preterm infants and contributes to improved food tolerance [62].

Research by N. van Best et al. (2020) showed that probiotics may be most effective in preterm newborns before stable colonization of the gut microbiota is established. Administration of probiotic formulas in the experimental group was associated with a higher relative abundance of *Bifidobacteria* and *Enterobacteria*, combined with a lower abundance of *Escherichia*, *Enterococcus*, and *Klebsiella*. Probiotic *Bifidobacteria* colonization was observed in 50% of infants, although it was often transient. Newborns receiving probiotic formulas showed a significant reduction in the incidence of necrotizing enterocolitis [63].

In a randomized intervention study by J. Samara et al. (2022) examining the effect of a probiotic product containing four strains of *Bifidobacterium* and one strain of *Lacticaseibacillus*. The researchers evaluated its impact on composition and functional trajectory of the gut microbiota in preterm infants who received the product daily starting at the onset of feeding until a gestational age of 36–37 weeks. The results demonstrated an accelerated transition to a mature microbiota similar to term infants. The results of this study indicate that *Bifidobacterium* strains, acting as "ecosystem engineers," accelerate microbiota maturation and exert an immunological effect on extremely preterm infants [64].

Currently, the use of probiotic supplements in preterm infants is considered a promising method for achieving initial "healthy colonization" of the gut during the neonatal period. Clinical data confirm their beneficial long-term effects, including anti-inflammatory effects [65, 66]. A systematic review by V.K. Batta et al. (2023), encompassing 67 randomized controlled trials, and a meta-analysis by H. Wang et al. (2023) of 70 studies showed that the use of probiotics in preterm newborns, especially those containing *B. infantis* strains, significantly reduces the risk of necrotizing enterocolitis and late-onset sepsis, thereby lowering the overall mortality rate in preterm infants [67, 68].

Despite the encouraging results obtained from the use of probiotics in newborns, questions remain unresolved regarding the algorithm for selecting strains, dosages, and regimens for probiotic use.

CONCLUSION

The gut microbiota plays a crucial role in protecting infants from infectious diseases from the very first days of life. The formation of microbial communities begins immediately after birth and depends on the mode of delivery, type of feeding, and use of antibiotics. These factors determine resistance to pathogens and effectiveness of the immune response.

Premature newborns experience a delay in microbiota establishment. Reduced diversity and stability of microbial communities increase the risk of developing severe infections, including sepsis and necrotizing enterocolitis. Intestinal dysbiosis at this age is often accompanied by overgrowth of opportunistic bacteria (*Klebsiella* spp., *Enterococcus* spp., *Pseudomonas* spp.), leading to inflammatory complications and systemic infection.

A key focus of infection prevention in newborns is maintaining a healthy microbiota. The use of probiotics and prebiotics in newborns has proven effective in reducing the incidence of late-onset neonatal sepsis and necrotizing enterocolitis, especially in preterm infants. Probiotic strains (*Bifidobacterium* spp., *Lactobacillus* spp., *E. faecium* L3) help restore normal microbial balance, strengthen the intestinal barrier function, and reduce inflammation.

Nevertheless, questions regarding the selection of optimal probiotic strains, dosages, and duration of use remain subjects for further research.

Thus, studying the development of the gut microbiota in newborns is a pressing issue and serves as the foundation for preventing infectious complications and improving disease outcomes in children at risk of dysbiosis. A deep understanding of microbiota-immune system interactions will enable the development of personalized strategies to prevent and treat infectious diseases in the early neonatal period.

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ADDITIONAL INFORMATION

Author contribution. D.M. Konyukhov — development of the article concept, search and analysis of literary sources, and writing of the article; N.V. Gonchar — development of the article concept, assistance in writing, and editing of the article; K.D. Ermolenko — development of the scientific concept of the article and editing of the text; A.N. Suvorov — participation in research planning, editing of the article, and approval of the final version.

All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Д.М. Конюхов — разработка концепции статьи, поиск и анализ литературных источников, написание статьи; Н.В. Гончар — разработка концепции статьи, содействие в написании и редактирование текста статьи; К.Д. Ермоленко — разработка научной концепции статьи и редактирование текста; А.Н. Суворов — участие в планировании исследования, редактирование статьи и одобрение финальной версии.

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REFERENCES

1. Dierikx T.H., Visser D.H., Benninga M.A. et al. The influence of prenatal and intrapartum antibiotics on intestinal microbiota colonisation in infants: A systematic review. *J Infect*. 2020;81(2):190–204. https://doi.org/10.1016/j.jinf.2020.05.002.
2. Chen Y., Zhou J., Wang L. Role and Mechanism of Gut Microbiota in Human Disease. *Front Cell Infect Microbiol*. 2021;11:625913. https://doi.org/10.3389/fcimb.2021.625913.
3. Novikova V.P., Gurova M.M., Khavkin A.I. Intestinal microbiota as a regulator of the functioning of organs and systems of the human body. Moscow: GEOTAR-Media; 2025. (In Russ.). https://doi.org/10.33029/9704-8926-0-IMR-2025-1-360.
4. Andersen V., Møller S., Jensen P.B. et al. Caesarean delivery and risk of chronic inflammatory diseases (inflammatory bowel disease, rheumatoid arthritis, coeliac disease, and diabetes mellitus): a population based registry study of 2,699,479 births in Denmark during 1973–2016. *Clin Epidemiol*. 2020;12:287–293. https://doi.org/10.2147/CLEP.S229056.
5. Zhong H., Wang X.G., Wang J. et al. Impact of probiotics supplement on the gut microbiota in neonates with antibiotic exposure: an open-label single-center randomized parallel controlled study. *World J Pediatr*. 2021;17(4):385–393. https://doi.org/10.1007/s12519-021-00443-y.
6. Das T.K., Pradhan S., Chakrabarti S. et al. Current status of probiotic and related health benefits. *Applied Food Research*. 2022;2(2):100185. https://doi.org/10.1016/j.afres.2022.100185.
7. Blanchetière A., Dolladille C., Goyer I., Join-Lambert O., Fazilleau L. State of the art of probiotic use in neonatal intensive care units in french-speaking european countries. *Children*. 2023;10(12):1889. https://doi.org/10.3390/children10121889.
8. Kara V.V., Grachev A.N. Methods for assessing the human gut microbiota. *Nauchnoe Obrazovanie*. 2023;1(18):68–73. (In Russ.). EDN: CKGPFV.
9. Jiao L., Kourkoumpetis T., Hutchinson D. et al. Spatial characteristics of colonic mucosa-associated gut microbiota in humans. *Microb Ecol*. 2022;83(3):811–821. https://doi.org/10.1007/s00248-021-01789-6.
10. Reygner J., Charrueau C., Delannoy J. et al. Freeze-dried fecal samples are biologically active after long-lasting storage and suited to fecal microbiota transplantation in a preclinical murine model of Clostridioides difficile infection. *Gut Microbes*. 2020;11(5):1405–1422. https://doi.org/10.1080/19490976.2020.1759489.
11. Tang Q., Jin G., Wang G. et al. Current sampling methods for gut microbiota: a call for more precise devices. *Front Cell Infect Microbiol*. 2020;10:151. https://doi.org/10.3389/fcimb.2020.00151.
12. Neuberger-Castillo L., Hamot G., Marchese M. et al. Method validation for extraction of dna from human stool samples for downstream microbiome analysis. *Biopreserv Biobank*. 2020;18(2):102–116. https://doi.org/10.1089/bio.2019.0112.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

13. Mordant A., Kleiner M. Evaluation of sample preservation and storage methods for metaproteomics analysis of intestinal microbiomes. *Microbiol Spectr*. 2021;9(3):e0187721. https://doi.org/10.1128/Spectrum.01877-21.
14. Williams G.M., Leary S.D., Ajami N.J. et al. Gut microbiome analysis by post: Evaluation of the optimal method to collect stool samples from infants within a national cohort study. *PLoS One*. 2019;14(6):e0216557. https://doi.org/10.1371/journal.pone.0216557.
15. Lee S.M., Park K.H., Hong S. et al. Identification of cultivable bacteria in amniotic fluid using cervicovaginal fluid protein microarray in preterm premature rupture of membranes. *Reprod Sci*. 2020;27(4):1008–1017. https://doi.org/10.1007/s43032-020-00143-4.
16. Kennedy K.M., de Goffau M.C., Perez-Muñoz M.E. et al. Questioning the fetal microbiome illustrates pitfalls of low-biomass microbial studies. *Nature*. 2023;613(7945):639–649. https://doi.org/10.1038/s41586-022-05546-8.
17. Sterpu I., Fransson E., Hugerth L.W. et al. No evidence for a placental microbiome in human pregnancies at term. *Am J Obstet Gynecol*. 2021;224(3):296.e1–296.e23. https://doi.org/10.1016/j.ajog.2020.08.103.
18. Stupak A., Kwiatek M., Gęca T. et al. A virome and proteomic analysis of placental microbiota in pregnancies with and without fetal growth restriction. *Cells*. 2024;13(21):1753. https://doi.org/10.3390/cells13211753.
19. He Q., Kwok L.Y., Xi X. et al. The meconium microbiota shares more features with the amniotic fluid microbiota than the maternal fecal and vaginal microbiota. *Gut Microbes*. 2020;12(1):1794266. https://doi.org/10.1080/19490976.2020.1794266.
20. Sajdel-Sulkowska E.M. The impact of maternal gut microbiota during pregnancy on fetal gut-brain axis development and life-long health outcomes. *Microorganisms*. 2023;11(9):2199. https://doi.org/10.3390/microorganisms11092199.
21. Laursen M.F., Bahl M.I., Licht T.R. Settlers of our inner surface — factors shaping the gut microbiota from birth to toddlerhood. *FEMS Microbiol Rev*. 2021;45(4):fuab001. https://doi.org/10.1093/femsre/fuab001.
22. Gonchar N.V., Babachenko I.V., Gostev V.V., Ibragimova O.M. Characteristics of intestinal microbiota of infants according to data of sequencing of the 16s RRNA gene. *Journal Infectology*. 2017;9(2):23–28. (In Russ.). https://doi.org/10.22625/2072-6732-2017-9-2-23-28.
23. Kaplina A.V., Azarov D.V., Petrova N.A. et al. Features of intestinal microbiome in necrotizing enterocolitis in preterm neonates and full-term neonates with congenital heart disease based on metagenomic sequencing. *Clinical Practice in Pediatrics*. 2023;18(6):68–83. (In Russ.). https://doi.org/10.20953/1817-7646-2023-6-68-83.
24. Graspeuntner S., Lupatsii M., van Zandbergen V. et al. Infants <90 days of age with late-onset sepsis display disturbances of the microbiome-immunity interplay. *Infection*. 2025;53(3):921–934. https://doi.org/10.1007/s15010-024-02396-6.
25. Chistyakova G.N., Remizova I.I., Ustyuzhanin A.V. et al. Expression of $CD14^+CD282^+$, $CD14^+CD284^+$, $CD14^+HLA\text{-}DR^+$, $CD14^+CD11b^+$ receptors and sIgA level in premature infants with. *K. pneumoniae*. *Medical Immunology (Russia)*. 2024;26(5):983–992. (In Russ.). https://doi.org/10.15789/1563-0625-EOC-16944.
26. Alcazar C.G., Paes V.M., Shao Y. et al. The association between early-life gut microbiota and childhood respiratory diseases: a systematic review. *Lancet Microbe*. 2022;3(11):e867–e880. https://doi.org/10.1016/S2666-5247(22)00184-7.
27. Gao Y., Nanan R., Macia L. et al. The maternal gut microbiome during pregnancy and offspring allergy and asthma. *J Allergy Clin Immunol*. 2021;148(3):669–678. https://doi.org/10.1016/j.jaci.2021.07.011.
28. Yuan X., Wang R., Han B. et al. Functional and metabolic alterations of gut microbiota in children with new-onset type 1 diabetes. *Nat Commun*. 2022;26;13(1):6356. https://doi.org/10.1038/s41467-022-33656-4.
29. Qadri H., Shah A.H., Almilaibary A., Mir M.A. Microbiota, natural products, and human health: exploring interactions for therapeutic insights. *Front Cell Infect Microbiol*. 2024;14:1371312. https://doi.org/10.3389/fcimb.2024.1371312.
30. Jia Q., Yu X., Chang Y. et al. Dynamic Changes of the gut microbiota in preterm infants with different gestational age. *Front Microbiol*. 2022;13:923273. https://doi.org/10.3389/fmicb.2022.923273.
31. Chen Y., Lu Y., Wang T., Yu B. Changes in gut microbiota at 1-60 days in 92 preterm infants in a neonatal intensive care unit using 16S rRNA gene sequencing. *Med Sci Monit*. 2023;29:e941560. https://doi.org/10.12659/MSM.941560.
32. Chi C., Xue Y., Lv N. et al. Longitudinal gut bacterial colonization and its influencing factors of low birth weight infants during the first 3 months of life. *Front Microbiol*. 2019;10:1105. https://doi.org/10.3389/fmicb.2019.01105.
33. Blakstad E.W., Korpela K., Lee S. et al. Enhanced nutrient supply and intestinal microbiota development in very low birth weight infants. *Pediatr Res*. 2019;86(3):323–332. https://doi.org/10.1038/s41390-019-0412-x.
34. Princisval L., Rebelo F., Williams B.L. et al. Association between the mode of delivery and infant gut microbiota composition up to 6 months of age: a systematic literature review considering the role of breastfeeding. *Nutr Rev*. 2021;80(1):113–127. https://doi.org/10.1093/nutrit/nuab008.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

35. Chen Y.Y., Zhao X., Moeder W. et al. Impact of maternal intrapartum antibiotics, and caesarean section with and without labour on bifidobacterium and other infant gut microbiota. *Microorganisms*. 2021;9(9):1847. https://doi.org/10.3390/microorganisms9091847.
36. Inchingolo F., Inchingolo A., Palumbo I. et al. The impact of cesarean section delivery on intestinal microbiota: mechanisms, consequences, and perspectives — a systematic review. *Int J Mol Sci*. 2024;25:1055. https://doi.org/10.3390/ijms25021055.
37. Li L., Wan W., Zhu C. Breastfeeding after a cesarean section: A literature review. *Midwifery*. 2021;103:103117. https://doi.org/10.1016/j.midw.2021.103117.
38. Mallick L.M., Shenassa E.D. Variation in breastfeeding initiation and duration by mode of childbirth: a prospective, population-based study. *Breastfeed Med*. 2024;19(4):262–274. https://doi.org/10.1089/bfm.2023.0180.
39. Chin N., Méndez-Lagares G., Taft D.H. et al. Transient effect of infant formula supplementation on the intestinal microbiota. *Nutrients*. 2021;13(3):807. https://doi.org/10.3390/nu13030807.
40. Beller L., Deboutte W., Falony G. et al. Successional stages in infant gut microbiota maturation. *mBio*. 2021;12(6):e0185721. https://doi.org/10.1128/mBio.01857-21.
41. Cuxart I., Coines J., Esquivias O. et al. Enzymatic hydrolysis of human milk oligosaccharides. the molecular mechanism of *Bifidobacterium bifidum* Lacto-N-biosidase. *ACS Catal*. 2022;12(8):4737–4743. https://doi.org/10.1021/acscatal.2c00309.
42. Kumar H., Collado M.C., Wopereis H. et al. The bifidogenic effect revisited-ecology and health perspectives of bifidobacterial colonization in early life. *Microorganisms*. 2020;8(12):1855. https://doi.org/10.3390/microorganisms8121855.
43. Kurata A., Yamasaki-Yashiki S., Imai T. et al. Enhancement of IgA production by membrane vesicles derived from Bifidobacterium longum subsp. infantis. *Biosci Biotechnol Biochem*. 2022;87(1):119–128. https://doi.org/10.1093/bbb/zbac172.
44. Boudry G., Charton E., Le Huerou-Luron I. et al. The relationship between breast milk components and the infant gut microbiota. *Front Nutr*. 2021;8:629740. https://doi.org/10.3389/fnut.2021.629740.
45. Vélez-Ixta J.M., Juárez-Castelán C.J., Ramírez-Sánchez D. et al. Post natal microbial and metabolite transmission: the path from mother to infant. *Nutrients*. 2024;16(13):1990. https://doi.org/10.3390/nu16131990.
46. Notarbartolo V., Giuffrè M., Montante C. et al. Composition of human breast milk microbiota and its role in children's health. *Pediatr Gastroenterol Hepatol Nutr*. 2022;25(3):194–210. https://doi.org/10.5223/pghn.2022.25.3.194.
47. Ingram K., Gregg C., Tegge A. et al. Metagenomic assessment of the bacterial breastfeeding microbiome in mature milk across lactation. *Front Pediatr*. 2024;11:1275436. https://doi.org/10.3389/fped.2023.1275436.
48. Komatsu Y., Kumakura D., Seto N. et al. Dynamic associations of milk components with the infant gut microbiome and fecal metabolites in a mother-infant model by microbiome, NMR metabolomic, and time-series clustering analyses. *Front Nutr*. 2022;8:813690. https://doi.org/10.3389/fnut.2021.813690.
49. Fabiano V., Indrio F., Verduci E. et al. Term infant formulas influencing gut microbiota: An overview. *Nutrients*. 2021;13(12):4200. https://doi.org/10.3390/nu13124200.
50. Morreale C., Giaroni C., Baj A. et al. Effects of perinatal antibiotic exposure and neonatal gut microbiota. *Antibiotics (Basel)*. 2023;12(2):258. https://doi.org/10.3390/antibiotics12020258.
51. Argentini C., Mancabelli L., Alessandri G. et al. Exploring the ecological effects of naturally antibiotic-insensitive bifidobacteria in the recovery of the resilience of the gut microbiota during and after antibiotic treatment. *Appl Environ Microbiol*. 2022;88(12):e0052222. https://doi.org/10.1128/aem.00522-22.
52. Ozkul C., Ruiz V. E., Battaglia T. et al. A single early-in-life antibiotic course increases susceptibility to DSS-induced colitis. *Genome Med*. 2020;12(1):65. https://doi.org/10.1186/s13073-020-00764-z.
53. Mancabelli L., Mancino W., Lugli G.A. et al. Amoxicillin-clavulanic acid resistance in the genus bifidobacterium. *Appl Environ Microbiol*. 2021;87(7):e03137-20. https://doi.org/10.1128/AEM.03137-20.
54. Zimmermann P., Curtis N. Effect of intrapartum antibiotics on the intestinal microbiota of infants: a systematic review. *Arch Dis Child Fetal Neonatal Ed*. 2020;105(2):201–208. https://doi.org/10.1136/archdischild-2018-316659.
55. Qiu J., Wu S., Huang R. et al. Effects of antibiotic therapy on the early development of gut microbiota and butyrate-producers in early infants. *Front Microbiol*. 2025;15:1508217. https://doi.org/10.3389/fmicb.2024.1508217.
56. Ventin-Holmberg R., Saqib S., Korpela K. et al. The effect of antibiotics on the infant gut fungal microbiota. *J Fungi (Basel)*. 2022;8(4):328. https://doi.org/10.3390/jof8040328.
57. Tashlanova V.V., Kataeva L.V., Stepanova T.F. Species characteristics of bacteria of the genus *Lactobacillus* identified in different loci of the human body (literature review). *Journal of microbiology, epidemiology and immunobiology*. 2023;100(4):364–375. (In Russ.). https://doi.org/10.36233/0372-9311-332.
58. Davis E.C., Castagna V.P., Sela D.A. et al. Gut microbiome and breast-feeding: Implications for early immune deve-

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

lopment. *J Allergy Clin Immunol*. 2022;150(3):523–534. https://doi.org/10.1016/j.jaci.2022.07.014.
59. Damaceno Q.S., Gallotti B., Reis I.M.M. et al. Isolation and identification of potential probiotic bacteria from human milk. *Probiotics Antimicrob Proteins*. 2023;15(3):491–501. https://doi.org/10.1007/s12602-021-09866-5.
60. Nguyen M., Holdbrooks H., Mishra P. et al. Impact of probiotic B. infantis EVC001 feeding in premature infants on the gut microbiome, nosocomially acquired antibiotic resistance, and enteric inflammation. *Front Pediatr*. 2021;9:618009. https://doi.org/10.3389/fped.2021.618009.
61. Gonchar N.V., Fedorova M.S., Alekhina G.G., Suvorov A.N. Experience of using a probiotic strain of Enterococcus in long-term nutritional support for premature children. *Russian Bulletin of Perinatology and Pediatrics*. 2021;66(6):115–120. (In Russ.). https://doi.org/10.21508/1027-4065-2021-66-6-115-120.
62. Deshpande G.C., Rao S.C., Keil A.D., Patole S.K. Evidence-based guidelines for use of probiotics in preterm neonates. *BMC Med*. 2011;9:92. https://doi.org/10.1186/1741-7015-9-92.
63. van Best N., Trepels-Kottek S., Savelkoul P. et al. Influence of probiotic supplementation on the developing microbiota in human preterm neonates. *Gut Microbes*. 2020;12(1):1–16. https://doi.org/10.1080/19490976.2020.1826747.
64. Samara J., Moossavi S., Alshaikh B. et al. Supplementation with a probiotic mixture accelerates gut microbiome maturation and reduces intestinal inflammation in extremely preterm infants. *Cell Host Microbe*. 2022;30(5):696–711.e5. https://doi.org/10.1016/j.chom.2022.04.005.
65. Underwood M.A., Umberger E., Patel R.M. Safety and efficacy of probiotic administration to preterm infants: ten common questions. *Pediatr Res*. 2020;88(Suppl 1):48–55. https://doi.org/10.1038/s41390-020-1080-6.
66. Guitor A.K., Yousuf E.I., Raphenya A.R. et al. Capturing the antibiotic resistome of preterm infants reveals new benefits of probiotic supplementation. *Microbiome*. 2022;10(1):136. https://doi.org/10.1186/s40168-022-01327-7.
67. Batta V.K., Rao S.C., Patole S.K. Bifidobacterium infantis as a probiotic in preterm infants: a systematic review and meta-analysis. *Pediatr Res*. 2023;94(6):1887–1905. https://doi.org/10.1038/s41390-023-02716-w.
68. Wang H., Meng X., Xing S. et al. Probiotics to prevent necrotizing enterocolitis and reduce mortality in neonates: A meta-analysis. *Medicine (Baltimore)*. 2023;102(8):e32932. https://doi.org/10.1097/MD.0000000000032932.

ЛИТЕРАТУРА

1. Dierikx T.H., Visser D.H., Benninga M.A. et al. The influence of prenatal and intrapartum antibiotics on intestinal microbiota colonisation in infants: A systematic review. *J Infect*. 2020;81(2):190–204. https://doi.org/10.1016/j.jinf.2020.05.002.
2. Chen Y., Zhou J., Wang L. Role and Mechanism of Gut Microbiota in Human Disease. *Front Cell Infect Microbiol*. 2021;11:625913. https://doi.org/10.3389/fcimb.2021.625913.
3. Новикова В.П., Гурова М.М., Хавкин А.И. Кишечная микробиота как регулятор работы органов и систем человека. М.: ГЭОТАР-Медиа; 2025. https://doi.org/10.33029/9704-8926-0-IMR-2025-1-360.
4. Andersen V., Møller S., Jensen P.B. et al. Caesarean delivery and risk of chronic inflammatory diseases (inflammatory bowel disease, rheumatoid arthritis, coeliac disease, and diabetes mellitus): a population based registry study of 2,699,479 births in Denmark during 1973–2016. *Clin Epidemiol*. 2020;12:287–293. https://doi.org/10.2147/CLEP.S229056.
5. Zhong H., Wang X.G., Wang J. et al. Impact of probiotics supplement on the gut microbiota in neonates with antibiotic exposure: an open-label single-center randomized parallel controlled study. *World J Pediatr*. 2021;17(4):385–393. https://doi.org/10.1007/s12519-021-00443-y.
6. Das T.K., Pradhan S., Chakrabarti S. et al. Current status of probiotic and related health benefits. *Applied Food Research*. 2022;2(2):100185. https://doi.org/10.1016/j.afres.2022.100185.
7. Blanchetière A., Dolladille C., Goyer I., Join-Lambert O., Fazilleau L. State of the art of probiotic use in neonatal intensive care units in french-speaking european countries. *Children*. 2023;10(12):1889. https://doi.org/10.3390/children10121889.
8. Кара В.В., Грачев А.Н. Методы оценки микробиоты кишечника человека. *Научное образование*. 2023;1(18):68–73. EDN: CKGPFV.
9. Jiao L., Kourkoumpetis T., Hutchinson D. et al. Spatial characteristics of colonic mucosa-associated gut microbiota in humans. *Microb Ecol*. 2022;83(3):811–821. https://doi.org/10.1007/s00248-021-01789-6.
10. Reygner J., Charrueau C., Delannoy J. et al. Freeze-dried fecal samples are biologically active after long-lasting storage and suited to fecal microbiota transplantation in a preclinical murine model of Clostridioides difficile infection. *Gut Microbes*. 2020;11(5):1405–1422. https://doi.org/10.1080/19490976.2020.1759489.
11. Tang Q., Jin G., Wang G. et al. Current sampling methods for gut microbiota: a call for more precise devices. *Front Cell Infect Microbiol*. 2020;10:151. https://doi.org/10.3389/fcimb.2020.00151.
12. Neuberger-Castillo L., Hamot G., Marchese M. et al. Method validation for extraction of dna from human stool samples for downstream microbiome analysis. *Biopreserv*

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

Biobank. 2020;18(2):102–116. https://doi.org/10.1089/bio.2019.0112.
13. Mordant A., Kleiner M. Evaluation of sample preservation and storage methods for metaproteomics analysis of intestinal microbiomes. *Microbiol Spectr*. 2021;9(3):e0187721. https://doi.org/10.1128/Spectrum.01877-21.
14. Williams G.M., Leary S.D., Ajami N.J. et al. Gut microbiome analysis by post: Evaluation of the optimal method to collect stool samples from infants within a national cohort study. *PLoS One*. 2019;14(6):e0216557. https://doi.org/10.1371/journal.pone.0216557.
15. Lee S.M., Park K.H., Hong S. et al. Identification of cultivable bacteria in amniotic fluid using cervicovaginal fluid protein microarray in preterm premature rupture of membranes. *Reprod Sci*. 2020;27(4):1008–1017. https://doi.org/10.1007/s43032-020-00143-4.
16. Kennedy K.M., de Goffau M.C., Perez-Muñoz M.E. et al. Questioning the fetal microbiome illustrates pitfalls of low-biomass microbial studies. *Nature*. 2023;613(7945):639–649. https://doi.org/10.1038/s41586-022-05546-8.
17. Sterpu I., Fransson E., Hugerth L.W. et al. No evidence for a placental microbiome in human pregnancies at term. *Am J Obstet Gynecol*. 2021;224(3):296.e1-296.e23. https://doi.org/10.1016/j.ajog.2020.08.103.
18. Stupak A., Kwiatek M., Gęca T. et al. A virome and proteomic analysis of placental microbiota in pregnancies with and without fetal growth restriction. *Cells*. 2024;13(21):1753. https://doi.org/10.3390/cells13211753.
19. He Q., Kwok L.Y., Xi X. et al. The meconium microbiota shares more features with the amniotic fluid microbiota than the maternal fecal and vaginal microbiota. *Gut Microbes*. 2020;12(1):1794266. https://doi.org/10.1080/19490976.2020.1794266.
20. Sajdel-Sulkowska E.M. The impact of maternal gut microbiota during pregnancy on fetal gut-brain axis development and life-long health outcomes. *Microorganisms*. 2023;11(9):2199. https://doi.org/10.3390/microorganisms11092199.
21. Laursen M.F., Bahl M.I., Licht T.R. Settlers of our inner surface — factors shaping the gut microbiota from birth to toddlerhood. *FEMS Microbiol Rev*. 2021;45(4):fuab001. https://doi.org/10.1093/femsre/fuab001.
22. Гончар Н.В., Бабаченко И.В., Гостев В.В., Ибрагимова О.М. Характеристика микробиоты кишечника детей первого года жизни поданным секвенирования гена 16S рибосомальной РНК. *Журнал инфектологии*. 2017;9(2):23–28. https://doi.org/10.22625/2072-6732-2017-9-2-23-28.
23. Каплина А.В., Азаров Д.В., Петрова Н.А. и др. Особенности микробиома кишечника при некротизирующем энтероколите у недоношенных новорожденных и доношенных новорожденных с врожденными пороками сердца по данным метагеномного секвенирования. *Вопросы практической педиатрии*. 2023;18(6):68–83. https://doi.org/10.20953/1817-7646-2023-6-68-83.
24. Graspeuntner S., Lupatsii M., van Zandbergen V. et al. Infants <90 days of age with late-onset sepsis display disturbances of the microbiome-immunity interplay. *Infection*. 2025;53(3):921–934. https://doi.org/10.1007/s15010-024-02396-6.
25. Чистякова Г.Н., Ремизова И.И., Устюжанин А.В. и др. Экспрессия CD14+CD282+, CD14+CD284+, CD14+HLA-DR+, CD14+CD11b+ рецепторов и уровень sIgA, у недоношенных детей, с K. pneumoniae. *Медицинская иммунология*. 2024;26(5):983–992. https://doi.org/10.15789/1563-0625-EOC-16944.
26. Alcazar C.G., Paes V.M., Shao Y. et al. The association between early-life gut microbiota and childhood respiratory diseases: a systematic review. *Lancet Microbe*. 2022;3(11):e867–e880. https://doi.org/10.1016/S2666-5247(22)00184-7.
27. Gao Y., Nanan R., Macia L. et al. The maternal gut microbiome during pregnancy and offspring allergy and asthma. *J Allergy Clin Immunol*. 2021;148(3):669–678. https://doi.org/10.1016/j.jaci.2021.07.011.
28. Yuan X., Wang R., Han B. et al. Functional and metabolic alterations of gut microbiota in children with new-onset type 1 diabetes. *Nat Commun*. 2022;26;13(1):6356. https://doi.org/10.1038/s41467-022-33656-4.
29. Qadri H., Shah A.H., Almilaibary A., Mir M.A. Microbiota, natural products, and human health: exploring interactions for therapeutic insights. *Front Cell Infect Microbiol*. 2024;14:1371312. https://doi.org/10.3389/fcimb.2024.1371312.
30. Jia Q., Yu X., Chang Y. et al. Dynamic Changes of the gut microbiota in preterm infants with different gestational age. *Front Microbiol*. 2022;13:923273. https://doi.org/10.3389/fmicb.2022.923273.
31. Chen Y., Lu Y., Wang T., Yu B. Changes in gut microbiota at 1-60 days in 92 preterm infants in a neonatal intensive care unit using 16S rRNA gene sequencing. *Med Sci Monit*. 2023;29:e941560. https://doi.org/10.12659/MSM.941560.
32. Chi C., Xue Y., Lv N. et al. Longitudinal gut bacterial colonization and its influencing factors of low birth weight infants during the first 3 months of life. *Front Microbiol*. 2019;10:1105. https://doi.org/10.3389/fmicb.2019.01105.
33. Blakstad E.W., Korpela K., Lee S. et al. Enhanced nutrient supply and intestinal microbiota development in very low birth weight infants. *Pediatr Res*. 2019;86(3):323–332. https://doi.org/10.1038/s41390-019-0412-x.
34. Princisval L., Rebelo F., Williams B.L. et al. Association between the mode of delivery and infant gut microbiota

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

composition up to 6 months of age: a systematic literature review considering the role of breastfeeding. *Nutr Rev*. 2021;80(1):113–127. https://doi.org/10.1093/nutrit/nuab008.
35. Chen Y.Y., Zhao X., Moeder W. et al. Impact of maternal intrapartum antibiotics, and caesarean section with and without labour on bifidobacterium and other infant gut microbiota. *Microorganisms*. 2021;9(9):1847. https://doi.org/10.3390/microorganisms9091847.
36. Inchingolo F., Inchingolo A., Palumbo I. et al. The impact of cesarean section delivery on intestinal microbiota: mechanisms, consequences, and perspectives — a systematic review. *Int J Mol Sci*. 2024;25:1055. https://doi.org/10.3390/ijms25021055.
37. Li L., Wan W., Zhu C. Breastfeeding after a cesarean section: A literature review. *Midwifery*. 2021;103:103117. https://doi.org/10.1016/j.midw.2021.103117.
38. Mallick L.M., Shenassa E.D. Variation in breastfeeding initiation and duration by mode of childbirth: a prospective, population-based study. *Breastfeed Med*. 2024;19(4):262–274. https://doi.org/10.1089/bfm.2023.0180.
39. Chin N., Méndez-Lagares G., Taft D.H. et al. Transient effect of infant formula supplementation on the intestinal microbiota. *Nutrients*. 2021;13(3):807. https://doi.org/10.3390/nu13030807.
40. Beller L., Deboutte W., Falony G. et al. Successional stages in infant gut microbiota maturation. *mBio*. 2021;12(6):e0185721. https://doi.org/10.1128/mBio.01857-21.
41. Cuxart I., Coines J., Esquivias O. et al. Enzymatic hydrolysis of human milk oligosaccharides. the molecular mechanism of *Bifidobacterium bifidum* Lacto-N-biosidase. *ACS Catal*. 2022;12(8):4737–4743. https://doi.org/10.1021/acscatal.2c00309.
42. Kumar H., Collado M.C., Wopereis H. et al. The bifidogenic effect revisited-ecology and health perspectives of bifidobacterial colonization in early life. *Microorganisms*. 2020;8(12):1855. https://doi.org/10.3390/microorganisms8121855.
43. Kurata A., Yamasaki-Yashiki S., Imai T. et al. Enhancement of IgA production by membrane vesicles derived from Bifidobacterium longum subsp. infantis. *Biosci Biotechnol Biochem*. 2022;87(1):119–128. https://doi.org/10.1093/bbb/zbac172.
44. Boudry G., Charton E., Le Huerou-Luron I. et al. The relationship between breast milk components and the infant gut microbiota. *Front Nutr*. 2021;8:629740. https://doi.org/10.3389/fnut.2021.629740.
45. Vélez-Ixta J.M., Juárez-Castelán C.J., Ramírez-Sánchez D. et al. Post natal microbial and metabolite transmission: the path from mother to infant. *Nutrients*. 2024;16(13):1990. https://doi.org/10.3390/nu16131990.
46. Notarbartolo V., Giuffrè M., Montante C. et al. Composition of human breast milk microbiota and its role in children's health. *Pediatr Gastroenterol Hepatol Nutr*. 2022;25(3):194–210. https://doi.org/10.5223/pghn.2022.25.3.194.
47. Ingram K., Gregg C., Tegge A. et al. Metagenomic assessment of the bacterial breastfeeding microbiome in mature milk across lactation. *Front Pediatr*. 2024;11:1275436. https://doi.org/10.3389/fped.2023.1275436.
48. Komatsu Y., Kumakura D., Seto N. et al. Dynamic associations of milk components with the infant gut microbiome and fecal metabolites in a mother-infant model by microbiome, NMR metabolomic, and time-series clustering analyses. *Front Nutr*. 2022;8:813690. https://doi.org/10.3389/fnut.2021.813690.
49. Fabiano V., Indrio F., Verduci E. et al. Term infant formulas influencing gut microbiota: An overview. *Nutrients*. 2021;13(12):4200. https://doi.org/10.3390/nu13124200.
50. Morreale C., Giaroni C., Baj A. et al. Effects of perinatal antibiotic exposure and neonatal gut microbiota. *Antibiotics (Basel)*. 2023;12(2):258. https://doi.org/10.3390/antibiotics12020258.
51. Argentini C., Mancabelli L., Alessandri G. et al. Exploring the ecological effects of naturally antibiotic-insensitive bifidobacteria in the recovery of the resilience of the gut microbiota during and after antibiotic treatment. *Appl Environ Microbiol*. 2022;88(12):e0052222. https://doi.org/10.1128/aem.00522-22.
52. Ozkul C., Ruiz V.E., Battaglia T. et al. A single early-in-life antibiotic course increases susceptibility to DSS-induced colitis. *Genome Med*. 2020;12(1):65. https://doi.org/10.1186/s13073-020-00764-z.
53. Mancabelli L., Mancino W., Lugli G.A. et al. Amoxicillin-clavulanic acid resistance in the genus bifidobacterium. *Appl Environ Microbiol*. 2021;87(7):e03137-20. https://doi.org/10.1128/AEM.03137-20.
54. Zimmermann P., Curtis N. Effect of intrapartum antibiotics on the intestinal microbiota of infants: a systematic review. *Arch Dis Child Fetal Neonatal Ed*. 2020;105(2):201–208. https://doi.org/10.1136/archdischild-2018-316659.
55. Qiu J., Wu S., Huang R. et al. Effects of antibiotic therapy on the early development of gut microbiota and butyrate-producers in early infants. *Front Microbiol*. 2025;15:1508217. https://doi.org/10.3389/fmicb.2024.1508217.
56. Ventin-Holmberg R., Saqib S., Korpela K. et al. The effect of antibiotics on the infant gut fungal microbiota. *J Fungi (Basel)*. 2022;8(4):328. https://doi.org/10.3390/jof8040328.
57. Ташланова В.В., Катаева Л.В., Степанова Т.Ф. Видовая характеристика бактерий рода Lactobacillus, циркулирующих в различных локусах организма человека

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(обзор литературы). *Журнал микробиологии, эпидемиологии и иммунобиологии*. 2023;100(4):364–375. https://doi.org/10.36233/0372-9311-332.
58. Davis E.C., Castagna V.P., Sela D.A. et al. Gut microbiome and breast-feeding: Implications for early immune development. *J Allergy Clin Immunol*. 2022;150(3):523–534. https://doi.org/10.1016/j.jaci.2022.07.014.
59. Damaceno Q.S., Gallotti B., Reis I.M.M. et al. Isolation and identification of potential probiotic bacteria from human milk. *Probiotics Antimicrob Proteins*. 2023;15(3):491–501. https://doi.org/10.1007/s12602-021-09866-5.
60. Nguyen M., Holdbrooks H., Mishra P. et al. Impact of probiotic B. infantis EVC001 feeding in premature infants on the gut microbiome, nosocomially acquired antibiotic resistance, and enteric inflammation. *Front Pediatr*. 2021;9:618009. https://doi.org/10.3389/fped.2021.618009.
61. Гончар Н.В., Федорова М.С., Алехина Г.Г., Суворов А.Н. Опыт использования пробиотического штамма энтерококка в длительной нутриционной поддержке детей, родившихся недоношенными. *Российский вестник перинатологии и педиатрии*. 2021;66(6):115–120. https://doi.org/10.21508/1027-4065-2021-66-6-115-120.
62. Deshpande G.C., Rao S.C., Keil A D., Patole S.K. Evidence-based guidelines for use of probiotics in preterm neonates. *BMC Med*. 2011;9:92. https://doi.org/10.1186/1741-7015-9-92.
63. van Best N., Trepels-Kottek S., Savelkoul P. et al. Influence of probiotic supplementation on the developing microbiota in human preterm neonates. *Gut Microbes*. 2020;12(1):1–16. https://doi.org/10.1080/19490976.2020.1826747.
64. Samara J., Moossavi S., Alshaikh B. et al. Supplementation with a probiotic mixture accelerates gut microbiome maturation and reduces intestinal inflammation in extremely preterm infants. *Cell Host Microbe*. 2022;30(5):696–711.e5. https://doi.org/10.1016/j.chom.2022.04.005.
65. Underwood M.A., Umberger E., Patel R.M. Safety and efficacy of probiotic administration to preterm infants: ten common questions. *Pediatr Res*. 2020;88(Suppl 1):48–55. https://doi.org/10.1038/s41390-020-1080-6.
66. Guitor A.K., Yousuf E.I., Raphenya A.R. et al. Capturing the antibiotic resistome of preterm infants reveals new benefits of probiotic supplementation. *Microbiome*. 2022;10(1):136. https://doi.org/10.1186/s40168-022-01327-7.
67. Batta V.K., Rao S.C., Patole S.K. Bifidobacterium infantis as a probiotic in preterm infants: a systematic review and meta-analysis. *Pediatr Res*. 2023;94(6):1887–1905. https://doi.org/10.1038/s41390-023-02716-w.
68. Wang H., Meng X., Xing S. et al. Probiotics to prevent necrotizing enterocolitis and reduce mortality in neonates: A meta-analysis. *Medicine (Baltimore)*. 2023;102(8):e32932. https://doi.org/10.1097/MD.0000000000032932.

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Review

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Celiac disease in various types of diabetes mellitus

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ABSTRACT. The co-occurrence of celiac disease and diabetes mellitus, particularly in young children, is characterized by a severe clinical course, extreme metabolic lability, a tendency toward ketosis, and recurrent severe hypoglycemia, which requires modifications to the standard treatment protocol. Timely diagnosis of celiac disease in patients with diabetes mellitus is essential for correcting overt and potential metabolic disorders caused by malabsorption syndrome. This article presents a literature review that examines, from an evidence-based medicine perspective, the shared genetic factors and autoimmune mechanisms common to both celiac disease and type 1 diabetes mellitus. Particular attention is given to the epidemiological and pathogenetic aspects of the relationship between celiac disease and type 1 diabetes mellitus. The central focus is on the alteration in the clinical presentation of these diseases under conditions of comorbidity. The authors review the association of celiac disease with diabetes mellitus in autoimmune polyglandular syndrome and with latent autoimmune diabetes in adults. Special emphasis is placed on topics debated in the literature, including early diagnosis of celiac disease in various types of diabetes mellitus and the impact of malabsorption syndrome on patients' quality of life when control of either or both conditions is poor.

KEYWORDS: *diabetes mellitus, malabsorption syndrome, celiac disease, gluten-free diet, autoimmune diseases*

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Обзор

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Целиакия при различных типах сахарного диабета

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РЕЗЮМЕ. Сочетание целиакии и сахарного диабета, особенно у детей раннего возраста, характеризуется тяжестью течения и крайней лабильностью, склонностью к развитию кетоза, повторяющимися тяжелыми гипогликемиями, что вносит коррективу в лечебный протокол. Своевременная диагностика целиакии у пациентов с сахарным диабетом необходима для коррекции явных и потенциальных метаболических нарушений, вызванных синдромом мальабсорбции. В статье представлен обзор литературы, описывающий с позиций доказательной медицины общность генетических факторов и аутоиммунных процессов, характерных для целиакии и сахарного диабета 1-го типа. Особое внимание уделено эпидемиологическим и патогенетическим аспектам взаимосвязи целиакии и сахарного диабета 1-го типа. В фокусе проблемы – изменение клинической картины этих заболеваний в случае коморбидности. Авторами представлены литературные данные о сопряженности целиакии и сахарного диабета в структуре аутоиммунного полигландулярного синдрома, а также целиакии и латентного аутоиммунного сахарного диабета у взрослых. Особый акцент сделан на обсуждаемых в литературе вопросах ранней диагностики целиакии при различных типах сахарного диабета, влиянии синдрома мальабсорбции на качество жизни пациентов в случае нарушения компенсации той или иной патологии. В статье приведены рекомендации, касающиеся дифференциальной диагностики, диетотерапии и медикаментозного лечения пациентов при сочетании у них целиакии и сахарного диабета.

КЛЮЧЕВЫЕ СЛОВА: *сахарный диабет, синдром мальабсорбции, целиакия, безглютеновая диета, аутоиммунные заболевания*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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INTRODUCTION

Malabsorption syndrome (MS) is a major cause of impaired metabolic control in patients with diabetes mellitus, particularly in children [1–4]. At the same time, malabsorption syndrome in diabetes mellitus may be a consequence of autonomic neuropathy [1]. Along with pancreatic insufficiency, liver dysfunction, changes in the gut microbiota, and functional impairments in small intestine enzyme production, celiac disease may be a cause of MS [3–5]. Celiac disease is currently considered a systemic immune-mediated disorder manifested by gluten-dependent symptoms and specific antibodies in genetically predisposed individuals [5, 6]. Taking into account that clinical manifestations of this disease are characterized by significant polymorphism, the diagnosis of celiac disease in patients with diabetes mellitus is often difficult [7].

The literature discusses associations between celiac disease and such autoimmune diseases of the endocrine system as type 1 diabetes mellitus (T1D), autoimmune thyroiditis (AIT), and gonadal involvement, as well as pathologies of the gastrointestinal tract (GIT): autoimmune gastritis, hepatitis, cholangitis, and others [8–12].

AIM

The aim of this review is to describe main mechanisms underlying the relationship between celiac disease and various types of diabetes mellitus, as well as specific features of therapeutic management in patients with celiac disease and diabetes.

MATERIALS AND METHODS

A literature search was conducted in international databases (PubMed, eLIBRARY, NCBI) using such keywords as “diabetes mellitus,” “malabsorption syndrome,” “celiac disease,” “gluten-free diet,” and “autoimmune diseases.” A total of 76 medical literature sources were selected for the literature review.

RESULTS AND DISCUSSION

Celiac disease, being a chronic immune-mediated condition, may be accompanied by extraintestinal manifestations and diseases affecting various organs. Moreover, exocrine pancreatic insufficiency (EPI) may be observed in one-third of children diagnosed with celiac disease and, as a rule, resolves after switching to a gluten-free diet (GFD). At the same time, chronic pancreatitis, including autoimmune forms, is an extremely rare comorbid condition in children with celiac disease, and very few cases in children have been described in the literature. Type 1 diabetes mellitus (T1DM) is a well-known and common comorbid condition in children with celiac disease. The main determinant of this association is a common predisposing factor related to HLA, although non-HLA-related genetic and environmental factors (viruses, gut microbiota, etc.) have also been identified and may be involved in the development of both autoimmune diseases [12].

EPIDEMIOLOGY OF CELIAC DISEASE ASSOCIATED WITH TYPE 1 DIABETES

The prevalence of T1D is 86.73 per 100,000 children and 203.29 per 100,000 adolescents [13]. The prevalence of celiac disease in T1D, according to various authors, ranges from 3–10% [14, 15]. Antibodies to tissue transglutaminase (anti-tTG) are detected in children with T1D with the same frequency [16–19]. The incidence of T1D has been rising in recent years parallel to celiac disease [20, 21]. In most patients, T1D diagnosis precedes celiac disease. However, there is evidence suggesting that early-onset celiac disease (before 20 years of age) is associated with a higher risk of developing diabetes [21]. Studies have shown that T1D develops in 0.14% of individuals with celiac disease compared to 0.06% in a control group of patients without celiac disease or autoimmune diseases, with the highest risk observed among children under 18 years of age. These results confirm that it is necessary to screen individuals at high-risk groups [18].

PATHOGENIC LINKS BETWEEN CELIAC DISEASE AND TYPE 1 DIABETES

The relationship between type 1 diabetes and celiac disease still requires further study. A common autoimmune mechanism is hypothesized, but it is associated with various genetic features determined by differences in the major histocompatibility complex (MHC), including *HLA* and *non-HLA* genes [22, 23].

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According to the European Society of Gastroenterology Guidelines and the Draft Clinical Recommendations for the Diagnosis and Treatment of Celiac Disease in Children, it is important to note that the HLA-DQ2 haplotype is detected in 90–95% of patients, and HLA-DQ8 in the remaining 5–10%. The absence of alleles typical of celiac disease in the genotype makes the development of the disease extremely unlikely [2, 3]. A strong link has been established between this disease and human HLA antigens located on chromosome 6p21. Literature analysis indicates that inflammatory bowel diseases, rheumatoid arthritis, and type 1 diabetes often involve mutations in the regulatory regions of genes located near HLA genes, which may explain the association of celiac disease with autoimmune processes [2, 4, 24].

A study conducted in Southern Iran among children with celiac disease showed that the DQ4a*4b allele also has a high frequency in samples from the main group of patients (78%, $p < 0.01$), followed by the DQ5a*5b allele (12%, $p < 0.01$). In other words, a higher prevalence of DQ4/DQ5 is observed in children with celiac disease compared to the control group (odds ratio 6.5, confidence interval 0.84–69.46, $p < 0.01$), which indicates the need for more extensive genetic studies in celiac disease, not limited to identifying HLA-DQ2/DQ8 haplotypes [25].

At the same time, T1D is a complex polygenic disease for which more than two dozen genetic regions have been identified, each designated IDDM (insulin-dependent diabetes mellitus) and assigned a serial number. The IDDM1 (MHC) and IDDM2 (insulin gene) loci have the most significant influence on T1D [23]. Various genetic markers also confirm the role of genetic predisposition in type 2 diabetes [26]. Genetic testing for gene polymorphisms that contribute to impaired carbohydrate and/or fat metabolism in patients with overweight and obesity is currently relevant as well. It is possible to create personalized recommendations for dietary therapy and physical activity to prevent diabetes in patients with a family history of the disease [27].

HLA molecules play a role in celiac disease pathogenesis due to their involvement in antigen presentation to antigen-presenting cells (T-lymphocytes, macrophages, dendritic cells) in the small intestinal mucosa (SIM), which begin to produce numerous biologically active substances (e.g., interleukin-15). These substances have a damaging effect on the intestinal epithelium and ultimately enter the systemic circulation. Genetic typing of *HLA* genes is diagnostically significant in identifying the disease among individuals belonging to risk groups (first-degree relatives) or exhibiting signs of an atypical form of celiac disease [3–5].

Type 1 diabetes is characterized by destruction of β-cells, which typically leads to absolute insulin deficiency. Autoimmune processes play a crucial role in the pathogenesis of T1D. Type 2 diabetes mellitus is a group of heterogeneous disorders of carbohydrate metabolism characterized by a predominance of either insulin resistance or impaired insulin secretion. In children, T2D is usually detected incidentally during routine screening for obesity or a family history of diabetes [13]. In individuals over 35 years of age, T2D is often accompanied by T1D, which is characterized by very slow progression. This distinct subtype has been termed LADA (latent autoimmune diabetes mellitus in adults). In the World Health Organization classification, this subtype of diabetes is considered a variant of T1D [23]. The autoimmune process in LADA has several distinctive features. The main types of autoantibodies in patients with LADA are antibodies to glutamic acid decarboxylase (GAD) and islet cell cytoplasmic autoantibodies (ICA), with the former being detected much more frequently. Other autoimmune diseases are frequently detected in LADA. For example, AIT occurs in 4% of patients with T1D and in 25% of patients with LADA. Celiac disease is detected in 10% of patients with T1D and in 19% with LADA [13, 14].

It should be noted that T1D may occur alongside other endocrine and non-endocrine diseases of autoimmune origin. This cluster of diseases is known as “polyglandular autoimmune syndrome (PAS). Decompensation of autoimmune thyroid disease, the development of adrenal insufficiency, and worsening of celiac disease, autoimmune gastritis, and pernicious anemia in patients with T1D can lead to impaired metabolic control. The increased risk of these diseases is associated with the presence of genetic markers such as HLA class II complex haplotypes, and the *CTLA-4, PTPN22, FOXP3* genes, etc. [14]. According to current data, PAS-1 is a rare hereditary autoimmune disease resulting from mutations in the Autoimmune REgulator (AIRE) gene and characterized by multiple organ dysfunction. Diabetes is a compo-

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nent of this disease. The prevalence of diabetes in patients with PAS-1 in Russia is high (14.1%) [15]. According to a Finnish study, which includes the largest number of patients with Type PAS-1 and the longest follow-up periods, 18% of patients with PAS-1 have diabetes. A low prevalence of diabetes is observed in countries such as China, Thailand, Korea, and Japan [14].

Almost all forms of diabetes are characterized by potential complications resulting from impaired glucose and lipid metabolism. Elevated levels of total lipids, triglycerides, and phospholipids are frequently detected in patients with diabetes and enteropathy. Steatorrhea is observed in the stool lipid profile of 50% of patients. This is associated both with increased triglyceride excretion due to impaired pancreatic exocrine function and insufficient lipase secretion, as well as with impaired absorption of phospholipids and monoglycerides in the small intestine resulting from disruption of the gut microbiota [1].

CHARACTERISTICS OF THE CLINICAL PRESENTATION

Clinical symptoms of celiac disease in patients with T1D may be absent or minimal. In such cases, recurrences of hypoglycemia or uncontrolled hyperglycemia may be sole manifestations of the disease, which may pass unnoticed due to dominant symptoms of T1D, particularly when the patient is on insulin therapy. Most researchers emphasize the need for timely diagnosis of celiac disease in T1D to ensure effective management of these conditions [26]. It is noted that the risk of celiac disease is higher in cases of early-onset T1D (before age 4) and late-onset T1D (around age 45) [27]. Screening is recommended in these groups [28].

Studies have shown that patients with celiac disease and T1D have an increased risk of developing diabetic retinopathy and nephropathy. At the same time, patients with T1D and undiagnosed celiac disease had a higher prevalence of retinopathy (58% vs. 25%) and nephropathy (42% vs. 4%) [22].

According to the All-Russian Consensus on the Diagnosis and Treatment of Celiac Disease in Children and Adults, patients with T1D should be screened for celiac disease, especially if they have any gastrointestinal complaints or laboratory abnormalities that suggest celiac disease [3, 5]. It is advisable to conduct periodic examinations of patients with T1D to identify signs of PAS and to promptly address potential metabolic and vascular complications [14]. Patients with T1D, autoimmune, and endocrine diseases may be classified as high risk for celiac disease and require serological screening tests [3, 28]. Point-of-care rapid tests for diagnosing celiac disease to detect a spectrum of anti-tTG antibodies, as well as antibodies to deamidated gliadin peptides (anti-DGP) and antibodies to endomysium (anti-EMA), are recommended for use in clinical practice [29]. The clinical presentation of celiac disease may be dominated by gastrointestinal manifestations, such as diarrhea (voluminous, foul-smelling stools), steatorrhea, abdominal pain, flatulence, abdominal distension, vomiting, and loss of appetite [3–5]. Nonspecific symptoms include delayed physical development, weight loss, muscle hypotonia, and apathy. Clinical symptoms of celiac disease appear gradually in most cases. Appetite disturbances, unexplained vomiting, and weight loss are noted [27].

Previously, there were four forms of the disease: typical (classic) celiac disease, characterized by clinical symptoms of malabsorption (chronic diarrhea, wasting, and “deficiency” symptoms resulting from impaired absorption of minerals and vitamins), and atypical celiac disease, in which gastrointestinal symptoms are absent or mild, while extraintestinal manifestations such as osteoporosis, anemia, infertility, neurological symptoms, and others take center stage in the clinical picture [2, 4, 12]. In modern medicine, the division of celiac disease into classic and atypical forms appears unfounded, since atypical variants occur much more frequently than classic ones. It is recommended to distinguish between cases with pronounced symptoms (both those related to the gastrointestinal tract or extraintestinal symptoms) and asymptomatic conditions. People with the asymptomatic (latent) form of the disease show no signs of the disease, and it is detected during preventive screenings or when family members are examined [3].

DIAGNOSIS

Non-invasive serological tests are currently used to diagnose celiac disease.

It is important to perform such testing before starting a gluten-free diet, when patients are con-

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suming their usual number of gluten-containing foods. Restricting or eliminating gluten from the diet can cause a rapid decrease in specific antibody levels, which may complicate or prevent further testing [2–4, 12]. For example, anti-DPG, anti-tTG, and anti-EMA antibodies (IgA and IgG) are detected in blood samples from patients consuming gluten. IgA antibodies produced by B-lymphocytes of the small intestine's own tissue are the most valuable for diagnosis. However, if the total IgA level in serum is reduced, IgG antibodies become more informative [3, 4].

The high probability of coexisting type 1 diabetes, autoimmune diseases, and celiac disease is demonstrated by the studies of E.O. Hennessy et al. (2012), M.S. Popoviciu et al. (2023) [11, 30]. For example, seropositive individuals with an anti-tTG titer >100 were significantly more frequently identified among patients with T1D and concomitant autoimmune diseases. Individuals homozygous for the DR3-DQ2 haplotype have a 33% risk of testing positive for anti-tTG, whereas those with the same haplotype but without T1D have only a 2% probability.

However, when testing for celiac disease, it should be noted that false-negative results may occur in cases of minor inflammatory processes in the small intestinal mucosa in latent forms of celiac disease, when antibody production is reduced due to low activity of type 2 tissue transglutaminase [2, 4]. Anti-tTG antibodies may not be produced even in the presence of clinical and morphological changes characteristic of celiac disease if the patient has hypogammaglobulinemia. So-called seronegative celiac disease can be diagnosed based on the results of a thorough examination, and according to the literature, it occurs in 6–22% of cases [2–5]. The rapid celiac disease test is an immunochromatographic assay designed to detect anti-tTG IgA and IgG in human whole blood. The use of a rapid celiac disease test may be useful for screening high-risk patients. Testing in a non-laboratory setting took 10 minutes and did not cause adverse effects in children. The prevalence of seropositive patients was 3.3% [30]. Earlier studies have demonstrated the high diagnostic value of such assays in screening for atypical forms of celiac disease in patients with type 1 diabetes [31, 32].

As for endoscopic markers of celiac disease, they are highly nonspecific. During endoscopy, celiac disease may be suspected upon detection of characteristic changes: flattening or absence of annular folds in the duodenum, the appearance of transverse grooves, a honeycomb pattern, or micronodularity of the mucosa. The characteristic complex of changes associated with this disease includes an increase in the number of lymphocytes between epithelial cells, varying degrees of villus shortening, and crypt hyperplasia. Nevertheless, the macroscopic appearance of the mucosa may be normal, which limits the utility of endoscopy as the primary diagnostic method [3, 33]. According to official guidelines for diagnosing celiac disease, if patients with symptoms have Anti-tTG IgA levels exceeding the upper limit of normal by more than 10-fold, along with elevated Anti-EMA levels and positive HLA DQ2/DQ8 markers, a diagnosis of celiac disease can be established without a biopsy [3]. In order to reliably assess the condition, morphological studies must be conducted while the patient continues their usual consumption of gluten-containing foods. Morphological diagnosis becomes more accurate when five or more tissue samples are taken, including the duodenal bulb region. Eliminating gluten from the diet can rapidly restore the normal structure of the mucosa, which will significantly complicate or even preclude the possibility of confirming the diagnosis through morphological analysis [3, 34].

An increase in the number of interepithelial lymphocytes may be observed in various pathological conditions (such as food allergies, viral intestinal infections, giardiasis, autoimmune diseases, and inflammatory bowel diseases) associated with changes in the histological structure of the small intestinal villi corresponding to Marsh–Oberhuber type 1. Such changes in the SIM cannot serve as a basis for diagnosing celiac disease without corresponding immunohistochemical analysisю They must be evaluated only in combination with the clinical picture and data from serological and genetic testing [3, 35]. It should be noted that a distinctive feature of interepithelial lymphocytes in celiac disease is the presence of a specific T-cell receptor on the surface of most enterocytes, which is utilized in immunohistochemical studies to determine the predominant type of lymphocytes in the SIM [2, 4]. The identification of type 2 and 3 lesions during microscopic examination (type 2—hyperplastic, type 3—destructive, in accordance with the Marsh–Oberhuber pathomorphological classification of enteropathy severity) is sufficient grounds for diagnosing celiac disease in seropositive patients,

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even in the absence of clinical manifestations of the disease [3].

In cases serological test are negative, some researchers believe that a gluten-free diet (GFD) should be initiated. If a patient responds to the diet, a diagnosis of seronegative celiac disease is rendered [36].

Other authors argue that patients with seronegative celiac disease should not be prescribed a GFD because the diet does not improve quality of life, and they describe acute nutrient deficiencies in patients with seronegative celiac disease [5].

Diagnosis of seronegative celiac disease, especially when combined with type 1 diabetes, anemia, chronic gastritis of mixed etiology (autoimmune and Helicobacter pylori-associated), and a family history of autoimmune diseases such as type 1 diabetes, AIT, presents certain challenges. Differential diagnosis with other pathological conditions is necessary. For example, it is necessary to rule out gluten sensitivity not associated with celiac disease and common variable immunodeficiency [37].

When a patient has both celiac disease and T1D, adherence to a diet is indicated, as a gluten-free diet forms the basis for treating celiac disease, while controlling carbohydrate intake is crucial for T1D. The dilemma of combining diets for these conditions stems from the fact that recommended gluten-free foods often have a high glycemic index and contain elevated amounts of added sugars and fats, which can negatively impact blood glucose control [26].

However, it is believed that GFD in children with T1D and celiac disease improves control of the disease and prevents growth retardation, even though in some cases there is a slight increase in insulin dosage in response to corrected malabsorption and the higher glycemic index of gluten-free foods.

A gluten-free diet has a preventive effect on vascular complications of type 1 diabetes [38]. Low adherence to dietary therapy in patients in this group is associated with osteopenia and various disorders of osteogenesis. A gluten-free diet and improved glycemic control play an important role in preventing osteopenia complications, diagnosed by a decrease in bone mineral density [2, 4, 39, 40].

TREATMENT

Treatment of celiac disease in patients with T1D involves dietary therapy that includes foods that are gluten-free and do not worsen glycemic control. Processed gluten-free foods are low in certain vitamins and minerals, such as B vitamins, vitamin D, calcium, iron, zinc, and magnesium, which will require dietary optimization and supplemental intake of vitamins and minerals.

It is essential to avoid not only foods that contain “obvious” gluten (bread, baked goods and pastries, pasta, wheat/semolina, barley/pearl barley, bulgur, couscous, spelt, triticale, kamut), but also those containing “hidden” gluten. This refers to gluten used as a food additive during production. Safe grains for people with celiac disease include rice, buckwheat, corn, millet, amaranth, quinoa, montina, chumiza, sago, sorghum, and teff. Flours and starches made from root vegetables such as potatoes, cassava, tapioca, and sweet potatoes as well as legumes (beans, peas, soybeans) and various nuts are safe as well. Specialized gluten-free products such as substitutes for bread, pasta, and baked goods are recommended for patients with celiac disease. In Russia, the consumption of oats is not recommended for celiac disease because oat groats are often contaminated with impurities from other grains [3].

Patients with type 1 diabetes and celiac disease are advised to follow a long-term low-carbohydrate diet, while taking into account the glycemic index of foods. Insulin therapy, in conjunction with dietary therapy, must be administered under strict monitoring of blood glucose levels. Frequent, small meals (5–6 times a day) are recommended, taking into account the principles of mechanical, thermal, and chemical sparing [26]. Given the need for frequent meals and strict monitoring of carbohydrate intake, the use of an insulin pump to administer ultra-short-acting insulin is the most optimal approach for patients with type 1 diabetes, especially for children and adolescents. This method of insulin administration expands opportunities for dose adjustment in cases of gastrointestinal disorders [39, 41].

However, it is important to remember that adherence to a restrictive diet by children with celiac disease and T1D affects their quality of life. For example, children face emotional and behavioral challenges in schools as they adapt to their condition and dietary needs. Therefore, parents and teachers must work together to implement necessary changes in school practices to ensure comprehensive care for these children [41–44].

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Drug therapy for celiac disease is secondary, but in some cases it can be vital. Long-term, repeated courses of highly active microencapsulated pancreatic enzymes are often indicated to correct digestive processes and are mandatory during periods of acute diarrhea. During exacerbations of diarrhea, adsorbents that neutralize organic acids, astringents, and coating agents are widely used; for example, Smecta, which is administered as a suspension before meals. The use of loperamide is contraindicated [3]. The most common differences in the microbiota in children with T1D compared to healthy children include changes in the abundance of *Bacteroides, Streptococcus, Clostridium, Bifidobacterium, Prevotella, Staphylococcus, Blautia, Faecalibacterium, Roseburia, and Lactobacillus* spp. [44]. Disruptions in gut microbiota in patients with T2D reach 60% [45]. To restore the microbial composition in cases of recurrent diarrhea, courses of prebiotics, probiotics, and symbiotics are indicated. According to specialists' observations, in two-thirds of patients, disturbances in the aerobic flora resolve, and in 50% of cases, Bifidobacteria reappear or their titer increases. In this regard, it is advisable to conduct repeated courses of treatment with probiotics and prebiotics during recurrent episodes of diarrhea [3]. According to leading endocrinologists, it is advisable to assess the influence of the gut microbiota not at the level of types, but of specific species and the way they cause certain changes in patients with diabetes [46].

Nutritional status disorders in children and adolescents on long-term GFD are manifested primarily by a decrease in body mass index, which was observed in 34.4%. Grade I protein-energy malnutrition and obesity are rare (8.6% and 2.8%, respectively). With long-term adherence to a low-carbohydrate diet, vitamin B6 deficiency was detected in 14.3%, decreased ionized calcium in 40.0%, decreased serum iron in 11.4%, and mild anemia in 5.7% of children [47]. To correct serious protein metabolism disorders, such as severe protein deficiency, plasma and albumin are administered intravenously. In some cases, anabolic hormones are used to improve protein absorption [45]. The use of glucocorticoid medications in celiac disease is indicated in cases of severe disease with pronounced protein-energy malnutrition and as replacement therapy to correct adrenal insufficiency [3]. The above-mentioned features of celiac disease treatment must be taken into account in patients with type 1 diabetes, as both anabolic hormones and glucocorticoids are counterinsular hormones [13].

Patients with celiac disease who have calcium metabolism disorders (rickets-like syndrome, hypocalcemic seizures, osteopenia, and osteoporosis) are prescribed calcium and vitamin D_3 supplements [48]. Studies evaluating densitometry results in children have revealed a decrease in bone mineral density not only at the time of celiac disease diagnosis but also during subsequent follow-up of these patients. It is important to note that patients with type 1 diabetes, even without celiac disease, are at risk of decreased levels of total and ionized serum calcium. In cases of long-standing decompensated diabetes, bone metabolism is impaired [48, 49].

In cases of pellagra syndrome associated with celiac disease, nicotinic acid preparations are used. Preventive treatment with nicotinic acid preparations is also relevant for patients with diabetes [50]. For the primary and secondary prevention of cardiovascular complications in diabetes among adult patients with and without dyslipidemia, statins are recommended as first-line medications. To treat and prevent vitamin deficiencies in both patients with diabetes and those with celiac disease, courses of B-complex vitamins, vitamin C, and fat-soluble vitamins (A, D, K, and E) are recommended [3, 9, 51].

CONCLUSION

The management of patients with a combination of diabetes and enteropathy requires a multidisciplinary approach involving a gastroenterologist, an endocrinologist, and a dietitian.

Even such an advanced and expensive method of treating T1D as insulin pump therapy may not be effective without proper dietary correction and medication, in case of uncontrolled celiac disease. It is impossible to predict the correlation between insulinemia and glycemia in cases of impaired intestinal absorption. Both medical and economic factors listed above and maintaining a good quality of life for require accurate and timely diagnosis of celiac disease in patients with diabetes. This is the only way to ensure patient compliance, which will improve the quality of their treatment and ensure the effective use of medical and economic resources.

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ADDITIONAL INFORMATION

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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REFERENCES

1. Dedov I.I., Kuraeva T.L., Peterkova V.A. Diabetes mellitus in children and adolescents. Moscow: GEOTAR-Media; 2007. (In Russ.).
2. Averkina N.A., Baranov A.A., Bel'mer S.V., Boraeva T.T., Borovik T.A. et al. "Celiac Disease-2025": Project of clinical guidelines for the diagnosis and treatment of celiac disease in children. *Pediatric pharmacology*. 2025;22(4):495–522. (In Russ.). https://doi.org/10.15690/pf.v22i4.2941.
3. Husby S., Koletzko S., Korponay-Szabo I. et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. *J Pediatr Gastroenterol Nutr*. 2020;70(1):141–156. https://doi.org/10.1097/MPG.0000000000002497.
4. Roslavtseva E.A., Dmitrieva Yu.A., Zakharova I.N., Borovik T.E., Potapov A.S., Surkov A.N. et al. Celiac disease in children: draft clinical guidelines. *Experimental and Clinical Gastroenterology*. 2021;188(4):199–227. (In Russ.). https://doi.org/10.31146/1682-8658-ecg-188-4-199-227.
5. Parfenov A.I., Bykova S.V., Sabelnikova E.A., Maev I.V., Baranov A.A., Bakulin I.G. et al. All-Russian consensus on diagnosis and treatment of celiac disease in children and adults. *Therapeutic Archive*. 2017;89(3):94–107. (In Russ.). https://doi.org/10.17116/terarkh201789394-107.
6. Triolo T.M., Armstrong T.K., McFann K., Yu L., Rewers M.J., Klingensmith G.J. et al. Additional autoimmune disease found in 33% of patients at type 1 diabetes onset. *Diabetes Care*. 2011;34(5):1211–1213. https://doi.org/10.2337/dc10-1756.
7. Greco D., Pisciotta M., Gambina F., Maggio F. Celiac disease in subjects with type 1 diabetes mellitus: a prevalence study in western Sicily (Italy). *Endocrine*. 2013;43(1):108–111. https://doi.org/10.1007/s12020-012-9718-8.
8. Bulatova E.M., Lagno O.V, Shabalov A.M., Polunovskiy V.V., Seledtsova L.A. Possibilities of genetic research in the prevention of the development of excess mass of the body and obesity in children. *Archives of Disease in Childhood*. 2019;104(S3):A273–A274. https://doi.org/10.1136/archdischild-2019-epa.640.
9. Bulatova E.M., Lagno O.V., Shabalov A.M., Polunovsky V.V., Seledtsova L.A. Possibilities of genetic research in the prevention of overweight and obesity in children. In: Current issues in pediatrics. Collection of abstracts of the XX Congress of pediatricians of Russia with international participation. Moscow; 2018. P. 44. (In Russ.). EDN: FXLUPE.
10. Khavkin A.I., Bystrova V.I., Schreiner E.V. et. al. Celiac disease: old problem, new solutions. *Nutrition*. 2023;13(4):64–71. (In Russ.). https://doi.org/10.20953/2224-5448-2023-4-64-71.
11. Hennesy E.O., Kuraeva T.L., Prokofyev S.A., Smirnova N.B., Tishina Y.V., Titovic E.V., Peterkova V.A. Serological markers of celiac disease and hla ii antigens in children and adolescents with diabetes mellitus type 1. *Current Pediatrics*. 2012;11(1):14–17. (In Russ.). https://doi.org/10.15690/vsp.v11i1.128.
12. Poddighe D. Pancreatic comorbidities in pediatric celiac disease: exocrine pancreatic insufficiency, pancreatitis, and diabetes mellitus. *Diagnostics*. 2025;15(10):1243. https://doi.org/10.3390/diagnostics15101243.
13. Diagnostics and treatment of endocrine diseases in children and adolescents. N.P. Shabalov, ed. 3rd ed., corrected and enlarged. Moscow: MEDpress-inform; 2017. (In Russ.).
14. Libman I., Haynes A., Lyons S., Pradeep P., Rwagasor E., Tung J.Y. et al. ISPAD clinical practice consensus guidelines 2022: Definition, epidemiology, and classification of diabetes in children and adolescents. *Pediatr Diabetes*. 2022;23(8):1160–1174. https://doi.org/10.1111/pedi.13454.
15. Sozaeva L.S., Zilberman L.I., Svetlova G.N., Andrianova E.A., Kareva M.A. et al. Clinical and immunological characteristics of diabetes mellitus in patients with

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

autoimmune polyglandular syndrome type 1 in Russia. *Diabetes Mellitus*. 2018;21(1):48–57. (In Russ.). https://doi.org/10.14341/DM9347. EDN: YTHLOX.
16. Tikhonovich Yu.V., Petryaikina E.E., Rybkina I.G., Garyaeva I.V., Tyul'pakov A.N. X-linked immune dysregulation, polyendocrinopathy and enteropathy (IPEX syndrome): the description of a clinical case and a short literature review. *Problems of Endocrinology*. 2014;60(5):29–33. (In Russ.). https://doi.org/10.14341/probl201460529-33. EDN: THSTZL.
17. Lampasona V., Passerini L., Barzaghi F., Lombardoni C., Bazzigaluppi E., Brigatti C. et al. Autoantibodies to harmonin and villin are diagnostic markers in children with IPEX syndrome. *PLoS ONE*. 2013;8(11):e78664. URL: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0078664 (accessed 15.07.2020). https://doi.org/10.1371/journal.pone.0078664.
18. Edelman S.V., Agardh D., Cui N., Hao L., Wieloch M., Meneghini L. Risk of new-onset type 1 diabetes in individuals with celiac disease and thyroid disease — An observational study. *Diabetes Obes Metab*. 2025;27(8):4229–4238. https://doi.org/10.1111/dom.16454.
19. Rubio-Cabezas O., Minton J.A., Caswell R., Shield J.P., Deiss D., Sumnik Z., Cayssials A., Herr M., Loew A., Lewis V., Ellard S., Hattersley A.T. Clinical heterogeneity in patients With FOXP3 mutations presenting with permanent neonatal diabetes. *Diabetes Care*. 2009;32(1):111–116. https://doi.org/10.2337/dc08-1188.
20. Turkunova M.E., Ditkovskaya L.V., Suspitsin E.N. et al. Neonatal diabetes mellitus in the structure of ipex syndrome. *Pediatrician (St Petersburg)*. 2017;8(2):99–104. (In Russ.). https://doi.org/10.17816/PED8299-104. EDN: YPSABV.
21. Gambineri E., Ciullini Mannurita S., Hagin D., Vignoli M., Anover-Sombke S., DeBoer S. et al. Clinical, immunological, and molecular heterogeneity of 173 patients with the phenotype of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. *Front Immunol*. 2018;9:2411. https://doi.org/10.3389/fimmu.2018.02411.
22. Safi M.A. Celiac disease in type 1 diabetes mellitus in the Kingdom of Saudi Arabia. Characterization and meta-analysis. *Saudi Med J*. 2019;40(7):647–656. https://doi.org/10.15537/smj.2019.7.24293.
23. Dedov I.I., Shestakova M.V., Vikulova O.K., Zheleznyakova A.V., Isakov M.A. Epidemiological characteristics of diabetes mellitus in the Russian Federation: clinical and statistical analysis according to the Federal diabetes register data of 01.01.2021. *Diabetes Mellitus*. 2021;24(3):204–221. (In Russ.). https://doi.org/10.14341/DM12759.
24. XV All-Russian Conference of Pediatric Endocrinologists "Optimization of Diagnostics, Treatment, and Medical and Social Rehabilitation in Pediatric Endocrinology". April 27–28, 2019, St. Petersburg. Collection of reports and articles. *Problems of Endocrinology*. 2029; 65(1S). URL: https://www.probl-endojournals.ru/jour/issue/viewIssue/814/17 (accessed: 03.02.2026).
25. Keshtkari A., Danaei M., Mollaali M. Association of HLA-DQ4/5 genotype polymorphisms with celiac disease in a group of children in Southwest Iran: Acase-control study. *Health Sci Rep*. 2024;7(7):e2242. https://doi.org/10.1002/hsr2.2242.
26. Livzan M.A., Gaus O.V., Kolbina M.V., Karasaeva F.Zh., Ratnikova O.A. Celiac disease in a patient with type 1 diabetes. *Experimental and Clinical Gastroenterology*. 2019;169(9):107–112. (In Russ.). https://doi.org/10.31146/1682-8658-ecg-169-9-107-112. EDN: TZQVQL.
27. Hakami M., Yafei S., Hummadi A., Abutaleb R., Khawaji A., Solan Y. et al. Clinical characteristics and prevalence of celiac disease in a large cohort of type 1 diabetes from Saudi Arabia. *Medicina (Kaunas)*. 2024;60(12):1940. https://doi.org/10.3390/medicina60121940.
28. Shah A.S., Zeitler P.S., Wong J. et al. ISPAD Clinical Practice Consensus Guidelines 2022: Type 2 diabetes in children and adolescents. *Pediatr Diabetes*. 2022;23(7):872–902. https://doi.org/10.1111/pedi.13409.
29. Novikova V.P., Khavkin A.I., Shapovalova N.S. Extra-laboratory diagnosis of coeliac disease. Clinical Practice in Pediatrics. 2018;13(5):62–67. (In Russ.). https://doi.org/10.20953/1817-7646-2018-5-62-67. EDN: VQBSGU.
30. Popoviciu M.S., Kaka N., Sethi Y., Patel N., Chopra H., Cavalu S. Type 1 diabetes mellitus and autoimmune diseases: a critical review of the association and the application of personalized medicine. *J Pers Med*. 2023;13(3):422. https://doi.org/10.3390/jpm13030422.
31. Pokhlebkina A.A., Tyrtova L.V. Experience of using non-laboratory tests in screening for celiac disease in children with type 1 diabetes mellitus. *Medicine: Theory and Practice*. 2019;4(1):287. (In Russ.). EDN: GLIDGM.
32. Kaur N., Minz R.W., Bhadada S.K., Saikia B., Dayal D., Anand S. et al. Role of anti-tissue transglutaminase IgA+IgG antibodies in detection of potential celiac disease in patients with type 1 diabetes. *Indian J Med Res*. 2019;149(1):18–25. https://doi.org/10.4103/ijmr.IJMR_1136_16.
33. Sakhuja S., Holtz L.R. Progression of pediatric celiac disease from potential celiac disease to celiac disease: a retrospective cohort study. *BMC Pediatr*. 2021;21(1):149. https://doi.org/10.1186/s12887-021-02625-z.
34. Raiteri A., Granito A., Giamperoli A., Catenaro T., Negrini G., Tovoli F. Current guidelines for the management of celiac disease: A systematic review with comparative analysis. *World J Gastroenterol*. 2022;28(1):154–175. https://doi.org/10.3748/wjg.v28.i1.154.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

35. Christodoulidis G., Agko S.E., Kouliou M.N., Koumarelas K.E., Zacharoulis D. Advances and challenges in diagnosing and managing adult autoimmune enteropathy. *World J Gastroenterol*. 2025;31(2):99118. https://doi.org/10.3748/wjg.v31.i2.99118.
36. Caio G., Volta U., Sapone A., Leffler D.A., De Giorgio R., Catassi C., Fasano A. Celiac disease: a comprehensive current review. *BMC Med*. 2019;17(1):142. https://doi.org/10.1186/s12916-019-1380-z.
37. Shapovalova N.S., Novikova V.P., Revnova M.O. et al. Seronegative coeliac disease in the light of the guidelines by the European Society for the Study of Coeliac Disease (ESsCD) 2019. *Pediatric Nutrition*. 2019;17(6):14–22. (In Russ.). https://doi.org/10.20953/1727-5784-2019-6-14-22. EDN: HKDVYD.
38. Leeds J.S., Hopper A.D., Hadjivassiliou M., Tesfaye S., Sanders D.S. High prevalence of microvascular complications in adults with type 1 diabetes and newly diagnosed celiac disease. *Diabetes Care*. 2011;34(10):2158–2163. https://doi.org/10.2337/dc11-0149.
39. Endocrine diseases in children and adolescents: a guide for doctors. E.B. Bashnina, ed. Moscow: GEOTAR-Media; 2017. (In Russ.).
40. Tye-Din J.A. Evolution in coeliac disease diagnosis and management. *JGH Open*. 2024;8(7):e13107. https://doi.org/10.1002/jgh3.13107.
41. Dreval A.V. Insulin pump therapy and continuous glucose monitoring in the current practice of diabetes treatment (lecture). *RMJ. Medical Review*. 2019;3(1-1):2–4. (In Russ.). EDN: LJHWNP.
42. Khan A., Rani S., Verma A., Verma S., Singh V. Impact of food distribution practices on school children with coeliac disease and type 1 diabetes mellitus. *J Clin Sci Res*. 2025;14(1):68–69. https://doi.org/10.4103/jcsr.jcsr_126_24.
43. Brusco M., Trivellini S., Cozzali R. et al. The environmental impact of pediatric celiac disease diagnosis and follow-up. *JPGN Rep*. 2025;6(3):236–240. https://doi.org/10.1002/jpr3.70048.
44. Razavi S., Amirmozafari N., Zahedi bialvaei A., Navab-Moghadam F., Khamseh M. E., Alaei-Shahmiri F., Sedighi M. Gut microbiota composition and type 2 diabetes: Are these subjects linked Together? *Heliyon*. 2024;10(20):e39464. https://doi.org/10.1016/j.heliyon.2024.e39464.
45. Han H., Li Y., Fang J., Liu G., Yin J., Li T., Yin Y. Gut microbiota and type 1 diabetes. *Int J Mol Sci*. 2018;19(4):995. https://doi.org/10.3390/ijms19040995.
46. Arhire A.I., Papuc T., Ioacără S., Gradisteanu Pircalabioru G., Barbu C.G. Unveiling the gut connection: Exploring the link between microbiota and type 1 diabetes onset in pediatric patients. *Biomed Rep*. 2025;24(1):1. https://doi.org/10.3892/br.2025.2074.
47. Pokrovskaya E.V., Shamkhalova M.S., Shestakova M.V. The new views on the state of the gut microbiota in obesity and diabetes mellitus type 2. *Diabetes mellitus*. 2019;22(3):253–262. (In Russ.). https://doi.org/10.14341/DM10194. EDN: LWRKYK.
48. Bavykina I.A., Zvyagin A.A. Nutritional status of children on a long-term gluten-free diet. *Voprosy prakticheskoi pediatrii*. 2015;10(2):20–25. (In Russ.). EDN: RWERML.
49. Bavykina I.A., Zvyagin A.A., Bavykin D.V., Yurova I.Yu. Densitometry in the assessment of bone metabolism in children with celiac disease. *Children's Medicine of the North-West*. 2024;12(2):89–94. (In Russ.). https://doi.org/10.56871/CmN-W.2024.71.22.007.
50. Capasso G., Guarino S., Tirelli P., Di Sessa A., Pietropaolo G., Auricchio F. et al. Adrenal response at the onset of type 1 diabetes mellitus in children and its association with acute metabolic and kidney complications. *BMC Endocr Disord*. 2025;25(1):272. https://doi.org/10.1186/s12902-025-02095-9.
51. Tye-Din J.A. Evolution in coeliac disease diagnosis and management. *JGH Open*. 2024;8(7):e13107. https://doi.org/10.1002/jgh3.13107.

ЛИТЕРАТУРА

1. Дедов И.И., Кураева Т.Л., Петеркова В.А. Сахарный диабет у детей и подростков. М.: ГЭОТАР-Медиа; 2007.
2. Аверкина Н.А., Баранов А.А., Бельмер С.В., Бораева Т.Т., Боровик Т.Э. и др. «Целиакия-2025»: проект клинических рекомендаций по диагностике и лечению целиакии у детей. *Педиатрическая фармакология*. 2025;22(4):495–522. https://doi.org/10.15690/pf.v22i4.2941.
3. Husby S., Koletzko S., Korponay-Szabo I. et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. *J Pediatr Gastroenterol Nutr*. 2020;70(1):141–156. https://doi.org/10.1097/MPG.0000000000002497.
4. Рославцева Е.А., Дмитриева Ю.А., Захарова И.Н., Боровик Т.Э., Потапов А.С., Сурков А.Н. и др. Целиакия у детей: проект клинических рекомендаций. *Экспериментальная и клиническая гастроэнтерология*. 2021;188(4):199–227. https://doi.org/10.31146/1682-8658-ecg-188-4-199-227.
5. Парфенов А.И., Быкова С.В., Сабельникова Е.А., Маев И.В., Баранов А.А., Бакулин И.Г. и др. Всероссийский консенсус по диагностике и лечению целиакии у детей и взрослых. *Терапевтический архив*. 2017;89(3):94–107. https://doi.org/10.17116/terarkh201789394-107.
6. Triolo T.M., Armstrong T.K., McFann K., Yu L., Rewers M.J., Klingensmith G.J. et al. Additional autoim-

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

mune disease found in 33% of patients at type 1 diabetes onset. *Diabetes Care*. 2011;34(5):1211–1213. https://doi.org/10.2337/dc10-1756.
7. Greco D., Pisciotta M., Gambina F., Maggio F. Celiac disease in subjects with type 1 diabetes mellitus: a prevalence study in western Sicily (Italy). *Endocrine*. 2013;43(1):108–111. https://doi.org/10.1007/s12020-012-9718-8.
8. Bulatova E.M., Lagno O.V., Shabalov A.M., Polunovskiy V.V., Seledtsova L.A. Possibilities of genetic research in the prevention of the development of excess mass of the body and obesity in children. *Archives of Disease in Childhood*. 2019;104(S3):A273–A274. https://doi.org/10.1136/archdischild-2019-epa.640.
9. Булатова Е.М., Лагно О.В., Шабалов А.М., Полуновский В.В., Селедцова Л.А. Возможности генетического исследования в профилактике развития избыточной массы тела и ожирения у детей. В кн.: Актуальные проблемы педиатрии. Сборник тезисов XX Конгресса педиатров России с международным участием. М.; 2018. С. 44. EDN: FXLUPE.
10. Хавкин А.И., Быстрова В.И., Шрайнер Е.В. и др. Целиакия: старая проблема, новые решения. *Вопросы диетологии*. 2023;13(4):64–71. https://doi.org/10.20953/2224-5448-2023-4-64-71. EDN: KBJCFO.
11. Хеннесси Е.О., Кураева Т.Л., Прокофьев С.А., Смирнова Н.Б., Тишина Ю.В., Титович Е.В., Петеркова В.А. Серологические маркеры целиакии и антигены HLA класса II у детей и подростков с сахарным диабетом 1 типа. *Вопросы современной педиатрии*. 2012;11(1):14–17. https://doi.org/10.15690/vsp.v11i1.128. EDN: OXJALH.
12. Poddighe D. Pancreatic comorbidities in pediatric celiac disease: exocrine pancreatic insufficiency, pancreatitis, and diabetes mellitus. *Diagnostics*. 2025;15(10):1243. https://doi.org/10.3390/diagnostics15101243.
13. Диагностика и лечение эндокринных заболеваний у детей и подростков. Н.П. Шабалов, ред. 3-е изд., испр. и доп. М.: МЕДпресс-информ; 2017.
14. Libman I., Haynes A., Lyons S., Pradeep P., Rwagasor E., Tung J.Y. et al. ISPAD clinical practice consensus guidelines 2022: Definition, epidemiology, and classification of diabetes in children and adolescents. *Pediatr Diabetes*. 2022;23(8):1160–1174. https://doi.org/10.1111/pedi.13454.
15. Созаева Л.С., Зильберман Л.И., Светлова Г.Н., Андрианова Е.А., Карева М.А., Иванова О.Н. и др. Клинические и иммунологические особености сахарного диабета у пациентов с аутоиммунным полигландулярным синдромом 1 типа в России. *Сахарный диабет*. 2018;21(1): 48–57. https://doi.org/10.14341/DM9347. EDN: YTHLOX.
16. Тихонович Ю.В., Петряйкина Е.Е., Рыбкина И.Г., Гаряева И.В., Тюльпаков А.Н. Х-сцепленные иммунная дисрегуляция, полиэндокринопатия и энтеропатия (IPEX-синдром): описание клинического случая и краткий обзор литературы. *Проблемы эндокринологии*. 2014;60(5):29–33. https://doi.org/10.14341/probl201460529-33. EDN: THSTZL.
17. Lampasona V., Passerini L., Barzaghi F., Lombardoni C., Bazzigaluppi E., Brigatti C. et al. Autoantibodies to harmonin and villin are diagnostic markers in children with IPEX syndrome. *PLoS ONE*. 2013;8(11):e78664. URL: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0078664 (accessed 15.07.2020). https://doi.org/10.1371/journal.pone.0078664.
18. Edelman S.V., Agardh D., Cui N., Hao L., Wieloch M., Meneghini L. Risk of new-onset type 1 diabetes in individuals with celiac disease and thyroid disease — An observational study. *Diabetes Obes Metab*. 2025;27(8):4229–4238. https://doi.org/10.1111/dom.16454.
19. Rubio-Cabezas O., Minton J.A., Caswell R., Shield J.P., Deiss D., Sumnik Z., Cayssials A., Herr M., Loew A., Lewis V., Ellard S., Hattersley A.T. Clinical heterogeneity in patients With FOXP3 mutations presenting with permanent neonatal diabetes. *Diabetes Care*. 2009;32(1):111–116. https://doi.org/10.2337/dc08-1188.
20. Туркунова М.Е., Дитковская Л.В., Суспицын Е.Н. и др. Неонатальный сахарный диабет в структуре IPEX-синдрома. *Педиатр*. 2017;8(2):99–104. https://doi.org/10.17816/PED8299-104. EDN: YPSABV.
21. Gambineri E., Ciullini Mannurita S., Hagin D., Vignoli M., Anover-Sombke S., DeBoer S. et al. Clinical, Immunological, and Molecular Heterogeneity of 173 Patients With the Phenotype of Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-Linked (IPEX) Syndrome. *Front Immunol*. 2018;9:2411. https://doi.org/10.3389/fimmu.2018.02411.
22. Safi M.A. Celiac disease in type 1 diabetes mellitus in the Kingdom of Saudi Arabia. Characterization and meta-analysis. *Saudi Med J*. 2019;40(7):647–656. https://doi.org/10.15537/smj.2019.7.24293.
23. Дедов И.И., Шестакова М.В., Викулова О.К., Железнякова А.В., Исаков М.А. Эпидемиологические характеристики сахарного диабета в Российской Федерации: клинико-статистический анализ по данным Регистра сахарного диабета на 01.01.2021. *Сахарный диабет*. 2021;24(3):204–221. https://doi.org/10.14341/DM12759.
24. XV Всероссийская конференция детских эндокринологов «Оптимизация диагностики лечения и медико-социальной реабилитации в детской эндокринологии». 27–28 апреля 2019 г., Санкт-Петербург. Сборник докладов и статей. *Проблемы эндокриноло-*

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

гии. 2029;65(1S). URL: https://www.probl-endojournals.ru/jour/issue/viewIssue/814/17 (дата обращения: 03.02.2026).
25. Keshtkari A., Danaei M., Mollaali M. Association of HLA-DQ4/5 genotype polymorphisms with celiac disease in a group of children in Southwest Iran: Acase-control study. *Health Sci Rep*. 2024;7(7):e2242. https://doi.org/10.1002/hsr2.2242.
26. Ливзан М.А., Гаус О.В., Колбина М.В., Карасаева Ф.Ж., Ратникова О.А. Целиакия у больной сахарным диабетом 1 типа. *Экспериментальная и клиническая гастроэнтерология*. 2019;169(9):107–112. https://doi.org/10.31146/1682-8658-ecg-169-9-107-112. EDN: TZQVQL.
27. Hakami M., Yafei S., Hummadi A., Abutaleb R., Khawaji A., Solan Y. et al. Clinical characteristics and prevalence of celiac disease in a large cohort of type 1 diabetes from Saudi Arabia. *Medicina (Kaunas)*. 2024;60(12):1940. https://doi.org/10.3390/medicina60121940.
28. Shah A.S., Zeitler P.S., Wong J. et al. ISPAD Clinical Practice Consensus Guidelines 2022: Type 2 diabetes in children and adolescents. *Pediatr Diabetes*. 2022;23(7):872–902. https://doi.org/10.1111/pedi.13409.
29. Новикова В.П., Хавкин А.И., Шаповалова Н.С. Внелабораторная диагностика целиакии. *Вопросы практической педиатрии*. 2018;13(5):62–67. https://doi.org/10.20953/1817-7646-2018-5-62-67. EDN: VQBSGU.
30. Popoviciu M.S., Kaka N., Sethi Y., Patel N., Chopra H., Cavalu S. Type 1 diabetes mellitus and autoimmune diseases: a critical review of the association and the application of personalized medicine. *J Pers Med*. 2023;13(3):422. https://doi.org/10.3390/jpm13030422.
31. Похлебкина А.А., Тыртова Л.В. Опыт использования внелабораторных тестов в скрининге на целиакию у детей с сахарным диабетом 1 типа. *Медицина: теория и практика*. 2019;4(1):287. EDN: GLIDGM.
32. Kaur N., Minz R.W., Bhadada S.K., Saikia B., Dayal D., Anand S. et al. Role of anti-tissue transglutaminase IgA+IgG antibodies in detection of potential celiac disease in patients with type 1 diabetes. *Indian J Med Res*. 2019;149(1):18–25. https://doi.org/10.4103/ijmr.IJMR_1136_16.
33. Sakhuja S., Holtz L.R. Progression of pediatric celiac disease from potential celiac disease to celiac disease: a retrospective cohort study. *BMC Pediatr*. 2021;21(1):149. https://doi.org/10.1186/s12887-021-02625-z.
34. Raiteri A., Granito A., Giamperoli A., Catenaro T., Negrini G., Tovoli F. Current guidelines for the management of celiac disease: A systematic review with comparative analysis. *World J Gastroenterol*. 2022;28(1):154–175. https://doi.org/10.3748/wjg.v28.i1.154.
35. Christodoulidis G., Agko S.E., Kouliou M.N., Koumarelas K.E., Zacharoulis D. Advances and challenges in diagnosing and managing adult autoimmune enteropathy. *World J Gastroenterol*. 2025;31(2):99118. https://doi.org/10.3748/wjg.v31.i2.99118.
36. Caio G., Volta U., Sapone A., Leffler D.A., De Giorgio R., Catassi C., Fasano A. Celiac disease: a comprehensive current review. *BMC Med*. 2019;17(1):142. https://doi.org/10.1186/s12916-019-1380-z.
37. Шаповалова Н.С., Новикова В.П., Ревнова М.О. и др. Серонегативная целиакия в свете рекомендаций европейского общества изучения целиакии (ESsCD) 2019 года. *Вопросы детской диетологии*. 2019;17(6):14–22. https://doi.org/10.20953/1727-5784-2019-6-14-22. EDN: HKDVYD.
38. Leeds J.S., Hopper A.D., Hadjivassiliou M., Tesfaye S., Sanders D.S. High prevalence of microvascular complications in adults with type 1 diabetes and newly diagnosed celiac disease. *Diabetes Care*. 2011;34(10):2158–2163. https://doi.org/10.2337/dc11-0149.
39. Эндокринные заболевания у детей и подростков: руководство для врачей. Е.Б. Башнина, ред. М.: ГЭОТАР-Медиа; 2017.
40. Tye-Din J.A. Evolution in coeliac disease diagnosis and management. *JGH Open*. 2024;8(7):e13107. https://doi.org/10.1002/jgh3.13107.
41. Древаль А.В. Место помповой инсулинотерапии и непрерывного мониторирования гликемии в современной практике лечения сахарного диабета. *РМЖ. Медицинское обозрение*. 2019;3(1-1):2–4. EDN: LJHWNP.
42. Khan A., Rani S., Verma A., Verma S., Singh V. Impact of food distribution practices on school children with coeliac disease and type 1 diabetes mellitus. *J Clin Sci Res*. 2025;14(1):68–69. https://doi.org/10.4103/jcsr.jcsr_126_24.
43. Brusco M., Trivellini S., Cozzali R. et al. The environmental impact of pediatric celiac disease diagnosis and follow-up. *JPGN Rep*. 2025;6(3):236–240. https://doi.org/10.1002/jpr3.70048.
44. Razavi S., Amirmozafari N., Zahedi bialvaei A., Navab-Moghadam F., Khamseh M. E., Alaei-Shahmiri F., Sedighi M. Gut microbiota composition and type 2 diabetes: Are these subjects linked together? *Heliyon*. 2024;10(20):e39464. https://doi.org/10.1016/j.heliyon.2024.e39464.
45. Han H., Li Y., Fang J., Liu G., Yin J., Li T., Yin Y. Gut microbiota and type 1 diabetes. *Int J Mol Sci*. 2018;19(4):995. https://doi.org/10.3390/ijms19040995.
46. Arhire A.I., Papuc T., Ioacără S., Gradisteanu Pircalabioru G., Barbu C.G. Unveiling the gut connection: Exploring the link between microbiota and type 1 diabetes onset in pediatric patients. *Biomed Rep*. 2025;24(1):1. https://doi.org/10.3892/br.2025.2074.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

47. Покровская Е.В., Шамхалова М.Ш., Шестакова М.В. Новые взгляды на состояние кишечной микробиоты при ожирении и сахарном диабете 2 типа. *Сахарный диабет*. 2019;22(3):253–262. https://doi.org/10.14341/DM10194. EDN: LWRKYK.
48. Бавыкина И.А., Звягин А.А. Нутритивный статус детей при длительной безглютеновой диете. *Вопросы практической педиатрии*. 2015;10(2):20–25. EDN: RWERML.
49. Бавыкина И.А., Звягин А.А., Бавыкин Д.В., Юрова И.Ю. Денситометрия в оценке костного метаболизма у детей с целиакией. *Children's Medicine of the North-West*. 2024;12(2):89–94. https://doi.org/10.56871/CmN-W.2024.71.22.007. EDN: NGSJKY.
50. Capasso G., Guarino S., Tirelli P., Di Sessa A., Pietropaolo G., Auricchio F. et al. Adrenal response at the onset of type 1 diabetes mellitus in children and its association with acute metabolic and kidney complications. *BMC Endocr Disord*. 2025;25(1):272. https://doi.org/10.1186/s12902-025-02095-9.
51. Tye-Din J.A. Evolution in coeliac disease diagnosis and management. *JGH Open*. 2024;8(7):e13107. https://doi.org/10.1002/jgh3.13107.

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An assessment of knowledge about celiac disease based on an anonymous survey among first- and sixth-year medical students at Saint Petersburg State Pediatric Medical University, as well as Medical College students

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ABSTRACT. ***Introduction.*** Celiac disease is currently one of the most common chronic immune-mediated diseases, characterized by polymorphism of clinical manifestations and the complexity of early diagnosis. Despite improvements in diagnostic methods, the disease often remains unrecognized, largely due to insufficient awareness among healthcare professionals and future doctors. ***The aim*** of the study was to assess the level of knowledge about celiac disease among 6th-year, 1st-year students, and medical college students. ***Materials and methods.*** An anonymous online survey was conducted, consisting of 19 questions grouped into 7 thematic blocks. A total of 1261 participants took part in the survey, including: 6th-year students — 418 people, medical college students — 69, 1st-year students — 774. Statistical data processing was performed using SPSS for Windows 13.0 and Microsoft Excel 2019 software. ***Results.*** The study revealed an unsatisfactory level of knowledge among medical students. Students primarily made errors in questions related to clinical presentation, specific serological diagnosis, diseases associated with celiac disease, genetic markers, and complications. The data indicate an insufficient understanding of the topic and the need to develop methods to increase knowledge and interest among students. ***Conclusions.*** The obtained results highlight the relevance of implementing additional educational activities. Effective measures may include: conducting additional lecture courses, scientific conferences, utilizing clinical case discussions in student practice, and disseminating reliable informational materials through university resources. A comprehensive educational approach and student discipline will improve the quality of training and enhance early diagnosis of the disease.

KEYWORDS: *celiac disease, student awareness, anonymous online survey*

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Знание о целиакии на основании анонимного опроса студентов 6-го и 1-го курсов Санкт-Петербургского государственного педиатрического медицинского университета и медицинского колледжа

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РЕЗЮМЕ. ***Введение.*** В настоящее время целиакия является одним из наиболее распространенных хронических иммуноопосредованных заболеваний, которое характеризуется полиморфизмом клинических проявлений и сложностью ранней диагностики. Несмотря на совершенствование методов диагностики, заболевание нередко остается нераспознанным, что во многом связано с недостаточной осведомленностью медицинских работников и будущих врачей. ***Цель исследования*** — оценить уровень знаний о целиакии среди студентов 6-го и 1-го курсов Санкт-Петербургского государственного педиатрического медицинского университета и медицинского колледжа. ***Материалы и методы.*** Проведено анонимное онлайн-тестирование, включавшее 19 вопросов, сгруппированных в 7 тематических блоков. В анкетировании принимал участие 1261 человек, из них 6-й курс — 418 человек, медицинский колледж — 69, 1-й курс — 774 обучающихся. Статистическая обработка данных выполнена с помощью программного обеспечения SPSS for Windows 13.0 и Microsoft Excel 2019. ***Результаты.*** Исследование выявило неудовлетворительный уровень знаний среди студентов-медиков. В основном студенты допускают ошибки в вопросах клинической картины, специфической серологической диагностики, заболеваний, связанных с целиакией, генетических маркеров и осложнений. Данные свидетельствуют о недостаточном понимании темы и необходимости разработки методов повышения знаний и интереса среди студентов. ***Выводы.*** Полученные результаты подчеркивают актуальность внедрения дополнительных образовательных мероприятий. Эффективными мерами могут быть: проведение дополнительных лекционных курсов, научных конференций, разборы клинических случаев в практике студентов, распространение достоверных информационных материалов через университетские ресурсы. Комплексный образовательный подход и дисциплина обучающихся позволят повысить качество подготовки и улучшить раннюю диагностику заболевания.

КЛЮЧЕВЫЕ СЛОВА: *целиакия, осведомленность студентов, анонимный онлайн-опрос*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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INTRODUCTION

Currently, celiac disease is one of the most pressing issues in pediatrics and gastroenterology. Over the past few years, its prevalence has increased significantly [1]. Increased awareness of celiac disease among physicians of various specialties (including dentists, gynecologists, dermatologists, and others), screening of children in high-risk groups, and public education through the media have contributed to increased numbers of diagnosed cases. The public organization "Emilia," which supports people with celiac disease, is actively involved in this educational work. According to the World Gastroenterology Organization, the prevalence of celiac disease in various populations ranges from 1 in 100 to 1 in 300 [1, 2]. Long-term studies indicate that gluten enteropathy occurs in 0.5–2% of the population, with an average prevalence of about 1% [3].

Celiac disease can develop at any age; the clinical picture is characterized by polymorphism and includes both intestinal symptoms (abdominal pain, loose stools, bloating) and extraintestinal symptoms (including failure to thrive, anemia, osteopenia, dermatitis herpetiformis, peripheral neuropathy, and others) [4, 5], which is why timely diagnosis is often difficult. The symptoms are so diverse that the disease has been dubbed the "Great Mimic."

Currently, serological tests are used for celiac disease screening: detection of specific antibodies to tissue transglutaminase (tTG) in serum samples [6, 7]. A major advantage of mass screening is the identification of mild and asymptomatic cases of celiac disease. Celiac disease is diagnosed through esophagogastroduodenoscopy (EGD) with a biopsy of the small intestine mucosa [8], and treatment consists of strict, lifelong adherence to a gluten-free diet [4, 9].

The percentage of diagnosed cases of celiac disease varies significantly from country to country, which is associated with both genetic factors and the level of awareness among physicians and the availability of diagnostic testing. In Finland, it ranges from 60–80%, in Italy from 30–40%, in the U.S. from 17–30%, in Germany from 10–20%, and in Russia from 5–10% [1, 10]. Scandinavian countries have the highest detection rates due to active population-based screening. Countries in Western Europe and North America are improving their diagnostic capabilities, but a significant proportion of cases (50–80%) still go undiagnosed [11]. In Asian, African, and Eastern European countries, the percentage of diagnosed cases is extremely low, which is associated with low public awareness and limited access to diagnostic tests (serology, biopsy) [12].

Thus, celiac disease remains a significant medical problem worldwide, affecting people of all age groups. Given the high prevalence and difficulties in timely diagnosis, studying this topic is vitally important for physicians and medical students, as it forms the foundation of their clinical experience, enhances their knowledge, and guides further scientific research in this field.

AIM

The aim of this study was to assess students' knowledge of celiac disease among first- and sixth-year students in the Faculty of Pediatrics and the Medical College of St. Petersburg State Pediatric Medical University (SPbSPMU) based on an anonymous online survey.

MATERIALS AND METHODS

This study was conducted among medical students in an anonymous online survey using Yandex Forms during lectures. Respondents were informed about the purpose of the survey, confidentiality, and the non-disclosure of individual results.

There were 19 questions in total, divided into seven thematic sections. The first section contained questions about the basics and general information regarding the disease, including its definition, duration, and age-related characteristics. In the second section, respondents were asked to identify the clinical manifestations of celiac disease and its complications. The third section focused on testing knowledge of diseases and conditions associated with an increased risk of developing celiac disease, as well as understanding of genotypes associated with it. The fourth extensive section assessed students' awareness of high-quality and timely diagnosis of celiac disease, including laboratory and imaging tests. The fifth section included questions on treatment, namely dietary therapy. It was important to assess whether students understood which foods can be consumed by patients with this diagnosis without harming their health, and

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which must be completely excluded. The sixth section addressed the topic of follow-up care and treatment monitoring: how often patients should be monitored and whether a follow-up biopsy is necessary. In the final, seventh section, we analyzed the prevalence of celiac disease among respondents, their close and distant relatives, to compare it with statistics in Russia, and also identified the sources of information used by students at SPSPMU.

A total of 1,261 people participated in the survey, including 418 sixth-year medical students, 69 medical college students, and 774 first-year students.

Statistical analysis was performed using SPSS for Windows 13.0 and Microsoft Excel 2019. The means of independent sample populations were compared using the Wilcoxon p-test. Changes were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

The study revealed an insufficient level of knowledge among medical students. Figure 1 shows the difference in correct answers among students in different years.

The following percentages of students answered all questions correctly: 56.6% (237) — 6th year; 45.1% (31) — Medical College (M/C); 46.9% (363) — 1st year. The difference between the students' answers is as follows: 6th year and M/C — 11.5% ($p < 0.05$); 6th and 1st years — 9.7% ($p < 0.05$); 1st year and M/C — 1.8% ($p > 0.05$). The data are presented in Figure 2.

When comparing results among students from different years, we can say that the difference between the 1st year, M/C, and the 6th year is quite small and amounts to approximately 10%. The level of knowledge increases as students' progress toward graduation; however, even among upperclassmen, there remains a significant number of gaps. Lower-year students demonstrate lower scores in understanding this topic.

Difficulties with answers mainly arise in questions regarding clinical manifestations. Most respondents are unaware that celiac disease manifests not only with intestinal but also with extraintestinal symptoms [13–16], and may also be asymptomatic [17]. According to the survey results, the following percentages of students selected intestinal symptoms: 6th year—62% (259), M/C—47% (32), 1st year—50% (387); and extraintestinal symptoms: 6th year—34% (142), M/C — 31% (21), 1st year — 29% (224). The difference is: 6th year — $p < 0.05$; M/C — $p > 0.05$; 1st year — $p < 0.05$.

Students know significantly less about complications of celiac disease. The percentage of students who answered correctly was: 6th year — 11.2% (47), M/C — 4.5% (3), 1st year — 4.3% (33) (6th year and M/C: $p < 0.05$; 6th and 1st years: $p < 0.05$; M/C and 1st year: $p > 0.05$).

In addition, students have low awareness of risk groups. Autoimmune thyroiditis, atopic dermatitis, first-degree relatives with celiac disease, type 1 diabetes, Down syndrome, Turner syndrome, Williams syndrome, and total immunoglobulin A deficiency [13, 18] represent an increased risk of developing celiac disease. Identifying risk

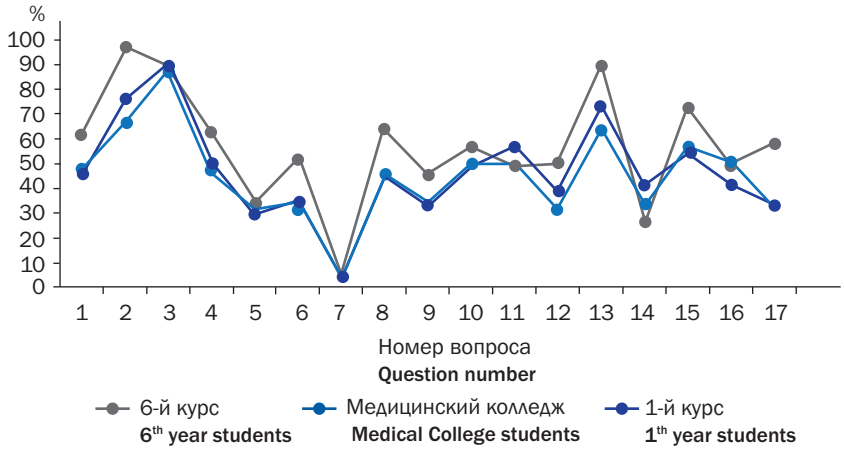

Fig. 1. Proportion of correct answers among students (the figure is prepared by the authors)

Рис. 1. Соотношение правильных ответов между студентами (рисунок подготовлен авторами)

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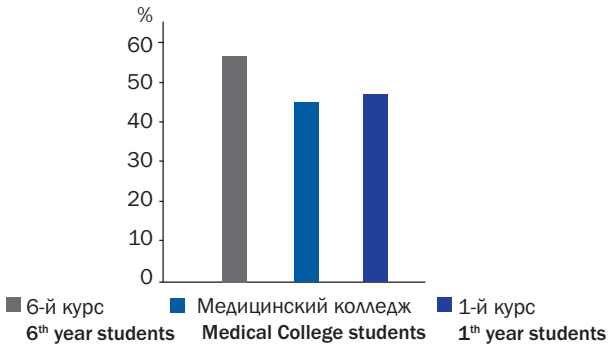

Fig. 2. Comparison of students achieving perfect scores across different courses, % (the figure is prepared by the authors)

Рис. 2. Сравнение студентов, правильно ответивших на все вопросы, среди разных курсов, % (рисунок подготовлен авторами)

groups can significantly aid in diagnosis, so this information should be relevant to medical students. More than half of the 6th-year students are aware of this (52% (217)), while students in lower years are less familiar with this information (M/C – 32% (22), 1st year – 35% (271)) (6th year and M/C: p <0.05; 6th and 1st years: p <0.05; M/C and 1st year: p >0.05).

Questions regarding genetic markers for celiac disease also posed a challenge. A high prevalence of celiac disease has been demonstrated in families with the presence of the HLA DQ2 and DQ8 haplotypes [8, 19–21]. The correct answer was given by students: 6th year – 50% (208), M/C – 32% (22), 1st year – 39% (305) (6th year and M/C: p <0.05; 6th and 1st years: p <0.05; M/C and 1st year: p >0.05).

In addition, students found it difficult to answer the question regarding diagnosis, which indicates an insufficient understanding of the complete diagnostic algorithm. The diagnosis of celiac disease is based on data from laboratory and instrumental studies. The most informative methods are serological and specific genetic tests [20, 22]. This option was chosen by: 6th-year students – 46% (192), M/C – 35% (24), 1st-year students – 33% (255) (6th-year students and M/C: p >0.05; 6th-year and 1st-year students: p <0.05; M/C and 1st year: p >0.05). The "gold standard" for definitive confirmation in patients with positive immunological tests is small bowel biopsy followed by histopathological examination [16, 23–25]. The students demonstrated the best knowledge on this question: 6th year – 65% (272), M/C – 46% (32), 1st year – 48% (371) (6th year and M/C: p <0.05; 6th and 1st years: p <0.05; M/C and 1st year: p >0.05).

The study allowed us to estimate the prevalence of celiac disease at our university. It turned out that in the 6th year, 5 out of 418 students (1.2%) had celiac disease, which almost corresponds to the estimated prevalence of the disease in Russia – 1:100 [1]. However, based on the responses of first-year medical students, 3 out of 69 students were found to have celiac disease (4.3%), and in the first year, 41 out of 774 students (5.3%). These figures already differ significantly from the aforementioned data for our country and lead to the conclusion that either the prevalence of celiac disease has indeed increased substantially, or the students' responses simply do not reflect reality. In total, 49 (3.9%) out of 1,261 people have the disease – a ratio of 1:25.

To learn about celiac disease, most students use online resources (86% (1,089)), as this method offers a vast amount of information nowadays and is also more accessible and user-friendly for the younger generation. However, the abundance of information and the prevalence of unofficial data lead to unreliable, incorrect, and outdated knowledge about the disease. Fortunately, there are still those who use books and medical journals (37% (469) and 24% (299), respectively), distance learning (12% (150)), and brochures (7% (94)), but the percentage of such students is significantly lower than those using the internet. One of the most prioritized and reliable sources is information from the St. Petersburg Celiac Disease Society "Emilia," but, unfortunately, our study's data showed that only a small number of students (7.5% (95)) are aware of this disease.

Thus, these results indicate a lack of understanding and the need to develop methods to increase knowledge and interest among students, as well as to implement additional educational initiatives.

CONCLUSION

In conclusion, we would like to note that celiac disease has a significant impact on people's health and quality of life. Every year, more and more cases of the disease are identified. Therefore, it is very important to raise public awareness and vigilance regarding celiac disease. Based on the results of our study, it is clear that not only

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underclassmen but also graduates are insufficiently aware of celiac disease. To address this issue, it is necessary to improve the professional training of future physicians. Holding additional classes, lectures, and scientific conferences on this topic helps increase knowledge. In addition, real clinical cases and interaction with patients contribute to better retention of information, the acquisition of valuable experience, and increased interest in the disease. An important way to improve awareness is to disseminate reliable information about celiac disease: posters in universities and hospitals, educational videos, and sections on the university's website with a library of materials for self-study. May 16 is World Celiac Disease Day. Thematic events and quizzes held on this day will also help broaden students' horizons and increase their interest in the disease. The prevalence of celiac disease is high, so knowledge of this condition will help in making an accurate diagnosis in a timely and effective manner, differentiating it from other diseases associated with malabsorption syndrome, and immediately prescribing targeted treatment.

ADDITIONAL INFORMATION

Authors' contribution. A.A. Kalinina — formulating the idea, research goals, and objectives; M.O. Revnova — preparing and creating the manuscript, commenting on or revising it; V.P. Novikova — editing the manuscript, providing commentary, and preparing it for publication; L.V. Sakhno — commenting on or revising the manuscript, including the stages before or after publication; E.V. Sousova — formulating the research idea, assisting in conducting testing among medical college students; P.V. Kan — formulating research goals, and objectives, conducting the research process; Kh.M. Khamchieva — creating a Yandex Form, conducting testing and analyzing the obtained data.

All authors read and approved the final version before publication.

Competing interests. The authors declare that they have no competing interests.

Consent for publication. The authors received written consent from the respondents to publish the data.

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REFERENCES

1. Singh P., Arora A., Strand T.A., Leffler D.A., Catassi C., Green P.H. et al. global prevalence of celiac disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2018;16(6):823–836.e2. https://doi.org/10.1016/j.cgh.2017.06.037.
2. Averkina N.A., Baranov A.A., Bel'mer S.V. et al. "Celiac Disease-2025": Project of clinical guidelines for the diagnosis and treatment of celiac disease in children. *Pediatric pharmacology*. 2025;22(4):495–522. (In Russ.). https://doi.org/10.15690/pf.v22i4.2941.
3. Bai J.C., Ciacci C. World Gastroenterology Organisation Global Guidelines: Celiac Disease February 2017. *J Clin Gastroenterol.* 2017;51(9):755–768. https://doi.org/10.1097/MCG.0000000000000919.
4. Revnova M.O. Celiac disease in children: clinical manifestations, diagnosis, and the effectiveness of a gluten-free diet. MD thesis. Saint Petersburg; 2005. 39 p. (In Russ.).

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

5. Al-Toma A., Volta U., Auricchio R., Castillejo G., Sanders D.S., Cellier C. et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. *United European Gastroenterol J*. 2019;7(5):583–613. https://doi.org/10.1177/2050640619844125.
6. Hopper A.D., Hadjivassiliou M., Hurlstone D.P., Lobo A.J., McAlindon M.E., Egner W. et al. What is the role of serologic testing in celiac disease? A prospective, biopsy-confirmed study with economic analysis. *Clin Gastroenterol Hepatol*. 2008;6(3):314–320. https://doi.org/10.1016/j.cgh.2007.12.008.
7. Volta U., Fabbri A., Parisi C., Piscaglia M., Caio G., Tovoli F., Fiorini E. Old and new serological tests for celiac disease screening. *Expert Rev Gastroenterol Hepatol*. 2010;4(1):31–35. https://doi.org/10.1586/egh.09.66.
8. Shchelochenkov S.V., Egorova I.V., Bordin D.S. et al. Modern possibilities of endoscopic diagnostics of celiac disease: from macroscopic signs to artificial intelligence. *Effective Pharmacotherapy*. 2025;21(22):78–85. (In Russ.). https://doi.org/10.33978/2307-3586-2025-21-22-78-85.
9. Aljada B., Zohni A., El-Matary W. The gluten-free diet for celiac disease and beyond. *Nutrients*. 2021;13(11):3993. https://doi.org/10.3390/nu13113993.
10. Mustalahti K., Catassi C., Reunanen A., Fabiani E., Heier M., McMillan S. et al. The prevalence of celiac disease in Europe: Results of a centralized, international mass screening project. *Ann Med*. 2010;42(8):587–595. https://doi.org/10.3109/07853890.2010.505931.
11. Rubio-Tapia A., Hill I.D., Semrad C., Kelly C.P., Greer K.B., Limketkai B.N. et al. American College of Gastroenterology Guidelines Update: diagnosis and management of celiac disease. *Am J Gastroenterol*. 2023;118(1):59–76. https://doi.org/10.14309/ajg.0000000000002075.
12. Theethira T.G., Kelly C.P. Coeliac disease. Missing villi? The search for coeliac disease in the Asia-Pacific region. *Nat Rev Gastroenterol Hepatol*. 2014;11(4):204–205. https://doi.org/10.1038/nrgastro.2014.26.
13. Celiac disease in children and adults. S.V. Bel'mer, M.O. Revnova, eds. Moscow: GEOTAR-Media; 2024. 295 p. (In Russ.)
14. Ait Said H., Elmoumou L., Guennouni M., Rherissi B., El Kadmiri N. IgE mediated food allergy and celiac disease: An updated review. *Russian Journal of Allergy*. 2023;20(4):488–500. (In Russ.). https://doi.org/10.36691/RJA16499.
15. Parfenov A.I. Celiac disease. Evolution of concepts on prevalence, clinical manifestations, and the significance of etiotropic therapy. Moscow: Anakharsis; 2007. 376 p. (In Russ.).
16. Majmudar V.H., Nguyen-Ngo K., Tadros M. Pitfalls in the diagnosis of celiac disease: bridging gaps from serology to clinical practice. *J Transl Gastroenterol*. 2025. https://doi.org/10.14218/JTG.2025.00038.
17. Auricchio R., Tosco A., Piccolo E., Galatola M., Izzo V., Maglio M. et al. Potential celiac children: 9-year follow-up on a gluten-containing diet. *Am J Gastroenterol*. 2014;109(6):913–921. https://doi.org/10.1038/ajg.2014.77.
18. Zakharova I.N., Osmanov I.M., Samsonova L.N., Okminyan G.F., Vorobyova A.S. et al. Celiac disease and associated endocrine diseases. *Pediatrician's Practice*. 2022;(2):23–31. EDN: HFBCCK. (In Russ.).
19. Kowalski M.K., Domżał-Magrowska D., Małecka-Wojciesko E. Celiac disease — narrative review on progress in celiac disease 11 March 2025. *Foods*. 2025;14(6):959. https://doi.org/10.3390/foods14060959.
20. Shapovalova N.S., Novikova V.P., Revnova M.O., Kalinina E.Yu., Belmer S.V., Khavkin A.I. Seronegative coeliac disease in the light of the guidelines by the European Society for the Study of Coeliac Disease (ESsCD) 2019. *Pediatric Nutrition*. 2019;17(6):14–22. (In Russ.). https://doi.org/10.20953/1727-5784-2019-6-14-22.
21. Aboulaghras S., Piancatelli D., Taghzouti K., Balahbib A., Alshahrani M.M., Al Awadh A.A. et al. Meta-analysis and systematic review of HLA DQ2/DQ8 in adults with celiac disease. *Int J Mol Sci*. 2023 ;24(2):1188. https://doi.org/10.3390/ijms24021188.
22. Rashid M., Lee J. Serologic testing in celiac disease: practical guide for clinicians. *Can Fam Physician*. 2016;62(1):38–43.
23. Blom J.J., Gidrewicz D., Turner J., Duerksen D.R., Pinto-Sánchez M.I. Diagnosis and management of celiac disease. *CMAJ*. 2025;197(38):E1258–E1265. https://doi.org/10.1503/cmaj.230091.
24. Rubio-Tapia A., Hill I.D., Kelly C.P., Calderwood A.H., Murray J.A.; American College of Gastroenterology. ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterol*. 2013;108(5):656–676; quiz 677. https://doi.org/10.1038/ajg.2013.79.
25. Ludvigsson J.F., Bai J.C., Biagi F. et al. BSG Coeliac Disease Guidelines Development Group; British Society of Gastroenterology. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. *Gut*. 2014;63(8):1210–1228. https://doi.org/10.1136/gutjnl-2013-306578.

ЛИТЕРАТУРА

1. Singh P., Arora A., Strand T.A., Leffler D.A., Catassi C., Green P.H. et al. global prevalence of celiac disease: systematic review and meta-analysis. *Clin Gastroenterol*

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

Hepatol. 2018;16(6):823–836.e2. https://doi.org/10.1016/j.cgh.2017.06.037.
2. Аверкина Н.А., Баранов А.А., Бельмер С.В. и др. «Целиакия-2025»: проект клинических рекомендаций по диагностике и лечению целиакии у детей. *Педиатрическая фармакология*. 2025;22(4):495–522. https://doi.org/10.15690/pf.v22i4.2941.
3. Bai J.C., Ciacci C. World Gastroenterology Organisation Global Guidelines: Celiac Disease February 2017. *J Clin Gastroenterol*. 2017;51(9):755–768. https://doi.org/10.1097/MCG.0000000000000919.
4. Ревнова М.О. Целиакия у детей: клинические проявления, диагностика, эффективность безглютеновой диеты. Автореф. дис. … д-ра мед. наук. СПб.; 2005. 39 с.
5. Al-Toma A., Volta U., Auricchio R., Castillejo G., Sanders D.S., Cellier C. et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. *United European Gastroenterol J.* 2019;7(5):583–613. https://doi.org/10.1177/2050640619844125.
6. Hopper A.D., Hadjivassiliou M., Hurlstone D.P., Lobo A.J., McAlindon M.E., Egner W. et al. What is the role of serologic testing in celiac disease? A prospective, biopsy-confirmed study with economic analysis. *Clin Gastroenterol Hepatol.* 2008;6(3):314–320. https://doi.org/10.1016/j.cgh.2007.12.008.
7. Volta U., Fabbri A., Parisi C., Piscaglia M., Caio G., Tovoli F., Fiorini E. Old and new serological tests for celiac disease screening. *Expert Rev Gastroenterol Hepatol.* 2010;4(1):31–35. https://doi.org/10.1586/egh.09.66.
8. Щелоченков С.В., Егорова И.В., Бордин Д.С. и др. Современные возможности эндоскопической диагностики целиакии: от макроскопических признаков до искусственного интеллекта. *Эффективная фармакотерапия*. 2025;21(22):78–85. https://doi.org/10.33978/2307-3586-2025-21-22-78-85.
9. Aljada B., Zohni A., El-Matary W. The gluten-free diet for celiac disease and beyond. *Nutrients*. 2021;13(11):3993. https://doi.org/10.3390/nu13113993.
10. Mustalahti K., Catassi C., Reunanen A., Fabiani E., Heier M., McMillan S. et al. The prevalence of celiac disease in Europe: Results of a centralized, international mass screening project. *Ann Med*. 2010;42(8):587–595. https://doi.org/10.3109/07853890.2010.505931.
11. Rubio-Tapia A., Hill I.D., Semrad C., Kelly C.P., Greer K.B., Limketkai B.N. et al. American College of Gastroenterology Guidelines Update: diagnosis and management of celiac disease. *Am J Gastroenterol*. 2023;118(1):59–76. https://doi.org/10.14309/ajg.0000000000002075.
12. Theethira T.G., Kelly C.P. Coeliac disease. Missing villi? The search for coeliac disease in the Asia-Pacific region. *Nat Rev Gastroenterol Hepatol*. 2014;11(4):204–205. https://doi.org/10.1038/nrgastro.2014.26.
13. Целиакия у детей и взрослых. С.В. Бельмер, М.О. Ревнова, ред. М.: ГЭОТАР-Медиа; 2024. 295 с.
14. AitSaid H., Elmoumou L., Guennouni M., Rherissi B., El Kadmiri N. IgE-опосредованная пищевая аллергия и целиакия: обновленный обзор. *Российский аллергологический журнал*. 2023;20(4):488–500. https://doi.org/10.36691/RJA16499.
15. Парфенов А.И. Целиакия. Эволюция представлений о распространенности, клинических проявлениях и значимости этиотропной терапии. М.: Анахарсис; 2007. 376 с.
16. Majmudar V.H., Nguyen-Ngo K., Tadros M. Pitfalls in the diagnosis of celiac disease: bridging gaps from serology to clinical practice. *J Transl Gastroenterol*. 2025. https://doi.org/10.14218/JTG.2025.00038.
17. Auricchio R., Tosco A., Piccolo E., Galatola M., Izzo V., Maglio M. et al. Potential celiac children: 9-year follow-up on a gluten-containing diet. *Am J Gastroenterol.* 2014;109(6):913–921. https://doi.org/10.1038/ajg.2014.77.
18. Дмитриева Ю.А., Захарова И.Н., Османов И.М., Самсонова Л.Н., Окминян Г.Ф., Воробьева А.С. и др. Целиакия и ассоциированные эндокринные заболевания. *Практика педиатра*. 2022;(2):23–31. EDN: HFBCCK.
19. Kowalski M.K., Domżał-Magrowska D., Małecka-Wojciesko E. Celiac disease — narrative review on progress in celiac disease 11 March 2025. *Foods*. 2025;14(6):959. https://doi.org/10.3390/foods14060959.
20. Шаповалова Н.С., Новикова В.П., Ревнова М.О., Калинина Е.Ю., Бельмер С.В., Хавкин, А.И. Серонегативная целиакия в свете рекомендаций Европейского общества изучения целиакии (ESsCD) 2019 года. *Вопросы детской диетологии.* 2019;17(6):14–22. https://doi.org/10.20953/1727-5784-2019-6-14-22.
21. Aboulaghras S., Piancatelli D., Taghzouti K., Balahbib A., Alshahrani M.M., Al Awadh A.A. et al. Meta-analysis and systematic review of HLA DQ2/DQ8 in adults with celiac disease. *Int J Mol Sci*. 2023 ;24(2):1188. https://doi.org/10.3390/ijms24021188.
22. Rashid M., Lee J. Serologic testing in celiac disease: practical guide for clinicians. *Can Fam Physician*. 2016;62(1):38–43.
23. Blom J.J., Gidrewicz D., Turner J., Duerksen D.R., Pinto-Sánchez M.I. Diagnosis and management of celiac disease. *CMAJ*. 2025;197(38):E1258–E1265. https://doi.org/10.1503/cmaj.230091.
24. Rubio-Tapia A., Hill I.D., Kelly C.P., Calderwood A.H., Murray J.A.; American College of Gastroenterology. ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterol*. 2013;108(5):656–676; quiz 677. https://doi.org/10.1038/ajg.2013.79.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

25. Ludvigsson J.F., Bai J.C., Biagi F. et al. BSG Coeliac Disease Guidelines Development Group; British Society of Gastroenterology. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. *Gut.* 2014;63(8):1210–1228. https://doi.org/10.1136/gutjnl-2013-306578.

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Review

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The role of tryptofan in celiac disease: review

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ABSTRACT. The analysis of the peculiarities of tryptophan metabolism in children suffering from celiac disease is presented. Tryptophan is one of the eight essential amino acids that are not produced in the human body, and their intake from food is necessary for protein synthesis and cell proliferation, including cells of the immune system. Tryptophan is metabolized by the human body to a large number of different signaling molecules and it occurs in three ways: indole, serotonin, kynurenine pathways. Tryptophan metabolism catabolites play a signaling role in the human body and in the intestinal microbial community. It is noted that tryptophan and its metabolites play a key role in suppressing inflammation and maintaining the integrity of the intestinal barrier. Tryptophan metabolites, especially kynurenine, also contribute significantly to immune regulation. In turn, a decrease in tryptophan intake in the body can affect the psychological state of patients with celiac disease through the serotonin pathway of amino acid metabolism, causing the development of depression and anxiety. Therefore, changes in tryptophan metabolism may potentially underlie the impaired immune response in celiac disease, affecting both the development of the disease and the persistence of symptoms, despite following a gluten-free diet.

KEYWORDS: *children, celiac disease, tryptophan, kynurenine, serotonin*

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Обзор

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Роль триптофана при целиакии: обзор литературы

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РЕЗЮМЕ. Представлен анализ особенностей метаболизма триптофана у детей, страдающих целиакией. Триптофан является одной из восьми незаменимых (эссенциальных) аминокислот, которые не вырабатываются в организме человека, и их поступление с пищей необходимо для синтеза белка, пролиферации клеток, включая клетки иммунной системы. Триптофан метаболизируется организмом человека до большого количества различных сигнальных молекул, и происходит это тремя путями: индольный, серотониновый, кинурениновый пути. Катаболиты триптофанового обмена играют сигнальную роль в организме человека и в микробном сообществе кишечника. Отмечено, что триптофан и его метаболиты играют ключевую роль в подавлении воспаления и поддержании целостности кишечного барьера. Также метаболиты триптофана, особенно кинуренин, вносят значительный вклад в иммунную регуляцию. В свою очередь, снижение поступления триптофана в организм может влиять на психологическое состояние пациентов с целиакией через серотониновый путь метаболизма аминокислоты, вызывая развитие депрессии и тревоги. Следовательно, изменения метаболизма триптофана потенциально могут лежать в основе нарушенного иммунного ответа при целиакии, влияя как на развитие заболевания, так и на сохранение симптомов, несмотря на соблюдение безглютеновой диеты.

КЛЮЧЕВЫЕ СЛОВА: *дети, целиакия, триптофан, кинуренин, серотонин*

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INTRODUCTION

Celiac disease is a chronic autoimmune enteropathy caused by gluten intolerance in patients with the HLA-DQ2 or HLA-DQ8 haplotypes [1, 2]. The disease is characterized by gastrointestinal symptoms (abdominal bloating, diarrhea), as well as involvement of other organs and systemic disorders such as osteoporosis, infertility, anemia, depression, skin lesions, and neurological disorders [3]. Currently, the only effective treatment for celiac disease is the complete elimination of gluten from the diet. A gluten-free diet (GFD) can lead to regression of clinical symptoms and serological and histological remission in most patients [1]. However, adhering to strict dietary restrictions is a challenge for some patients due to the limited availability and high cost of gluten-free products, as well as their taste characteristics, which reduces the effectiveness of the GFD [4, 5]. In addition, a patient's self-imposed adherence to dietary restrictions without prior consultation with a dietitian may lead to a reduction in several important nutrients [1, 3].

Essential amino acids play a crucial role in immune system function, maintaining intestinal integrity, and regulating metabolism. Insufficient absorption of these amino acids during an inflammatory process in the intestine, as well as adherence to strict dietary restrictions in GFD, may play a role in the pathogenesis of the disease. Moreover, changes in the amino acid composition of plasma and feces correlate with disease progression [6, 7].

The gastrointestinal tract (GIT) is the first to come into contact with antigens entering our body along with food. Furthermore, the GIT initiates the processes of nutrient metabolism with the participation of the gut microbiota. The intestinal immune system, together with the mucosal epithelium, provides a protective barrier that prevents toxins and antigens from entering the systemic circulation and causing damage [8]. The nature of the immune response to antigens derived from food or produced as a result of nutrient metabolism is largely determined by the phenotype of intestinal dendritic cells and their degree of maturation, which is shaped by their interaction with regulatory T cells (Treg) [9, 10]. Dendritic cells are distributed throughout the intestine, in addition to mesenteric lymph nodes, lymphoid follicles, and Peyer's patches. The function of dendritic cells is to take up antigens for subsequent presentation to naive T cells. Based on their functional activity, dendritic cells are classified as immunogenic and tolerogenic. The former activates T-cell immunity, while the latter participate in inducing tolerance in peripheral T cells [11]. The primary function of Tregs is to control the intensity and duration of the immune response by regulating the function of T-effector cells (T-helpers and T-killers) [12]. To suppress the immune response, Tregs secrete transforming growth factor β, interleukins (IL) 10 and 35. Additionally, Tregs express cytotoxic T-lymphocyte glycoprotein 4 (CTLA-4), that is a membrane protein that serves as a cell receptor of the immunoglobulin superfamily and inhibits T-cell activation by binding to B7 ligands (CD80/CD86) on the surface of dendritic cells. It has been suggested that tryptophan catabolism is an important factor influencing Treg function [9]. Furthermore, it has been established that low concentrations of this amino acid limit T-cell proliferation while simultaneously increasing Treg production [13]. In turn, tryptophan catabolism is limited by the cytosolic heme protein indoleamine 2,3-dioxygenase (IDO). This enzyme participates in inhibiting the immune response, preventing a potential exacerbation of inflammatory reactions and inducing antigen tolerance [14].

The aim of this review was to analyze data in the latest literature devoted to tryptophan metabolism in patients with celiac disease.

MECHANISMS OF TRYPTOPHAN METABOLISM IN HUMANS

Tryptophan is one of the eight essential amino acids that cannot be produced. Their intake through food is necessary for protein synthesis and cell proliferation, including immune system cells. Catabolites of tryptophan metabolism play a signaling role in the human body and in the gut microbiome. Receptors and signaling pathways for so-called tryptophan signaling molecules (TSMs), their cellular targets, and their physiological and metabolic effects are currently being actively studied. It has been established that virtually all catabolites of tryptophan metabolism are signaling molecules. Many of them exert their signaling role through aryl hydrocarbon receptors (AhR). The dominant pathway of tryptophan metabolism is the kynurenine pathway, which is

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the source of universal signaling molecules: kynurenine, quinolinic acid, and kynurenic acid. The indole pathway of tryptophan catabolism is the primary for microbes, with the exception of indole formation reactions in immune cells. It serves as a source of interkingdom and interspecies signaling molecules such as indole and its derivatives: indole-3-pyruvate, indole-3-lactate, indole-3-acetate, indole-3-propionate, indole-3-acrylate, indole-3-butyrate, and indole-3-acetaldehyde. Serotonin and melatonin are also universal signaling molecules and have been extensively studied in various diseases of the nervous system [15]. A decrease in tryptophan concentration in biological fluids will affect cellular functions and the state of homeostasis. Various factors can influence tryptophan bioavailability, ranging from the composition of the gut microbiome to systemic inflammatory signals. Gut microorganisms can absorb tryptophan themselves and thus limit its availability to the host organism. Formed metabolites exert a local effect on both the microbiome and the host's cells. Tryptophan can also be formed through microbial synthesis and recycling of other amino acids resulting from peptide breakdown [16]. This amino acid is found in bread, chocolate, cheese, cottage cheese, yogurt, oatmeal, peanuts, bananas, beans, milk, fish, turkey, chicken, and dried prunes, and in small amounts in corn [17]. Consequently, a strict restrictive gluten-free diet, impaired absorption, as well as prolonged stress which contributes to elevated cortisol levels that compete with tryptophan in celiac disease, can lead to a reduction in tryptophan intake in the patient.

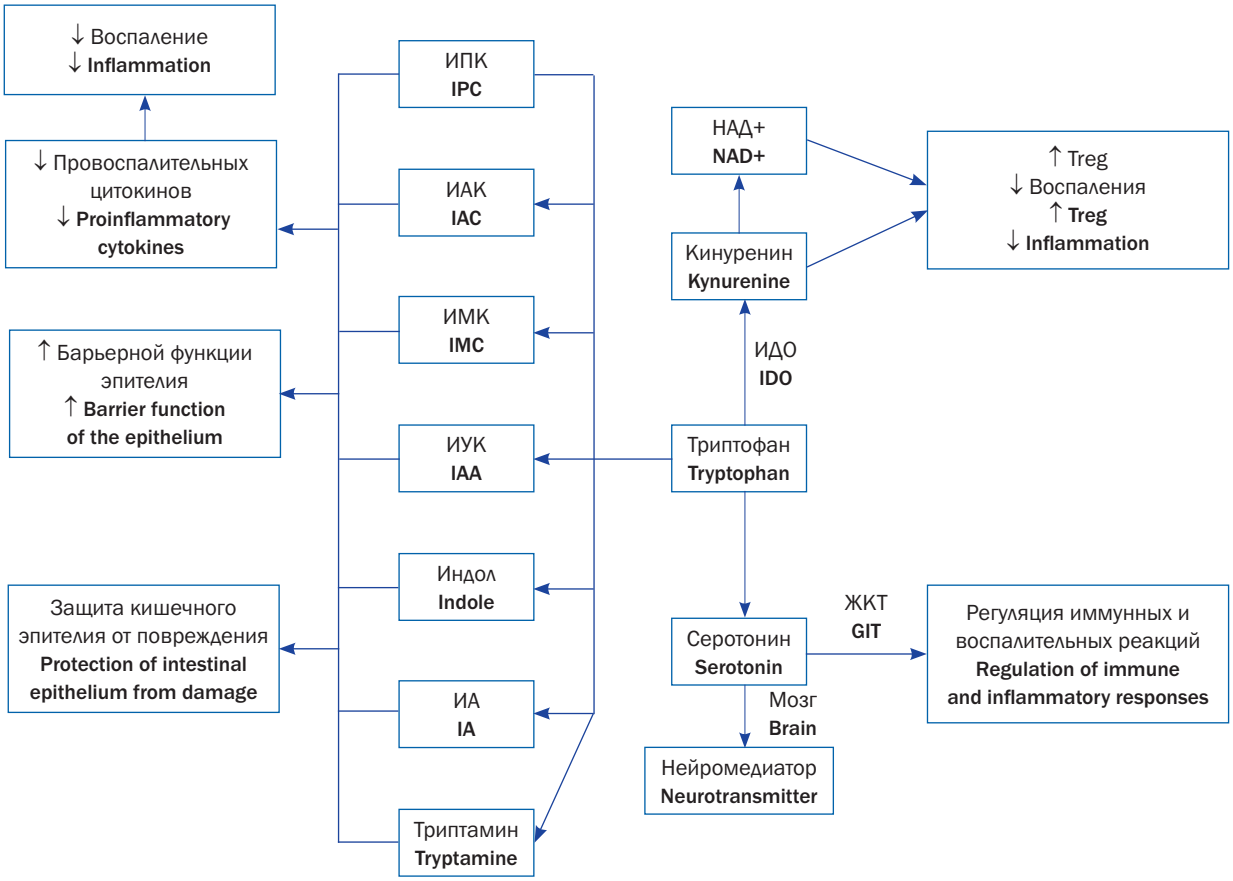

Fig. 1. The main pathways and effects of tryptophan metabolism: GIT — gastrointestinal tract; IA — indole-3-aldehyde; IAC — indoleacrylic acid; IDO — indoleamine-2,3-dioxygenase; IMC — indolelactic acid; IPC — indolepropionic acid; IAA — indole-3-acetic acid; NAD+ — nicotinamide adenine dinucleotide; Treg — regulatory T cells (borrowed from [20], with modifications)

Рис. 1. Основные пути и эффекты метаболизма триптофана: ЖКТ — желудочно-кишечный тракт; ИА — индол-3-альдегид; ИАК — индолакриловая кислота; ИДО — индоламин-2,3-диоксигеназа; ИМК — индолмолочная кислота; ИПК — индолпропионовая кислота; ИУК — индол-3-уксусная кислота; НАД+ — никотинамидадениндинуклеотид; Treg — регуляторные Т-клетки (заимствовано из [20], с изменениями)

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Tryptophan is metabolized into a large number of different signaling molecules [18, 19], and this occurs via three pathways (Fig. 1).

INDOLE PATHWAY

The indole metabolic pathway involves the gut microbiota, which converts tryptophan into indole and its derivatives, which in turn act as ligands for aryl hydrocarbon receptors (AhR) [20]. Indole is the most common microbial indole catabolite of tryptophan and is synthesized by *Proteus vulgaris, Bacteroides thetaiotaomicron*, and *Escherichia coli* [15, 17, 21]. *Clostridium sporogenes* converts tryptophan into tryptamine, indole-lactic acid (ILA), and indolepropionic acid (IPA). ILA is also produced by *Bifidobacterium* spp. and *Ruminococcus gnavus* [20, 22]. IPA contributes to the expression of tight junction proteins, zonulin-1 and occludin, maintaining the integrity of the intestinal epithelium, which reduces the entry of bacterial lipopolysaccharides into the bloodstream [20]. *Peptostreptococcus* spp. metabolize tryptophan into indole-acrylic acid (IAcrA), which also improves the intestinal barrier function and reduces inflammatory responses of immune cells. M. Wlodarska et al. found that treatment of mouse bone marrow macrophages stimulated by bacterial lipopolysaccharide with IAcrA resulted in increased anti-inflammatory cytokine IL-10, accompanied by a decrease in IL-1β and IL-6 [23]. Some members of *Bacteroides* spp. and *Clostridium* spp. produce ILA and indole-3-acetic acid (IAA), which is decarboxylated to form skatole. *Lactobacillus* spp. metabolize tryptophan into indole-3-aldehyde (IA) and ILA [20].

Indole has a beneficial effect on intestinal mucosal cells, increasing the expression of genes involved in maintaining the intestinal barrier function, and also inhibits inflammatory processes [24]. In addition, indole stimulates the secretion of glucagon-like peptide 1 by enteroendocrine cells, suppressing gastric secretion and peristalsis, which creates a feeling of satiety [25].

The AhR (aryl hydrocarbon receptor) signaling pathway is activated, serving as a key system of cellular regulation. Inactive AhR in the cytoplasm can bind various ligands and translocate to the nucleus, activating genes responsible for xenobiotic metabolism, immunity, and maintenance of barrier function, which is essential for regulating immune mechanisms, regeneration, growth, and differentiation of immunocompetent cells. Impaired activation of this pathway underlies the pathogenesis of certain metabolic diseases as well as malignant neoplasms [26]. AhR ligands include not only indoles but also flavonoids, polyphenols, and other compounds involved in maintaining the integrity of the intestinal barrier [27]. Activation of AhR by indole and its derivatives, such as the tryptophan metabolite tryptamine, regulates intestinal motility [26]. In addition, tryptamine interacts with IDO and AhR, participating in immunological control and reducing the expression of pro-inflammatory cytokines, normalizing the expression of the epithelial tight junction protein zonulin-1, which leads to improved barrier function of the intestinal wall and reduced inflammation [25]. Furthermore, AhR expression by intestinal mucosal cells decreases during periods of celiac disease exacerbation. However, interaction between the intestinal microbiota and AhR in patients with celiac disease remains not fully established [28].

SEROTONIN PATHWAY

The gut-brain axis is a bidirectional system of communication, linking the brain's emotional and cognitive centers with the peripheral functioning of the digestive tract. It is becoming increasingly evident that the gut microbiota influences behavior, as do tryptophan and serotonin, suggesting that changes in the gut may play a significant role in the pathophysiology of human central nervous system (CNS) disorders [29]. It is known that more than 90% of serotonin is synthesized in the enterochromaffin cells of the intestine and in the brain. There, through a series of chemical reactions, 5-hydroxylation and decarboxylation by tryptophan decarboxylase in the presence of iron ions and the pteridine cofactor, tryptophan is converted into serotonin and 5-hydroxyindoleacetic acid [17]. Serotonin (5-hydroxytryptamine) is a key regulator of adaptive responses to environmental factors, as well as states and changes in the central nervous system, including mood, libido, cognitive abilities, aggression, anxiety, nociception, body temperature, and eating behavior. Up to 3% of dietary tryptophan is used for serotonin synthesis. The blood-brain barrier is considered impermeable to serotonin, and its primary function is to regulate inflammatory and immune processes in the gastrointestinal tract [17, 30].

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The gut microbiota controls the serotonin pathway of tryptophan metabolism by synthesizing deoxycholic acid, a stimulator of serotonin synthesis [31]. Since *Escherichia, Streptococcus, Enterococcus, Pseudomonas*, and *Candida* are capable of synthesizing serotonin, it can be assumed that modulating the gut microbiota may be effective for normalizing the levels of this biogenic amine [17].

K.Z. Sanidad found that serotonin signals T cells to increase intracellular IA levels and suppress mTOR activation, thereby promoting Treg differentiation both *ex vivo* and *in vivo* in the intestines of newborn mice. Oral administration of serotonin to newborn mice led to the formation of long-term antigen-specific immune tolerance, mediated by T cells, to both food antigens and commensal bacteria [30].

THE KYNURENINE PATHWAY

More than 90% of all tryptophan in the body is metabolized in the liver via the kynurenine pathway, forming nicotinic acid via kynurenine with the participation of IDO. This enzyme is expressed throughout the human body depending on the concentration of pro-inflammatory cytokines, primarily interferon γ. However, its maximum expression is found in the brain, gastrointestinal tract, and liver [16]. Through the catabolic products of IDO, kinurenines, tryptophan suppresses immune processes by modulating the activity of T-effector cells and stimulating the proliferation of Tregs, thereby inducing immunological tolerance [32]. In addition, tryptophan participates in regulating neuronal functions and maintaining intestinal homeostasis via the kynurenine pathway [15, 17]. Kynurenine is considered a signaling molecule that exerts effects via AhR. It can also be metabolized into signaling molecules that regulate inflammation and promote increased immunological tolerance [33]. Creating a local or systemic environment with high kynurenine levels and low tryptophan levels alters the function of surrounding cells. T-lymphocytes are also susceptible to these changes, as tryptophan exerts immunomodulatory and immunosuppressive effects on T-cells, regulating their activation and function, including the induction of tolerance via the AhR receptor. Tryptophan also influences the differentiation of T-regulatory cells, which is important in the context of inflammation, autoimmune diseases, and neuroimmune processes [15]. Tryptophan catabolism occurs in inflamed tissue areas, reducing their damage [34]. Pro-inflammatory cytokines shift tryptophan metabolism toward kynurenine formation [34, 35].

It is believed that tryptophan catabolism via the kynurenine pathway is one of the mechanisms that ensures tolerance of the human immune system. The breakdown of tryptophan reduces the levels and availability of this amino acid, thereby suppressing T-cell proliferation. In addition, products of tryptophan catabolism, such as kynurenine, 3-hydroxykinurenine, and 3-hydroxyanthranilate, inhibit T-cell proliferation, possibly through apoptotic mechanisms [36].

A high nicotinamide content in the diet likely deactivates the mechanism that halts the body's production of nicotinamide from tryptophan via kynurenine and causes immune intolerance, including in the fetus, and infertility. It is hypothesized that the decline in birth rates in certain regions may be associated with the consumption of meat low in tryptophan [37].

TRYPTOPHAN INFLUENCES IMMUNO-INFLAMMATORY PROCESS

The described functions of tryptophan enable control of immune and inflammatory reactions in the gut by altering its concentration and inducing its biologically active metabolites. Enzymes that limit the rate of amino acid metabolism play an important role in each of its degradation pathways. The role of certain amino acids and vitamins in modulating the immune response and inflammatory reactions in immunopathological diseases of the gastrointestinal tract has now been established [7, 12]. For example, changes in the metabolism of essential amino acids have been identified in patients with celiac disease, which may result from a combination of genetic predisposition, dietary changes, and the activity of the gut microbiota [38, 39]. The gut microbiome participates in regulating the production of tryptophan-derived bioactive metabolites, utilizing both dietary and microorganism-synthesized amino acids [31].

Tryptophan metabolism can potentially influence an immune response in several ways. First, the conversion of tryptophan to kynurenine via IDO can lead to local depletion of the amino acid, which

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inhibits the proliferation of T cells, which are key players in the immune response. Second, certain tryptophan metabolites formed via the kynurenine pathway promote the production of Tregs, which perform an important role in maintaining immune tolerance [7].

TRYPTOPHAN DEFICIENCY AND CELIAC DISEASE

Adherence to a strict gluten-free diet by patients with celiac disease can lead to reduced tryptophan intake, which alters amino acid metabolism and may potentially exacerbate inflammatory processes in patients with celiac disease [40].

Thus, according to N. Van Hees et al., long-term adherence to a gluten-free diet led to reduced plant protein intake in patients with celiac disease. The blood levels of essential amino acids, including tryptophan, were lower in these patients compared to those who did not follow any dietary restrictions [41]. A study by V. Lamas et al. found that patients with celiac disease experience a decrease in AhR ligand concentrations during disease exacerbation, which reduces the activity of this signaling pathway [42]. S. Nikolaus et al. reported that serum tryptophan concentrations in patients with inflammatory bowel diseases were significantly lower than in the control group. The lowest tryptophan concentrations were observed in patients with Crohn's disease. Analysis of tryptophan metabolite concentrations reveals high degradation activity in patients with inflammatory bowel disease, suggesting that tryptophan deficiency may contribute to the development or exacerbation of the disease. S. Nikolaus et al. conclude that the administration of high doses of tryptophan metabolites (nicotinamide, IA) as dietary supplements may alter the state of the gut microbiome, thereby enhancing the anti-inflammatory effect of tryptophan [43].

A study by F. Asgari showed that gliadin enhances the expression of maturation markers such as CD83, CD86, and HLA-DR, and promotes the secretion of tumor necrosis factor-α and IL-12 in dendritic cells. Vitamin A, tryptophan, and their metabolites increase the expression of CD103 while simultaneously limiting the expression of HLA-DR, CD83, and CD86. They also enhance the expression of RALDH2 and IDO and promote the secretion of TGF-β (transforming growth factor β) and IL-10, while simultaneously limiting the secretion of IL-12 and TNF-α (tumor necrosis factor α). The data obtained indicate that vitamin A and tryptophan have a beneficial effect on the course of celiac disease, highlighting their potential as therapeutic agents for this condition [12].

Given that tryptophan is a precursor of serotonin, a neurotransmitter that plays a key role in mood regulation, its reduced consumption may lead to the onset of depressive symptoms in patients with celiac disease [44].

CONCLUSION

Tryptophan metabolism plays an important role in maintaining physiological processes in the gastrointestinal tract. Tryptophan derivatives produced via the indole pathway have a significant effect on the integrity and function of the intestinal barrier, increasing the expression of tight junction proteins and reducing inflammation. The conversion of tryptophan to kynurenine via IDO can lead to local depletion of the amino acid, which inhibits the proliferation of T cells, key participants in the immune response in celiac disease (see Fig. 1). In addition, certain metabolites formed via the kynurenine pathway promote the generation of Tregs, which play a crucial role in maintaining immune tolerance. A strict gluten-free diet may lead to reduced consumption of tryptophan-rich foods. In turn, decreased dietary tryptophan intake and disturbances in its metabolism may potentially influence the immune response in celiac disease. These factors contribute to the pathogenesis of the disease and the persistence of clinical symptoms despite adherence to a gluten-free diet. Dietary adjustments and increased consumption of tryptophan-rich foods, on the one hand, and modulation of the gut microbiota to normalize the metabolism of this amino acid, on the other, may represent promising therapeutic strategies for patients with inflammatory bowel diseases.

ADDITIONAL INFORMATION

Authors' contribution. A.I. Khavkin — formulation and development of the idea, main goal and objectives of the study, final editing; A.V. Nalyotov, S.I. Sitkin — preparation and writing of the initial version of the manuscript.

All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and re-

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vising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. А.И. Хавкин — формулирование и развитие идеи, основной цели и задач исследования, финальное редактирование; А.В. Налетов, С.И. Ситкин — подготовка, написание первоначального варианта рукописи.

Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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REFERENCES

1. Averkina N.A., Baranov A.A., Bel'mer S.V., Boraeva T.T., Borovik T.A. et al. Project of clinical guidelines for the diagnosis and treatment of celiac disease in children. *Pediatric pharmacology*. 2025;22(4):495–522. (In Russ.). https://doi.org/10.15690/pf.v22i4.2941.
2. Khavkin A.I., Nalyotov A.V., Kuropyatnik P.I. The role of viruses in celiac disease pathogenesis: current status. *Pediatric pharmacology*. 2024;21(4):369–374. (In Russ.). https://doi.org/10.15690/pf.v21i4.2771.
3. Zingone F., Bai J.C., Cellier C., Ludvigsson J.F. Celiac diseaserelated conditions: who to test. *Gastroenterology*. 2024;167(1):64–78. https://doi.org/10.1053/j.gastro.2024.02.044.
4. Khavkin A.I., Nalyotov A.V., Pavlovskaya E.V., Yablokova E.A., Kur'yaninova V.A. et al. Quality of life of patients with celiac disease on gluten-free diet: narrative review. *Current Pediatrics*. 2025;24(3):157–161. (In Russ.). https://doi.org/10.15690/vsp.v24i3.2923.
5. Khavkin A.I., Grechanyi S.V., Malakhova A.A., Odinaeva N.D., Kondratyeva E.I. et al. Psychological factors influencing the adherence to a gluten-free diet in children and adolescents. *Pediatric Nutrition*. 2025;23(5):18–30. (In Russ.). https://doi.org/10.20953/1727-5784-2025-5-18-30.
6. Bakhtiari S., Asri N., Masotti A., Jahani-Sherafat S., Tavirani M.R. et al. Essential amino acids in celiac disease: key roles in immunogenicity, pathogenesis, and therapeutic approaches. *Crit Rev Clin Lab Sci*. 2025:1–16. https://doi.org/10.1080/10408363.2025.2551656.
7. Ding X., Bin P., Wu W., Yajie Chang Y., Zhu G. Tryptophan metabolism, regulatory T cells, and inflammatory bowel disease: a mini review. *Mediators Inflamm*. 2020;2020:9706140. https://doi.org/10.1155/2020/9706140.
8. Khavkin A.I., Nalyotov A.V., Sitkin S.I., Boraeva T.T., Matsynina M.A. et al. Characteristics of the gut microbiota in patients with celiac disease. *Pediatric Nutrition*. 2025; 23(4):47–54. (In Russ.). https://doi.org/10.20953/1727-5784-2025-4-47-54.
9. Asgari F., Khodadoust M., Nikzamir A., Sherafat S.J., Tavirani M.R. et al. The role of tryptophan metabolism and tolerogenic dendritic cells in maintaining immune tolerance: Insights into celiac disease pathogenesis. *Immun Inflamm Dis*. 2024;12(8):e1354. https://doi.org/10.1002/iid3.1354.
10. Chernykh E.R., Tyrinova T.V., Leplina O.Yu., Tikhonova M.A., Kurochkina Yu.D., Oleynik E.A. et al. Phenotype and functions of human dendritic cells derived from CD14+ monocyte subsets opposed to CD16 expression. *Bulletin of Siberian Medicine*. 2019;18(1):266–276. (In Russ.). https://doi.org/10.20538/1682-0363-2019-1-266-276.
11. Soto J.A., Gálvez N.M.S., Andrade C.A., Pacheco G.A., Bohmwald K. et al. The role of dendritic cells during infections caused by highly prevalent viruses. *Front Immunol*. 2020;11:1513. https://doi.org/10.3389/fimmu.2020.01513.
12. Asgari F., Nikzamir A., Baghaei K., Salami S., Masotti A. et al. Immunomodulatory and anti-inflammatory effects of Vitamin A and tryptophan on monocyte-derived dendritic cells stimulated with gliadin in celiac disease patients. *Inflammation*. 2024;47(5):1706–1727. https://doi.org/10.1007/s10753-024-02004-7.
13. Blagih J., Hennequart M., Zani F. Tissue nutrient environments and their effect on regulatory T cell biology. *Front Immunol*. 2021;12:637960. https://doi.org/10.3389/fimmu.2021.637960.
14. Kozlov V.A., Demina D.V. Tryptophan and indoleamine-2,3-dioxygenase (IDO) in pathogenesis of immunosuppressive clinical conditions. *Medical Immunology*. 2017;19(3):225–240. (In Russ.). https://doi.org/10.15789/1563-0625-2017-3-225-240.
15. Shatova O.P., Shestopalov A.V. Tryptophan metabolism: a new look at the role of tryptophan derivatives in the human body. *Advances in Current Biology*. 2023;143(1):3–15. (In Russ.). https://doi.org/10.31857/S0042132423010076.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

16. Cervenka I., Agudelo L.Z., Ruas J.L. Kynurenines: Tryptophan's metabolites in exercise, inflammation, and mental health. *Science*. 2017;357(6349):eaaf9794. https://doi.org/10.1126/science.aaf9794.
17. Shatova O.P., Zabolotneva A.A., Mikin I.E., Bril D.V., Shestopalov A.V. et al. The role of tryptophan metabolites in metabolism and pathogenesis of obesity. *Russian Journal of Preventive Medicine*. 2022;25(10):97–103. (In Russ.) https://doi.org/10.17116/profmed20222510197.
18. Gao K., Mu C., Farzi A., Zhu W.Y. Tryptophan metabolism: a link between the gut microbiota and brain. *Adv Nutr*. 2020;11(3):709–723. https://doi.org/10.1093/advances/nmz127.
19. Kumar P., Lee J.H., Lee J. Diverse roles of microbial indole compounds in eukaryotic systems. *Biol Rev Camb Philos Soc*. 2021;96(6):2522–2545. https://doi.org/10.1111/brv.12765.
20. Shcherbakova E.S., Sall T.S., Sitkin S.I., Vakhitov T.Ya., Demyanova E.V. The role of bacterial metabolites derived from aromatic amino acids in non-alcoholic fatty liver disease. *Almanac of Clinical Medicine*. 2020;48(6):375–386. (In Russ.). https://doi.org/10.18786/2072-0505-2020-48-066.
21. Philips C.A., Augustine P., Yerol P.K., Ramesh G.N., Ahamed R. et al. Modulating the intestinal microbiota: Therapeutic opportunities in liver disease. *J Clin Transl Hepatol*. 2020;8(1):87–99. https://doi.org/10.14218/JCTH.2019.00035.
22. Roager H.M., Licht T.R. Microbial tryptophan catabolites in health and disease. *Nat Commun*. 2018;9(1):3294. https://doi.org/10.1038/s41467-018-05470-4.
23. Wlodarska M., Luo C., Kolde R., d'Hennezel E., Annand J.W. et al. Indoleacrylic acid produced by commensal peptostreptococcus species suppresses inflammation. *Cell Host Microbe*. 2017;22(1):25–37.e6. https://doi.org/10.1016/j.chom.2017.06.007.
24. Portune K., Beaumont M., Davila A., Tomé D., Blachier F., Sanz Y. Gut microbiota role in dietary protein metabolism and health-related outcomes: The two sides of the coin. *Trends Food Sci Technol*. 2016;57:213–232. https://doi.org/10.1016/j.tifs.2016.08.011.
25. Oliphant K., Allen-Vercoe E. Macronutrient metabolism by the human gut microbiome: major fermentation by-products and their impact on host health. *Microbiome*. 2019;7(1):91. https://doi.org/10.1186/s40168-019-0704-8.
26. Vyhlidalova B., Krrasulova K., Pecinkova P., Marcalíková A., Vrzal R. et al. Gut microbial catabolites of tryptophan are ligands and agonists of the aryl hydrocarbon receptor: a detailed characterization. *Int J Mol Sci*. 2020;21(7):2614. https://doi.org/10.3390/ijms21072614.
27. Khavkin A.I., Nalyotov A.V., Matsynina M.A. Anti-inflammatory effects of olive oil and its components. prospects of application in the treatment of inflammatory bowel diseases. *Pediatric pharmacology*. 2024;21(3):249–255. (In Russ.). https://doi.org/10.15690/pf.v21i3.2754.
28. Dinallo V., Marafini I., Di Fusco D., Di Grazia A., Laudisi F. et al. Protective effects of aryl hydrocarbon receptor signaling in celiac disease mucosa and in poly I:C-induced small intestinal atrophy mouse model. *Front Immunol*. 2019;10:91. https://doi.org/10.3389/fimmu.2019.00091.
29. Jenkins T.A., Nguyen J.C., Polglaze K.E., Bertrand P.P. Influence of tryptophan and serotonin on mood and cognition with a possible role of the gut-brain. *Nutrients*. 2016;8(1):56. https://doi.org/10.3390/nu8010056.
30. Sanidad K.Z., Rager S.L., Carrow H.C., Ananthanarayanan A., Callaghan R. et al. Gut bacteria-derived serotonin promotes immune tolerance in early life. *Sci Immunol*. 2024;9(93):eadj4775. https://doi.org/10.1126/sciimmunol.adj4775.
31. Grifka-Walk H.M., Jenkins B.R., Kominsky D.J. Amino acid TRP: the far out impacts of host and commensal tryptophan metabolism. *Front Immunol*. 2021;12:2005. https://doi.org/10.3389/fimmu.2021.653208.
32. Asgari F., Mahinpour R., Moradi L., Haghighipour N. The chromene derivative 4-Clpgc inhibits cell proliferation and induces apoptosis in the K562 cell line. *J Cell Commun Signal*. 2020;14(1):77–91. https://doi.org/10.1007/s12079-019-00530-w.
33. Marszalek-Grabska M., Katarzyna Walczak K., Gawel K., Wicha-Komsta K., Wnorowska S. et al. Kynurenine emerges from the shadows — current knowledge on its fate and function. *Pharmacol Therap*. 2021;225:107845. https://doi.org/10.1016/j.pharmthera.2021.107845.
34. Sorgdrager F.J.H., Naudé P.J.W., Kema I.P., Nollen E.A., De Deyn P.P. et al. Tryptophan metabolism in inflammaging: from biomarker to therapeutic target. *Front Immunol*. 2019;10:2565. https://doi.org/10.3389/fimmu.2019.02565.
35. Mondanelli G., Ugel S., Grohmann U., Bronte V. The immune regulation in cancer by the amino acid metabolizing enzymes ARG and IDO. *Curr Opin Pharmacol*. 2017;35:30–39. https://doi.org/10.1016/j.coph.2017.05.002.
36. Stone T.W., Williams R.O. Modulation of T-cells by tryptophan metabolites in the kynurenine pathway. *Trends Pharmacol Sci*. 2023;44(7):442–456. https://doi.org/10.1016/j.tips.2023.04.006.
37. Williams A.C., Hill L.J. Meat and nicotinamide: a causal role in human evolution, history, and demographics. *Int J Tryptophan Res*. 2017;10:1178646917704661. https://doi.org/10.1177/1178646917704661.
38. Olivares M., Walker A.W., Capilla A., Benítez-Páez A., Palau F. et al. Gut microbiota trajectory in early life may predict development of celiac disease. *Microbiome*. 2018;6(1):36. https://doi.org/10.1186/s40168-018-0415-6.
39. Gao J., Xu K., Liu H., Liu G., Bai M. et al. Impact of the gut microbiota on intestinal immunity mediated by tryp-

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

tophan metabolism. *Front Cell Infect Microbiol*. 2018;8:13. https://doi.org/10.3389/fcimb.2018.00013.
40. Fallah S., Asri N., Nikzamir A. Ahmadipour Sh., Sadeghi A. et al. Investigating the impact of vitamin A and amino acids on immune responses in celiac disease patients. *Diseases*. 2024;12(1):13. https://doi.org/10.3390/diseases12010013.
41. Van Hees N.J.M., Giltay E.J., Tielemans S.M.A.J., Geleijnse J.M., Puvill T. et al. Essential amino acids in the gluten-free diet and serum in relation to depression in patients with celiac disease. *PLoS One*. 2015;10(4):e0122619. https://doi.org/10.1371/journal.pone.0122619.
42. Lamas B., Hernandez-Galan L., Galipeau H.J., Constante M., Clarizio A. et al. Aryl hydrocarbon receptor ligand production by the gut microbiota is decreased in celiac disease leading to intestinal inflammation. *Sci Transl Med*. 2020;12(566):eaba0624. https://doi.org/10.1126/scitranslmed.aba0624.
43. Nikolaus S., Schulte B., Al-Massad N., Thieme F., Schulte D.M. et al. Increased tryptophan metabolism is associated with activity of inflammatory bowel diseases. *Gastroenterology*. 2017;153(6):1504–1516.e2. https://doi.org/10.1053/j.gastro.2017.08.028.
44. Dochat C., Afari N., Satherley R.S., Coburn S., McBeth J.F. Celiac disease symptom profiles and their relationship to gluten-free diet adherence, mental health, and quality of life. *BMC Gastroenterology*. 2024;24(1):9. https://doi.org/10.1186/s12876-023-03101-x.

ЛИТЕРАТУРА

1. Аверкина Н.А., Баранов А.А., Бельмер С.В., Бораева Т.Т., Боровик Т.Э. и др. «Целиакия-2025»: проект клинических рекомендаций по диагностике и лечению целиакии у детей. *Педиатрическая фармакология*. 2025;22(4):495–522. https://doi.org/10.15690/pf.v22i4.2941.
2. Хавкин А.И., Налетов А.В., Куропятник П.И. Роль вирусов в патогенезе целиакии: современное состояние вопроса. *Педиатрическая фармакология*. 2024;21(4):369–374. https://doi.org/10.15690/pf.v21i4.2771.
3. Zingone F., Bai J.C., Cellier C., Ludvigsson J.F. Celiac diseaserelated conditions: who to test. *Gastroenterology*. 2024;167(1):64–78. https://doi.org/10.1053/j.gastro.2024.02.044.
4. Хавкин А.И., Налетов А.В., Павловская Е.В., Яблокова Е.А., Курьянинова В.А. и др. Качество жизни пациентов с целиакией, соблюдающих безглютеновую диету: обзор литературы. *Вопросы современной педиатрии*. 2025;24(3):157–161. https://doi.org/10.15690/vsp.v24i3.2923.
5. Хавкин А.И., Гречаный С.В., Малахова А.А., Одинаева Н.Д., Кондратьева Е.И. и др. Психологические факторы приверженности безглютеновой диете у детей и подростков. *Вопросы детской диетологии*. 2025;23(5):18–30. https://doi.org/10.20953/1727-5784-2025-5-18-30.
6. Bakhtiari S., Asri N., Masotti A., Jahani-Sherafat S., Tavirani M.R. et al. Essential amino acids in celiac disease: key roles in immunogenicity, pathogenesis, and therapeutic approaches. *Crit Rev Clin Lab Sci*. 2025:1–16. https://doi.org/10.1080/10408363.2025.2551656.
7. Ding X., Bin P., Wu W., Yajie Chang Y., Zhu G. Tryptophan metabolism, regulatory T cells, and inflammatory bowel disease: a mini review. *Mediators Inflamm*. 2020;2020:9706140. https://doi.org/10.1155/2020/9706140.
8. Хавкин А.И., Налетов А.В., Ситкин С.И., Бораева Т.Т., Мацынина М.А. и др. Особенности состояния кишечной микробиоты у пациентов с целиакией. *Вопросы детской диетологии*. 2025;23(4):47–54. https://doi.org/10.20953/1727-5784-2025-4-47-54.
9. Asgari F., Khodadoust M., Nikzamir A., Sherafat S.J., Tavirani M.R. et al. The role of tryptophan metabolism and tolerogenic dendritic cells in maintaining immune tolerance: Insights into celiac disease pathogenesis. *Immun Inflamm Dis*. 2024;12(8):e1354. https://doi.org/10.1002/iid3.1354.
10. Черных Е.Р., Тыринова Т.В., Леплина О.Ю., Тихонова М.А., Курочкина Ю.Д., Олейник Е.А. и др. Фенотип и функции дендритных клеток человека, генерированных из субпопуляций моноцитов CD14+, оппозитных по экспрессии CD16. *Бюллетень сибирской медицины*. 2019;18(1):266–276. https://doi.org/10.20538/1682-0363-2019-1-266-276.
11. Soto J.A., Gálvez N.M.S., Andrade C.A., Pacheco G.A., Bohmwald K. et al. The role of dendritic cells during infections caused by highly prevalent viruses. *Front Immunol*. 2020;11:1513. https://doi.org/10.3389/fimmu.2020.01513.
12. Asgari F., Nikzamir A., Baghaei K., Salami S., Masotti A. et al. Immunomodulatory and anti-inflammatory effects of Vitamin A and tryptophan on monocyte-derived dendritic cells stimulated with gliadin in celiac disease patients. *Inflammation*. 2024;47(5):1706–1727. https://doi.org/10.1007/s10753-024-02004-7.
13. Blagih J., Hennequart M., Zani F. Tissue nutrient environments and their effect on regulatory T cell biology. *Front Immunol*. 2021;12:637960. https://doi.org/10.3389/fimmu.2021.637960.
14. Козлов В.А., Демина Д.В. Триптофан и indoleamine-2,3-dioxygenase (IDO) в патогенезе иммунокомпрометированных заболеваний. *Медицинская иммунология*. 2017;19(3):225–240. https://doi.org/10.15789/1563-0625-2017-3-225-240.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

15. Шатова О.П., Шестопалов А.В. Метаболизм триптофана: новый взгляд на роль триптофановых производных в организме человека. *Успехи современной биологии*. 2023;143(1):3–15. https://doi.org/10.31857/S0042132423010076.
16. Cervenka I., Agudelo L.Z., Ruas J.L. Kynurenines: Tryptophan's metabolites in exercise, inflammation, and mental health. *Science*. 2017;357(6349):eaaf9794. https://doi.org/10.1126/science.aaf9794.
17. Шатова О.П., Заболотнева А.А., Микин И.Е., Бриль Д.В., Шестопалов А.В. и др. Роль метаболитов триптофана в обмене веществ и патогенезе ожирения. *Профилактическая медицина*. 2022;25(10):97–103. https://doi.org/10.17116/profmed20222510197.
18. Gao K., Mu C., Farzi A., Zhu W.Y. Tryptophan metabolism: a link between the gut microbiota and brain. *Adv Nutr*. 2020;11(3):709–723. https://doi.org/10.1093/advances/nmz127.
19. Kumar P., Lee J.H., Lee J. Diverse roles of microbial indole compounds in eukaryotic systems. *Biol Rev Camb Philos Soc*. 2021;96(6):2522–2545. https://doi.org/10.1111/brv.12765.
20. Щербакова Е.С., Салль Т.С., Ситкин С.И., Вахитов Т.Я., Демьянова Е.В. Роль бактериальных производных ароматических аминокислот в развитии неалкогольной жировой болезни печени. *Альманах клинической медицины*. 2020;48(6):375–386. https://doi.org/10.18786/2072-0505-2020-48-066.
21. Philips C.A., Augustine P., Yerol P.K., Ramesh G.N., Ahamed R. et al. Modulating the intestinal microbiota: Therapeutic opportunities in liver disease. *J Clin Transl Hepatol*. 2020;8(1):87–99. https://doi.org/10.14218/JCTH.2019.00035.
22. Roager H.M., Licht T.R. Microbial tryptophan catabolites in health and disease. *Nat Commun*. 2018;9(1):3294. https://doi.org/10.1038/s41467-018-05470-4.
23. Wlodarska M., Luo C., Kolde R., d'Hennezel E., Annand J.W. et al. Indoleacrylic acid produced by commensal peptostreptococcus species suppresses inflammation. *Cell Host Microbe*. 2017;22(1):25–37.e6. https://doi.org/10.1016/j.chom.2017.06.007.
24. Portune K., Beaumont M., Davila A., Tomé D., Blachier F., Sanz Y. Gut microbiota role in dietary protein metabolism and health-related outcomes: The two sides of the coin. *Trends Food Sci Technol.* 2016;57:213–232. https://doi.org/10.1016/j.tifs.2016.08.011.
25. Oliphant K., Allen-Vercoe E. Macronutrient metabolism by the human gut microbiome: major fermentation by-products and their impact on host health. *Microbiome*. 2019;7(1):91. https://doi.org/10.1186/s40168-019-0704-8.
26. Vyhlidalova B., Krrasulova K., Pecinkova P., Marcalíková A., Vrzal R. et al. Gut microbial catabolites of tryptophan are ligands and agonists of the aryl hydrocarbon receptor: a detailed characterization. *Int J Mol Sci*. 2020;21(7):2614. https://doi.org/10.3390/ijms21072614.
27. Хавкин А.И., Налетов А.В., Мацынина М.А. Противовоспалительные эффекты оливкового масла и его компонентов. Перспективы применения в лечении воспалительных заболеваний кишечника. *Педиатрическая фармакология*. 2024;21(3):249–255. https://doi.org/10.15690/pf.v21i3.2754.
28. Dinallo V., Marafini I., Di Fusco D., Di Grazia A., Laudisi F. et al. Protective effects of aryl hydrocarbon receptor signaling in celiac disease mucosa and in poly I:C-induced small intestinal atrophy mouse model. *Front Immunol*. 2019;10:91. https://doi.org/10.3389/fimmu.2019.00091.
29. Jenkins T.A., Nguyen J.C., Polglaze K.E., Bertrand P.P. Influence of tryptophan and serotonin on mood and cognition with a possible role of the gut-brain. *Nutrients*. 2016;8(1):56. https://doi.org/10.3390/nu8010056.
30. Sanidad K.Z., Rager S.L., Carrow H.C., Ananthanarayanan A., Callaghan R. et al. Gut bacteria-derived serotonin promotes immune tolerance in early life. *Sci Immunol*. 2024;9(93):eadj4775. https://doi.org/10.1126/sciimmunol.adj4775.
31. Grifka-Walk H.M., Jenkins B.R., Kominsky D.J. Amino acid TRP: the far out impacts of host and commensal tryptophan metabolism. *Front Immunol*. 2021;12:2005. https://doi.org/10.3389/fimmu.2021.653208.
32. Asgari F., Mahinpour R., Moradi L., Haghighipour N. The chromene derivative 4-Clpgc inhibits cell proliferation and induces apoptosis in the K562 cell line. *J Cell Commun Signal*. 2020;14(1):77–91. https://doi.org/10.1007/s12079-019-00530-w.
33. Marszalek-Grabska M., Katarzyna Walczak K., Gawel K., Wicha-Komsta K., Wnorowska S. et al. Kynurenine emerges from the shadows — current knowledge on its fate and function. *Pharmacol Therap*. 2021;225:107845. https://doi.org/10.1016/j.pharmthera.2021.107845.
34. Sorgdrager F.J.H., Naudé P.J.W., Kema I.P., Nollen E.A., De Deyn P.P. et al. Tryptophan metabolism in inflammaging: from biomarker to therapeutic target. *Front Immunol*. 2019;10:2565. https://doi.org/10.3389/fimmu.2019.02565.
35. Mondanelli G., Ugel S., Grohmann U., Bronte V. The immune regulation in cancer by the amino acid metabolizing enzymes ARG and IDO. *Curr Opin Pharmacol*. 2017;35:30–39. https://doi.org/10.1016/j.coph.2017.05.002.
36. Stone T.W., Williams R.O. Modulation of T-cells by tryptophan metabolites in the kynurenine pathway. *Trends Pharmacol Sci*. 2023;44(7):442–456. https://doi.org/10.1016/j.tips.2023.04.006.
37. Williams A.C., Hill L.J. Meat and nicotinamide: a causal role in human evolution, history, and demographics. *Int*

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

J Tryptophan Res. 2017;10:1178646917704661. https://doi.org/10.1177/1178646917704661.
38. Olivares M., Walker A.W., Capilla A., Benítez-Páez A., Palau F. et al. Gut microbiota trajectory in early life may predict development of celiac disease. *Microbiome*. 2018;6(1):36. https://doi.org/10.1186/s40168-018-0415-6.
39. Gao J., Xu K., Liu H., Liu G., Bai M. et al. Impact of the gut microbiota on intestinal immunity mediated by tryptophan metabolism. *Front Cell Infect Microbiol*. 2018;8:13. https://doi.org/10.3389/fcimb.2018.00013.
40. Fallah S., Asri N., Nikzamir A. Ahmadipour Sh., Sadeghi A. et al. Investigating the impact of vitamin A and amino acids on immune responses in celiac disease patients. *Diseases*. 2024;12(1):13. https://doi.org/10.3390/diseases12010013.
41. Van Hees N.J.M., Giltay E.J., Tielemans S.M.A.J., Geleijnse J.M., Puvill T. et al. Essential amino acids in the gluten-free diet and serum in relation to depression in patients with celiac disease. *PLoS One*. 2015;10(4):e0122619. https://doi.org/10.1371/journal.pone.0122619.
42. Lamas B., Hernandez-Galan L., Galipeau H.J., Constante M., Clarizio A. et al. Aryl hydrocarbon receptor ligand production by the gut microbiota is decreased in celiac disease leading to intestinal inflammation. *Sci Transl Med*. 2020;12(566):eaba0624. https://doi.org/10.1126/scitranslmed.aba0624.
43. Nikolaus S., Schulte B., Al-Massad N., Thieme F., Schulte D.M. et al. Increased tryptophan metabolism is associated with activity of inflammatory bowel diseases. *Gastroenterology*. 2017;153(6):1504–1516.e2. https://doi.org/10.1053/j.gastro.2017.08.028.
44. Dochat C., Afari N., Satherley R.S., Coburn S., McBeth J.F. Celiac disease symptom profiles and their relationship to gluten-free diet adherence, mental health, and quality of life. *BMC Gastroenterology*. 2024;24(1):9. https://doi.org/10.1186/s12876-023-03101-x.

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Quality of life of children with functional abdominal pain disorders: a cross-sectional study

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ABSTRACT. ***Introduction.*** Functional abdominal pain disorders are widespread in pediatric practice and have a significant impact on the quality of life of patients. ***Aim*** — to evaluate the quality of life of children aged 8–17 years with functional abdominal pain disorders compared to healthy peers. ***Materials and methods.*** A one-stage study was conducted with the participation of 193 children with functional abdominal pain disorders (functional dyspepsia, irritable bowel syndrome, functional abdominal pain, biliary dysfunction) aged 8–17 years and 183 healthy children (control group). The quality of life was assessed using the Russian version of the PedsQL 4.0 questionnaire. Nonparametric methods and a generalized linear model adjusted for age and gender were used for statistical analysis. ***Results.*** Children with functional abdominal pain disorders demonstrated a significantly lower overall quality of life compared to healthy peers (69.6 vs. 85.9; p <0.001). A decrease in scores was observed in all quality of life domains: physical activity (71.9 vs. 87.5 in the control group) and psychosocial functioning (68.3 vs. 83.3) were significantly lower in the functional abdominal pain disorders group. The school functioning scale was the most significantly affected (65.0 vs. 80.0; p <0.001). In the functional abdominal pain disorders group, lower quality of life scores were associated with female gender and adolescence (13–17 years). A generalized linear model confirmed that the presence of functional abdominal pain disorders was the most powerful independent predictor of lower quality of life. Healthy children had higher quality of life by 12.34 points (B=12.34, p <0.001), after adjusting for gender and age. ***Conclusion.*** The presence of functional abdominal pain disorders is associated with a significant decrease in the quality of life in children. Adolescents and girls with functional abdominal pain disorders represent the most vulnerable groups. Comprehensive management of such patients should be aimed not only at relieving pain, but also at improving the quality of life.

KEYWORDS: *functional gastrointestinal disorders, abdominal pain, functional dyspepsia, irritable bowel syndrome, biliary dysfunction, functional abdominal pain, quality of life, PedsQL*

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Оригинальная статья

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Качество жизни детей с функциональными расстройствами органов пищеварения с абдоминальной болью: одномоментное исследование

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РЕЗЮМЕ. ***Введение.*** Функциональные расстройства органов пищеварения с абдоминальной болью широко распространены в педиатрической практике и оказывают значительное влияние на качество жизни пациентов. ***Цель*** — оценить качество жизни детей в возрасте 8–17 лет с функциональными расстройствами органов пищеварения с абдоминальной болью по сравнению со здоровыми сверстниками. ***Материалы и методы.*** Проведено одномоментное исследование с участием 193 детей с функциональными расстройствами органов пищеварения с абдоминальной болью (функциональная диспепсия, синдром раздраженного кишечника, функциональная абдоминальная боль, билиарная дисфункция) в возрасте 8–17 лет и 183 здоровых детей (контрольная группа). Качество жизни оценивалось с помощью русскоязычной версии опросника PedsQL 4.0. Для статистического анализа использовались непараметрические методы и обобщенная линейная модель с поправкой на возраст и пол. ***Результаты.*** Дети с функциональными расстройствами органов пищеварения с абдоминальной болью продемонстрировали значительно более низкое общее качество жизни по сравнению со здоровыми сверстниками (69,6 против 85,9; p <0,001). Снижение показателей отмечено по всем доменам качества жизни: физическая активность (71,9 против 87,5 у контроля) и психосоциальное функционирование (68,3 против 83,3) были достоверно ниже в группе

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функциональных расстройств органов пищеварения с абдоминальной болью. Наиболее существенно страдала шкала школьного функционирования (65,0 против 80,0; p <0,001). В группе функциональных расстройств органов пищеварения с абдоминальной болью более низкие показатели качества жизни были ассоциированы с женским полом и подростковым возрастом (13–17 лет). Обобщенная линейная модель подтвердила, что наличие функциональных расстройств органов пищеварения с абдоминальной болью является наиболее мощным независимым предиктором снижения качества жизни. У здоровых детей общий балл был на 12,34 пункта выше (B=12,34, p <0,001) после коррекции на пол и возраст. ***Заключение.*** Функциональные расстройства органов пищеварения с абдоминальной болью ассоциированы со значительным снижением качества жизни у детей. Подростки и девочки с функциональными расстройствами органов пищеварения с абдоминальной болью представляют наиболее уязвимые группы. Комплексное ведение таких пациентов должно быть направлено не только на купирование боли, но и на улучшение качества жизни.

КЛЮЧЕВЫЕ СЛОВА: *функциональные расстройства органов пищеварения, боль в животе, функциональная диспепсия, синдром раздраженного кишечника, билиарная дисфункция, функциональная абдоминальная боль, качество жизни, PedsQL*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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INTRODUCTION

In modern medicine, when conducting clinical trials designed to compare the effectiveness of different therapeutic approaches, particular attention is paid to a comprehensive assessment of treatment outcomes. Alongside traditional biomedical indicators, such as laboratory data and instrumental studies, the assessment of a patient's quality of life (QL) is becoming increasingly important. This indicator can serve both as a supplementary assessment tool and as a key criterion in analyzing the effectiveness of various treatment and monitoring regimens at different stages of clinical trials [1].

Special questionnaires have been developed for a comprehensive assessment of QL in children and adults with various diseases. An important advantage of these questionnaires is that they are universal and not tied to specific diseases, which allows for comparing results across different patient groups [2].

In pediatric practice, two versions of the questionnaire are often used. The first version is completed by the child, and the second by the parents. It is important to note that there is a significant discrepancy between the data provided by parents and the information provided by the children themselves. This discrepancy is due to a number of factors: differences in perception of the situation, varying levels of understanding of the phenomena being described, or insufficient awareness on the part of one of the respondents. Given the above, it is recommended to consider children's self-reports as more reliable [3, 4].

The most widely used QL questionnaire in pediatrics is the Pediatric Quality of Life Inventory 4.0 (PedsQL 4.0). The questionnaire was developed in 1998, and its adaptation for the Russian-speaking population was completed in 2005. It consists of 23 questions divided into four sections: physical functioning, emotional well-being, social functioning, and role or school functioning. Scores are transformed to a 0–100 scale, with higher scores indicating better quality of life. [4, 5].

The PedsQL 4.0 questionnaire has demonstrated high effectiveness as a tool for the comprehensive assessment of QL in children with inflammatory bowel disease. This questionnaire provides valuable information on the health status of children with Crohn's disease and ulcerative colitis, including their physical, psychological, and emotional well-being, and is recommended for use in follow-up care and monitoring of disease activity [6–8].

In recent years, specialized programs have also been developed in Russia to monitor the condition of patients with GIT disorders, incorporating quality-of-life questionnaires [9].

Functional gastrointestinal disorders with abdominal pain (FGID-AB) in children significantly affect their quality of life. One study assessed the quality of life of children with FGID-AB using the PedsQL 4.0 questionnaire. The sample included patients with FGID-AB, organic GIT diseases, and healthy children. The results showed that children with FGID-AB had lower scores on all aspects of quality of life compared to healthy children and children with organic GIT diseases [10].

However, a review of the literature has revealed a number of significant gaps. First, although there are studies demonstrating a decline in quality of life among children with FGID-AB, data collected in outpatient settings that reflect Russian clinical practice remain limited. Second, a significant portion of the studies rely on the Rome criteria and, as a rule, do not consider patients with biliary dysfunction (BD), which frequently appears in Russian pediatric gastroenterology as a clinically significant diagnosis. Third, quality of life assessment is often conducted using specialized but more extensive questionnaires (KIDSCREEN, CHQ, KINDL), the use of which increases the burden on the respondent and makes them difficult to use for rapid assessment in the practice of a community pediatrician. Thus, there remains a lack of data obtained using a brief, universal tool for assessing quality of life in children with FGID-AB, covering the entire spectrum of nosological forms as defined in Russian guidelines.

This study assessed the quality of life of children aged 8–17 years with FGID-AB, including patients with BD, using the PedsQL 4.0 questionnaire (child self-report). The analysis covered key health-related quality-of-life components (physical, emotional, social, and school functioning), as well as summary measures. The results obtained can be used to optimize the referral process and follow-up of children with FGID-AB in outpatient settings.

AIM

To assess the quality of life of children aged 8 to 17 with functional gastrointestinal disorders and abdominal pain.

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MATERIALS AND METHODS

Study design

A cross-sectional study was conducted to assess the quality of life of children aged 8 to 17 years with functional gastrointestinal disorders and abdominal pain, using the PedsQL 4.0 questionnaire.

Study setting

Our study included children aged 8 to 17 who were treated at the pediatric clinic of the Dolgoprudny Central City Hospital (DCCH), a municipal healthcare institution in Dolgoprudny. The study began on February 18, 2025, and was completed on May 31, 2025.

Participants

The study included two groups of children aged 8 to 17 years: children with functional gastrointestinal disorders presenting with abdominal pain (the observation group) and healthy children (the control group). The observation group included children diagnosed with one of the following functional gastrointestinal disorders: functional dyspepsia, irritable bowel syndrome, functional abdominal pain, or biliary dysfunction, diagnosed in accordance with the recommendations of the Russian Society of Pediatric Gastroenterologists, Hepatologists, and Nutritionists [11–14]. The inclusion criterion for the study was the absence of organic gastrointestinal diseases and other chronic conditions that could affect quality of life. The control group consisted of essentially healthy children without any chronic diseases. A sample was selected from among all children in both groups.

Variables

The primary dependent variable is quality of life, which was assessed using the Russian-language version of the PedsQL 4.0 questionnaire, which includes an overall score and a score for each domain (physical, emotional, social, and school functioning). The independent variables include the following: the presence of a functional gastrointestinal disorder accompanied by abdominal pain, and the child's age and gender.

Data sources

Quality of life was assessed using standardized PedsQL 4.0 questionnaires designed for children aged 8 to 12 and 13 to 17. Based on these questionnaires, two electronic versions were developed and posted on the Yandex Forms platform. We contacted the children's legal guardians by phone and invited them to participate in the study. Upon receiving consent from the child's guardian, a link to the corresponding questionnaire was sent to them via messenger or email.

The observation group was created from a database of outpatient records that we compiled in a previous study [15].

The control group consisted of children who had undergone routine medical examinations and were classified as health groups I or II.

Systematic mistakes

For several reasons, the electronic medical records of the children who participated in the study may have lacked information regarding organic gastrointestinal disorders or any other chronic conditions. First, some of them may have received medical care at private clinics, regional referral centers, or other healthcare facilities. Second, some study participants may have recently been assigned to a pediatric clinic, and data on their medical conditions had not yet been entered into their electronic medical records. To avoid such errors, before sending the link to the questionnaire, we confirmed with the legal guardian during a phone call that the child did not have any chronic diseases.

Scope of the study

A preliminary calculation of the sample size for the observation group was performed using the classical formula, taking into account the prevalence of FGID-AB obtained in our study [15]:

$$n = t^2 \cdot P \cdot Q/\Delta^2,$$

where P = 0.136 (the prevalence of FGID-AB obtained in our previous study), Q = 1 − P, t = 1.96, Δ = 0.05. The minimum required number of children with FGID-AB (n=180) was increased to 220 to account for possible refusals and incomplete questionnaires. A similar number of children (n=220) was selected for the control group.

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Statistical methods

Statistical analysis was performed using IBM SPSS Statistics 26.0 (IBM Corp., USA) and Microsoft Excel 2021. Quantitative indicators are presented as the median (Me) and interquartile range (Q_1–Q_3), since the data distribution deviated from the normal distribution (verified using the Shapiro–Wilk test). The Mann–Whitney U test was used for pairwise comparisons of two independent groups. Statistical significance of differences was determined at a significance level of $p < 0.05$.

To assess the independent contribution of factors to the overall quality-of-life score, we used a generalized linear model (GLM) for a continuous dependent variable, which was the total PedsQL 4.0 score. The model included the presence of FGID-AB (healthy vs. children with FGID-AB), gender (girls vs. boys), and age group (8–12 vs. 13–17 years). Comparison categories were defined using reference values (boys, FGID-AB, 13–17 years). The regression coefficient B reflected the difference in the expected mean total QL score (in PedsQL points) between the compared categories while holding the other covariates constant; 95% confidence intervals and p-values were calculated using standard model methods. The level of statistical significance was set at 0.05.

RESULTS

Participants

The sample was selected in stages. In the first stage, 220 children with FGID-AB and 220 apparently healthy children for the control group, who met the selection criteria, were selected from the population of children aged 8 to 17. The parents of the children participating in the study received verbal information over the phone about the study's objectives, confidentiality, and anonymity, after which they gave verbal informed consent for their child's participation in the survey. After consent to participate in the study was obtained, parents were sent a link to a questionnaire on Yandex Forms, which the child was required to complete themselves.

Of the 440 invited participants (220 children with FGID-AB and 220 healthy children), 376 completed the questionnaire in full — 193 children with FGID-AB and 183 healthy children, who constituted the control group. The dropout rate was 14.5% (27 children with FGID-AB and 37 healthy children), which was due to subsequent withdrawal from the study.

The median age of the children in the observation group was Me=12.00 [10.0–13.0] years, and in the control group, Me=13.00 [10.0–14.0] years. The groups were comparable in terms of age (U=18039.5; p=0.717). The gender distribution was

Table 1. Comparison of quality of life scores between children with functional abdominal pain disorders and healthy controls

Таблица 1. Сравнение показателей качества жизни детей с функциональными расстройствами органов пищеварения с абдоминальной болью и здоровых

Показатель качества жизни **Quality of life indicator**	**Дети с ФРОП-АБ** **Children with FAPD** **Me [Q_1–Q_3]**	**Здоровые дети** **Healthy children** **Me [Q_1-Q_3]**	**U**	**p**
Общий балл качества жизни Overall quality of life score	69,6 [62,0–79,3]	85,9 [73,4–90,2]	8016,5	<0,001
Физическое функционирование Physical functioning	71,9 [62,5–81,3]	87,5 [76,6–93,8]	7990,0	<0,001
Психосоциальное функционирование Psychosocial functioning	68,3 [58,3–78,3]	83,3 [70,8–90,0]	8826,0	<0,001
Эмоциональное функционирование Emotional functioning	70,0 [55,0–80,0]	80,0 [65,0–90,0]	12076,5	<0,001
Социальное функционирование Social functioning	75,0 [65,0–85,0]	85,0 [77,5–95,0]	8707,0	<0,001
Школьное функционирование School functioning	65,0 [50,0–75,0]	80,0 [70,0–85,0]	7746,5	<0,001

The table is prepared by the authors using their own data

Таблица составлена авторами по собственным данным

Note: FAPD — functional abdominal pain disorders (here and further in tables).

Примечание: ФРОП-АБ — функциональное расстройство органов пищеварения с абдоминальной болью (здесь и далее в таблицах).

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as follows: in the observation group, there were 109 girls (56.5%) and 84 boys (43.5%), and in the control group, there were 96 girls (52.5%) and 87 boys (47.5%). The groups were comparable in terms of gender (χ^2=0.46; p=0.498).

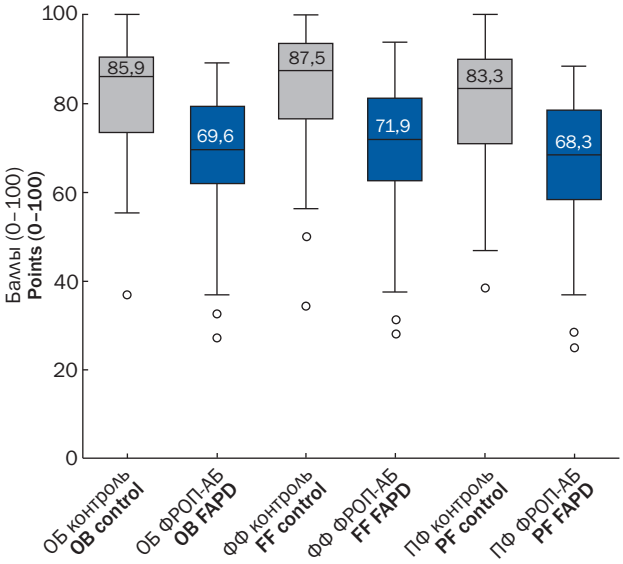

Fig. 1. Comparison of the main indicators of the quality of life of children with functional abdominal pain disorders (FAPD) and healthy children: OB — overall quality of life score; PF — psychosocial functioning; FF — physical functioning (the figure is prepared by the authors)

Рис. 1. Сравнение основных показателей качества жизни детей с функциональными расстройствами органов пищеварения с абдоминальной болью (ФРОП-АБ) и здоровых: ОБ — общий балл качества жизни; ПФ — психосоциальное функционирование; ФФ — физическое функционирование (рисунок подготовлен авторами)

The study group consisted of 67 children (34.7%) with functional dyspepsia, 30 children (15.5%) with irritable bowel syndrome, 31 children (16.1%) with functional abdominal pain, and 65 children (33.7%) with biliary dysfunction.

Children with FGID-AB had lower quality-of-life scores on all scales of the PedsQL questionnaire compared with healthy children (Mann–Whitney U test; p <0.001 for all comparisons).

The median values of quality-of-life scores are presented in Table 1 and Figure 1. The most pronounced differences were observed on the "School Functioning" and "Physical Functioning" scales.

When comparing quality-of-life indicators among children with FGID-AB (the main group) by gender, statistically significant differences were found on several scales. The median total QL score for boys was higher than for girls — 75.0 [65.2–81.2] versus 67.4 [58.7–78.8] (U=5597.5; p=0.008).

The most pronounced differences were observed on the physical functioning scale — 78.1 [66.4–84.4] for boys versus 68.8 [59.4–79.7] for girls (U=5979.0; p <0.001). Differences in indicators of psychosocial, emotional, social and school functioning did not reach statistical significance (p >0.05).

Thus, boys with FGID-AB have a higher quality of life, primarily due to the physical component (Table 2).

Table 2. Comparison of quality of life scores between children with functional abdominal pain disorders, depending on their gender

Таблица 2. Сравнение показателей качества жизни детей с функциональными расстройствами органов пищеварения с абдоминальной болью в зависимости от пола

Показатель качества жизни **Quality of life indicator**	**Девочки** **Girls** **Me [Q_1–Q_3]**	**Мальчики** **Boys** **Me [Q_1–Q_3]**	**U**	**p**
Общий балл качества жизни Overall quality of life score	67,4 [58,7–78,8]	75,0 [65,2–81,2]	5597,5	0,008
Физическое функционирование Physical functioning	68,8 [59,4–79,7]	78,1 [66,4–84,4]	5979,0	<0,001
Психосоциальное функционирование Psychosocial functioning	66,7 [55,0–78,3]	73,3 [61,7–78,3]	5258,5	0,077
Эмоциональное функционирование Emotional functioning	65,0 [50,0–80,0]	75,0 [60,0–83,8]	5242,0	0,083
Социальное функционирование Social functioning	75,0 [65,0–82,5]	75,0 [70,0–85,0]	5183,0	0,113
Школьное функционирование School functioning	60,0 [50,0–75,0]	65,0 [55,0–75,0]	5111,0	0,164

The table is prepared by the authors using their own data
Таблица составлена авторами по собственным данным

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When comparing quality of life indicators among children with FGID-AB by age group, statistically significant differences were found across all scales of the PedsQL questionnaire. The median total quality of life scores for younger schoolchildren were higher than those for adolescents — 76.1 [66.9–82.6] versus 65.2 [56.8–75.0] (p <0.001). A similar trend was observed for physical, psychosocial, emotional, social, and school functioning (Table 3).

Thus, younger schoolchildren with FGID-AB have a higher quality of life than adolescents, reflecting the age-related intensification of the influence of psychoemotional factors, academic workload, and social stress.

A generalized linear model was constructed to assess the independent contributions of FGID-AB status, gender, and age to quality of life. The following were selected as reference categories: FGID-AB status, male gender, and the older age group (13–17 years). The model showed that membership in the FGID-AB group was associated with the most pronounced differences in quality of life scores after adjusting for gender and age. Thus, in healthy children, the total quality of life score was

Table 3. Comparison of quality of life scores between children with functional abdominal pain disorders, depending on their age group

Таблица 3. Сравнение показателей качества жизни детей с функциональными расстройствами органов пищеварения с абдоминальной болью в зависимости от возрастной группы

Показатель качества жизни **Quality of life indicator**	**Дети 8–12 лет** **Children 8–12 years old** **Me [Q_1–Q_3]**	**Дети 13–17 лет** **Children 13–17 years old** **Me [Q_1–Q_3]**	**U**	**p**
Общий балл качества жизни Overall quality of life score	76,1 [66,9–82,6]	65,3 [56,8–75,0]	2802,0	<0,001
Физическое функционирование Physical functioning	78,1 [68,8–87,5]	65,6 [59,4–77,3]	2534,5	<0,001
Психосоциальное функционирование Psychosocial functioning	75,0 [63,3–81,7]	63,3 [52,1–75,0]	2945,5	<0,001
Эмоциональное функционирование Emotional functioning	75,0 [65,0–85,0]	65,0 [45,0–75,0]	2817,5	<0,001
Социальное функционирование Social functioning	75,0 [70,0–85,0]	70,0 [65,0–80,0]	3790,0	0,026
Школьное функционирование School functioning	70,0 [55,0–75,0]	60,0 [45,0–70,0]	2881,0	<0,001

The table is prepared by the authors using their own data
Таблица составлена авторами по собственным данным

Table 4. Factors associated with the overall quality of life score: results of the generalized linear model

Таблица 4. Влияние различных факторов на общий балл качества жизни по данным обобщенной линейной модели

Фактор **Factor**	**Категория сравнения** **Comparison category**	**B**	**95% ДИ** **95% CI**	**p**
ФРОП-АБ FAPD	Здоровые (референс: ФРОП-АБ) Healthy (reference: FAPD)	+12,34	10,07–14,61	<0,001
Возрастная группа Age group	8–12 лет (референс: 13–17 лет) 8–12 years (reference: 13–17 years)	+8,22	5,96–10,49	<0,001
Пол Sex	Девочки (референс: мальчики) Girls (reference: boys)	–3,69	–5,97...–1,41)	0,001
Константа Constant	–	67,16	64,78–69,54	<0,001

The table is prepared by the authors using their own data
Таблица составлена авторами по собственным данным

Note: CI — confidence interval; FAPD — functional abdominal pain disorders; B — regression coefficient showing the change in the quality of life score, a positive B value indicates a higher quality of life in the first comparison group.

Примечание: ДИ — доверительный интервал; ФРОП-АБ — функциональное расстройство органов пищеварения с абдоминальной болью; B — коэффициент регрессии, показывающий изменение балла качества жизни, положительное значение B указывает на более высокое качество жизни в первой группе сравнения.

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12.34 points higher than in patients with FGID-AB (B=12.336; 95% CI 10.068–14.605; p <0.001).

Age also had a significant independent effect: among younger schoolchildren (8–12 years), quality of life was 8.22 points higher than among adolescents (13–17 years) (B=8.224; 95% CI 5.957–10.491; p <0.001).

The child's gender had a statistically significant but less pronounced effect: girls had a quality of life score that was 3.69 points lower than that of boys (B=–3.691; 95% CI –5.968…–1.414; p=0.001).

Thus, the generalized linear model showed that differences in the total quality of life score between the groups of healthy children and patients with FGID-AB persist after adjusting for age and gender (Table 4).

DISCUSSION

Key findings

The results of our cross-sectional study demonstrate that the presence of FGID-AB is an independent factor associated with a significant reduction in QL among children aged 8–17 years. The most pronounced differences compared to the group of healthy peers were observed in the areas of academic and psychosocial functioning. Within the group of children with FGID-AB, lower QL scores were found among girls and adolescents.

LIMITATIONS

The main limitation of this study is its cross-sectional design, which does not allow for conclusions regarding causal relationships between the presence of functional gastrointestinal disorders with abdominal pain (FGID-AB) and reduced QL.

Furthermore, the assessment was based on children's self-reports, which could potentially lead to subjective distortions in the perception of symptoms and overall condition. Nevertheless, the use of the standardized and validated PedsQL instrument, adapted for the pediatric population, ensures sufficient reliability and reproducibility of the data obtained.

Another limitation is that the survey was conducted during a period of seasonal increase in the incidence of acute respiratory infections, which may have temporarily affected self-reported quality of life, particularly on the school functioning scale, which reflects a child's attendance and participation in the educational process.

Limitations of the study include the lack of an assessment of the current severity of clinical symptoms at the time the questionnaire was completed, as well as information on ongoing treatment (pharmacological and non-pharmacological) during the survey period. Given the possible variability of symptoms in FGID-AB, these factors could have influenced quality-of-life indicators and partially accounted for the observed differences.

Interpretation of the results

Our findings regarding a significant reduction in QL among children with FGID-AB are fully consistent with the results of major international and Russian studies. Our key observation that children with FGID-AB have significantly lower QL scores compared to healthy peers not only replicates the findings of H. Karami et al. (2022), but also confirms the data from a larger study by J.W. Varni et al. (2015), which also demonstrated that children with functional gastrointestinal disorders have lower QOL scores compared to healthy peers [10, 16].

Similar results were obtained in the Russian population: in a study by T.V. Polivanova et al. (2023), which included school-aged children, a significant decrease in QL was also noted in the presence of abdominal pain, with the children themselves reporting deterioration across a greater number of parameters compared to their parents' assessments [17]. The data obtained confirm the validity of our methodological approach, according to which priority in assessing QL is given to the children's own reports, since their perception of the illness may differ significantly from their parents' perspective.

Our study provides a detailed breakdown of this decline: the most pronounced differences were found in the areas of school and psychosocial functioning. This focus on school maladjustment complements the findings of T.V. Polivanova et al., who also identified behavioral problems and reduced family cohesion in children, and expands upon the conclusions of H. Karami et al. (2022), where the greatest differences concerned social and emotional aspects.

In contrast to the work by T.V. Polivanova et al. [17], where gender differences did not reach statistical significance, our study revealed lower QL scores among girls and adolescents with FGID-AB.

A key methodological strength of our study is the regression analysis we conducted, which confirmed that the negative impact of FGID-AB on quality of life is independent and remains significant after ad-

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justing for gender and age. Thus, our study not only confirms the findings of international and domestic authors regarding reduced quality of life in children with FGID-AB but also expands upon them, demonstrating the independent contribution of the core symptoms of these disorders to reduced QL.

The significant reduction in the total quality of life score in children with FGID-AB identified in our study is consistent with the biopsychosocial model of these disorders, within which chronic abdominal pain acts not merely as an isolated symptom, but as a constant stressor that triggers a cascade of interrelated physical and psychoemotional disturbances.

The most pronounced decline was observed in academic performance. This key finding has a logical pathophysiological basis. Chronic pain, acting as a constant distraction, directly disrupts the cognitive processes necessary for successful learning. A vicious cycle develops: against a backdrop of missed classes and declining academic performance, academic debt accumulates, which in itself becomes a powerful source of chronic stress and anxiety. These negative emotions, in turn, through the gut-brain axis mechanisms, potentiate visceral hypersensitivity and intensify pain perception, closing the vicious cycle.

A decline in physical functioning scores may be associated with a direct limitation of activity caused by chronic abdominal pain. Children often consciously avoid games, sports, and other physical activities for fear of triggering pain or other symptoms of FGID-AB, which leads to physical inactivity and, in the long term, to reduced exercise tolerance and a deterioration in overall physical condition.

The decline in emotional well-being is a direct consequence of constant psychological and emotional stress. Living with the unpredictability of FGID-AB symptoms contributes to the development of anxiety and impairments in social functioning.

The identified intra-group differences — namely, a more significant decline in QL among girls and adolescents — can also be explained. Adolescence is characterized by a sharp increase in academic workload, more complex social relationships, and hormonal changes, all of which increase the nervous system's vulnerability to chronic stress. Gender imbalance, in turn, may be associated with a higher prevalence of anxiety and depression among girls, which are closely linked to FGID-AB and exacerbate the subjective perception of the illness.

The findings have direct practical implications for improving care for children with FGID-AB. They clearly demonstrate that the goal of treatment for FGID-AB should be not only to relieve abdominal pain but also to comprehensively improve the patient's quality of life. Standardized assessment of QL using questionnaires such as the PedsQL should be considered an integral part of dynamic monitoring, allowing for the identification of the areas of the child's life most affected and the quantitative evaluation of treatment effectiveness.

Generalizability

Despite these limitations, the findings have important practical implications. They not only confirm the significant negative impact of FGID-AB on children's quality of life, but also help identify the most vulnerable groups (adolescents and girls) that require special attention.

The data obtained indicate the need for a comprehensive approach to the management of patients with FGID-AB. Treatment strategies should be aimed not only at relieving abdominal pain but also at actively improving quality of life. To develop and validate such strategies, prospective studies are needed in which the comparative assessment of the effectiveness of various treatment methods will be conducted using validated instruments, such as the PedsQL questionnaire, as a key objective outcome measure.

CONCLUSION

Functional gastrointestinal disorders accompanied by abdominal pain are an independent factor contributing to a significant decline in quality of life among children aged 8–17, particularly in school and psychosocial settings, with girls and adolescents being the most vulnerable. The results obtained support the need for a comprehensive therapeutic approach aimed not only at pain relief but also at improving quality of life.

ADDITIONAL INFORMATION

Author contribution. N.Z. Zokirov — study conception and design, analysis of results, manuscript writing; E.I. Alieva — study design, participation in discussion of the results, manuscript editing; A.V. Krasnov — organization of questionnaire administration, data analysis and processing, statistical analysis, participation in discussion of the results; A.I. Khavkin — study conception, final manuscript editing, approval of the final version;

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V.V. Sytkov — data analysis and processing, statistical analysis, manuscript writing.

All authors read and approved the final version before publication.

Competing interests. The authors declare that they have no competing interests.

Ethical aspects. The study protocol was reviewed and approved by the local ethics committee. Participation of children and their parents was voluntary. Before completing the questionnaire, parents were given verbal information about the study's objectives, confidentiality, and anonymity, and then provided verbal informed consent for their child to participate. The questionnaire did not contain personal data and did not allow for the identification of respondents. The study was observational and did not involve any interventions in the participants' health.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Н.З. Зокиров — разработка концепции и дизайна исследования, анализ результатов, написание текста рукописи; Э.И. Алиева — разработка дизайна исследования, участие в обсуждении результатов, редактирование текста; А.В. Краснов — организация анкетирования, анализ и обработка данных, статистический анализ, участие в обсуждении результатов; А.И. Хавкин — разработка концепции исследования, окончательное редактирование рукописи, утверждение финальной версии; В.В. Сытьков — анализ и обработка данных, статистическая обработка, написание текста рукописи.

Все авторы прочли и одобрили финальную версию перед публикацией.

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Этические аспекты. Протокол исследования был рассмотрен и одобрен локальным этическим комитетом. Участие детей и их родителей было добровольным. Перед заполнением анкеты родители получили устную информацию о целях исследования, принципах конфиденциальности и анонимности, после чего дали устное информированное согласие на участие ребенка в опросе. Анкета не содержала персональных данных и не позволяла идентифицировать респондентов. Исследование носило наблюдательный характер и не включало вмешательств в здоровье участников.

REFERENCES

1. Novik A.A., Ionova T.I. Handbook of quality of life research in medicine. Yu.A. Shevchenko, ed. 4th edition, revised and enlarged. Moscow: National Medical and Surgical Center named after N.I. Pirogov; 2021. (In Russ.).
2. Agrba A.V., Ildarova A.A., Stetsenko M.S. The importance of using quality of life questionnaires in assessing the effectiveness of therapy for children with chronic gastroduodenal pathology. In: Modern animal husbandry and innovations in food production technology, aspects of environmental, industrial and hygienic safety. Proceedings of the international scientific and practical conference. Persianovsky, November 22, 2024. Persianovsky: Don State Agrarian University; 2024. P. 472–478. EDN: WFKXUC.
3. Rajmil L., López A.R., López-Aguilà S., Alonso J. Parent-child agreement on health-related quality of life (HRQOL): a longitudinal study. Health Qual Life Outcomes. 2013;11:1–10. https:/doi.org/10.1186/1477-7525-11-101.
4. Arsiwala T., Afroz N., Kordy K., Naujoks C., Patalano F. Measuring what matters for children: a systematic review of frequently used pediatric generic PRO instruments. *Ther Innov Regul Sci*. 2021;55(5):1082–1095. https:/doi.org/10.1007/s43441-021-00311-x.
5. Varni J.W., Seid M., Rode C.A. The PedsQL™: measurement model for the pediatric quality of life inventory. *Med Care*.1999;37(2):126–139.
6. Silonyan A.L., Surkov A.N., Chernikov V.V. Quality of life of children with inflammatory bowel diseases. *Russian Pediatric Journal***.** 2021;24(S):55–56. (In Russ.). EDN: OMDRWB.
7. Arakelian L., Surkov A.N., Namazova-Baranova L.S. et al. Assessment of the quality of life of children with inflammatory bowel diseases. *University Therapeutic Journal*.2024;6(S2):9–10. (In Russ.). EDN: IAKZIA.
8. Tagirova A.R. Quality of life in children with inflammatory bowel diseases. PhD dissertation. Moscow; 2021. 177 p. (In Russ.). EDN: PRFIQL.
9. Certificate of state registration of computer program No. 2024615192 Russian Federation. Namazova-Baranova L.S., Surkov A.N., Bessonov E.E. et al. Program for monitoring the condition of pediatric patients with gastrointestinal tract pathology: No. 2024613598: declared. 20.02.2024: published. 04.03.2024; applicant Federal State Budgetary Scientific Institution "Russian Scientific

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

Center of Surgery named after Academician B.V. Petrovsky". (In Russ.). EDN: IKNWLL.
10. Varni J.W., Bendo C.B., Denham J. et al. PedsQL™ Gastrointestinal Symptoms Scales and Gastrointestinal Worry Scales in pediatric patients with functional and organic gastrointestinal diseases in comparison to healthy controls. *Qual Life Res*. 2015;24(2):363–378. https:/doi.org/10.1007/s11136-014-0781-x.
11. Belmer S.V., Volynets G.V., Gorelov A.V., Gurova M.M., Zvyagin A.A. et al. Functional digestive disorders in children. Guidelines of Society of Pediatric Gastroenterologists, Hepatologists and Nutritionists. Part 1. *Russian Bulletin of Perinatology and Pediatrics*. 2020;65(4):150–161. (In Russ.). https://doi.org/10.21508/1027-4065-2020-65-4-150-161.
12. Belmer S.V., Volynets G.V., Gorelov A.V., Gurova M.M., Zvyagin A.A. et al. Functional digestive disorders in children. Guidelines of the Society of Pediatric Gastroenterologists, Hepatologists and Nutritionists. Part 2. *Russian Bulletin of Perinatology and Pediatrics*. 2020;65(5):100–111. (In Russ.). https://doi.org/10.21508/1027-4065-2020-65-5-100-111.
13. Belmer S.V., Volynets G.V., Gorelov A.V., Gurova M.M., Zvyagin A.A. et al. functional disorders of digestive system in children. Guidelines of Society of Pediatric Gastroenterology, Hepatology and Nutrition. Part 3. *Russian Bulletin of Perinatology and Pediatrics*. 2020;65(6):133–144. (In Russ.). https://doi.org/10.21508/1027-4065-2020-65-6-133-144.
14. Pediatric Gastroenterology. National Guidelines. Belmer S.V., Razumovsky A.Yu., eds. Moscow: GEOTAR-Media; 2022. 864 p.
15. Zokirov N.Z., Alieva E.I., Krasnov A.V., Sytkov V.V., Yablokova E.A. Prevalence of functional gastrointestinal disorders with abdominal pain in children aged 8–17 years: cross-sectional study. *Pediatric pharmacology*. 2025;22(6):655–662. (In Russ.). https://doi.org/10.15690/pf.v22i6.2991.
16. Karami H., Charati J.Ya., Aghaee B.L. et al. Quality of life for children with functional abdominal pain and their parents copmared to healthy individuals. *J Ped Rev*. 2022;10(3):267–272. https://doi.org/0.32598/jpr.10.3.1018.1.
17. Polivanova T.V., Kasparov E.V., Vshivkov V.A. Indicators of quality of life in schoolchildren with abdominal pain. *Experimental and Clinical Gastroenterology*. 2023;1(209):158–164. (In Russ.). https://doi.org/10.31146/1682-8658-ecg-209-1-158-164. EDN: TLQTGP.

ЛИТЕРАТУРА

1. Новик А.А., Ионова Т.И. Руководство по исследованию качества жизни в медицине. Ю.А. Шевченко, ред. 4-е изд., перераб. и доп. М.: Изд-во НМХЦ им Н.И. Пирогова; 2021.
2. Агрба А.В., Ильдарова А.А., Стеценко М.С. Значение использования опросников качества жизни при оценке эффективности терапии детей с хронической гастродуоденальной патологией. В кн.: Современное животноводство и инновации в технологии производства продуктов питания, аспекты экологической, производственной и гигиенической безопасности. Материалы международной научно-практической конференции. Персиановский, 22 ноября 2024 года. Персиановский: Донской государственный аграрный университет; 2024. С. 472–478. EDN: WFKXUC.
3. Rajmil L., López A.R., López-Aguilà S., Alonso J. Parent-child agreement on health-related quality of life (HRQOL): a longitudinal study. *Health Qual Life Outcomes*. 2013;11:1–10. https:/doi.org/10.1186/1477-7525-11-101.
4. Arsiwala T., Afroz N., Kordy K., Naujoks C., Patalano F. Measuring what matters for children: a systematic review of frequently used pediatric generic PRO instruments. *Ther Innov Regul Sci*. 2021;55(5):1082–1095. https:/doi.org/10.1007/s43441-021-00311-x.
5. Varni J.W., Seid M., Rode C.A. The PedsQL™: measurement model for the pediatric quality of life inventory. *Med Care*.1999;37(2):126–139.
6. Силонян А.Л., Сурков А.Н., Черников В.В. Качество жизни детей с воспалительными заболеваниями кишечника. *Российский педиатрический журнал*. 2021;24(S):55–56. EDN: OMDRWB.
7. Аракелян Л., Сурков А.Н., Намазова-Баранова Л.С. и др. Оценка качества жизни детей с воспалительными заболеваниями кишечника. *University Therapeutic Journal*. 2024;6(S2):9–10. EDN: IAKZIA.
8. Тагирова А.Р. Качество жизни у детей с воспалительными заболеваниями кишечника. Дис. … канд. мед. наук. М.; 2021. 177 с. EDN: PRFIQL.
9. Свидетельство о государственной регистрации программы для ЭВМ № 2024615192 Российская Федерация. Намазова-Баранова Л.С., Сурков А.Н., Бессонов Е.Е. и др. Программа для мониторинга состояния пациентов детского возраста с патологией органов желудочно-кишечного тракта: № 2024613598: заявл. 20.02.2024: опубл. 04.03.2024; заявитель Федеральное государственное бюджетное научное учреждение «Российский научный центр хирургии имени академика Б.В. Петровского». EDN: IKNWLL.
10. Varni J.W., Bendo C.B., Denham J. et al. PedsQL™ Gastrointestinal Symptoms Scales and Gastrointestinal Worry Scales in pediatric patients with functional and organic gastrointestinal diseases in comparison to healthy controls. *Qual Life Res*. 2015;24(2):363–378. https:/doi.org/10.1007/s11136-014-0781-x.
11. Бельмер С.В., Волынец Г.В., Горелов А.В., Гурова М.М., Звягин А.А. и др. Функциональные расстройства органов пищеварения у детей. Рекомендации

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

Общества детских гастроэнтерологов, гепатологов и нутрициологов. Часть 1. Российский вестник перинатологии и педиатрии. 2020;65(4):150–161. https:/doi.org/10.21508/1027-4065-2020-65-4-150-161.
12. Бельмер С.В., Волынец Г.В., Горелов А.В., Гурова М.М., Звягин А.А. и др. Функциональные расстройства органов пищеварения у детей. Рекомендации Общества детских гастроэнтерологов, гепатологов и нутрициологов. Часть 2. Российский вестник перинатологии и педиатрии. 2020;65(5):100–111. https://doi.org/10.21508/1027-4065-2020-65-5-100-111.
13. Бельмер С.В., Волынец Г.В., Горелов А.В., Гурова М.М., Звягин А.А. и др. Функциональные расстройства органов пищеварения у детей. Рекомендации Общество детских гастроэнтерологов, гепатологов и нутрициологов. Часть 3. *Российский вестник перинатологии и педиатрии*. 2020;65(6):133–144. https://doi.org/10.21508/1027-4065-2020-65-6-133-144.
14. Детская гастроэнтерология. Национальное руководство. Бельмер С.В., Разумовский А.Ю., ред. М.: ГЭОТАР-Медиа; 2022. 864 с.
15. Зокиров Н.З., Алиева Э.И., Краснов А.В., Сытьков В.В., Яблокова Е.А. Распространенность функциональных расстройств органов пищеварения с абдоминальной болью у детей в возрасте 8–17 лет: поперечное исследование. *Педиатрическая фармакология*. 2025;22(6):655–662. https://doi.org/10.15690/pf.v22i6.2991.
16. Karami H., Charati J.Ya., Aghaee B.L. et al. Quality of life for children with functional abdominal pain and their parents copmared to healthy individuals. *J Ped Rev*. 2022;10(3):267–272. https://doi.org/0.32598/jpr.10.3.1018.1.
17. Поливанова Т.В., Каспаров Э.В., Вшивков В.А. Показатели качества жизни школьников с болями в животе. *Экспериментальная и клиническая гастроэнтерология*. 2023;1(209):158–164. https://doi.org/10.31146/1682-8658-ecg-209-1-158-164. EDN: TLQTGP.

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Prevalence of gastroesophageal reflux disease symptoms in school-age children

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ABSTRACT. ***Introduction.*** The Montreal Consensus Meeting defined gastroesophageal reflux disease as a condition that develops when reflux of gastric contents causes bothersome symptoms and/or complications. The global prevalence of gastroesophageal reflux disease is 13.3% and continues to increase. Data on the prevalence of gastroesophageal reflux disease in the pediatric population are significantly scarcer. Study. ***Aim*** – to study the prevalence of gastroesophageal reflux disease symptoms in school-aged children using the Gerd-Q questionnaire. ***Materials and methods.*** A study was conducted to assess the prevalence of gastroesophageal reflux disease symptoms among schoolchildren in Barnaul. The study included 291 schoolchildren, including 131 boys (45.0%) and 160 girls (55.0%), studying in grades 7–11 of comprehensive schools. The validated Gerd-Q questionnaire was used to quantitatively assess the prevalence of gastroesophageal reflux disease symptoms in the pediatric population. The statistical significance of differences in qualitative characteristics was assessed using the Pearson χ^2 goodness-of-fit test. Differences at $p < 0.05$ were considered significant. ***Results.*** According to a study of gastroesophageal reflux disease symptoms conducted using the Gerd-Q questionnaire, the prevalence of gastroesophageal reflux disease in school-aged children was 8.2%. Heartburn and regurgitation, with a frequency of at least once a week, were reported by 19.6% and 35.7% of schoolchildren, respectively. Nocturnal gastroesophageal reflux disease symptoms were observed in 2.7% of schoolchildren. Periodic self-administration of antacids to relieve symptoms was used by 4.1% of those surveyed. ***Conclusion.*** The use of the Gerd-Q questionnaire allows to improve the frequency of detection of gastroesophageal reflux disease symptoms, and the most frequent, among school-age children, is determined by heartburn, which bothers boys predominantly.

KEYWORDS: *gastroesophageal reflux disease, children, Gerd-Q questionnaire*

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Распространенность симптомов гастроэзофагеальной рефлюксной болезни у детей школьного возраста

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РЕЗЮМЕ. ***Введение.*** Монреальское консенсусное совещание определило гастроэзофагеальную рефлюксную болезнь как состояние, развивающееся, когда рефлюкс содержимого желудка вызывает беспокоящие симптомы и/или осложнения. Общемировая распространенность гастроэзофагеальной рефлюксной болезни составляет 13,3% и продолжает расти. Данных о распространенности гастроэзофагеальной рефлюксной болезни в педиатрической популяции значительно меньше. ***Цель исследования*** – установить распространенность симптомов гастроэзофагеальной рефлюксной болезни у детей школьного возраста с помощью опросника Gerd-Q. ***Материалы и методы.*** Проведено исследование распространенности симптомов гастроэзофагеальной рефлюксной болезни среди школьников города Барнаула. В исследование включен 291 школьник, из них 131 мальчик (45,0%) и 160 девочек (55,0%), учащиеся 7–11 классов общеобразовательных учреждений. Для количественной оценки распространенности симптомов гастроэзофагеальной рефлюксной болезни в детской популяции применяли валидированный опросник Gerd-Q. Статистическая значимость различий качественных признаков оценивалась с использованием критерия согласия χ^2 Пирсона. Различия при $p < 0,05$ расценивали как значимые. ***Результаты.*** По данным исследования симптомов гастроэзофагеальной рефлюксной болезни, проведенного с применением анкеты Gerd-Q, распространенность гастроэзофагеальной рефлюксной болезни у детей школьного возраста составила 8,2%. Жалобы на изжогу и регургитацию с частотой не менее 1 раза в неделю предъявляли 19,6 и 35,7% школьников. Ночные симптомы гастроэзофагеальной рефлюксной болезни отмечались у 2,7% школьников. К периодическому самостоятельному приему антацидов для купирования симптомов прибегали 4,1% обследованных. ***Заключение.*** Использование анкеты Gerd-Q позволяет увеличить частоту выявления симптомов гастроэзофагеальной рефлюксной болезни, причем наиболее частым среди симптомов определяется изжога, которая беспокоит преимущественно мальчиков.

КЛЮЧЕВЫЕ СЛОВА: *гастроэзофагеальная рефлюксная болезнь, дети, анкета Gerd-Q*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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INTRODUCTION

The Montreal Consensus Meeting defined gastroesophageal reflux disease (GERD) as a condition that develops when reflux of stomach contents causes bothersome symptoms and/or complications. Common esophageal signs and symptoms include peptic stricture, esophageal ulcer, Barrett's esophagus, esophageal adenocarcinoma, retrosternal pain, heartburn, regurgitation, and dysphagia [1, 2]. The prevalence of GERD among the adult population is high and continues to rise. The highest prevalence of GERD symptoms was observed in a single study in Central America (19.6%), while the lowest was in Asia (10.0%; 23 studies), particularly in Southeast Asia (7.4%; 18 studies) [3]. The global prevalence of GERD is 13.3% (95% CI 12.0–14.6) [3]. The prevalence is higher among individuals over 50 years of age (OR 1.32; 95% CI 1.12–1.54) [4].

There is significantly less data on the prevalence of GERD in the pediatric population [5]. According to the results of some studies, the prevalence of GERD symptoms among school-aged children and adolescents may be comparable to that in adults. For example, the prevalence of heartburn in the "weekly" category among adolescents, according to data from Novosibirsk authors for 2009, was 6.9% among boys, 4.4% among girls, and 5.5% overall [6]. The prevalence of troublesome heartburn in the school-age population of Krasnoyarsk was reported as 10.4% in one study; other GERD symptoms—a sensation of acidity and/or bitterness in the throat, regurgitation, and difficulty swallowing — were observed less frequently and were associated with heartburn in most patients; heartburn was reported 1.4 times more often in boys than in girls, and 1.6 times more often in older schoolchildren than in younger schoolchildren [7]. According to other data, 21.3% of schoolchildren experienced heartburn at least once in the past year. Heartburn was significantly more common among boys than among girls. The prevalence of heartburn was 26.2% among older school-aged children and 14.3% among younger school-aged children. Weekly heartburn was reported in 2.7% of children [8]. In a survey of older children and adolescents, the frequency of typical subjective manifestations of GERD was 19.4% (95% CI 17.7–21.1%); sour belching was the most common symptom (in 8.2% (95% CI 7.0–9.4) of the examined children and adolescents, heartburn (in 7.4% (95% CI 6.3–8.6) of respondents), and regurgitation (in 7.3% (95% CI 6.2–8.4) [9]. In a survey of 55 adolescents in the Republic of Belarus, clinical symptoms of GERD of varying duration were identified in 65% (95% CI 51.4–77.8) of the 17-year-old adolescents surveyed. Based on diagnostic clinical criteria, GERD was diagnosed in 3.6% of cases (95% CI 0.4–12.5) [10].

When planning a survey, the choice of questionnaire is crucial. One of the tools used to diagnose GERD is the GERD-Q questionnaire. In adult patients, the GERD-Q questionnaire has a sensitivity of 65.4% and a specificity of 91.7% [11]. Another study showed that the most satisfactory results for detecting erosive esophagitis in school-aged children were obtained using the GERD-Q questionnaire with a cutoff score of 8; in this case, sensitivity and specificity were 64.1% and 82.9%, respectively [12]. The prevalence of GERD can also be studied based on endoscopic findings. In 2008, a large-scale study was conducted involving 7,188 children and adolescents under the age of 17 (mean age 12.7±4.9 years); erosive esophagitis was detected in 12.4% of them. Its prevalence increased with age, reaching 19.6% by age 17 [13]. In another study, during fibrogastroscopy of 2,935 children with symptoms of dyspepsia aged 7 to 18 years, changes consistent with epithelialized esophageal erosions were detected in 20.2%, and non-epithelialized erosions in an additional 7.6% of children. Among patients with erosive esophagitis across all age groups, stage A according to the Los Angeles classification was predominant — 67.1% of children, stage B — 28.4%, stage C in only 3.5% of those examined; erosive changes in the esophagus were more common in boys, and the proportion of children with erosive esophagitis was similar across all age groups from 7 to 18 years [14].

Thus, the data on the prevalence of GERD in children are inconclusive and require further research in this area.

AIM

To investigate the prevalence of symptoms of gastroesophageal reflux disease in school-aged children using the GERD-Q questionnaire.

MATERIALS AND METHODS

A study was conducted on the prevalence of GERD symptoms among schoolchildren in Barnaul. Surveys

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were conducted in each of the four administrative districts. In each district, a school and a class were selected by random draw. A total of 400 questionnaires were distributed; of these, 109 were incomplete or incorrectly filled out and were therefore excluded from the study. Thus, the analysis included data from 291 schoolchildren, of whom 131 were boys (45.0%) and 160 were girls (55.0%), students in grades 7–11 of general education institutions. The mean age of the surveyed children was 15.3±1.25 years. The inclusion criteria for the study were:

- school-age;
- enrollment in a general education school;
- the presence of informed voluntary consent for children's participation in the study.

To quantitatively assess the prevalence of GERD symptoms in the pediatric population, the validated GERD-Q questionnaire (Russian-language version) was used. It is based on six indicators: "heartburn," "regurgitation," "pain," "nausea," "nocturnal GERD symptoms," and "use of medications to relieve heartburn." A score of 8 points or more serves as the basis for a diagnosis of GERD. The statistical significance of differences in qualitative characteristics was assessed using Pearson's χ^2 test. Differences at $p < 0.05$ were considered significant.

RESULTS

According to international consensus and Russian clinical guidelines, the main clinical manifestations of GERD are heartburn and regurgitation. When evaluating the survey results, 57 out of 291 (19.6%) school-aged children experienced heartburn, with an equal frequency among boys—24 out of 131 (18.3%) — and girls — 33 out of 160 (20.6%), p=0.623. Heartburn occurring at least once a week was reported by 43 out of 291 (14.8%) respondents, with 17 out of 131 (13.0%) boys and 26 out of 160 (16.3%) girls, p=0.434. Complaints of heartburn occurring 2–3 times a week were reported by a significantly smaller number of children: 13/291 (4.5%), 6/131 (4.6%) among boys, and 7/160 (4.4%) among girls, p=0.933. Frequent heartburn 4–7 times a week was observed in only one boy — 1/291 (0.3%). The data are presented in Table 1.

Complaints of regurgitation were reported by 104/291 (35.7%) of the examined schoolchildren, which is nearly twice as common as heartburn. Boys reported this symptom slightly more often — 54/131 (41.2%) — than girls — 50/160 (31.3%), p=0.078. Regurgitation at least once a week was experienced by 76/291 (26.1%) children; boys also reported it slightly more often — 40/131 (30.5%) — than girls — 36/160 (22.5%), p=0.121. Regurgitation 2–3 times a week was reported by 21/291 (7.2%) schoolchildren, with boys accounting for 12/131 (9.2%) and girls for 9/160 (5.6%), p=0.247. Complaints of frequent regurgitation were reported by 7/291 (2.4%) children, girls — 5/160 (3.1%), boys — 2/131 (1.5%), p=0.376. The results are presented in Table 2.

Less prominent symptoms of GERD include abdominal pain and nausea, as reflected in the GERD-Q questionnaire scoring. The total number of children reporting abdominal pain was 98/291 (33.7%); girls reported it significantly more often — 68/160 (42.5%) — than boys — 30/131 (22.9%), p <0.001. At least once a week, 66 out of 291 (22.7%) children experienced abdominal pain, with girls accounting

Table 1. Proportion of schoolchildren complaining of heartburn

Таблица 1. Доля школьников, предъявляющих жалобы на изжогу

Пациенты Patients	Проявление симптома Symptom manifestation			
	симптом отсутствует there is no symptom	1 раз в неделю once a week	2–3 раза в неделю 2–3 times a week	4–7 раз в неделю 4–7 times a week
Мальчики Boys (n=131)	107/131 (81,7%)	17/131 (13,0%)	6/131 (4,6%)	1/131 (0,8%)
Девочки Girls (n=160)	127/160 (79,4%)	26/160 (16,3%)	7/160 (4,4%)	0/160 (0,0%)
Всего Total	234/291 (80,4%)	43/291 (14,8%)	13/291 (4,5%)	1/291 (0,3%)
p_{1-2}	0,623	0,434	0,933	0,269

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Таблица составлена авторами по собственным данным

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Table 2. Proportion of schoolchildren complaining about regurgitation

Таблица 2. Доля школьников, предъявляющих жалобы на регургитацию

Пациенты Patients	Проявление симптома Symptom manifestation			
	симптом отсутствует there is no symptom	1 раз в неделю once a week	2–3 раза в неделю 2–3 times a week	4–7 раз в неделю 4–7 times a week
Мальчики Boys (n=131)	77/131 (58,8%)	40/131 (30,5%)	12/131 (9,2%)	2/131 (1,5%)
Девочки Girls (n=160)	110/160 (68,8%)	36/160 (22,5%)	9/160 (5,6%)	5/160 (3,1%)
Всего Total (n=291)	187/291 (64,3%)	76/291 (26,1%)	21/291 (7,2%)	7/291 (2,4%)
p_{1-2}	0,078	0,121	0,247	0,376

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Таблица составлена авторами по собственным данным

Table 3. Frequency of abdominal pain syndrome in school-age children

Таблица 3. Частота абдоминального болевого синдрома у детей школьного возраста

Пациенты Patients	Проявление симптома Symptom manifestation			
	симптом отсутствует there is no symptom	1 раз в неделю once a week	2–3 раза в неделю 2–3 times a week	4–7 раз в неделю 4–7 times a week
Мальчики Boys (n=130)	101/131 (77,1%)	21/131 (16,0%)	7/131 (5,3%)	2/131 (1,5%)
Девочки Girls (n=160)	92/160 (57,5%)	45/160 (28,1%)	18/160 (11,3%)	5/160 (3,1%)
Всего Total	193/291 (66,3%)	66/291 (22,7%)	25/291 (8,6%)	7/291 (2,4%)
p_{1-2}	<0,001	0,015	p=0,074	0,376

The table is prepared by the authors using their own data

Таблица составлена авторами по собственным данным

Table 4. Proportion of schoolchildren complaining of nausea

Таблица 4. Доля школьников, предъявляющих жалобы на тошноту

Пациенты Patients	Проявление симптома Symptom manifestation			
	симптом отсутствует there is no symptom	1 раз в неделю once a week	2–3 раза в неделю 2–3 times a week	4–7 раз в неделю 4–7 times a week
Мальчики Boys (n=130)	98/131 (74,8%)	25/131 (19,1%)	6/131 (4,6%)	2/131 (1,5%)
Девочки Girls (n=160)	86/160 (53,8%)	39/160 (24,4%)	28/160 (17,5%)	8/160 (5,0%)
Всего Total	184/291 (63,2%)	64/291 (22,0%)	34/291 (11,7%)	10/291 (3,4%)
p_{1-2}	<0,001	0,279	<0,001	0,123

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for 45 out of 160 (28.1%), which was also significantly more common than in boys – 21 out of 131 (16.0%), p=0.015. Abdominal pain was observed in 25/291 (8.6%) children 2–3 times a week; it was also slightly more common in girls – 18/160 (11.3%) – than in boys – 7/131 (5.3%), p=0.074. Frequent abdominal pain was noted in only 7/291 (2.4%) of those examined, with equal frequency among boys – 2/131 (1.5%) – and girls – 5/160 (3.1%), p=0.376. The results are presented in Table 3.

The total number of children who reported nausea was 107 out of 291 (36.8%), with a higher proportion of girls – 74 out of 160 (46.3%) – than boys – 33 out of 131 (25.2%) – p <0.001. At least once a week, 64 out of 291 (22.0%) schoolchildren reported nausea, with an equal frequency among boys – 25 out of 131 (19.1%) – and girls – 39 out of 160 (24.4%), p=0.279. More frequent episodes of nausea (2–3 times a week) were reported by 34/291 (11.7%) respondents, with girls reporting it significantly more often – 28/160 (17.5%) – than boys – 6/131 (4.6%), p <0.001. A small number of schoolchildren – 10/291 (3.4%) – reported frequent episodes of nausea, occurring 4–7 times a week; among girls – 8/160 (5.0%), among boys – 2/131 (1.5%), p=0.123. The data are presented in Table 4.

In addition, to more accurately assess the likelihood of gastroesophageal reflux disease, the GERD-Q questionnaire includes an assessment of nocturnal symptoms of the disease and the frequency of self-administration of antacids and other medications to relieve heartburn. Nocturnal GERD symptoms in children were noted in only 8/291 (2.7%) children, with equal frequency among boys – 4/131 (3.1%) – and girls – 4/160 (2.5%), p=0.774. At least once a week, 5 out of 291 (1.7%)

Table 5. Frequency of nocturnal symptoms of gastroesophageal reflux disease in school-age children

Таблица 5. Частота ночных симптомов гастроэзофагеальной рефлюксной болезни у детей школьного возраста

Пациенты Patients	Проявление симптома Symptom manifestation			
	симптом отсутствует there is no symptom	1 раз в неделю once a week	2–3 раза в неделю 2–3 times a week	4–7 раз в неделю 4–7 times a week
Мальчики Boys (n=131)	127/131 (96,9%)	3/131 (2,3%)	0/131 (0,0%)	1/131 (0,8%)
Девочки Girls (n=160)	156/160 (97,5%)	3/160 (1,9%)	2/160 (1,3%)	0/160 (0,0%)
Всего Total	283/291 (97,3%)	5/291 (1,7%)	2/291 (0,7%)	1/291 (0,3%)
p_{1-2}	0,774	0,805	0,200	0,269

The table is prepared by the authors using their own data

Таблица составлена авторами по собственным данным

Table 6. Proportion of schoolchildren with heartburn taking antacid medication

Таблица 6. Доля школьников с изжогой, принимающих антацидные препараты

Пациенты Patients	Проявление симптома Symptom manifestation			
	нет no	1 раз в неделю once a week	2–3 раза в неделю 2–3 times a week	4–7 раз в неделю 4–7 times a week
Мальчики Boys (n=131)	127/131 (96,9%)	2/131 (1,5%)	1/131 (0,8%)	1/131 (0,8%)
Девочки Girls (n=160)	152/160 (95%)	3/160 (1,9%)	4/160 (2,5%)	1/160 (0,6%)
Всего Total	279/291 (95,9%)	5/291 (1,7%)	5/291 (1,7%)	2/291 (0,7%)
p_{1-2}	0,407	0,821	0,257	0,887

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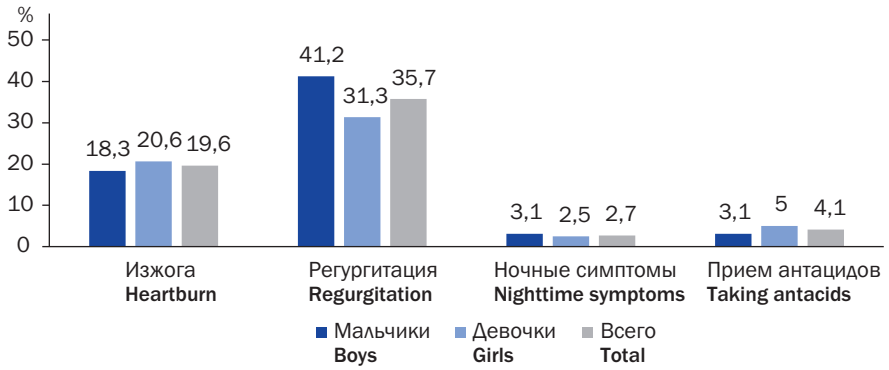

Fig. 1. Symptoms of gastroesophageal reflux disease in school-age children (%) (the figure is prepared by the authors)

Рис. 1. Симптомы гастроэзофагеальной рефлюксной болезни у детей школьного возраста (%) (рисунок подготовлен авторами)

Table 7. The proportion of children who scored eight or more points according to the Gerd-Q

Таблица 7. Доля детей, набравших по данным анкеты Gerd-Q 8 баллов и более

Показатель Indicator	<8 баллов <8 points	≥8 баллов ≥8 points
Мальчики Boys (n=131)	117/131 (89,3%)	14/131 (10,7%)
Девочки Girls (n=160)	150/160 (93,5%)	10/160 (6,5%)
Всего Total	267/291 (91,8%)	24/291 (8,2%)
p_{1-2}	0,172	

The table is prepared by the authors using their own data

Таблица составлена авторами по собственным данным

schoolchildren experienced nighttime symptoms. Periodic nighttime symptoms 2–3 times a week were reported in 2 out of 291 (0.7%) of the surveyed children. Frequent nocturnal symptoms 4–7 times a week were observed in only 1/291 (0.3%) child. No gender differences were found. The results are presented in Table 5.

The total number of children who occasionally took antacids was 12 out of 291 (4.1%), with an equal frequency among girls (8 out of 160, 5%) and boys (4 out of 131, 3.1%); p=0.407 (Fig. 1). Among the surveyed schoolchildren who took the medications at least once a week, there were 5/291 (1.7%) children, 2/131 (1.5%) boys, and 3/160 (1.9%) girls, p=0.821. Periodic use of antacids 2–3 times a week was reported by 5/291 (1.7%) of the respondents, 4/160 (2.5%) of whom were girls and 1/131 (0.8%) of whom were boys, p=0.257. Frequent use of antacids was observed in only 2/291 (0.7%) of respondents. The data are presented in Table 6.

A total score of 8 or higher on the questionnaire indicates a high probability of GERD. The proportion of schoolchildren who scored 8 points or more was 24/291 (8.2%), with 14/131 (10.7%) boys and 10/160 (6.59%) girls, p=0.172. The data are presented in Table 7.

DISCUSSION

The study found that 8.2% of school-aged children scored 8 points or higher on the GERD-Q questionnaire; 10.7% of boys and 6.5% of girls. This is slightly lower than in the adult population [1, 2], but higher than in one pediatric study [10]. The prevalence of individual GERD symptoms among schoolchildren was higher. Thus, 19.6% of those examined reported heartburn, 14.8% experienced heartburn episodes once a week, and in the remaining 4.8% of cases, 2 to 7 times a week. This is somewhat more frequent than in other studies, where the prevalence of weekly or troublesome heartburn among adolescents ranged from 2.7% to 10% [6, 7, 9]. At the same time, up to 21.3% of schoolchildren may experience less frequent

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episodes of heartburn (less than once a week) [8]. Unlike other pediatric studies, heartburn was reported with equal frequency among boys and girls. Regurgitation was observed significantly more frequently than heartburn—in 35.7% of those examined (also with equal frequency among boys and girls) — which is significantly more common than in other studies [9, 10]. As with heartburn, episodes of regurgitation occurring no more than once a week were most common, observed in 26.1% of the children examined. Nocturnal GERD symptoms, indicative of a more severe course of the disease, were observed in 2.7% of schoolchildren. 4.1% of the examined children resorted to periodically taking antacids on their own to relieve GERD symptoms.

CONCLUSION

Thus, the use of the GERD-Q questionnaire improves the detection rate of GERD symptoms, with heartburn being the most common symptom among school-aged children, affecting boys in particular.

ADDITIONAL INFORMATION

Authors'contribution. D.Yu. Latyshev, M.D. Lider, N.A. Tekutyeva — literature search, writing the draft of the article, descriptive part, data collection, correspondence with the editorial board; Yu.F. Lobanov, E.V. Skudarnov — scientific supervision, making comments on the draft version of the article, approval of the final version; V.S. Ponomaryov, I.Yu. Boldenkova — formal analysis, concept and conceptualization.

All authors made a substantial contribution to the acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Д.Ю. Латышев, М.Д. Лидер, Н.А. Текутьева — поиск литературы, написание черновика статьи, описательная часть, набор данных, переписка с редакцией журнала; Ю.Ф. Лобанов, Е.В. Скударнов — научное руководство, внесение замечаний в черновой вариант статьи, утверждение итоговой версии; В.С. Пономарёв, И.Ю. Болденкова — формальный анализ, концепция и концептуализация.

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REFERENCES

1. Vakil N., van Zanten S.V., Kahrilas P., Dent J., Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol*. 2006;101(8):1900–1920. https://doi.org/10.1111/j.1572-0241.2006.00630.x.
2. Ivashkin V.T., Maev I.V., Trukhmanov A.S., Lapina T.L., Storonova O.A., Zayratyants O.V. et al. Recommendations of the Russian Gastroenterological Association in Diagnosis and Treatment of Gastroesophageal Reflux Disease. *Russian Journal of Gastroenterology, Hepatology, Coloproctology*. 2020;30(4):70–97. (In Russ.). https://doi.org/10.22416/1382-4376-2020-30-4-70-97.
3. Fass R., Boeckxstaens G.E., El-Serag H. et al. Gastroesophageal reflux disease. *Nat Rev Dis Primers*. 2021;7(1):55. https://doi.org/10.1038/s41572-021-00287-w.
4. Eusebi L.H., Ratnakumaran R., Yuan Y., Solaymani-Dodaran M., Bazzoli F., Ford A.C. Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis. *Gut*. 2018;67(3):430–440. https://doi.org/10.1136/gutjnl-2016-313589.
5. El-Serag H.B., Sweet S., Winchester C.C., Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut*. 2014;63(6):871–880. https://doi.org/10.1136/gutjnl-2012-304269.
6. Reshetnikov O.V., Kurilovich S.A., Denisova D.V., Krotov S.A. Prevalence and risk factors of gerd in adoles-

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

cents in novosibirsk: ten-year trends. *Experimental and Clinical Gastroenterology*. 2016;(9):54–57. (In Russ.)
7. Vasyutin A.V., Tonkikh Yu.L., Tsukanov V.V. Crossover of heartburn and dyspepsia in school-age children. *Doctor.Ru*. 2022;21(7):52–55. (In Russ.). https://doi.org/10.31550/1727-2378-2022-21-7-52-55.
8. Vasyutin A.V., Tsukanov V.V., Kasparov E.V., Tonkikh Yu.L., Bronnikova E.P. The Influence of family Predisposition to heartburn in children. *Pharmateca*. 2016;(1):62–64. (In Russ.).
9. Zagorskiy S.E. Frequency of typical symptoms of gastroesophageal reflux disease in older children and adolescents in the Republic of Belarus, living in different urban conditions. *Practical Medicine*. 2013;6(75):119–121. (In Russ.).
10. Karchevsky A.A., Semukha A.R., Khvoynitskaya A.A., Yakovleva O.A. Assessment of the frequency of clinical symptoms of gastroesophageal reflux disease in children. Actual problems of medicine. Collection of materials of the final scientific and practical conference. S.B. Wolf, ed. Grodno: Grodno State Medical University; 2022. P. 117–120. (In Russ.).
11. Kaybysheva V.O., Trukhmanov A.S., Ivashkin V.T. Discussion of gastroesophageal reflux disease issue in World gastroenterological congress abstracts (Shanghai, 2013). Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2014;24(3):22–27. (In Russ.).
12. Latyshev D.Yu., Lobanov Yu.F., Strozenko L.A., Tekutyeva N.A., Orekhova A.K., Martirosyan M.S., Boldenkova I.Yu. Experience of using the GERD-Q questionnaire in the diagnosis of gastroesophageal reflux disease in pediatric practice. *Bulletin of Medical Science*. 2022;(3(27)):44–48. (In Russ.).
13. Gilger M.A., El-Serag H.B., Gold B.D. et al. Prevalence of endoscopic findings of erosive esophagitis in children: a population-based study. *J Pediatr Gastroenterol Nutr*. 2008;47(2):141–146. https://doi.org/10.1097/MPG.0b013e31815eeabe.
14. Latyshev D.Yu., Lobanov Yu.F., Strozenko L.A. Esophageal lesions in children with symptoms of dyspepsia. *Russian Pediatric Journal*. 2024;27(1):44–48. (In Russ.). https://doi.org/10.46563/1560-9561-2024-27-1-44-48.

ЛИТЕРАТУРА

1. Vakil N., van Zanten S.V., Kahrilas P., Dent J., Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol.* 2006;101(8):1900–1920. https://doi.org/10.1111/j.1572-0241.2006.00630.x.
2. Ивашкин В.Т., Маев И.В., Трухманов А.С., Лапина Т.Л., Сторонова О.А., Зайратьянц О.В. и др. Рекомендации Российской гастроэнтерологической ассоциации по диагностике и лечению гастроэзофагеальной рефлюксной болезни. *Российский журнал гастроэнтерологии, гепатологии, колопроктологии*. 2020;30(4):70–97. https://doi.org/10.22416/1382-4376-2020-30-4-70-97
3. Fass R., Boeckxstaens G.E., El-Serag H. et al. Gastroesophageal reflux disease. *Nat Rev Dis Primers*. 2021;7(1):55. https://doi.org/10.1038/s41572-021-00287-w.
4. Eusebi L.H., Ratnakumaran R., Yuan Y., Solaymani-Dodaran M., Bazzoli F., Ford A.C. Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis. *Gut*. 2018;67(3):430–440. https://doi.org/10.1136/gutjnl-2016-313589.
5. El-Serag H.B., Sweet S., Winchester C.C., Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut*. 2014;63(6):871–880. https://doi.org/10.1136/gutjnl-2012-304269.
6. Решетников О.В., Курилович С.А., Денисова Д.В., Кротов С.А. Распространенность и факторы риска ГЭРБ у подростков г. Новосибирска: десятилетние тренды. *Экспериментальная и клиническая гастроэнтерология*. 2016;(9):54–57.
7. Васютин А.В., Тонких Ю.Л., Цуканов В.В. Перекрест изжоги и диспепсии у детей школьного возраста. *Доктор.Ру*. 2022;21(7):52–55. https://doi.org/10.31550/1727-2378-2022-21-7-52-55.
8. Васютин А.В., Цуканов В.В., Каспаров Э.В., Тонких Ю.Л., Бронникова Е.П. Влияние семейной предрасположенности к возникновению изжоги у детей. *Фарматека.* 2016;(1):62–64.
9. Загорский С.Э. Частота типичных симптомов гастроэзофагеальной рефлюксной болезни у детей старшего возраста и подростков Республики Беларусь, проживающих в различных условиях урбанизации. *Практическая медицина*. 2013;6(75):119–121.
10. Карчевский А.А., Сёмуха А.Р., Хвойницкая А.А., Яковлева О.А. Оценка частоты клинических симптомов гастроэзофагеальной рефлюксной болезни у детей. Актуальные проблемы медицины. Сборник материалов итоговой научно-практической конференции. С.Б. Вольф, отв. ред. Гродно: Гродненский государственный медицинский университет; 2022. С. 117–120.
11. Кайбышева В.О., Трухманов А.С., Ивашкин В.Т. Обсуждение проблемы гастроэзофагеальной рефлюксной болезни в материалах Всемирного гастроэнтерологического конгресса (Шанхай, 2013). *Российский журнал гастроэнтерологии, гепатологии, колопроктологии*. 2014;24(3):22–27.
12. Латышев Д.Ю., Лобанов Ю.Ф., Строзенко Л.А., Текутьева Н.А., Орехова А.К., Мартиросян М.С., Болден-

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кова И.Ю. Опыт применения анкеты GERD-Q в диагностике гастроэзофагеальной рефлюксной болезни в педиатрической практике. *Бюллетень медицинской науки*. 2022;(3(27)):44–48.
13. Gilger M.A., El-Serag H.B., Gold B.D. et al. Prevalence of endoscopic findings of erosive esophagitis in children: a population-based study. *J Pediatr Gastroenterol Nutr*. 2008;47(2):141–146. https://doi.org/10.1097/MPG.0b013e31815eeabe.
14. Латышев Д.Ю., Лобанов Ю.Ф., Строзенко Л.А. Поражения пищевода у детей с симптомами диспепсии. *Российский педиатрический журнал*. 2024;27(1):44–48. https://doi.org/10.46563/1560-9561-2024-27-1-44-48.

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Current problems of nutrition in children with organic diseases of the central nervous system and possible solutions

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ABSTRACT. ***Introduction.*** The nutritional status of children with cerebral palsy has been described repeatedly, while children with severe organic damage to the central nervous system have similar changes. ***The aim*** — to determine the frequency of nutritional deficiency and possible ways of correction in children, pupils of the mercy department of the orphanage for the disabled. ***Materials and methods.*** The design of a single-center retrospective cohort study assessed the physical development and nutritional status of 113 mercy ward students with severe organic damage to the central nervous system from 4 to 18 years of age. ***Results.*** The study included equal proportions of children with cerebral palsy (n=38) and spastic tetraparesis (n=39). The study involved children fed through a gastrostomy tube, 33 of whom had cerebral palsy and three with organic central nervous system damage. Most children included in the study (n=56; 49.5%) had spastic tetraparesis, GMFCS level 5 of motor activity. According to the GMFCS scale, level 4 was diagnosed in 3 people (2.5%), and 1 child each with mobility at the GMFCS 2 and GMFCS 3 levels. Other variants of cerebral palsy included paraplegia and hemiplegia, ataxic-hyperkinetic and mixed variants. Children with cerebral palsy also had pronounced motor impairments. A third of the entire sample of children (n=36) had severe malnutrition, another third had mild and moderate severe malnutrition (n=37), satisfactory nutritional status was diagnosed in 35 children, obesity in 5. Growth retardation of varying degrees of severity was noted in 17 children. ***Conclusions.*** There is a cohort of children who, due to severe organic disorders, have significant, difficult-to-correct nutritional deficiencies. Nutrition for children with severe neurological pathology requires the work of a multidisciplinary team of highly qualified specialists (pediatrician, nutritionist, gastroenterologist, speech therapist, pulmonologist, clinical pharmacologist, kinesiologist, and occupational therapist).

KEYWORDS: *children, organic damage to the central nervous system, nutritional status, enteral nutrition, gastrostomy*

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Актуальные проблемы питания детей с органическим поражением центральной нервной системы и возможные пути решения

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РЕЗЮМЕ. ***Введение.*** Статус питания детей с детским церебральным параличом описан неоднократно, при этом дети с тяжелым органическим поражением центральной нервной системы имеют схожие изменения. ***Цель*** — определить частоту развития нутритивного дефицита и возможные пути его коррекции у детей — воспитанников отделения милосердия детского дома-интерната инвалидов. ***Материалы и методы.*** В дизайне одноцентрового ретроспективного когортного исследования оценено физическое развитие и нутритивный статус 113 воспитанников отделения милосердия с тяжелыми проявлениями органического поражения центральной нервной системы от 4 до 18 лет, преобладали дети подросткового и юношеского возраста. ***Результаты.*** В исследовании в равных долях присутствовали дети с органическим поражением центральной нервной системы (n=38) и детским церебральным параличом (n=39). В исследовании приняли участие дети, питающиеся через гастростому, из которых 33 имели детский церебральный паралич, а трое — органическое поражение центральной нервной системы. Большинство (n=56; 49,5%) характеризовались спастическим тетрапарезом с уровнем мобильности GMFCS 5, у троих (2,5%) отмечен уровень GMFCS 4, и по одному ребенку — с уровнями GMFCS 2 и GMFCS 3. Среди других вариантов детского церебрального паралича отмечены пара- и гемиплегии, атаксически-гиперкинетические и смешанные варианты. Дети с органическим поражением центральной нервной системы также имели выраженные двигательные нарушения. Треть всей выборки детей (n=36) имели тяжелую белково-энергетическую недостаточность, другая треть — легкую и умеренную белково-энергетическую недостаточность (n=37), удовлетворительный нутритивный статус диагностирован у 35 детей, ожирение у 5. Задержка роста разной степени выраженности отмечена у 17 детей. ***Выводы.*** Существует когорта детей, которые в силу своих тяжелых органических нарушений имеют значительные, трудно поддающиеся коррекции нарушения питания. Питание детей с тяжелой неврологической патологией требует работы мультидисциплинарной команды специалистов высокой квалификации (педиатр, диетолог, гастроэнтеролог, логопед, пульмонолог, клинический фармаколог, кинезиолог, эрготерапевт).

КЛЮЧЕВЫЕ СЛОВА: *дети, органическое поражение центральной нервной системы, нутритивный статус, энтеральное питание, гастростома*

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INTRODUCTION

Organic central nervous system disorders (OCNSD) is a collective term that encompasses a group of conditions, the most common of which are cerebral palsy (CP), congenital malformations (hydrocephalus, *spina bifida*, genetic abnormalities), and the consequences of perinatal hypoxia (congenital infections, toxic and mechanical factors, severe neonatal jaundice) [1–5]. In the current International Classification of Diseases (ICD-10), the term "organic lesion of the central nervous system" is coded under F06–F09 "Mental disorders due to brain injury or somatic disease," as well as G90–G99 "Other disorders of the nervous system." In clinical practice, specific diagnoses are used (e.g., "consequences of perinatal hypoxic-ischemic CNS damage," "symptomatic epilepsy," etc.). Statistical data worldwide are collected according to specific nosologies. Thus, the prevalence of cerebral palsy in developed countries and the Russian Federation (RF) is 2–3.5 per 1,000 live births [1–7].

In developed countries and the Russian Federation, the incidence of severe central nervous system (CNS) disorders has remained relatively stable over the past 20–30 years. The incidence of birth defects is declining due to preventive measures (folic acid supplementation, improved perinatal and neonatal screening). At the same time, with improved survival rates among extremely preterm infants, some of them develop CNS malformations due to genetic abnormalities or other perinatal causes [2, 7, 8]. According to Rosstat data, as of 2023, approximately 15,000–18,000 children with intellectual disabilities—most often severe or profound — reside in residential care facilities within the Russian Federation's social protection system; these disabilities are primarily caused by organic damage to the central nervous system[1]. Dysphagia[2] [9, 10], motor impairments [1, 10–12], an inability to communicate [12], and dependence on external care [13] create conditions conducive to the development of malnutrition [14–16].

The prevalence of nutritional deficiencies among children with severe neurological disorders ranges from 30% to 70%, depending on the child's age, the specific condition, and its severity, and represents a central challenge in the management of such patients[3] [10, 12, 14].Scientific data clearly indicate that protein-energy malnutrition is a significant independent factor that shortens the life expectancy of children with severe neurological disorders [17–21].

AIM

To determine the prevalence of nutritional deficiencies and possible ways to address them among children in the special care unit of a residential care home for children with disabilities.

MATERIALS AND METHODS

This single-center retrospective cohort study evaluated the physical development and nutritional status of 119 children aged 4 to 18 years with severe manifestations of cerebral palsy who were residents of a special care facility.

Somatometric measurements (height, weight) of low-mobility patients with pronounced body deformities, intellectual disability, and severe behavioral disorders sometimes present certain difficulties and can significantly distort the actual picture [22–28]. For children with severe motor impairments, a segmental method of measuring height based on lower leg length was used (Table 1) [26, 27, 29].

Estimated height was calculated using the provided formulas based on age, and during puberty, based on sex. Measurement errors could reach 1.5 cm [27, 29].

The children's body weight was measured using electronic floor scales, which were calibrated before each measurement. Children who were unable to stand were weighed using the tare method [27, 29] while held by staff, with the weight of the person weighing them subtracted. The frequency of measurements varied depending on the feeding method: once every 3 months for orally fed children; once a month for children receiving tube feeding and gastrostomy feeding; once a week or more frequently in cases of weight loss.

[1] Rosstat. Residential care institutions for children with disabilities [website]. Available from: https://www.rosstat.gov.ru/ (accessed: 15 Dec 2025).

[2] Common Gastrointestinal Problems in Children with Neurological Impairments (NI): Evaluation, Treatment and Monitoring. URL: http://odgru.ru/images/Common_Gastrointestinal_Problems_in_Children_with_Neurological_Impairments_NI._ESPGHAN_Advice_Guide._2019.pdf (accessed: 15.12.2025).

[3] Ibid.

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Table 1. Formulas for calculating body length by shin length in patients with limited mobility [27, 29]

Таблица 1. Формулы расчета длины тела по длине голени у маломобильных пациентов [27, 29]

Возраст **Age**	**Формула** **Formula**
До 12 лет Up to 12 years old	Рост (см) = (3,26 · ДГ (см) + 30,8 Height (cm) = (3.26 · SL (cm) + 30,8
Мальчики, старше 12 лет Boys over 12 years old	Рост (см) = 64,19 – 0,04 · Возраст (годы) + 2,2 · ДГ (см) Height (cm) = 64.19 – 0.04 · Age (years) + 2.2 · SL (cm)
Девочки, старше 12 лет Girls over 12 years old	Рост (см) = 84,88 – 0,24 · Возраст (годы) + 1,83 · ДГ (см) Height (cm) = 84.88 – 0.24 · Age (years) + 1.83 · SL (cm)

Note: SL — shin length.
Примечание: ДГ — длина голени.

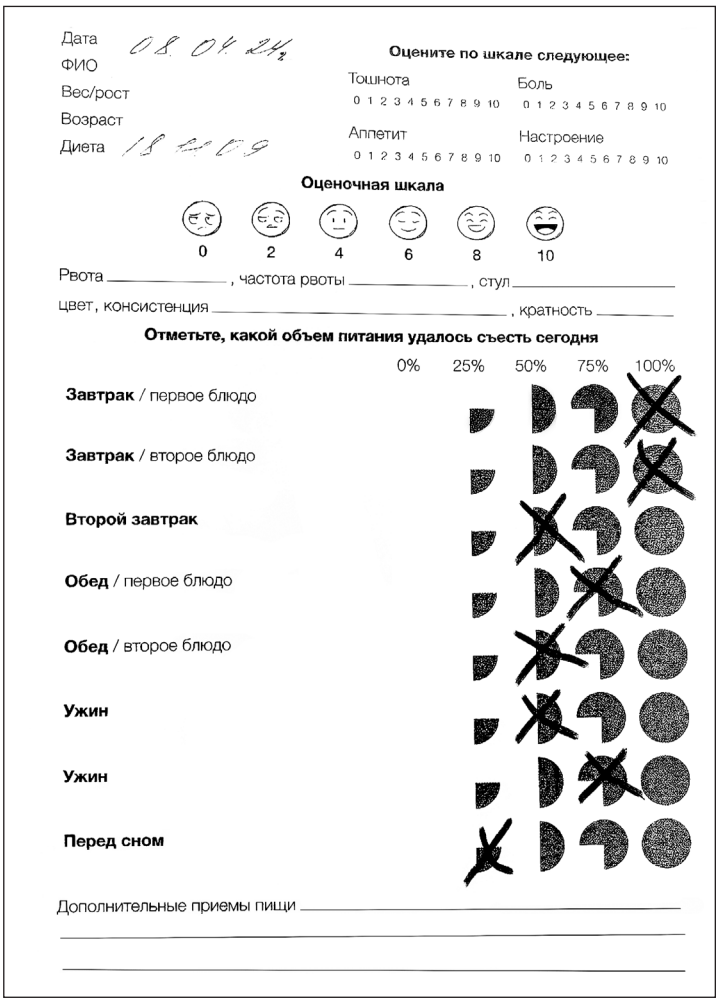

Fig. 1. Nutrition diary filled out by the nursing staff (figure provided by the author)

Рис. 1. Дневник питания, заполненный средним медицинским персоналом (рисунок предоставлен автором)

To assess the children's physical development, Z-scores were used with software recommended by the World Health Organization (WHO): WHO Antro (for children aged 0 to 5 years) and WHO Antro Plus (for children over 5 years of age), as well as a modified version of its mobile app, AntroCalc [27]. For children with cerebral palsy, in accordance with WHO recommendations, special percentile curves were used to assess height, age, and body mass index (BMI), depending on the

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degree of gross motor impairment, gender, and feeding method [27]. In our study, percentile values were converted to Z-scores according to the conversion table [27].

Meal provisions for children residing in social care facilities for people with disabilities are regulated by St. Petersburg Government Resolution No. 1284 of December 29, 2014, "On the Approval of Nutritional Standards in Social Service Organizations in St. Petersburg" (as amended on July 18, 2025)[1]. For patients requiring additional therapeutic nutrition, the amount of food consumed was assessed by nursing staff using a specialized food diary (Fig. 1), which was filled out daily. Subsequently, dietary analysis was conducted by a physician with a parallel assessment of nutritional status. The results of the two-week dietary log made it possible to identify children who regularly did not finish the offered portion of food, as well as children with dysphagia, and to determine its severity. Children who were fed orally, most often with pureed food, over a prolonged period and whose feeding did not meet physiological norms — as confirmed by low physical development indicators — became candidates for the introduction of supplemental therapeutic nutrition [28–30].

The diagnosis of malnutrition and its severity were determined in accordance with WHO recommendations [26].

Permission to conduct the study was obtained from the independent ethics committee of the St. Petersburg State Pediatric Medical University of Ministry of Health of Russia.

Statistical analysis of the results was performed using Microsoft Excel (Microsoft 365 version, 2025–2026) with descriptive statistical methods and nonparametric methods.

RESULTS

The study included equal numbers of orally fed children with OCNSD (n=41) and cerebral palsy (n=37). The group of children fed via gastrostomy was combined: it consisted primarily of children with cerebral palsy (n=38) and three children with OCNSD. The age distribution is presented in Table 2. Adolescents predominate in the groups.

Among patients with OCNSD, the majority of children have a history of hypoxic-ischemic CNS damage.

The following neurological disorders are included in the spectrum of this condition:

- moderate to severe intellectual disability, with or without behavioral disturbances;
- chromosomal disorders, such as Down syndrome, Pierre Robin syndrome, and Franceschetti syndrome;
- structural and symptomatic epilepsy, including drug-resistant epilepsy;
- Duchenne muscular dystrophy;
- an atypical form of adrenoleukodystrophy (inherited peroxisomal disorders);
- malformations of the brain and spinal cord.

Most of the children included in the study had spastic tetraparesis (n=654; 54.6%) and a GMFCS Level 5 motor activity score (n=68; 57.1%). According to the GMFCS scale, 6 (5.0%) patients were diagnosed with Level 4, 4 (3.4%) with Level 3 mobility, 2 (1.7%) with Level 2, and 40 (33.6%) with Level 1 or no motor impairments. Among other variants of cerebral palsy: ataxic-hyperkinetic (n=7; 5.9%), atonic-asthenic (n=2; 1.7%), and mixed variants (n=2; 1.7%). It should be noted that children with CNS disorders also had pronounced motor impairments.

Since 2019, patients with severe CNS damage who have reached the age of 18 have been transferred to psychoneurological residential facilities until they reach the age of 24[2, 3]. The longer stay of patients over the age of 18 in residential care facilities for people with disabilities is due to their physical and mental development, as well as significant limitations in their self-care skills. It should be noted that the latest WHO consensus documents

[1] Resolution of the Government of St. Petersburg of December 29, 2014 No. 1284 "On Approval of Nutrition Standards in Social Service Organizations of St. Petersburg" (as amended on July 18, 2025). URL: https://docs.cntd.ru/document/822404350 (accessed: 12.12.2025).

[2] Ministry of Labour and Social Protection of the Russian Federation. Order No. 305n of 14 May 2025 "On Approval of the Rules for Organizing the Activities of Social Service Organizations and Their Structural Units" [Internet]. Available from: https://legalacts.ru/doc/postanovlenie-mintruda-rf-ot-08082002-n-54/ (accessed: 15 Dec 2025).

[3] Ministry of Labour and Social Development of the Russian Federation. Resolution No. 54 of 8 August 2002 "On Approval of Methodological Recommendations for the Organization of Activities of State (Municipal) Residential Institutions for Children with Intellectual Disabilities" [Internet]. Available from: https://normativ.kontur.ru/document?moduleId=1&documentId=500399 (accessed: 15.12.2025).

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Table 2. Age composition of groups

Таблица 2. Возрастной состав групп

Признак Sign	Группа Group			Различия между группами Statistics
	№ 1 ОПЦНС OLCNS	№ 2 ДЦП CP	№ 3 ГСТ GST	
Первое детство First childhood n=13 (10,9%)	1 (2,4%)	3 (8,1%)	9 (22,0%)	0,013 P_{1-3}=0,021
Второе детство Second childhood n=39 (32,8%)	7 (17,1%)	13 (35,1%)	19 (46,3%)	0,017 P_{1-3}=0,025
Подростковый возраст Adolescence n=10 (8,4%)	3 (7,3%)	4 (10,8%)	3 (7,3%)	0,820
Юношеский возраст Youth age n=57 (47,9%)	30 (73,3%)	17 (45,9%)	10 (24,4%)	<0,001 P_{1-3} <0,001
Итого Total n=119 (100%)	41 (34,5%)	37 (31%)	41 (34,5%)	119 (100%)

The table is prepared by the authors using their own data

Таблица составлена авторами по собственным данным

Note: GST — gastrostomy; CP — cerebral palsy; OLCNS — organic lesion of the central nervous system.

Примечание: ГСТ — гастростома; ДЦП — детский церебральный паралич; ОПЦНС — органическое поражение центральной нервной системы.

Table 3. Structure of physical development and nutritional status of pupils of the nursing department

Таблица 3. Структура физического развития и нутритивного статуса воспитанников отделения милосердия

Нутритивный статус Nutritional status	Периоды детства Childhood periods				Всего Total n=119 (100%)
	первое детство first childhood n=13 (10,9%)	второе детство second childhood n=39 (32,8%)	подростковый возраст adolescence n=10 (8,4%)	юношеский возраст youth age n=57 (47,9%)	
Удовлетворительный Normal	7 (53,8%)	16 (41,0%)	3 (30,0%)	16 (28,0%)	42 (35,3%)
Легкая недостаточность питания Mild malnutrition	3 (23%)	7 (17,9%)	2 (20,0%)	12 (21,0%)	24 (20,2%)
Умеренная недостаточность питания Moderate malnutrition	1 (7,7%)	10 (25,6%)	1 (10,0%)	8 (14,0%)	20 (16,8%)
Тяжелая недостаточность питания Severe malnutrition	2 (15,4%)	4 (10,3%)	4 (40,0%)	20 (35%)	30 (25,2%)
Избыточная масса тела Overweight	0	0	0	0	0
Ожирение Obesity	0	2 (5,1%)	0	1 (1,75%)	3 (2,5%)
Задержка роста Stunting	2 (1,8%)	1 (0,9%)	0	1 (0,9%)	4 (3,4%)
Выраженная задержка роста Growth retardation	0	2 (1,8%)	3 (2,6%)	8 (7,1%)	13 (10,9%)

The table is prepared by the authors using their own data

Таблица составлена авторами по собственным данным

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on age categories define adolescence as extending up to age 25[1] [26, 27].

Deviations in physical development and nutritional status among children with CNS disorders are presented in Table 3. It should be noted that 35 (31%) children were diagnosed with average physical development and satisfactory nutritional status.

Among the study cohort, normal nutritional status was determined in 42 (35.3%) children. In percentage terms, children in the younger age group predominated (53.8%), while the lowest number of children without nutritional disorders was among adolescents (28%). Severe protein-energy malnutrition was diagnosed in 30 (25.2%) children, primarily among adolescents (n=4, 40%) and young adults (n=20, 35%). Obesity was observed in 5 patients from different age groups. Growth retardation was observed in every age group. Severe growth retardation was also characteristic of young adult residents — 8 (7.1%).

Motor impairments worsened the nutritional status of the children. In most cases, normal nutritional status was observed in children with minimal motor impairments (n=23; 53.7%). Severe motor impairments were mostly associated with severe malnutrition (n=27; 39.7%). Obesity was more common in the group of children with severe cerebral palsy (n=4; 5.9%) (Fig. 2).

Depending on the feeding method, the subjects were distributed as follows: 43 (36.1%) children characterized by limited mobility and severe dysphagia were fed via gastrostomy; 35 (29.4%) children with moderate and mild dysphagia received pureed food from the family table; 47 (39.5%) patients were fed according to age-appropriate standards. Among the children receiving feeding via a gastrostomy, 12 had a tracheostomy, and one child was on continuous mechanical ventilation. The feeding rate was determined by the child's physiological capabilities. However, frequent rumination, hyperkinesis, convulsive syndrome, maintenance of pathological muscle tone, and the tendency of children with severe neurological pathology to induce vomiting on their own led to severe nutritional deficiency.

Methods for correcting nutritional status disorders in neurological patients are currently not standardized, and there are no clinical guidelines for the nutrition of children with central nervous system disorders. At the same time, studying the nutritional status of children with central nervous system disorders and developing a general algorithm for its assessment and correction will improve the quality of life for these patients.

Choosing a feeding method. For children with no safety or efficacy restrictions regarding food intake, the diet was selected based on the presence of comorbid conditions. A standard diet was defined as one balanced in terms of caloric content and macronutrients — proteins, fats, and carbohydrates — in accordance with age-specific guidelines for residents of care facilities for people with disabilities[2] [31]. A general pureed diet was prescribed for children with an intact swallowing reflex but clear signs of dysphagia, rated at 2–3 on the EDACS scale. In cases of childhood obesity, restrictions on simple carbohydrates and fats were prescribed, along with an increase in fiber intake. In cases of low weight gain or nutritional deficiency, the possibility of supplemental feeding with a therapeutic formula was considered, either orally, via a feeding tube, or by adding it to foods (porridge, cottage cheese, yogurt) [32–34].

Meal frequency and portion size. Portion sizes and meal frequency are established in accordance with St. Petersburg Government Resolution No. 1284 of December 29, 2014, "On the Approval of Nutritional Standards in Social Service Organizations of St. Petersburg," which regulates the daily food intake for orphaned children in residential social service facilities[3]. Children who could feed themselves were fed 5 times a day; those fed via gastrostomy were fed 6 times a day; in cases of diagnosed nutritional deficiency, tube feeding was added to the 5-meal regimen [27, 33, 34].

Methods of feeding children with severe dysphagia. In children with severe impairments in the effectiveness and safety of oral feeding (EDACS IV–V), tube feeding was initiated. If the need for tube feeding persisted for more than a month, a gastrostomy was performed [10, 27, 34]. Balloon "tailed" gastrostomies were most commonly used for children with severe

[1] The WHO Child Growth Standards. URL: https://www.who.int/tools/child-growth-standards (accessed: 15.12.2025).

[2] Resolution of the Government of St. Petersburg of December 29, 2014 No. 1284 "On approval of nutrition standards in social service organizations of St. Petersburg" (as amended on July 18, 2025). URL: https://docs.cntd.ru/document/822404350 (accessed: 12.12.2025).

[3] Ibid.

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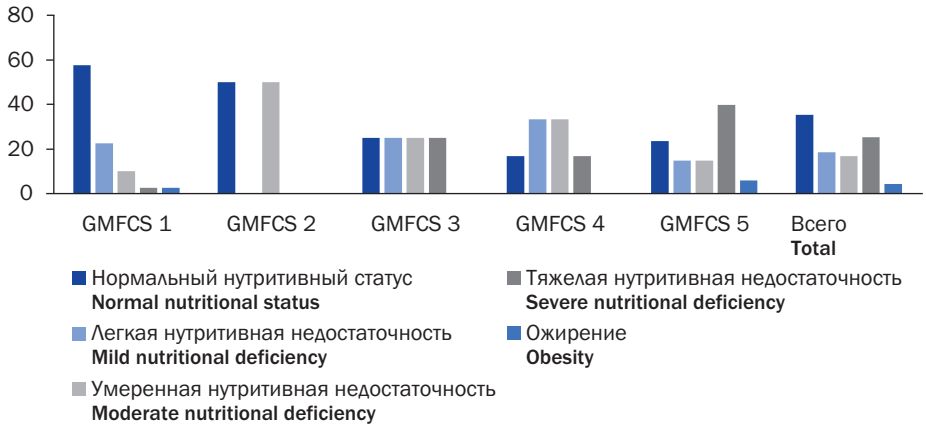

Fig. 2. Nutritional Status Characteristics Relative to the Degree of Gross Motor Function Impairment (the figure is prepared by the author using their own data)

Рис. 2. Характеристика нутритивного статуса в зависимости от степени нарушения больших моторных функций (рисунок подготовлен автором по собственным данным)

multiple impairments [34–36]. The more physiological bolus method of feeding formula was used most frequently. In cases of vomiting and regurgitation caused by frequent concomitant gastroesophageal reflux (GER), we switched to enteral drip feeding [36–39].

Nutritional guidelines for children with feeding tubes. Patients with stomas or feeding tubes were fed six times a day; between feedings, the children were given water. In cases of illness, GERD exacerbations, frequent regurgitation, or weight loss, we switched to frequent, small feedings, reducing the volume of formula per feeding and increasing the frequency of feedings while maintaining the daily volume and caloric intake. If frequent, small feedings were ineffective, we resorted to drip feeding. Difficulties with drip feeding may be due to the need for the patient to remain immobile; therefore, such feeding was performed more often at night[1] [29, 33, 34, 36]. The calculation of the volume of therapeutic formula provided in inpatient social care facilities is governed by St. Petersburg Government Resolution No.1284[2] of December 29, 2014, and was conducted taking individual characteristics into account.

DISCUSSION

There is evidence of differences in physical development [10, 12–16, 25], nutritional status [10, 16, 22–24, 28], and body composition in children with OCNSD [10, 13, 22, 28] compared to neurotypical children. Measurements of basic indicators of physical development (height and body weight) in children with limited mobility differ from those in typically developing children [12, 15, 29]. Methods for assessing physical development and nutritional status also differ [10, 12, 14, 15]. The WHO website provides charts and tables for assessing physical development and nutritional status in children with cerebral palsy based on motor activity levels on the scale GMFCS[3] [26, 27] and certain genetic syndromes (trisomy 21, Noonan syndrome)[4]. Previous studies on the nutritional status of children with cerebral palsy have shown that children with minimal motor impairments may be classified as typically developing according to AntroCalc, whereas children with limited mobility, when classified as typically developing, will exhibit significant nutritional deficiencies and severe growth retardation [12, 14, 23, 25]. Given the high prevalence of nutritional disorders in children with CP [12, 14, 23, 25] and OCNSD, the correction of malnutrition in this patient population is a critically important component of therapy, directly affecting prognosis and life expectancy [19, 20].

[1] Dietetic Management of Children with Neurological Impairments (NI). URL: http://odgru.ru/images/Dietetic_Management_of_Children_with_Neurological_Impairments_NI._ESPGHAN_Advice_Guide._2019.pdf (accessed: 15.12.2025).

[2] Government of Saint Petersburg. Resolution No. 1284 of 29 December 2014 "On Approval of Nutrition Standards in Social Service Organizations of Saint Petersburg" (as amended on 18 July 2025) [Internet]. Available from: https://docs.cntd.ru/document/822404350 (accessed: 12.12.2025).

[3] Growth Charts for Cerebral Palsy» Life Expectancy. Project. URL: https://www.lifeexpectancy.org/articles/GrowthCharts.shtml (accessed: 12.12.2025).

[4] The WHO Child Growth Standards. URL: https://www.who.int/tools/child-growth-standards (accessed: 15.12.2025).

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In Russia, there are no clinical guidelines for the nutrition of children with severe organic CNS disorders and cerebral palsy. Based on the regulatory framework and available scientific literature, the Miloserdie Department has developed a standardized algorithm for diagnosing malnutrition and selecting individualized nutrition plans for the facility's residents. There is a cohort of children who, due to their severe organic disorders, have significant nutritional disorders that are difficult to correct.

CONCLUSION

One-third of the residents (n=42; 35.3%) at the social care facility had a satisfactory nutritional status. Severe malnutrition was diagnosed in 30 (25.2%) residents, primarily among adolescents (n=4; 40%) and young adults (n=20; 35%). One-third of the residents with severe swallowing disorders — dysphagia — require additional feeding devices (gastrostomies). Feeding via gastrostomy is most commonly provided to children in late childhood (n=19; 46.3%), early childhood (n=9; 22%), and adolescence (n=10; 24.4%).

Feeding children with severe neurological disorders requires the work of a multidisciplinary team of highly qualified specialists (pediatrician, dietitian, gastroenterologist, speech therapist, pulmonologist, clinical pharmacologist, kinesiologist, occupational therapist). Providing adequate nutrition and treatment for children with neurological disorders entails very high financial costs. The organization of nutrition for children in social care facilities requires improvements to the regulatory framework, development of clinical guidelines, and further scientific research.

ADDITIONAL INFORMATION

The author read and approved the final version before publication.

Conflict of interest. The authors declare no obvious or potential conflicts of interest related to the publication of this article.

Consent for publication. The author obtained written consent from the patients' legal representatives for the publication of medical data.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Автор прочитал и одобрил финальную версию перед публикацией.

Конфликт интересов. Автор декларирует отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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REFERENCES

1. Graham H.K., Rosenbaum P., Paneth N., Dan B., Lin J.P., Damiano D.L. et al. Cerebral palsy. *Nat Rev Dis Primers*. 2016;(2):15082. https://doi.org/10.1038/nrdp.2015.82.
2. Salkov V.N., Khudoerkov R.M. Infantile cerebral palsy as a result of prenatal brain dysontogenesis. *Russian Bulletin of Perinatology and Pediatrics*. 2019;64(3):11–16. (In Russ.). https://doi.org/10.21508/1027-4065-2019-64-3-11-16. EDN: CVUEZS.
3. Crary M.A., Carnaby G.D., Mathijs L., Maes S., Gelin G., Ortibus E., Rommel N. Spontaneous swallowing frequency, dysphagia, and drooling in children with cerebral palsy. *Arch Phys Med Rehabil*. 2022;103(3):451–458. https://doi.org/10.1016/j.apmr.2021.09.014.
4. Koltsov A.A., Dzhomardly E.I. General Issues of Cerebral Palsy in Children: A Scientific Review. Part 1: Etiology, Pathogenesis and Clinical Features of Spastic Forms. *Physical and Rehabilitation Medicine*. 2021;3(1):36–47. (In Russ.). https://doi.org/10.26211/2658-4522-2021-3-1-36-47.
5. Dzhomardly E.I., Koltsov A.A. General issues of childhood cerebral palsy: a scientific review. Part 2: diagnostics and treatment. *Physical and Rehabilitation Medicine*. 2021;3(2):15–27. (In Russ.). https://doi.org/10.26211/2658-4522-2021-3-2-15-27.
6. Moiseeva K.E., Suslova G.A., Zastupova A.A., Glushchenko V.A., Bolotskikh V.M., Kolotova A.S. et al. Medical and social problems of the prevalence of infantile cerebral palsy (literature review). *Current Problems of Health Care and Medical Statistics*. 2024;(5):907–924. (In Russ.). https://doi.org/10.24412/2312-2935-2024-5-907-924.
7. McIntyre S., Goldsmith S., Webb A., Ehlinger V., Hollung S.J., McConnell K. et al.; Global CP Prevalence

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

Group*. Global prevalence of cerebral palsy: A systematic analysis. *Dev Med Child Neurol*. 2022;64(12):1494–1506. https://doi.org/10.1111/dmcn.15346.
8. Baibarina E.N., Antonov A.G., Degtyareva A.V. et al. Remote results of nursing children with extremely low birth weight in the Russian Federation. *Pediatrics. Consilium Medicum*. 2019;(2):47–53. (In Russ.).
9. Zavyalova A.N., Novikova V.P. Dysphagia in children: review. *University Therapeutic Journal*. 2023;5(1):64–84. (In Russ.). https://doi.org/10.56871/UTJ.2023.15.64.004.
10. Zavyalova A.N. Nutritional status of children with dysphagia and its correction. MD dissertation. Saint Petersburg: Saint Petersburg State Pediatric Medical University; 2023. (In Russ.).
11. Shalkevich L.V. Cerebral palsy: modern conception of classification systems. *Meditsinskie Novosti*. 2021;(1): 19–23. (In Russ.).
12. Rakhmaeva R.F. Diagnostics and correction of nutritional status disorders in children with cerebral palsy. PhD thesis. Kazan; 2021. 18 p. (In Russ.).
13. Zavyalova A.N., Novikova V.P., Klikunova K.A. Nutritional status and feeding problems in children with dysphagia and cerebral palsy in different social settings. *Experimental and Clinical Gastroenterology*. 2022;(2):21–29. (In Russ.). https://doi.org/10.31146/1682-8658-ecg-198-2-21-29.
14. Perfilova O.V. Features of nutritional status and prediction of the risk of malnutrition in children with cerebral palsy. PhD dissertation. Ekaterinburg; 2022. (In Russ.).
15. Rakhmaeva R.F., Kamalova A.A., Ayupova V.A. Evaluation of anthropometric parameters and body composition in children with cerebral palsy. *Russian Bulletin of Perinatology and Pediatrics*. 2019;64(5):204–208. (In Russ.). https://doi.org/10.21508/1027-4065-2019-64-5-204-208.
16. Titova O.N., Taran N.N., Matinyan I.A., Keleinikova A.V., Pavlovskaya E.V., Strokova T.V. Indicators of nutritional status in children with infantile cerebral paralysis in GMFCS IV–V classes of motor activity. *Child and Adolescent Rehabilitation*. 2021;1(44):30–39. (In Russ.).
17. da Silva D.C.G., de Sá Barreto da Cunha M., de Oliveira Santana A., Dos Santos Alves A.M., Pereira Santos M. Malnutrition and nutritional deficiencies in children with cerebral palsy: a systematic review and meta-analysis. *Public Health*. 2022;205:192–201. https://doi.org/10.1016/j.puhe.2022.01.024.
18. Tumanova U.N., Shuvalova M.P., Schegolev A.I. Analysis of statistical indicators of congenital anomalies as causes of early neonatal death in the Russian Federation. *Russian Bulletin of Perinatology and Pediatrics*. 2018;63(6):60–67. (In Russ.). https://doi.org/10.21508/1027-4065-2018-63-5-60-67.
19. Figueroa M.J., Rojas C., Barja S. Morbimortalidad asociada al estado nutricional y vía de alimentación en niños con parálisis cerebral [Morbimortality associated to nutritional status and feeding path in children with cerebral palsy]. *Rev Chil Pediatr*. 2017;88(4):478–486. (In Spanish). https://doi.org/10.4067/S0370-41062017000400006.
20. Aldharman S.S., Alhamad F.S., Alharbi R.M., Almutairi Y.S., Alhomsi M.W.M., Alzahrani S.A. et al. Risk factors for mortality in patients with cerebral palsy: a systematic review and meta-analysis. *Cureus*. 2023;15(5):e39327. https://doi.org/10.7759/cureus.39327.
21. Hansen T.W.B., Ersland L., Thimm C. et al. Swallowing disorders and mortality in adults with cerebral palsy: a systematic review. *Dev Med Child Neurol*. 2020;62(12): 1355–1361.
22. Pak L.A., Makarova S.G., Chumbadze T.R., Fisenko A.P. Disorders of the nutritional status and their correction in cerebral palsy children. *Russian Pediatric Journal*. 2019;1(22):23–27. (In Russ.). https://doi.org/10.18821/1560-9561-2019-22-1-23-27.
23. Leontyev I.A., Sitnikova E.P., Kovina M.V. Features of nutritional status and anthropometric indicators in children under 5 years of age with cerebral palsy. *Topical Issues of Medical Science*. 2023;1(1):34–44. (In Russ.).
24. Keleinikova A.V., Taran N.N., Titova O.N., Dremucheva T.A., Strokova T.V. Undernutrition in children: features of clinical manifestations and food intake. *Medical Alphabet*. 2022;(16):51–59. (In Russ.). https://doi.org/10.33667/2078-5631-2022-16-51-59.
25. Zavyalova A.N., Novikova V.P., Churakova I.Yu., Chuynyshena S.A., Turun D.P., Luzanova O.A. et al. Physical development and prevalence of malnutrition in children with cerebral palsy. *Preventive and Clinical Medicine*. 2022;1(82):42–52. (In Russ.). https://doi.org/10.47843/2074-9120_2022_1_42.
26. Gritsinskaya V.L., Zavyalova A.N., Kukes I.V., Lisitsa I.A., Lunegov T.D., Melnikova E.A. et al. Methods for diagnosing protein-energy malnutrition in children and adolescents. Saint Petersburg; 2024. (In Russ.).
27. Ivanov D.O., Strokova T.V., Kamalova A.A., Aleksandrovich Yu.S., Taran N.N., Zavyalova A.N. and others. Diagnosis and correction of nutritional status in children with cerebral palsy. St. Petersburg; 2020. 100 p. (In Russ.).
28. Titova O.N. Study of nutritional status and development of specialized diets in children with cerebral palsy. PhD dissertation. Moscow; 2024. (In Russ.).
29. Pyryeva E.A., Safronova A.I., Timoshina M.I., Netunaeva E.A. Methods of nutritional status assessment in children with neurological disorders. *Pediatric Nutrition*. 2023;21(6):38–43. (In Russ.). https://doi.org/10.20953/1727-5784-2023-6-38-43.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

30. Fedorushkina N.A., Borovik O.A., Zvonkova N.G., Bushueva T.V., Yatsyk S.P., Sokolov I. et al. Current possibilities for nutritional interventions in children with cerebral palsy. *Pediatrics. Journal named after G.N. Speransky*. 2023;102(6):140–151. (In Russ.). https://doi.org/10.24110/0031-403X-2023-102-6-140-151.
31. Lisovsky O.V., Gostimsky A.V., Lisitsa I.A., Zavyalova A.N., Karpatsky I.V., Gavshchuk M.V., Getsko N.V. Organization of therapeutic nutrition in a medical organization. Saint Petersburg; 2022. (In Russ.).
32. Potani I., Spiegel-Feld C., Brixi G., Bendabenda J., Siegfrie N., Bandsma R.H.J. et al. Ready-to-Use Therapeutic Food (RUTF) Containing Low or No Dairy Compared to Standard RUTF for Children with Severe Acute Malnutrition: A Systematic Review and Meta-Analysis. *Adv Nutr*. 2021;12(5):1930–1943. https://doi.org/10.1093/advances/nmab027.
33. Malnutrition in children. D.O. Ivanov, V.P. Novikova, A.N. Zavyalova, I.A. Lisitsa, eds. Moscow: GEOTAR-Media; 2025. (In Russ.). https://doi.org/10.33029/9704-9254-3-NPD-2025-1-480. EDN: TJTEYZ.
34. Zavyalova A.N., Ivanov D.O., Novikova V.P., Gavshchuk M.V. et al. Dysphagia in children. Moscow: GEOTAR-Media, 2025. 352 p. (In Russ.).
35. Zavyalova A.N., Gavshchuk M.V., Novikova V.P., Kuznetsova Yu.V., Lisovsky O.V., Gostimsky A.V. et al. Analysis of cases of gastrostomia in children according to the data of the system of compulsory health insurance in Saint Petersburg. *Nutrition*. 2021;11(4):15–22. (In Russ.). https://doi.org/10.20953/2224-5448-2021-4-15-22.
36. Zavyalova A.N., Novikova V.P., Orel V.I., Gavshchuk M.V., Kuznetsova Yu.V., Davletova L.A., Al-Hares M.M. Organization of the stomy patient nutrition. Choice of food substrate. *Pediatrician (St. Petersburg)*. 2023;14(2):93–104. (In Russ.). https://doi.org/10.17816/PED14293-104.
37. Zavyalova A.N., Novikova V.P., Gavshchyuk M.V., Kuznetsova Yu.V. Dysphagia: diagnosis, modern methods of diet therapy. *Pediatric Nutrition*. 2022;20(6):51–62. (In Russ.). https://doi.org/10.20953/1727-5784-2022-6-51-62.
38. Gavshchuk M.V., Lisovsky O.V., Zavyalova A.N., Gostimsky A.V., Klikunova K.A., Lisitsa I.A. et al. Method for administering enteral nutrition to the gastrointestinal tract. Patent for invention RU 2791497 C1. 09.03.2023. Application No. 2022108180 dated 28.03.2022. (In Russ.).
39. Lisitsa I.A., Zavyalova A.N., Alexandrovich Yu.S., Novikova V.P., Lisovskii O.V., Gavshchuk M.V. et al. Practical aspects of organization of enteral nutrition in pediatric intensive care unit patients. Part 1. Choosing a nutritional strategy. *Children's Medicine of the North-West*. 2024;12(4):39–57. (In Russ.). https://doi.org/10.56871/CmN-W.2024.50.45.003.

ЛИТЕРАТУРА

1. Graham H.K., Rosenbaum P., Paneth N., Dan B., Lin J.P., Damiano D.L. et al. Cerebral palsy. *Nat Rev Dis Primers*. 2016;(2):15082. https://doi.org/10.1038/nrdp.2015.82.
2. Сальков В.Н., Худоерков Р.М. Детский церебральный паралич как следствие пренатального дизонтогенеза головного мозга. *Российский вестник перинатологии и педиатрии*. 2019;64(3):11–16. https://doi.org/10.21508/1027-4065-2019-64-3-11-16. EDN: CVUEZS.
3. Crary M.A., Carnaby G.D., Mathijs L., Maes S., Gelin G., Ortibus E., Rommel N. Spontaneous swallowing frequency, dysphagia, and drooling in children with cerebral palsy. *Arch Phys Med Rehabil*. 2022;103(3):451–458. https://doi.org/10.1016/j.apmr.2021.09.014.
4. Кольцов А.А., Джомардлы Э.И. Общие вопросы детского церебрального паралича (научный обзор). Часть 1: этиология, патогенез и клинические особенности спастических форм. *Физическая и реабилитационная медицина*. 2021;3(1):36–47. https://doi.org/10.26211/2658-4522-2021-3-1-36-47.
5. Джомардлы Э.И., Кольцов А.А. Общие вопросы детского церебрального паралича (научный обзор). Часть 2: диагностика и лечение. *Физическая и реабилитационная медицина*. 2021;3(2):15–27. https://doi.org/10.26211/2658-4522-2021-3-2-15-27.
6. Моисеева К.Е., Суслова Г.А., Заступова А.А., Глущенко В.А., Болотских В.М., Колотова А.С. и др. Медико-социальные проблемы распространенности детского церебрального паралича (обзор литературы). *Современные проблемы здравоохранения и медицинской статистики*. 2024;(5):907–924. https://doi.org/10.24412/2312-2935-2024-5-907-924.
7. McIntyre S., Goldsmith S., Webb A., Ehlinger V., Hollung S.J., McConnell K. et al.; Global CP Prevalence Group*. Global prevalence of cerebral palsy: A systematic analysis. *Dev Med Child Neurol*. 2022;64(12):1494–1506. https://doi.org/10.1111/dmcn.15346.
8. Байбарина Е.Н., Антонов А.Г., Дегтярева А.В. и др. Отдаленные результаты выхаживания детей с экстремально низкой массой тела в Российской Федерации. *Педиатрия. Consilium Medicum*. 2019;(2):47–53.
9. Завьялова А.Н., Новикова В.П. Дисфагия у детей: обзор. *University Therapeutic Journal*. 2023;5(1):64–84. https://doi.org/10.56871/UTJ.2023.15.64.004.
10. Завьялова А.Н. Нутритивный статус детей с дисфагией и его коррекция. Дис. … д-ра мед. наук. СПб.: СПбГПМУ; 2023.
11. Шалькевич Л.В. Детский церебральный паралич: использование современных классификационных систем. *Медицинские новости*. 2021;(1):19–23.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

12. Рахмаева Р.Ф. Диагностика и коррекция нарушений нутритивного статуса у детей с детским церебральным параличом. Автореф. дис. … канд. мед. наук. Казань; 2021. 18 с.
13. Завьялова А.Н., Новикова В.П., Кликунова К.А. Нутритивный статус и проблемы при кормлении у детей с дисфагией и детским церебральным параличом, находящихся в разных социальных условиях. *Экспериментальная и клиническая гастроэнтерология*. 2022;(2):21–29. https://doi.org/10.31146/1682-8658-ecg-198-2-21-29.
14. Перфилова О.В. Особенности нутритивного статуса и прогнозирование риска развития недостаточности питания у детей с детским церебральным параличом. Дис. … канд. мед. наук. Екатеринбург; 2022.
15. Рахмаева Р.Ф., Камалова А.А., Аюпова В.А. Оценка антропометрических показателей и компонентного состава тела у детей с детским церебральным параличом. *Российский вестник перинатологии и педиатрии*. 2019;64(5):204–208. https://doi.org/10.21508/1027-4065-2019-64-5-204-208.
16. Титова О.Н., Таран Н.Н., Матинян И.А., Павловская Е.В., Келейникова А.В., Строкова Т.В. Показатели нутритивного статуса у детей с детским церебральным параличом в IV–V классах моторной активности GMFCS. *Детская и подростковая реабилитация*. 2021;1(44):30–39.
17. da Silva D.C.G., de Sá Barreto da Cunha M., de Oliveira Santana A., Dos Santos Alves A.M., Pereira Santos M. Malnutrition and nutritional deficiencies in children with cerebral palsy: a systematic review and meta-analysis. *Public Health*. 2022;205:192–201. https://doi.org/10.1016/j.puhe.2022.01.024.
18. Туманова У.Н., Шувалова М.П., Щеголев А.И. Анализ статистических показателей врожденных аномалий как причины ранней неонатальной смерти в Российской Федерации. *Российский вестник перинатологии и педиатрии*. 2018;63(6):60–67. https://doi.org/10.21508/1027-4065-2018-63-5-60-67.
19. Figueroa M.J., Rojas C., Barja S. Morbimortalidad asociada al estado nutricional y vía de alimentación en niños con parálisis cerebral [Morbimortality associated to nutritional status and feeding path in children with cerebral palsy]. *Rev Chil Pediatr*. 2017;88(4):478–486. (In Spanish). https://doi.org/10.4067/S0370-41062017000400006.
20. Aldharman S.S., Alhamad F.S., Alharbi R.M., Almutairi Y.S., Alhomsi M.W.M., Alzahrani S.A. et al. Risk factors for mortality in patients with cerebral palsy: a systematic review and meta-analysis. *Cureus*. 2023;15(5):e39327. https://doi.org/10.7759/cureus.39327.
21. Hansen T.W.B., Ersland L., Thimm C. et al. Swallowing disorders and mortality in adults with cerebral palsy: a systematic review. *Dev Med Child Neurol*. 2020;62(12):1355–1361.
22. Пак Л.А., Макарова С.Г., Чумбадзе Т.Р., Фисенко А.П. Нарушения нутритивного статуса и их коррекция у детей с детским церебральным параличом. *Российский педиатрический журнал*. 2019;22(1):23–27. https://doi.org/10.18821/1560-9561-2019-22-1-23-27.
23. Леонтьев И.А., Ситникова Е.П., Ковина М.В. Особенности нутритивного статуса и антропометрических показателей у детей в возрасте до 5 лет с детским церебральным параличом. *Актуальные вопросы медицинской науки*. 2023;1(1):34–44.
24. Келейникова А.В., Таран Н.Н., Титова О.Н., Дремучева Т.А., Строкова Т.В. Дефицит массы тела у детей: особенности клинических проявлений и фактического питания. *Медицинский алфавит*. 2022;(16):51–59. https://doi.org/10.33667/2078-5631-2022-16-51-59.
25. Завьялова А.Н., Новикова В.П., Чуракова И.Ю., Чуйнышена С.А., Турун Д.П. и др. Физическое развитие и выраженность белково-энергетической недостаточности у детей с детским церебральным параличом. *Профилактическая и клиническая медицина*. 2022;1(82):42–52. https://doi.org/10.47843/2074-9120_2022_1_42.
26. Грицинская В.Л., Завьялова А.Н., Кукес И.В., Лисица И.А., Лунегов Т.Д., Мельникова Е.А. и др. Методы диагностики белково-энергетической недостаточности у детей и подростков. СПб.; 2024.
27. Иванов Д.О., Строкова Т.В., Камалова А.А., Александрович Ю.С., Таран Н.Н., Завьялова А.Н. и др. Диагностика и коррекция нутритивного статуса у детей с детским церебральным параличом. СПб.; 2020. 100 с.
28. Титова О.Н. Изучение пищевого статуса и разработка специализированных рационов питания у детей с детским церебральным параличом. Дис. … канд. мед. наук. М.; 2024.
29. Пырьева Е.А., Сафронова А.И., Тимошина М.И., Нетунаева Е.А. Методы оценки нутритивного статуса у детей с неврологическими заболеваниями. *Вопросы детской диетологии*. 2023;21(6):38–43. https://doi.org/10.20953/1727-5784-2023-6-38-43.
30. Федорушкина Н.А., Боровик Т.Э., Звонкова Н.Г., Бушуева Т.В., Яцык С.П., Соколов И. и др. Современные возможности лечебного питания пациентов с детским церебральным параличом при нарушениях нутритивного статуса. *Педиатрия. Журнал им. Г.Н. Сперанского*. 2023;102(6):140–151. https://doi.org/10.24110/0031-403X-2023-102-6-140-151.
31. Лисовский О.В., Гостимский А.В., Лисица И.А., Завьялова А.Н., Карпатский И.В., Гавщук М.В., Гецко Н.В.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

Организация лечебного питания в медицинской организации. СПб.; 2022.
32. Potani I., Spiegel-Feld C., Brixi G., Bendabenda J., Siegfried N., Bandsma R.H.J. et al. Ready-to-Use Therapeutic Food (RUTF) Containing Low or No Dairy Compared to Standard RUTF for Children with Severe Acute Malnutrition: A Systematic Review and Meta-Analysis. *Adv Nutr*. 2021;12(5):1930–1943. https://doi.org/10.1093/advances/nmab027.
33. Недостаточность питания у детей. Д.О. Иванов, В.П. Новикова, А.Н. Завьялова, И.А. Лисица, ред. М.: ГЭОТАР-Медиа; 2025. 480 с. https://doi.org/10.33029/9704-9254-3-NPD-2025-1-480. EDN: TJTEYZ.
34. Завьялова А.Н., Иванов Д.О., Новикова В.П., Гавщук М.В. и др. Дисфагия у детей. М.: ГЭОТАР-Медиа, 2025. 352 с.
35. Завьялова А.Н., Гавщук М.В., Новикова В.П., Кузнецова Ю.В., Лисовский О.В., Гостимский А.В. и др. Анализ случаев гастростомии у детей по данным системы обязательного медицинского страхования в Санкт-Петербурге. *Вопросы диетологии*. 2021;11(4):15–22. https://doi.org/10.20953/2224-5448-2021-4-15-22.
36. Завьялова А.Н., Новикова В.П., Орел В.И., Гавщук М.В., Кузнецова Ю.В., Давлетова Л.А., Аль-Харес М.М. Организация питания стомированного пациента. Выбор пищевого субстрата. *Педиатр*. 2023;14(2):93–104. https://doi.org/10.17816/PED14293-104.
37. Завьялова А.Н., Новикова В.П., Гавщук М.В., Кузнецова Ю.В. Дисфагия: диагностика, современные методы диетотерапии. *Вопросы детской диетологии*. 2022;20(6):51–63. https://doi.org/10.20953/1727-5784-2022-6-51-62. EDN: ZUXUAE.
38. Гавщук М.В., Лисовский О.В., Завьялова А.Н., Гостимский А.В., Кликунова К.А., Лисица И.А. и др. Способ введения энтерального питания в желудочно-кишечный тракт. Патент на изобретение RU 2791497 C1. 09.03.2023. Заявка № 2022108180 от 28.03.2022.
39. Лисица И.А., Завьялова А.Н., Александрович Ю.С., Новикова В.П., Лисовский О.В., Гавщук М.В. и др. Практические аспекты организации энтерального питания пациентов педиатрических ОРИТ. Часть 1. Выбор способа питания. *Children's Medicine of the North-West*. 2024;12(4):39–57. https://doi.org/10.56871/CmN-W.2024.50.45.003.

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Evaluation of the effectiveness of using leucocyte indices in the differential diagnosis of acute abdominal pain in children in the first 6 years of life

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ABSTRACT. ***Introduction.*** Evaluation of diagnostic efficiency of leukocyte indices in differential diagnostics of acute abdominal pain in children under 6 years of age, with identification of the most informative indicators, is a highly relevant task of modern pediatrics. The solution to this problem can significantly improve the accuracy of diagnostics, reduce the incidence of complications and optimize patient management tactics. ***The aim*** — to evaluate the efficiency of integral leukocyte indices in differential diagnostics of acute abdominal pain in children of the first 6 years of life. ***Materials and methods.*** A retrospective cohort study of 130 children was conducted (acute appendicitis n=35; functional bowel disorders: n=40; control: n=55). Based on the general blood test data, 13 integral leukocyte indices were calculated. Statistical analysis was performed using nonparametric methods. ***Results.*** High differential potential was revealed for the following indices: erythrocyte loading coefficient (0.88±0.76 conventional units for acute appendicitis, compared with 0.53±0.33 conventional units for functional bowel disorders; p=0.006), immunolymphocytic potential (147.41±177.87 conventional units for acute appendicitis, compared with 287.21±272.83 conventional units for functional bowel disorders; p <0.001), leukocyte intoxication index (4.84±5.58 conventional units for acute appendicitis, compared with 0.86±1.29 conventional units for functional bowel disorders; p <0.0001), modified leukocyte intoxication index (4.32±3.24 conventional units for acute appendicitis, compared with 3.27±2.57 conventional units for functional bowel disorders; p <0.01), reactive neutrophil response (15.54±13.07 conventional units in acute appendicitis compared to 9.21±15.36 conventional units in functional bowel disorders; p >0.05), body resistance index (5.82±9.69 conventional units in acute appendicitis, compared to 33.59±13.66 conventional units in functional bowel disorders; p <0.001), lymphocyte-granulocyte index (2.45±3.31 conventional units in acute appendicitis, compared to 5.72±7.98 in functional bowel disorders; p <0.05). Moderate value was noted for blood leukocyte shift index and Krebs index, but with limitations. Low significance was revealed for cell-phagocytic potential, leukocyte ratio and erythrocyte sedimentation rate, nuclear index of endotoxicosis — no significant differences, for allergic predisposition of the body — nonspecificity. ***Conclusions***. The combination of erythrocyte loading coefficient, immunolymphocytic potential, leukocyte intoxication index, modified leukocyte intoxication index, body resistance index, blood leukocyte shift index, lymphocyte-granulocyte index demonstrated the greatest potential for differential diagnosis of acute appendicitis and functional bowel disorders in children under 6 years of age. Validation on an independent cohort and clarification of threshold values are necessary for implementation in clinical practice.

KEYWORDS: *acute abdominal pain, differential diagnosis, leukocyte indices, children*

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Оригинальная статья

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Оценка эффективности применения лейкоцитарных индексов при дифференциальной диагностике острой боли в животе у детей первых 6 лет жизни

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РЕЗЮМЕ. ***Введение.*** Оценка диагностической эффективности лейкоцитарных индексов при дифференциальной диагностике острой абдоминальной боли у детей в возрасте до 6 лет с выявлением наиболее информативных показателей – высокоактуальная задача современной педиатрии. Решение этой проблемы может существенно повысить точность диагностики, снизить частоту осложнений и оптимизировать тактику ведения пациентов. ***Цель*** – оценить эффективность интегральных лейкоцитарных индексов при дифференциальной диагностике острой боли в животе у детей первых 6 лет жизни. ***Материалы и методы.*** Проведено ретроспективное когортное исследование 130 детей (острый аппендицит: n=35; функциональные нарушения кишечника: n=40; контроль: n=55). На основе данных общего анализа крови рассчитаны 13 интегральных лейкоцитарных индексов. Статистический анализ выполнен с использованием непараметрических методов. ***Результаты.*** Высокий дифференциальный потенциал выявлен у следующих индексов: нагрузочный эритроцитарный коэффициент (0,88±0,76 усл. ед. при остром аппендиците в сравнении с 0,53±0,33 усл. ед. при функциональных нарушениях кишечника; p=0,006), иммунолимфоцитарный потенциал (147,41±177,87 усл. ед. при остром аппендиците в сравнении с 287,21±272,83 усл. ед. при функциональных нарушениях кишечника; p <0,001), лейкоцитарный индекс интоксикации (4,84±5,58 усл. ед. при остром аппендиците в сравнении с 0,86±1,29 усл. ед. при функциональных нарушениях кишечника; p <0,0001), лейкоцитарный индекс интоксикации модифицированный (4,32±3,24 усл. ед. при остром аппендиците в сравнении с 3,27±2,57 усл. ед. при функциональных нарушениях кишечника; p <0,01), реактивный ответ нейтрофилов (15,54±13,07 усл. ед. при остром аппендиците в сравнении с 9,21±15,36 усл. ед. при функциональных нарушениях кишечника; p >0,05), индекс резистентности организма (5,82±9,69 усл. ед. при остром аппендиците в сравнении с 33,59±13,66 усл. ед. при функциональных нарушениях кишечника; p <0,001), индекс лимфоцитарно-гранулоцитарный (2,45±3,31 усл. ед. при остром аппендиците в сравнении с 5,72±7,98 усл. ед. при функциональных нарушениях кишечника; p <0,05). Умеренная ценность отмечена у индекса сдвига лейкоцитов крови и индекса Кребса, но с ограничениями. Низкая значимость выявлена у клеточно-фагоцитарного потенциала, индекса соотношения лейкоцитов и скорости оседания эритроцитов, у ядерного индекса эндотоксикоза – отсутствие значимых различий, у аллергической настроенности организма – неспецифичность. ***Выводы.*** Комбинация нагрузочного эритроцитарного коэффициента, иммунолимфоцитарного потенциала, лейкоцитарного индекса интоксикации, лейкоцитарного индекса интоксикации модифицированного, реактивного ответа нейтрофилов, индекса резистентности организма, индекса сдвига лейкоцитов крови, индекса лимфоцитарно-гранулоцитарного продемонстрировала наибольший потенциал для дифференциальной диагностики острого аппендицита и функциональных нарушений кишечника у детей до 6 лет. Для внедрения в клиническую практику необходима валидация на независимой когорте и уточнение пороговых значений.

КЛЮЧЕВЫЕ СЛОВА: *острая абдоминальная боль, дифференциальная диагностика, лейкоцитарные индексы, дети*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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INTRODUCTION

Acute abdominal pain (AAP) is the most common reason for referral to a pediatric surgeon in children under 6 years of age [1, 2]. Between 10% and 25% of children experience recurrent episodes of abdominal pain over the course of a year, yet only 2% to 4% of them seek medical care [1–3]. In the breakdown of emergency surgical procedures on abdominal organs, appendectomy accounts for 80%, diagnostic laparoscopy for 11%, acute gynecological pathology for 5%, abdominal trauma for 2%, other conditions — 2%, of which 1% is intestinal obstruction [1–3]. Overall, complaints of abdominal pain in children rank second in frequency after infectious diseases in pediatric practice [2, 3]. This symptom serves as a nonspecific marker for a wide range of conditions — from transient functional disorders to life-threatening surgical pathologies — with up to 60% of episodes of acute abdominal pain remaining etiologically unrecognized at the initial stage [4, 5, 7].

The key diagnostic challenge is to distinguish conditions requiring urgent surgical intervention — such as acute appendicitis (AA), intussusception, and peritonitis — from conditions that can be managed conservatively or do not require active treatment (functional bowel disorders (FBD), gastroenteritis, mesadenitis) [6]. Delayed detection of surgical pathology or unwarranted surgical intervention is associated with high risks of complications and an unjustified burden on the child and the healthcare system [2, 4, 7].

The differential diagnosis of acute abdominal pain is particularly challenging in preschool-aged children (≤6 years) for the following reasons:

- the nonspecific nature of the clinical presentation (symptoms of AAP and other acute surgical conditions — such as pain, vomiting, fever, refusal to eat) are virtually indistinguishable from the manifestations of common viral infections, gastroenteritis, and functional abdominal pain) [8, 9];
- limited communication (a young child cannot accurately describe the nature, location, and intensity of pain) [8, 9];
- difficulties with physical examination (assessment of the abdomen is often hampered by the child's fear, restlessness, and muscle guarding, which reduces the informative value of physical findings, including signs of peritoneal irritation) [9, 10];
- high frequency of complications (due to diagnostic difficulties, children under 6 years of age with acute appendicitis are admitted to the hospital at the stage of perforation in 43–72% of cases, with the development of peritonitis and sepsis) [7];
- the standard diagnostic algorithm includes a clinical evaluation and a complete blood count (CBC), with a focus on leukocytosis; however, it has extremely low specificity [11]. Leukocytosis is observed in bacterial infections, viral diseases, stress reactions, and many non-surgical causes of AAP. Its level does not allow for reliable differentiation of AA from FBD or other inflammatory non-surgical conditions. The lack of accessible, rapid, and objective laboratory tests to distinguish between surgical and non-surgical causes of AAP in preschoolers remains one of the key unresolved problems, leading to delays in vital surgery or to unnecessary surgical interventions [9, 12].

In this context, the use of calculated leukocyte indices (LI) derived from standard CBC data appears to be a promising approach. These composite indices (such as the leukocyte shift index, leukocyte intoxication index, neutrophil-to-lymphocyte ratio, etc.) combine information about various leukocyte subpopulations and their ratios. In theory, they are capable of reflecting the degree and nature of the systemic inflammatory response (bacterial and viral, acute and chronic) and the severity of endogenous intoxication more accurately than isolated leukocytosis. Assessing the body's immunoreactivity allows for predicting the course of the process and evaluating the risk of postoperative complications [8–10].

Their advantages lie in their objectivity, accessibility, speed of results, and potentially higher specificity due to the simultaneous consideration of multiple parameters, which reduces the influence of individual variations [8–10]. LI make it possible to detect endogenous intoxication even in cases where standard CBC levels fall within the reference range. The use of LI should be viewed not as a replacement for existing comprehensive diagnostic algorithms, but as a valuable supplement to them in the early stages. Integrating LI into established assessment scales (e.g., the Alvarado scale) can enhance their objectivity and informative value, particularly in borderline cases or when diagnostic resources are limited [8–10].

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A critical barrier to incorporating LI into the differential diagnosis algorithm for AAP in young children is the lack of evidence specifically for this population. Their actual diagnostic effectiveness and differential diagnostic significance have not been studied specifically for distinguishing between surgical (AA) and nonsurgical (FBD) causes of AAP in this complex group of patients [8–10].

Thus, evaluating the diagnostic effectiveness of LI for the differential diagnosis of AAP, particularly the distinction between AA and FBD, in children under 6 years of age — including the determination of reference values and the identification of the most informative indicators — is a highly relevant task in modern pediatrics and pediatric surgery. Resolving this issue could significantly improve diagnostic accuracy, reduce the incidence of complications, and optimize patient management strategies.

AIM

To evaluate the effectiveness of comprehensive leukocyte indices in the differential diagnosis of acute abdominal pain in children under 6 years of age.

MATERIALS AND METHODS

A cohort, comparative, retrospective study was conducted involving 75 children with AAP (AA, n=35; FBD, n=40), aged 1 month to 6 years. The children were hospitalized within 1–72 hours of the onset of initial symptoms. Healthy children of the same age constituted the control group (CG) (n=55).

Inclusion criteria: clinical diagnosis of AA or FBD (at discharge from the hospital), hospitalized for elective surgical treatment of a pathological condition, age ranging from 1 month to 6 years, consent of parents or guardians to participate in the study.

Exclusion criteria: failure to meet inclusion criteria, congenital malformations and abdominal neoplasms, HIV infection.

Complete blood count (CBC) parameters were analyzed (performed within 1 hour of admission). Based on the complete blood count data, integral leukocyte indices (ILI) were calculated [9, 10]. In practice, calculating ILI data does not require special software and can be performed by a physician using Microsoft Excel (or similar software), as well as manually.

The data were analyzed using STATISTICA 13.3 with nonparametric methods. Continuous variables are expressed as medians (Me) with confidence intervals (95% CI) or means (M) and standard deviations. The Mann–Whitney U test was used to compare two independent samples in the absence of evidence of a normal distribution of the data. Differences were considered statistically significant at a p-value of less than 0.05.

RESULTS AND DISCUSSION

In CG patients ILI was studied, and reference values were established for children under 6 years of age. The status of the overall reactive potential was assessed based on the calculation of integral indices [9, 10].

Erythrocyte Load Coefficient (ELC). This indicator indirectly reflects the degree of endogenous intoxication and inflammatory processes in the body. It is based on the ability of erythrocyte membranes to adsorb toxic metabolites, inflammatory mediators, and tissue breakdown products on their surface. An increase in ELC indicates increased absorption of pathological substances on erythrocytes, which is a marker of toxic exposure [9, 10].

Cellular-Phagocytic Potential (CPP). This indicator reflects the overall ability of blood immune cells (primarily neutrophils and monocytes) to perform phagocytosis. The higher the CPP level, the greater the body's protective capacity [9, 10].

Immunolymphocytic Potential (ILP). This indicator reflects the functional activity and reserve capacity of lymphocytes. A decrease in ILP directly indicates functional insufficiency of the lymphocytic component [9, 10].

Allergic Predisposition of the Body (APB). This indicator is primarily based on the eosinophil level. It serves as an indirect marker of the presence and activity of an inflammatory process (parasitic, autoimmune) in the body. A decrease in APB indicates infectious inflammatory phenomena, while an increase in APB indicates an autoimmune or allergic process [9, 10].

The degree of endogenous intoxication was assessed according to the calculation of integral indices.

Leukocyte Intoxication Index (LII). This indicator takes into account changes in the leukocyte

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formula, the ratio of different types of leukocytes, and the appearance of immature and degenerative forms of neutrophils. An increase in LII is associated with an increase in toxic burden and severity of the condition [9, 10].

Modified Leukocyte Intoxication Index (MLII). This is an improved formula for assessing the severity of endogenous intoxication and the inflammatory process, calculated on the basis of the blood leukocyte formula. Its calculation also includes eosinophils and plasma cells, with correction for zero values [9, 10].

Neutrophil Reactive Response (NRR). This indicator reflects the intensity of the neutrophil response to inflammation or intoxication. Unlike LII, it focuses only on the neutrophilic component [9, 10].

Body Resistance Index (BRI). This indicator assesses the ability of the immune system for emergency mobilization during acute inflammation or intoxication. An increase in BRI indicates immune hyperreactivity (acute bacterial process, pronounced intoxication), while a decrease in BRI indicates depletion of reserves (severe sepsis, viral infections, immunodeficiency) [9, 10].

Blood Leukocyte Shift Index (BLSI). This index reflects the presence of immature forms of the neutrophilic component in response to inflammation or intoxication. An increase in BLSI indicates an acute bacterial process and the release of immature neutrophils from the bone marrow into the bloodstream, while a decrease in BLSI is observed in viral infections or depletion of the granulocytic lineage [9, 10].

Lymphocyte-Granulocyte Index (LGI). This indicator reflects the balance between lymphocytes and neutrophils, and the immune response in the hemogram. An increase in LGI indicates predominance of the lymphocytic component (typical of viral infections and autoimmune processes), while a decrease in LGI indicates dominance of the neutrophilic response (typical of acute bacterial infections and pronounced intoxication) [9, 10].

Garkavi Index (GI). This indicator reflects the relationship between two components of immunity—cellular and humoral. Its key essence is the assessment of the adaptive tension of the body during inflammation, intoxication, or stress. A decrease in GI indicates dominance of the neutrophilic component, characteristic of acute bacterial infections. An increase in GI indicates predominance of the lymphocytic response, typical of viral infections, chronic inflammation, and autoimmune processes. It is also observed in depletion of the neutrophilic lineage [9, 10].

Leukocyte-to-Erythrocyte Sedimentation Rate Ratio Index (LESRI). This indicator assesses the relationship between the cellular and humoral components of the inflammatory response. An increase in LESRI indicates predominance of an acute cellular response, where leukocytosis rises faster than ESR. A decrease in LESRI indicates dominance of the humoral immune response, where ESR is elevated despite normal or reduced leukocyte levels [9, 10].

Krebs Index (KI). This indicator reflects the ratio between neutrophils and lymphocytes in peripheral blood. An increase in KI indicates acute bacterial infections and stress conditions, while a decrease in KI is interpreted as a manifestation of viral infection or depletion of the neutrophilic component [9, 10].

Nuclear Endotoxicosis Index (NEI). This indicator assesses the degree of toxic damage to neutrophils during severe intoxication. An increase in NEI is associated with the severity of endotoxicosis and reflects the accumulation of toxins that damage blood cells [9, 10].

Comparing the groups of children with FBD and AA according to the above-mentioned ILI, the following results were obtained.

The ELC in the group of children with FBD was 0.53±0.33 conventional units, Me=0.43 (95% CI 0.28–0.41), which was significantly higher than in the CG (0.43±0.24 conventional units, $p < 0.05$) and indicated the presence of a moderate inflammatory process and intoxication. In the group of patients with AA, the ELC was 0.88±0.76 conventional units, Me=0.59 (95% CI 0.62–1.01), which sharply and significantly exceeded both the CG values and the values of the FBD group ($p < 0.01$) (Fig. 1). This indicates a pronounced inflammatory process and severe intoxication in AA. Objective confirmation of significant inflammation in the vermiform appendix in all patients with AA confirms the diagnostic value of ELC for this pathology in this age group.

The CPP in the group of children with FBD was 685.64±287.79 conventional units, Me=652.54 (95% CI 237.29–365.78), which was slightly higher than in the CG (604.10±238.14 conventional

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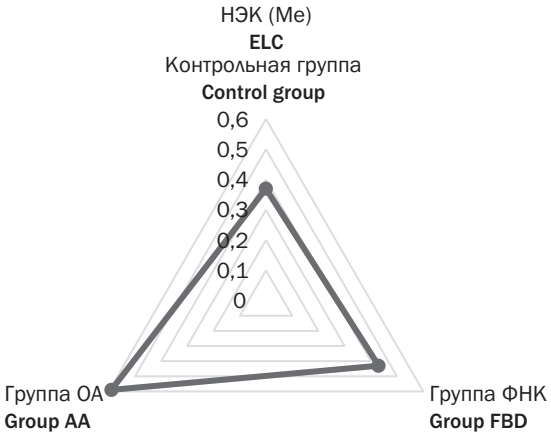

Fig. 1. Erythrocyte loading coefficient (ELC) levels in the study groups: OA — acute appendicitis; FBD — functional bowel disorders (here and further in the figures) (the figure is prepared by the authors)

Рис. 1. Уровень нагрузочного эритроцитарного коэффициента (НЭК) в исследуемых группах: ОА — острый аппендицит; ФНК — функциональные нарушения кишечника (здесь и далее на рисунках) (рисунок подготовлен авторами)

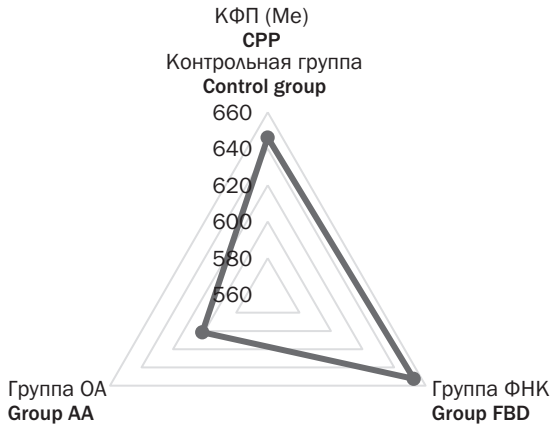

Fig. 2. Cell-phagocytic potential (CPP) levels in the study groups (the figure is prepared by the authors)

Рис. 2. Уровень клеточно-фагоцитарного потенциала (КФП) в исследуемых группах (рисунок подготовлен авторами)

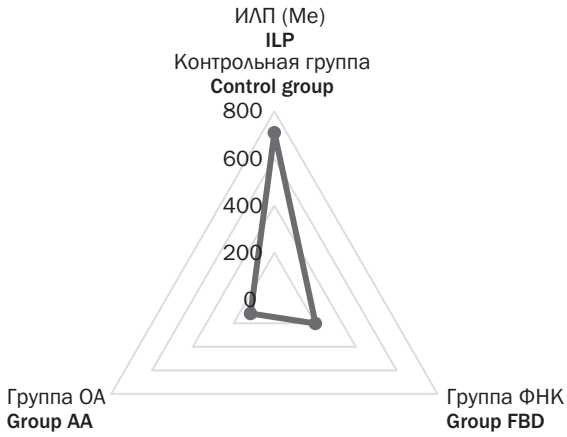

Fig. 3. Immunolymphocytic potential (ILP) levels in the study groups (the figure is prepared by the authors)

Рис. 3. Уровень иммунолимфоцитарного потенциала (ИЛП) в исследуемых группах (рисунок подготовлен авторами)

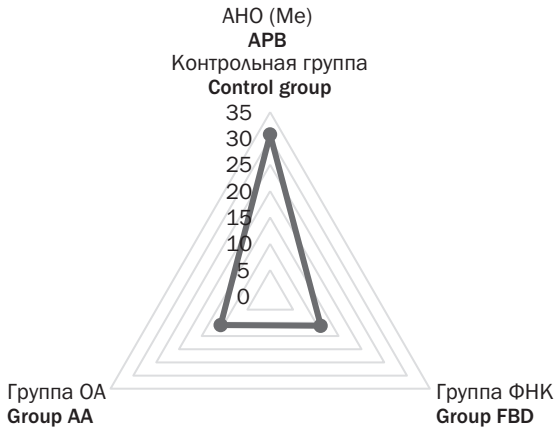

Fig. 4. Allergic predisposition of the body (APB) levels in the study groups (the figure is prepared by the authors)

Рис. 4. Уровень аллергической настроенности организма (АНО) в исследуемых группах (рисунок подготовлен авторами)

units, p >0.05) and indicated activation of nonspecific defense mechanisms in response to a moderate inflammatory process in FBD. In the group of patients with AA, the index was 641.7±195.6 conventional units, Me=601.45 (95% CI 159.85–252.09). These index values were slightly higher than in the CG but showed marked differences compared with the FBD group (p >0.05) (Fig. 2). These values may reflect either insufficient activation of phagocytosis to control acute inflammation (which contributed to the development of AA) or depletion of protective capacities (decompensation) against the background of a severe inflammatory process.

The ILP in the group of children with FBD was 287.21±272.83 conventional units, Me=201.92 (95% CI 224.96–346.77), which was significantly lower than in the CG (646.99±265.64 conventional units, p <0.001). In the group of patients with AA, the index was 147.41±177.87 conventional units, Me=116.79 (95% CI 145.37–229.24), and was even more significantly reduced compared with both the CG (p <0.001) and FBD (p <0.01) (Fig. 3). Since ILP reflects the activity of the

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lymphocytic component (specific immunity), a pronounced decrease in both groups, especially in AA, is characteristic of inflammatory processes of bacterial origin, where redistribution of immune resources and/or suppression of lymphopoiesis occurs.

The APB in the group of children with FBD was 16.02±12.11 conventional units, Me=11.10 (95% CI 8.62–19.25), which was significantly lower than in the CG (38.15±32.72 conventional units, p <0.001). In the group of patients with AA, the index was 15.17±11.25 conventional units, Me=10.86 (95% CI 6.29–17.69), which was also lower than in the CG (Fig. 4). Compared with the CG, both groups demonstrated more than a two-fold decrease in the index (p=0.01), which may be interpreted as an acute inflammatory process. The index values between the study groups differed insignificantly (p ≥0.05).

The LII in the group of children with FBD was 0.86±1.29 conventional units, Me=0.44 (95% CI 1.08–1.60), which was slightly higher than in the CG (0.33±0.59 conventional units, p <0.01). In the group of patients with AA, the index was 4.84±5.58 conventional units, Me=1.96 (95% CI 4.56–7.19), thus sharply and significantly exceeding both the CG and the FBD group values (p <0.001) (Fig. 5). This clearly demonstrates the severity of endogenous intoxication and inflammatory changes in AA compared with FBD.

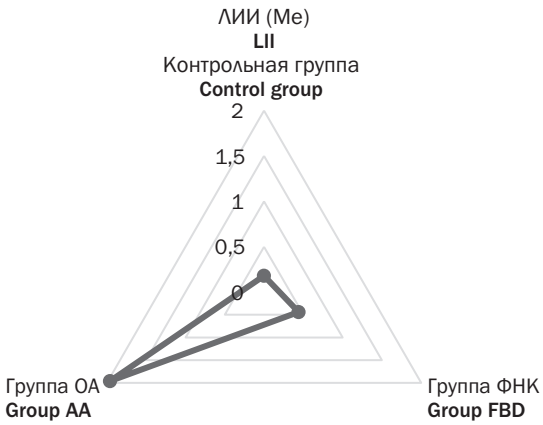

Fig. 5. Leukocyte intoxication index (LII) levels in the study groups (the figure is prepared by the authors)

Рис. 5. Уровень лейкоцитарного индекса интоксикации (ЛИИ) в исследуемых группах (рисунок подготовлен авторами)

Fig. 6. Modified leukocyte intoxication index (LIIm) levels in the study groups (the figure is prepared by the authors)

Рис. 6. Уровень лейкоцитарного индекса интоксикации модифицированного (ЛИИм) в исследуемых группах (рисунок подготовлен авторами)

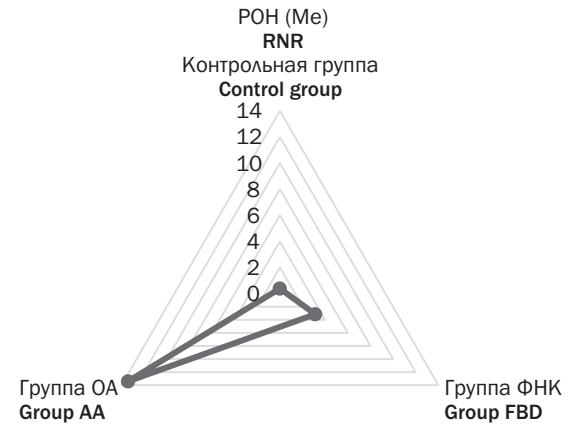

Fig. 7. Reactive neutrophil response (RNR) levels in the study groups (the figure is prepared by the authors)

Рис. 7. Уровень реактивного ответа нейтрофилов (РОН) в исследуемых группах (рисунок подготовлен авторами)

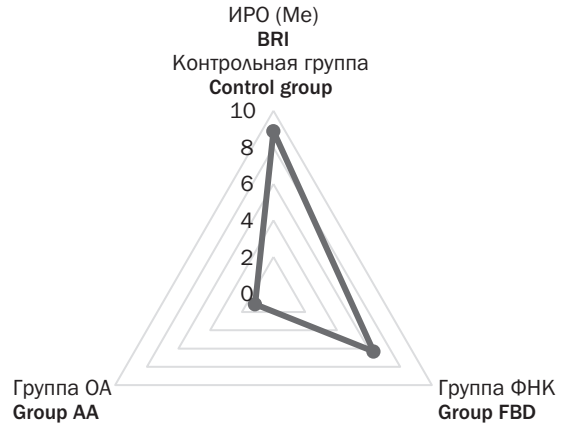

Fig. 8. Body resistance index (BRI) levels in the study groups (the figure is prepared by the authors)

Рис. 8. Уровень индекса резистентности организма (ИРО) в исследуемых группах (рисунок подготовлен авторами)

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The modified LII in the group of children with FBD was 3.27±2.57 conventional units, Me=2.57 (95% CI 1.78–3.76), which was slightly higher than in the CG (0.88±0.68 conventional units, p <0.001). In the group of patients with AA, the index was 4.32±3.24 conventional units, Me=3.29 (95% CI 2.92–5.25; p <0.001) (Fig. 6). Considering the differences in the obtained values, this index quite accurately (p <0.001) reflects the severity of the inflammatory process.

The NRR in the group of children with FBD was 9.21±15.36 conventional units, Me=3.13 (95% CI 12.19–20.78), which was significantly higher than in the CG (0.88±1.29 conventional units, p <0.001). In the group of patients with AA, the index was 15.54±13.07 conventional units, Me=13.43 (95% CI 9.81–19.59), which was also significantly higher than in the CG (p <0.001) and in the FBD group (p <0.05) (Fig. 7). As a modification of LII, NRR confirms the pattern: the severity of inflammatory changes and intoxication is maximal in AA, moderate in FBD, and minimal in the CG. A correlation was found between increased NRR and the severity of the process.

The BRI in the group of children with FBD was 33.59±13.66 conventional units, Me=6.32 (95% CI 105.14–156.19), and was significantly higher than in the CG (19.52±25.53 conventional units, p <0.05). This may be regarded as an adequate response of the body's defense systems to moderate inflammation in FBD. In the group of patients with AA, the index was 5.82±9.69 conventional units, Me=1.16 (95% CI 7.90–12.54), and was significantly lower than in the CG (p <0.001) (Fig. 8). Such a sharp decrease in BRI indicates suppression of the body's resistance in AA, reflecting the severity of the condition and decompensation of defense mechanisms.

The BLSI in the group of children with FBD was 3.02±2.57 conventional units, Me=2.33 (95% CI 2.15–3.19), and was significantly higher than in the CG (1.01±0.78 conventional units, p <0.001). In the group of patients with AA, the index was 4.51±2.88 conventional units, Me=3.76 (95% CI 2.36–3.72), exceeding the values in both the CG (p <0.001) and the FBD group (p <0.05) (Fig. 9). The obtained data confirm the presence of an inflammatory process in both groups, with greater severity in AA. However, the difference between FBD and AA is less pronounced than their difference from the CG, which may indicate relatively low specificity of BLSI for differentiating these two pathologies compared with other indices (e.g., ILP, LII, NRR).

The LGI in the group of children with FBD was 5.72±7.98 conventional units, Me=3.19 (95% CI 6.67–9.92), which was lower than in the CG (14.19±11.09 conventional units, p <0.001). In the group of patients with AA, the index was 2.45±3.31 conventional units, Me=1.84 (95% CI 2.71–4.27), which was significantly lower than in both the CG and the FBD group (p <0.001) (Fig. 10). A significant decrease in LGI in the

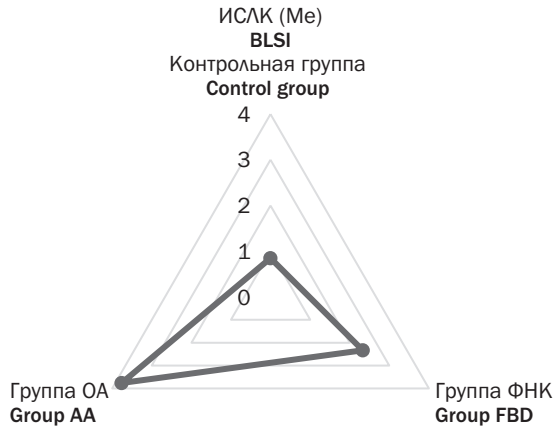

Fig. 9. Blood leukocyte shift index (BLSI) levels in the study groups (the figure is prepared by the authors)

Рис. 9. Уровень индекса сдвига лейкоцитов крови (ИСЛК) в исследуемых группах (рисунок подготовлен авторами)

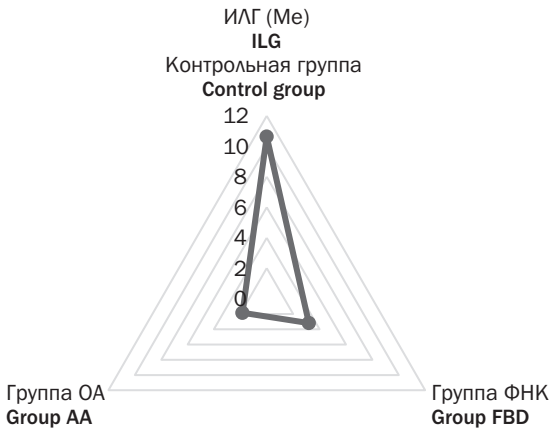

Fig. 10. Lymphocytic granulocytic index (ILG) levels in the study groups (the figure is prepared by the authors)

Рис. 10. Уровень индекса лимфоцитарно-гранулоцитарного (ИЛГ) в исследуемых группах (рисунок подготовлен авторами)

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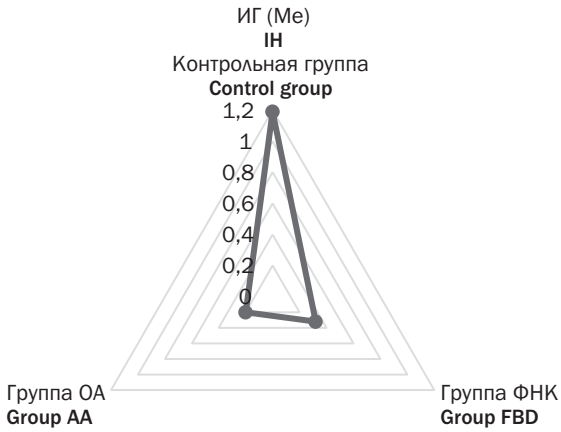

Fig. 11. Harkavi index (IH) levels in the study groups (the figure is prepared by the authors)

Рис. 11. Уровень индекса Гаркави (ИГ) в исследуемых группа (рисунок подготовлен авторами)

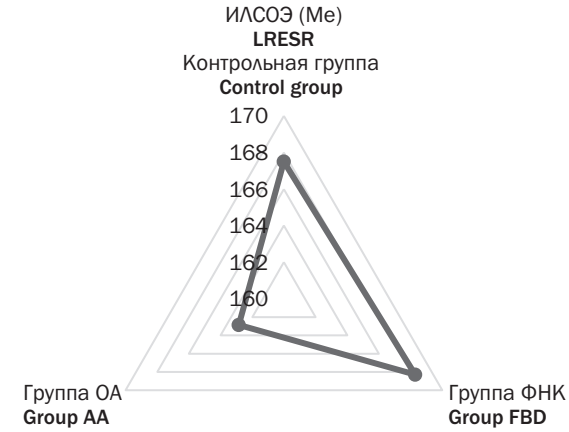

Fig. 12. Leukocyte ratio and ESR index (LRESR) levels in the study groups (the figure is prepared by the authors)

Рис. 12. Уровень индекса соотношения лейкоцитов и СОЭ (ИЛСОЭ) в исследуемых группах (рисунок подготовлен авторами)

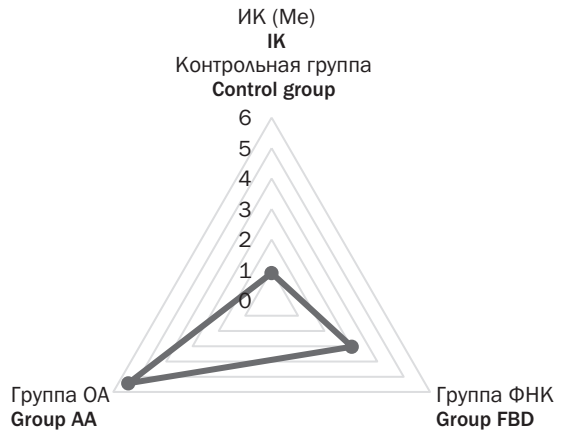

Fig. 13. Krebs index (IK) levels in the study groups (the figure is prepared by the authors)

Рис. 13. Уровень индекса Кребса (ИК) в исследуемых группах (рисунок подготовлен авторами)

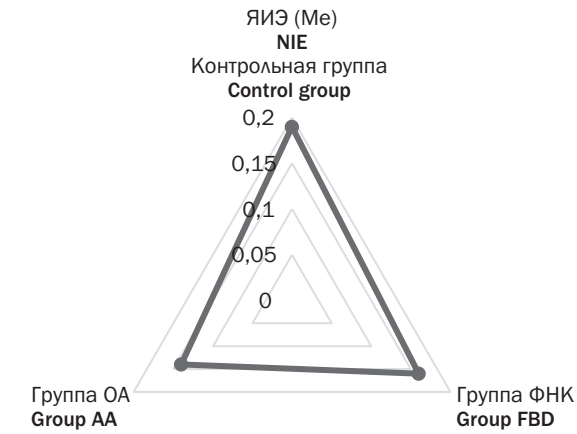

Fig. 14. Nuclear index of endotoxicosis (NIE) levels in the study groups (the figure is prepared by the authors)

Рис. 14. Уровень ядерного индекса эндотоксикоза (ЯИЭ) в исследуемых группах (рисунок подготовлен авторами)

pathological groups (especially in AA) compared with the CG indicates intoxication by autolysis products.

The GI in the group of children with FBD was 0.39±0.34 conventional units, Me=0.32 (95% CI 0.05–1.42), which was lower than in the CG (1.65±1.36 conventional units, p <0.001). In the group of patients with AA, the index was 0.29±0.41 conventional units, Me=0.20 (95% CI 0.09–0.56) (Fig. 11). The results in both groups were significantly lower than in the CG (p <0.001), indicating a reduced immune response to the inflammatory process (typical of acute bacterial infections); however, the difference between the FBD and AA groups was small (p >0.05).

The L/ESR ratio in the group of children with FBD was 202.41±106.51 conventional units, Me=168.29 (95% CI 88.66–133.41), which was slightly higher than in the CG (196.28±97.88 conventional units, p >0.05). In the group of patients with AA, the index was 188.66±111.88 conventional units, Me=162.85 (95% CI 90.50–146.59), which was slightly lower than in the CG. The differences between the FBD and AA groups were statistically insignificant (p >0.05) (Fig. 12). The observed fluctuations relative to the CG values do not provide a clear picture for differentiating the infectious nature of inflammation (where an increase would be expected) from the autoimmune nature (where a decrease would be expected) in

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either group. The results appear questionable. It is possible that studying a larger number of observations would reveal more significant patterns.

The KI in the group of children with FBD was 4.49±4.75 conventional units, Me=3.04 (95% CI 3.97–5.90), which was significantly higher than in the CG (1.09±0.91 conventional units, p <0.001). In the group of patients with AA, the index was 6.06±3.25 conventional units, Me=5.43 (95% CI 2.66–4.19), which was also significantly higher than in the CG (p <0.001) (Fig. 13). Exceeding the reference values in both groups indicates the presence of a certain degree of endogenous intoxication. Higher index values in AA compared with FBD (p >0.05) indicate greater severity of intoxication.

The NEI in the group of children with FBD was 0.22±0.16 conventional units, Me=0.16 (95% CI 0.13–0.19), which was slightly lower than in the CG (0.25±0.17 conventional units, p >0.05). In the group of patients with AA, the index was 0.19±0.14 conventional units, Me=0.14 (95% CI 0.11–0.18), which was also slightly lower than in the CG (p >0.01) (Fig. 14). The differences between the FBD and AA groups were statistically insignificant (p >0.05). The obtained results (a decrease relative to the CG in both groups) contradict the expected increase in the index in endotoxicosis. This may indicate either insufficient sensitivity of NEI in the studied processes or an insufficient sample size for evaluating this parameter.

A COMPARATIVE ANALYSIS OF THE DIAGNOSTIC EFFECTIVENESS OF THE LEUKOCYTE INDEX

For a comprehensive assessment of the diagnostic value of the ILI, a three-stage comparison was performed. The pathology groups (FBD, AA) and the control group (CG) were compared to assess sensitivity to inflammatory changes. The AA and FBD groups were compared with each other to evaluate differential diagnostic potential.

ELC in the FBD group (0.53±0.33 conventional units) did not differ statistically significantly from the CG (0.43±0.24 conventional units, p <0.05) (Fig. 15). In the AA group, a significant increase in the parameter to 0.88±0.77 conventional units was recorded. Differences compared with the CG (p <0.01) and the FBD group (p <0.01) were statistically significant, confirming the differential diagnostic potential of ELC for distinguishing these pathological conditions. The value in the

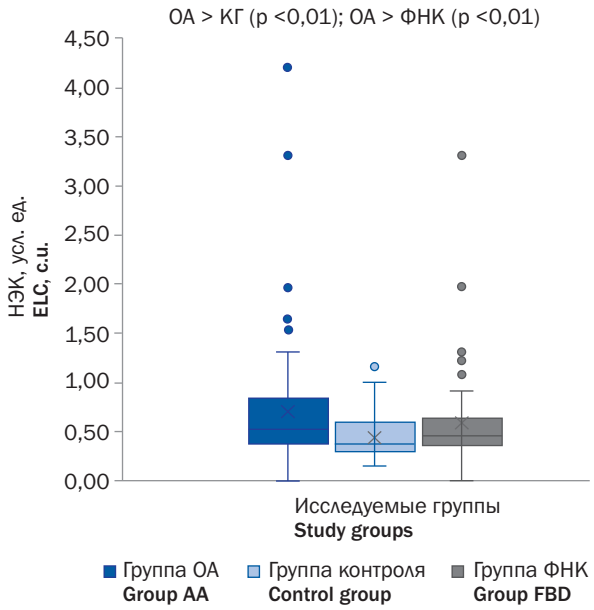

Fig. 15. Comparative characteristics of the erythrocyte loading coefficient (ELC) level in the studied groups (the figure is prepared by the authors)

Рис. 15. Сравнительная характеристика уровня нагрузочного эритроцитарного коэффициента (НЭК) в исследуемых группах (рисунок подготовлен авторами)

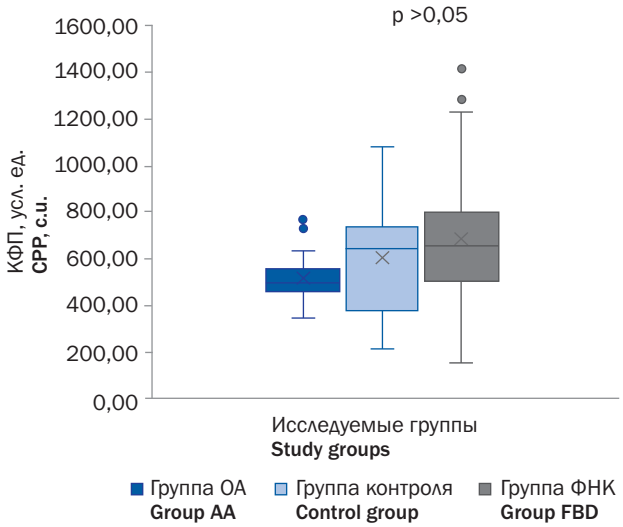

Fig. 16. Comparative characteristics of the cell-phagocytic potential (CPP) level in the studied groups (the figure is prepared by the authors)

Рис. 16. Сравнительная характеристика уровня клеточно-фагоцитарного потенциала (КФП) в исследуемых группах (рисунок подготовлен авторами)

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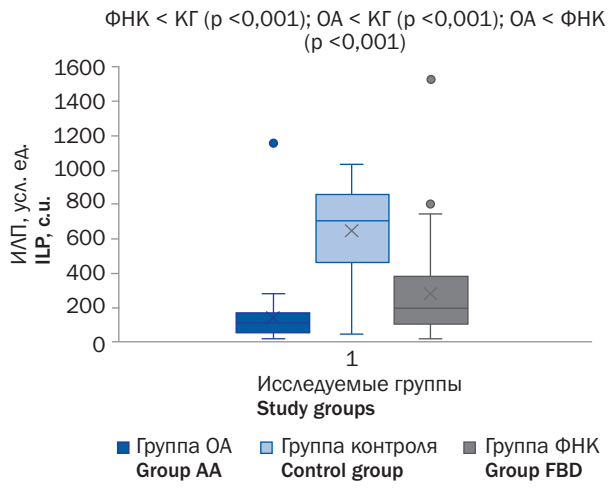

Fig. 17. Comparative characteristics of the immunolymphocytic potential (ILP) level in the studied groups (the figure is prepared by the authors)

Рис. 17. Сравнительная характеристика уровня иммунолимфоцитарного потенциала (ИЛП) в исследуемых группах (рисунок подготовлен авторами)

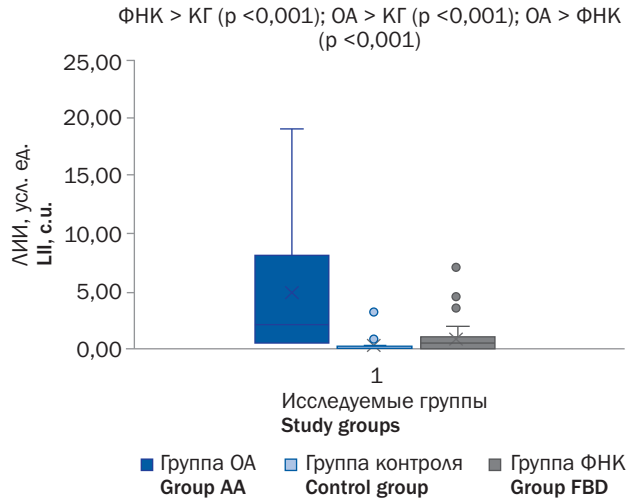

Fig. 18. Comparative characteristics of the leukocyte intoxication index (LII) level in the studied groups (the figure is prepared by the authors)

Рис. 18. Сравнительная характеристика уровня лейкоцитарного индекса интоксикации (ЛИИ) в исследуемых группах (рисунок подготовлен авторами)

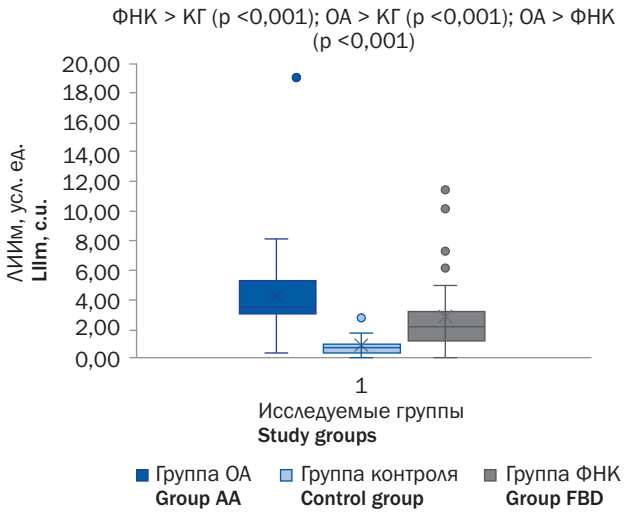

Fig. 19. Comparative characteristics of the leukocyte intoxication index (LIIm) level in the studied groups (the figure is prepared by the authors)

Рис. 19. Сравнительная характеристика уровня лейкоцитарного индекса интоксикации модифицированного (ЛИИм) в исследуемых группах (рисунок подготовлен авторами)

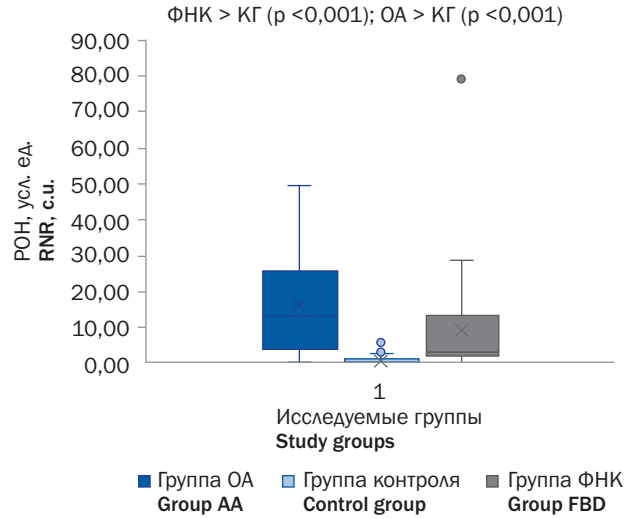

Fig. 20. Comparative characteristics of the reactive neutrophil response (RNR) level in the studied groups (the figure is prepared by the authors)

Рис. 20. Сравнительная характеристика уровня реактивного ответа нейтрофилов (РОН) в исследуемых группах (рисунок подготовлен авторами)

AA group exceeded the ELC in the CG by more than two standard deviations. These findings suggest that ELC may be considered a promising marker for differentiating surgical (AA) and functional (FBD) pathology. The statistically significant increase in ELC in the AA group compared with the FBD group is consistent with its potential role as an indicator of destructive processes.

CPP in the FBD group (685.64±287.79 conventional units) did not differ statistically significantly from the CG (604.11±238.14 conventional units, p >0.05) (Fig. 16). In the AA group

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(641.70±195.60 conventional units), the CPP level also showed no statistically significant difference compared with the CG (p >0.05). No statistically significant differences were observed between the groups either. At this stage of the study, these findings call into question the clinical utility of CPP as a diagnostic marker for differentiating the presented pathological conditions.

ILP in the FBD group (287.21±272.83 conventional units) was significantly lower than in the CG (646.99±265.64 conventional units, p <0.001) (Fig. 17). In the AA group, a pronounced decrease in the parameter was recorded (147.41±177.88 conventional units), statistically significant compared with both the CG (p <0.001) and the FBD group (p <0.01), corresponding to severe lymphopenia. The observed marked decrease in ILP in the AA group indicates its potential as a marker of immunosuppression in this pathology, consistent with the assumption that the degree of ILP reduction correlates with disease severity.

LII in the FBD group (0.86±1.29 conventional units) was statistically significantly higher than in the CG (0.33±0.59 conventional units, p <0.01), corresponding to a moderate increase (Fig. 18). In the AA group, a pronounced increase in the parameter was observed (4.84±5.58 conventional units), statistically significant compared with both the CG (p <0.001) and the FBD group (p <0.01), with a mean value exceeding the control by 14.4 times. These findings confirm the role of LII as an important indicator of intoxication severity, while its marked elevation in the AA group supports its potential value for identifying purulent-destructive forms.

Modified LII in the FBD group (2.88±2.42 conventional units) was statistically significantly higher than in the CG (0.88±0.68 conventional units, p <0.001) (Fig. 19). In the AA group, a pronounced increase in the parameter was recorded (4.37±2.92 conventional units), statistically significant compared with both the CG (p <0.001) and the FBD group (p <0.01). The observed marked elevation of modified LII in the AA group compared with both the CG and the FBD group is consistent with its potential role as a marker of inflammatory severity and endotoxicosis characteristic of AA. The high variability of this parameter in the studied groups (standard deviation comparable to the mean value) should be taken into account when interpreting individual measurements.

NRR in the FBD group (9.21±15.36 conventional units) was statistically significantly higher than in the CG (0.88±1.29 conventional units, p <0.001) (Fig. 20). In the AA group, a pronounced increase

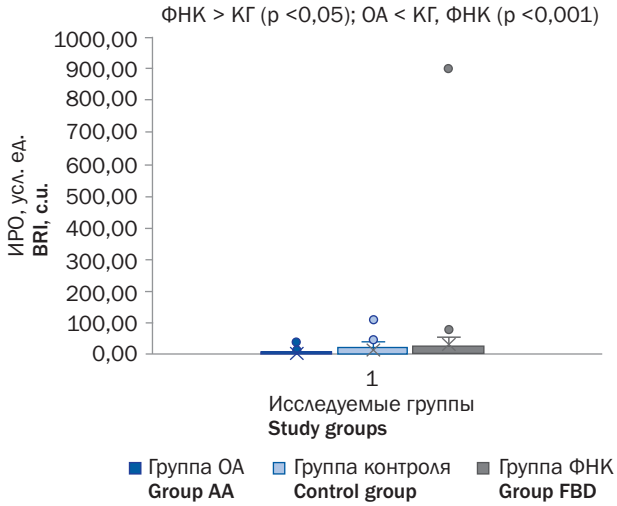

Fig. 21. Comparative characteristics of the body resistance index (BRI) level in the studied groups (the figure is prepared by the authors)

Рис. 21. Сравнительная характеристика уровня индекса резистентности организма (ИРО) в исследуемых группах (рисунок подготовлен авторами)

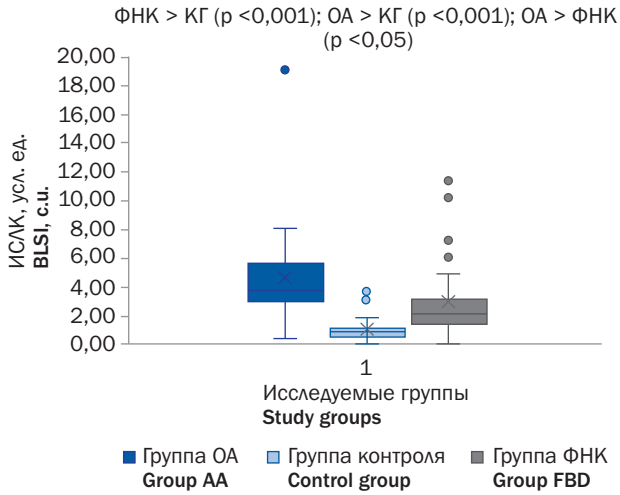

Fig. 22. Comparative characteristics of the blood leukocyte shift index (BLSI) level in the studied groups (the figure is prepared by the authors)

Рис. 22. Сравнительная характеристика уровня индекса сдвига лейкоцитов крови (ИСЛК) в исследуемых группах (рисунок подготовлен авторами)

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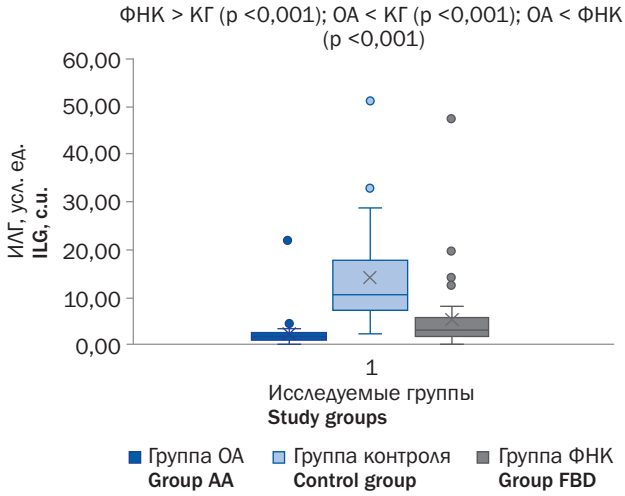

Fig. 23. Comparative characteristics of the lymphocytic granulocytic index (ILG) level in the studied groups (the figure is prepared by the authors)

Рис. 23. Сравнительная характеристика уровня индекса лимфоцитарно-гранулоцитарного (ИЛГ) в исследуемых группах (рисунок подготовлен авторами)

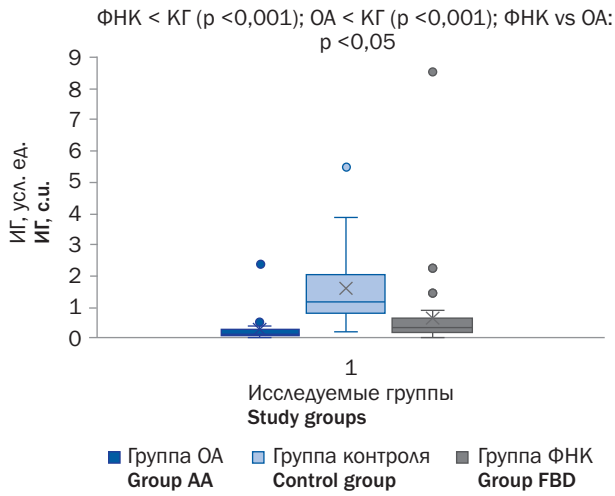

Fig. 24. Comparative characteristics of the Harkavi index (IH) level in the studied groups (the figure is prepared by the authors)

Рис. 24. Сравнительная характеристика уровня индекса Гаркави (ИГ) в исследуемых группах (рисунок подготовлен авторами)

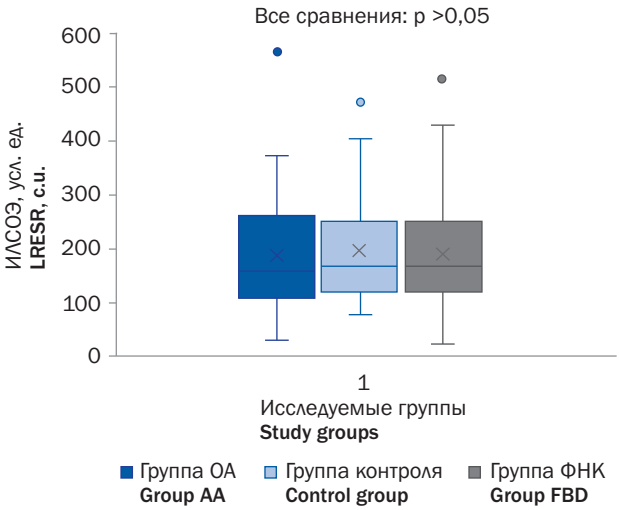

Fig. 25. Comparative characteristics of the leukocyte ratio and ESR index (LRESR) level in the studied groups (the figure is prepared by the authors)

Рис. 25. Сравнительная характеристика уровня индекса соотношения лейкоцитов и СОЭ (ИЛСОЭ) в исследуемых группах (рисунок подготовлен авторами)

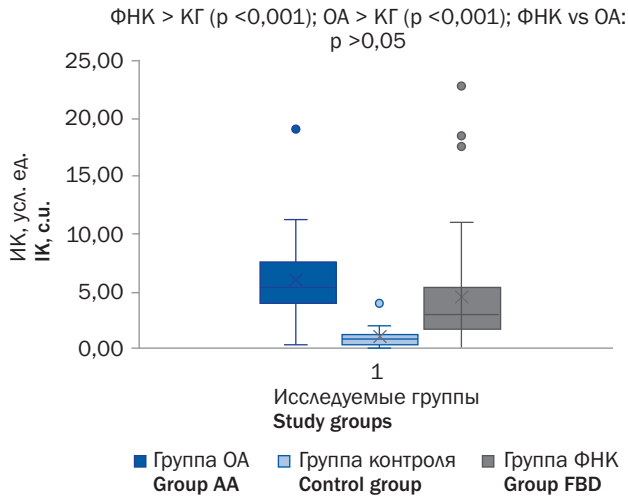

Fig. 26. Comparative characteristics of the Krebs index (IK) level in the studied groups (the figure is prepared by the authors)

Рис. 26. Сравнительная характеристика уровня индекса Кребса (ИК) в исследуемых группах (рисунок подготовлен авторами)

in the parameter was recorded (15.54±13.07 conventional units), statistically significant compared with the CG (p <0.001). Despite the significant increase in pathological conditions, the high variability of the parameter, with a standard deviation exceeding 100% of the mean value in both the FBD and AA groups, substantially reduces the diagnostic reliability of NRR in single measurements, suggesting its potential value mainly for dynamic monitoring.

BRI in the FBD group (33.59±12.66 conventional units) was slightly but statistically significantly higher than in the CG (19.52±25.53 conventional units, p <0.05) (Fig. 21). In the AA group, a significant decrease in the parameter was observed (5.82±9.69 conventional units),

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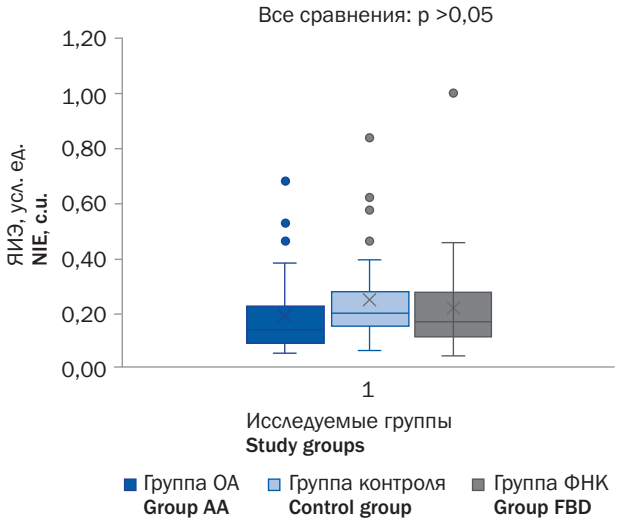

Fig. 27. Comparative characteristics of the nuclear index of endotoxicosis (NIE) level in the studied groups (the figure is prepared by the authors)

Рис. 27. Сравнительная характеристика уровня ядерного индекса эндотоксикоза (ЯИЭ) в исследуемых группах (рисунок подготовлен авторами)

statistically significant compared with both the CG and the FBD group (p <0.001). These findings reflect decreased body resistance in AA; however, the difference from FBD may be influenced by the high variability of the parameter in the FBD group, which limits the specificity of this index.

BLSI in the FBD group (3.02±2.57 conventional units) was statistically significantly higher than in the CG (1.01±0.78 conventional units, p <0.001) (Fig. 22). In the AA group, a pronounced increase in the parameter was recorded (4.51±2.88 conventional units), statistically significant compared with both the CG (p <0.001) and the FBD group (p <0.05). BLSI demonstrates the ability to reflect the intensity of the inflammatory process; however, overlapping values between the FBD (Me=2.33) and AA (Me=3.76) groups limit its specificity for differential diagnosis, suggesting that it is more appropriate when used in combination with other markers.

LGI in the FBD group (5.72±7.98 conventional units) was statistically significantly lower than in the CG (14.19±11.09 conventional units, p <0.001) (Fig. 23). In the AA group, a pronounced decrease in the parameter was recorded (2.45±3.31 conventional units), statistically significant compared with both the CG (p <0.001) and the FBD group (p <0.001). The observed marked decrease in LGI under pathological conditions contradicts the theoretical expectation of its increase during infectious-inflammatory processes, indicating the need to revise the interpretative criteria and methodological aspects of its application for this pathology within the present study.

GI in the FBD group (0.39±0.34 conventional units) was statistically significantly lower than in the CG (1.65±1.36 conventional units, p <0.001) (Fig. 24). In the AA group, a comparable decrease was observed (0.29±0.41 conventional units), also statistically significant compared with the CG (p <0.001), but without significant differences compared with the FBD group (p >0.05), making this index of limited value for differential diagnosis of these conditions.

L/ESR Index in the FBD group (202.41±106.51 conventional units) did not differ statistically significantly from the CG (196.28±97.88 conventional units, p >0.05) (Fig. 25). In the AA group, the parameter (188.66±111.89 conventional units) also did not differ significantly from the CG (p >0.05) or from the FBD group (p >0.05). The absence of significant changes in the studied groups indicates that the L/ESR Index cannot be used for differential diagnosis of abdominal syndrome in children.

KI in the FBD group (4.49±4.75 conventional units) was statistically significantly higher than in the CG (1.09±0.91 conventional units, p <0.001) (Fig. 26). In the AA group, a pronounced increase in the parameter was observed (6.06±3.26 conventional units), statistically significant compared with both the CG and the FBD group (p <0.001). The statistically significant increase in KI confirms its sensitivity as a marker of endotoxicosis; however, the absence of a significant difference between the FBD and AA groups (p >0.05) indicates limited differential diagnostic potential for distinguishing these conditions at this stage.

NEI in the FBD group (0.22±0.16 conventional units) did not differ statistically significantly from the CG (0.250±0.170 conventional units, p >0.05) (Fig. 27). In the AA group (0.189±0.139 conventional units), no significant differences were also observed compared with either the CG (p >0.05) or the FBD group (p >0.05). These results indicate that NEI is not an informative marker for these pathologies.

CONCLUSION

The conducted study revealed a high differential diagnostic potential of the combination of the indices ELC, ILP, LII, modified LII, NRR, BRI,

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BLSI, and LGI for distinguishing acute appendicitis and functional bowel disorders in children. Statistically significant differences in these markers between the acute appendicitis and functional bowel disorder groups, as well as characteristic dynamics (in acute appendicitis: a pronounced increase in ELC, LII, modified LII, NRR, and BLSI; a significant decrease in ILP, BRI, and LGI), indicate the promise of their combined use. Our findings require validation in an independent patient cohort, i.e., under the conditions of a new prospective study conducted prior to establishing a final diagnosis, followed by analysis of the new results.

ADDITIONAL INFORMATION

Authors' contribution. R.F. Makhmutov — formulation and development of the idea, research objectives, final editing; G.A. Novikov — preparation, writing of the initial draft of the manuscript.

All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Consent for publication. Written consent was obtained from legal representatives of the patients for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Р.Ф. Махмутов — формулирование и развитие идеи, цели исследования, финальное редактирование; Г.А. Новиков — подготовка, написание первоначального черновика рукописи.

Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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REFERENCES

1. Salö M., Ohlsson B., Arnbjörnsson E., Stenström P. Appendicitis in children from a gender perspective. *Pediatr Surg Int*. 2015;31(9):845–853. https://doi.org/10.1007/s00383-015-3729-5.
2. Mahmutov R.F., Novikov G.A. Topical issues of diagnosing acute appendicitis in children of pre-school age. *Practical Medicine*. 2025;23(1):33–36. (In Russ.).
3. Yang H.R., Wang Y.C., Chung P.K., Chen W.K., Jeng L.B., Chen R.J. Role of leukocyte count, neutrophil percentage, and C-reactive protein in the diagnosis of acute appendicitis in the elderly. *Am Surg*. 2005;71(4):344–347.
4. Mahmutov R.F., Novikov G.A. A modern approach to the diagnosis of acute abdominal pain in children. In: Proceedings of the XXXII Congress of Pediatric Gastroenterologists of Russia and the CIS Countries "Current Issues of Abdominal Pathology in Children". Moscow; 2025. P. 47–49. (In Russ.).
5. Almaramhy H.H. Acute appendicitis in young children less than 5 years: review article. *Ital J Pediatr*. 2017;43(1):15. https://doi.org/10.1186/s13052-017-0335-2.
6. Nance M.L., Adamson W.T., Hedrick H.L. Appendicitis in the young child: a continuing diagnostic challenge. *Pediatr Emerg Care*. 2000;16(3):160–162. https://doi.org/10.1097/00006565-200006000-00005.
7. Chang Y.J., Chao H.C., Kong M.S., Hsia S.H., Yan D.C. Misdiagnosed acute appendicitis in children in the emergency department. *Chang Gung Med J*. 2010;33(5):551–557.
8. Vlasov A.P., Leshchankina N.Yu., Vlasova T.I., Markin O.V., Myshkina N.A. Endogenous intoxication in emergency abdominal surgery. New approaches to correction. Moscow: GEOTAR-Media; 2022. (In Russ.).
9. Novikov G.A., Mahmutov R.F. On the importance of leukocyte indices in the diagnosis of acute abdominal pain in infants. In: Collection of articles from the VII Scientific and Practical Conference "Scientific Avant-garde". Moscow; 2025. P. 491–497. (In Russ.).
10. Nesterova I.V., Chudilova G.A., Lomtatidze L.V., Kovalyova S.V., Chapurina V.N., Teterin Yu.V. The calculated index of neutrophilic granulocytes in the differential diagnosis of the severity of bacterial infectious and inflammatory diseases. *Effektivnaya farmakoterapiya*. 2024;20(38):34–44.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

(In Russ.). https://doi.org/10.33978/2307-3586-2024-20-38-34-44.
11. Gromov M.I., Rysev A.V., Zhuravlev Yu.F., Pivovarova L.P., Ariskina O.B., Markelova E.V. Leukocyte index of intoxication according to V.K. Ostrovskii as a criterion for assessing bacterial infection. *Grekov's Bulletin of Surgery*. 2023;182(2):53–58. (In Russ.). https://doi.org/10.24884/0042-4625-2023-182-2-53-58.
12. Azzini A.M., Dorizzi R.M., Sette P., Vecchi M., Coledan I., Righi E., Tacconelli E. A 2020 review on the role of procalcitonin in different clinical settings: an update conducted with the tools of the Evidence Based Laboratory Medicine. *Ann Translational Medicine*. 2020;8(9):610. https://doi.org/10.21037/atm-20-1855.

ЛИТЕРАТУРА

1. Salö M., Ohlsson B., Arnbjörnsson E., Stenström P. Appendicitis in children from a gender perspective. *Pediatr Surg Int*. 2015;31(9):845–853. https://doi.org/10.1007/s00383-015-3729-5.
2. Махмутов Р.Ф., Новиков Г.А. Актуальные вопросы диагностики острого аппендицита у детей преддошкольного и дошкольного возраста. *Практическая медицина*. 2025;23(1):33–36.
3. Yang H.R., Wang Y.C., Chung P.K., Chen W.K., Jeng L.B., Chen R.J. Role of leukocyte count, neutrophil percentage, and C-reactive protein in the diagnosis of acute appendicitis in the elderly. *Am Surg*. 2005;71(4):344–347.
4. Махмутов Р.Ф., Новиков Г.А. Современный взгляд на диагностику острой абдоминальной боли у детей. В кн.: Материалы XXXII Конгресса детских гастроэнтерологов России и стран СНГ «Актуальные проблемы абдоминальной патологии у детей». М.; 2025. С. 47–49.
5. Almaramhy H.H. Acute appendicitis in young children less than 5 years: review article. *Ital J Pediatr*. 2017;43(1):15. https://doi.org/10.1186/s13052-017-0335-2.
6. Nance M.L., Adamson W.T., Hedrick H.L. Appendicitis in the young child: a continuing diagnostic challenge. *Pediatr Emerg Care*. 2000;16(3):160–162. https://doi.org/10.1097/00006565-200006000-00005.
7. Chang Y.J., Chao H.C., Kong M.S., Hsia S.H., Yan D.C. Misdiagnosed acute appendicitis in children in the emergency department. *Chang Gung Med J*. 2010;33(5):551–557.
8. Власов А.П., Лещанкина Н.Ю., Власова Т.И., Маркин О.В., Мышкина Н.А. Эндогенная интоксикация в неотложной абдоминальной хирургии. Новые подходы к коррекции. М.: ГЭОТАР-Медиа; 2022.
9. Новиков Г.А., Махмутов Р.Ф. К вопросу о значении лейкоцитарных индексов в диагностике острой абдоминальной боли у детей первых лет жизни. В кн.: Сборник статей VII Научно-практической конференции «Научный авангард». М.; 2025. С. 491–497.
10. Нестерова И.В., Чудилова Г.А., Ломтатидзе Л.В., Ковалёва С. В., Чапурина В. Н., Тетерин Ю.В. Расчетный индекс нейтрофильных гранулоцитов в дифференциальной диагностике степени тяжести бактериальных инфекционно-воспалительных заболеваний. *Эффективная фармакотерапия*. 2024;20(38):34–44. https://doi.org/10.33978/2307-3586-2024-20-38-34-44.
11. Громов М.И., Рысев А.В., Журавлев Ю.Ф., Пивоварова Л.П., Арискина О.Б., Маркелова Е.В. Лейкоцитарный индекс интоксикации по В.К. Островскому как критерий оценки бактериальной инфекции. *Вестник хирургии имени И.И. Грекова*. 2023;182(2):53–58. https://doi.org/10.24884/0042-4625-2023-182-2-53-58.
12. Azzini A.M., Dorizzi R.M., Sette P., Vecchi M., Coledan I., Righi E., Tacconelli E. A 2020 review on the role of procalcitonin in different clinical settings: an update conducted with the tools of the Evidence Based Laboratory Medicine. *Ann Translational Medicine*. 2020;8(9):610. https://doi.org/10.21037/atm-20-1855.

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Review

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The significance of microcirculation disorders and changes in blood rheological characteristics for the development of inflammatory bowel diseases

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ABSTRACT. The review provides an analysis of literature data on changes in the blood microcirculation system at inflammatory bowel diseases and their impact on the development of general disorders in the body. It explores the consequences of damage to the inner lining of blood vessels (endothelium) and the slowdown in capillary blood flow. These processes are being studied because the hemostasis system and blood fluidity (haemorheology) ensure normal blood supply to tissues, and when these systems are disrupted, perfusion is severely impaired. An analysis of scientific data allows us to draw a clear conclusion: disruptions in microcirculation and a decrease in blood fluidity, primarily due to increased clumping of red blood cells and a loss of their flexibility, play a crucial role in the development of inflammatory bowel diseases. These abnormalities create a vicious cycle: the worse the blood supply to tissues, the more pronounced the tissue ischemia is, and the more severe the inflammation is. This combination causes the disease to worsen.

KEYWORDS: *inflammatory bowel disease, IBD, viscosity, inflammation, red blood cells, blood supply*

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Обзор

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Значение расстройств микроциркуляции и изменений реологических характеристик крови для развития воспалительных заболеваний кишечника

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РЕЗЮМЕ. В обзоре представлен анализ данных литературы об изменениях в системе микроциркуляции крови при воспалительных заболеваниях кишечника и их влиянии на развитие общих нарушений в организме. Разобрано, чем может обернуться травма внутренней выстилки сосудов (эндотелия) и изменение скорости капиллярного кровотока на более медленное. Эти процессы исследуются, поскольку система гемостаза и текучесть крови (гемореология) обеспечивают нормальное кровоснабжение тканей, а при их расстройстве перфузия серьезно нарушается. Анализ научных данных позволяет сделать однозначный вывод: сбои в микроциркуляции и ухудшение текучести крови, в первую очередь из-за повышенного слипания красных клеток крови и потери ими гибкости, играют решающую роль в развитии воспалительных заболеваний кишечника. Эти нарушения провоцируют порочный круг: чем хуже кровоснабжение тканей, тем более выражена тканевая ишемия и тем сильнее в них протекает воспаление. Это в совокупности провоцирует обострение болезни.

КЛЮЧЕВЫЕ СЛОВА: *воспалительные заболевания кишечника, ВЗК, вязкость, воспаление, красные клетки крови, кровоснабжение*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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INTRODUCTION

Inflammatory bowel diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), represent a serious medical and social problem in modern gastroenterology. The relevance of this group of diseases is multifactorial: their etiology remains unclear, the incidence among the working-age population continues to rise, and the course of the disease becomes chronic and recurrent. The main risk factors include complications that pose a life-threatening risk to the patient. The situation is further exacerbated by the lack of curative treatments and the need for expensive, long-term therapy. Patients' quality of life is significantly reduced as a result [1].

Currently, there is a trend toward the disease affecting younger age groups — 20% of all newly diagnosed cases of IBD occur in children under 6 years of age, and among adolescents, the peak incidence is between 15 and 29 years of age [2]. Data from various regions of Russia confirm the global trend of an increasing number of these diseases in children.

The significance of Crohn's disease and ulcerative colitis in pediatric practice cannot be overstated. These conditions strike children during their most active period of growth and development, a time when the body's need for proteins, fats, and carbohydrates — as well as micronutrients and macronutrients — is heightened. As a result, there is a decrease in appetite, as well as impaired absorption and metabolism in general; in the long term, such disruptions in intestinal absorption inhibit growth, weight gain, and skeletal mineralization. This leads to delayed puberty, an imbalance in the child's psycho-emotional state, and, consequently, reduced social adaptation [3].

THE ROLE OF MICROCIRCULATORY ALTERATIONS IN THE DEVELOPMENT OF INFLAMMATORY BOWEL DISEASE

Despite extensive research, the exact causes of IBD remain unclear. According to current understanding, the disease develops due to a combination of genetic predisposition and environmental factors, leading to a disruption in the regulation of the immune response to the intestinal microbiota and a loss of control over the inflammatory reaction in the intestinal mucosa [4, 5].

An important link in the pathogenesis is damage to the epithelial barrier, increased permeability, and the development of endogenous intoxication. These processes have a variety of negative effects on cellular structures and contribute to the maintenance of metabolic disturbances in IBD [6–8].

Although the pathogenesis of IBD has been studied in considerable detail, there is still no unified concept explaining the mechanisms of development and progression of UC and CD. Improving therapeutic efficacy is directly linked to an in-depth investigation of currently emerging individual pathogenetic pathways [8]. One such insufficiently studied aspect is the role of microcirculatory disorders.

Chronic inflammation in IBD is a complex process involving both immune and non-immune cells, including components of the microcirculatory bed. The inflammatory process in the intestine differs fundamentally from that in other organs. First, UC and CD are characterized by the phenomenon of leukocyte hyperadhesion to the vascular endothelium against a background of microvascular dysfunction [9]. Second, microcirculatory alterations maintain chronic inflammation through reduced tissue perfusion, development of ischemia, activation of the coagulation system, and angiogenesis leading to structural tissue remodeling [10–12].

Structural changes include remodeling and proliferation of endothelial cells in capillaries and venules, which contributes to the persistence of inflammation in the gastrointestinal tract [13]. Experimental and clinical observations have demonstrated an increased reticular structure of microvessels, as well as an increase in their diameter and density in patients with IBD [14, 15].

The severity of endothelial dysfunction correlates with disease severity and activity in both adults and children [16–19]. Microvascular disturbances are also associated with increased oxidative stress and represent a specific feature of intestinal involvement in IBD [20].

Perfusion studies demonstrate a reduction in small intestinal blood flow in CD, depending on the degree of inflammation [21]. In children with UC, changes in capillary blood flow velocity in the duodenum have been identified, which are not associated with inflammatory markers or disease activity [22]. The most pronounced reductions in

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blood volume and flow are observed in CD when inflammation is combined with fibrosis [23]. In the active phase of IBD, a significant deterioration in microcirculatory function is observed compared with remission [24]. Even in UC remission, an imbalance in mucosal blood supply persists, and incomplete restoration correlates with local ischemia [25].

Experimental data confirm that a decrease in capillary blood flow occurs already in the early stages of colitis. Impaired microcirculation precedes chronic histological changes and contributes to functional disturbances during disease progression, whereas its improvement is associated with stabilization of intestinal permeability [26].

THE EFFECT OF BLOOD RHEOLOGICAL PARAMETERS ON MICROCIRCULATION FUNCTION

The functioning of the microcirculatory system largely depends on the rheological parameters of blood, with erythrocytes serving as a universal model for studying the state of cytoplasmic membranes and cellular metabolism [27]. The study of erythrocyte membrane characteristics and their functional properties in IBD is of fundamental importance for understanding the pathogenesis of these diseases.

As the most numerous blood cells, red blood cells play a key role in microcirculation, ensuring oxygen delivery to tissues and responding to changes in its local concentration [28]. They determine the rheological properties of blood in the microvascular bed due to their ability to aggregate and deform [29].

The process of erythrocyte aggregation is actively studied in both clinical and basic research [30–33]. A continuous dynamic "aggregation–disaggregation" process occurs in the blood, with disaggregation normally prevailing over aggregation. When blood flow velocity decreases, erythrocytes form linear aggregates, which are disrupted when shear rate increases [34]. Optimal aggregation is of great importance for the microcirculatory bed, as it regulates venous resistance and maintains the necessary hydrostatic pressure in capillaries [35].

The aggregation process is influenced both by plasma properties and by characteristics of the erythrocytes themselves. Albumin, immunoglobulins, prostaglandins, and other components possess pro-aggregatory activity [36, 38], with fibrinogen recognized as the most potent stimulator of aggregation [37]. The formation of "rouleaux" occurs with the participation of plasma proteins that create molecular "bridges" between cells [39–41]. According to the alternative "depletion layer" theory, aggregation is driven by an osmotic gradient [41]. The contradictions between existing theories indicate that the mechanisms of aggregation remain insufficiently studied [40].

Important determinants of aggregability include biochemical, geometric, and biomechanical properties of erythrocytes, including sialic acid content, membrane phospholipid composition, and cell shape [42–44]. Altered erythrocytes (e.g., echinocytes) can form particularly strong aggregates.

In pathological conditions, a syndrome of increased blood viscosity is observed, characterized by the formation of stable "clump-like" aggregates that persist even at high shear rates. Erythrocyte hyperaggregation is recorded in type 1 and type 2 diabetes mellitus, cardiovascular, oncological, and inflammatory diseases [44–47], leading to a reduction in the density of functioning capillaries, an increase in vascular resistance [48], and impaired tissue perfusion [49].

Of particular concern are pathologically strong aggregates that cannot pass through narrow capillaries, resulting in blood flow shunting and the formation of "plasma" capillaries devoid of erythrocytes [50, 51].

The second key rheological parameter is erythrocyte deformability, i.e., the ability of red blood cells to change shape under flow conditions [52, 53]. Deformability is of fundamental importance for gas exchange, as it enhances intracellular oxygen convection [54]. A reduction in deformability by as little as 10% significantly impairs tissue oxygenation [55].

Deformational properties are determined by the viscoelastic characteristics of the membrane, intracellular viscosity, and the surface-to-volume ratio of the cell [56]. Impaired deformability may be caused by activation of lipid peroxidation, changes in hemoglobin concentration, or adenosine triphosphate deficiency.

Thus, the rheological properties of blood, determined by erythrocyte aggregability and deformability, play a decisive role in ensuring adequate tissue perfusion, gas exchange, and metabolism.

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THE SIGNIFICANCE OF RHEOLOGICAL ABNORMALITIES IN INFLAMMATORY BOWEL DISEASES

Studies on the rheological properties of erythrocytes in inflammatory bowel disease remain limited. Existing data indicate increased erythrocyte aggregation in both active and inactive forms of CD in adult patients, accompanied by an increase in fibrinogen concentration during the active phase of the disease. A correlation has been established between rheological parameters and markers of systemic inflammation, allowing erythrocyte aggregation to be considered a nonspecific indicator of inflammatory activity in IBD [57].

A significant finding in 2009 was the discovery of increased strength of erythrocyte aggregates in IBD patients, correlating with disease activity, fibrinogen levels, and erythrocyte sedimentation rate [58]. At the same time, studies using dextran did not reveal differences in erythrocyte aggregative properties between patients and healthy individuals, indicating the preservation of the main cellular aggregation mechanisms in IBD. These findings suggest the presence of similar rheological disturbances in the intestinal microcirculation system, which, in combination with endothelial dysfunction, may lead to tissue hypoxia, intestinal wall damage, and compensatory angiogenesis.

Disorders of rheological properties in IBD are not limited to changes in aggregation. Experimental and clinical studies confirm a persistent reduction in erythrocyte deformability in both active and inactive forms of IBD, with the most pronounced changes during exacerbation [59].

An additional factor aggravating rheological disturbances in IBD is an increase in plasma viscosity, particularly pronounced in active CD. This parameter shows a close correlation with major markers of inflammatory activity [60]. The combination of these abnormalities such as increased plasma viscosity, enhanced erythrocyte aggregation, and reduced erythrocyte deformability leads to a significant deterioration in blood rheological properties, impaired tissue perfusion, and progression of intestinal inflammation.

CONCLUSION

Analysis of scientific data suggests that disturbances in microcirculation and blood rheological properties play a significant role in the mechanisms underlying the development of inflammatory bowel disease. Of key importance in this context are changes in erythrocyte aggregability and deformability. The resulting impairments of capillary blood flow initiate a vicious cycle of pathological processes: the development of ischemia and tissue hypoxia leads to the exacerbation of the inflammatory response, which in turn promotes disease progression.

Thus, disturbances in blood rheology and microcirculation create a pathological basis for the persistence of the inflammatory process in IBD, forming a self-sustaining mechanism of disease development.

ADDITIONAL INFORMATION

Authors' contribution. E.N. Fedulova — the concept and design of the study; A.N. Popovicheva, V.A. Tsarev — literature selection, writing and editing of the text.

All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Э.Н. Федулова — концепция и дизайн исследования; А.Н. Поповичева, В.А. Царев — подбор литературы, написание и редактирование текста.

Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

REFERENCES

1. Grover Z., De Nardi A., Lewindon P.J. Inflammatory bowel disease in adolescents. *Aust Fam Physician.* 2017;46(8):565–571.
2. Tyazheva A.A., Pechkurov D.V., Romanova A.A., Strepnev B.B., Kozarez E.V. A case of diagnosis of Crohn's dis-

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ease in an early child. *Practical Medicine*. 2018;2(113):74–76. (In Russ.). EDN: YXORSP.
3. Khavkin A.I., Bogdanova N.M., Nalyotov A.V., Matsynina M.A., Erokhina M.A. Inflammatory Bowel Diseases and Dairy Products. *Pediatric Pharmacology*. 2024;21(5):455–461. (In Russ.). https://doi.org/10.15690/pf.v21i5.2800.
4. Ivashkin V.T., Sheptulina A.F., Raikhelson K.L., Losik E.A., Ivashkin K.V., Okhlobystin A.V. et al. Autoimmune diseases of the digestive system. *Bulletin of the Russian Academy of Medical Sciences*. 2015;70(2):139–151. (In Russ.). https://doi.org/10.15690/vramn.v70i2.1306.
5. Khavkin A.I., Nalyotov A.V., Bogdanova N.M., Matsynin A.N. Etiological predictors in the development of inflammatory bowel diseases. *Nutrition*. 2024;14(4):28–34. (In Russ.). https://doi.org/10.20953/2224-5448-2024-4-28-34.
6. Zolotova N.A., Archiva H.M., Zairatyants O.V. Epithelial barrier of the colon in normal and ulcerative colitis. *Experimental and Clinical Gastroenterology*. 2019;162(2):4–13. (In Russ.). https://doi.org/10.31146/1682-8658-ecg-162-2-4-13. EDN: SUBULS.
7. Fedorova O.V., Fedulova E.N., Tutina O.A. Endogenous intoxication in chronic inflammatory bowel diseases in children: from pathogenesis to treatment. *Medical Almanac*. 2008;(3):84–88. (In Russ.). EDN: JTXKCB.
8. Fedorova O.V., Fedulova E.N., Tutina O.A., Kopeikin V.N., Korkotashvili L.V. Sorption pathogenetic therapy of endogenous intoxication of pediatric chronic inflammatory bowel diseases. *Pediatric Pharmacology*. 2009;6(5):34–37. (In Russ.). EDN: KYLVFN.
9. Rumyantsev V.G. Ulcerative colitis: a guide for doctors. Moscow: Medical Information Agency; 2009. 424 p.
10. Danese S. Inflammation and the mucosal microcirculation in inflammatory bowel disease: the ebb and flow. *Curr Opin Gastroenterol.* 2007;23(4):384–389. https://doi.org/10.1097/MOG.0b013e32810c8de3.
11. Deban L., Correale C., Vetrano S., Malesci A., Danese S. Multiple pathogenic roles of microvasculature in inflammatory bowel disease: a Jack of all trades. *Am J Pathol.* 2008;172(6):1457–1466. https://doi.org/10.2353/ajpath.2008.070593.
12. Kono T., Omiya Y., Hira Y., Kaneko A., Chiba S., Suzuki T., Noguchi M., Watanabe T. Daikenchuto (TU-100) ameliorates colon microvascular dysfunction via endogenous adrenomedullin in Crohn's disease rat model. *J Gastroenterol.* 2011;46(10):1187–1196. https://doi.org/10.1007/s00535-011-0438-2.
13. Cibor D., Domagala-Rodacka R., Rodacki T., Jurczyszyn A., Mach T., Owczarek D. Endothelial dysfunction in inflammatory bowel diseases: Pathogenesis, assessment and implications. *World J Gastroenterol.* 2016;22(3):1067–1077. https://doi.org/10.3748/wjg.v22.i3.1067.
14. Hagel S., Bruns T., Stallmach A., Schmidt C. A confocal view of the intestinal microcirculation in a patient with Crohn disease and portal vein thrombosis. *Endoscopy*. 2011;43(Suppl 2 UCTN):E126–E127. https://doi.org/10.1055/s-0030-1256161.
15. Harris N.R., Carter P.R., Yadav A.S., Watts M.N., Zhang S., Kosloski-Davidson M., Grisham M.B. Relationship between Inflammation and Tissue Hypoxia in a Mouse Model of Chronic Colitis. *Inflamm Bowel Dis.* 2011;17(3):742–746. https://doi.org/10.1002/ibd.21423.
16. Tityuk S.Yu., Pikhur O.L., Tishkov D.S., Iordanishvili A.K. Morphological and functional features of oral mucosa in persons with chronic inflammatory bowel diseases. *Kursk Scientific and Practical Bulletin "Man and His Health"*. 2016;(3):49–55. (In Russ.). https://doi.org/10.21626/vestnik/2016-3/08.
17. Danese S., Fiorino G., Angelucci E., Vetrano S., Pagano N., Rando G. et al. Narrow-band imaging endoscopy to assess mucosal angiogenesis in inflammatory bowel disease: a pilot study. *World J Gastroenterol.* 2010;16(19):2396–2400. https://doi.org/10.3748/wjg.v16.i19.2396.
18. Rakhmetov N.R., Rakhmetova K.U., Danilova Zh.A., Karzhauv A.N. Indicators of endothelial dysfunction in inflammatory bowel diseases. *Bulletin of KazNMU*. 2016;(4):7–11. (In Russ.). EDN: YOEUEG.
19. Khlynova O.V., Stepina E.A. Specific Features of Vascular Endothelium in Patients with Severe Forms of Inflammatory Bowel Diseases. *Russian Journal of Gastroenterology, Hepatology, Coloproctology*. 2018;28(5):98–104. (In Russ.). https://doi.org/10.22416/1382-4376-2018-28-5-98-104. EDN: YOCIWD.
20. Winderman R., Rabinowitz S.S., Vaidy K., Schwarz S.M. Measurement of Microvascular Function in Pediatric Inflammatory Bowel Disease. *J Pediatr Gastroenterol Nutr.* 2019;68(5):662–668. https://doi.org/10.1097/MPG.0000000000002252.
21. Hatoum O.A., Miura H., Binion D.G. The vascular contribution in the pathogenesis of inflammatory bowel disease. *Am J Physiol Heart Circ Physiol.* 2003;285(5):H1791–1796. https://doi.org/10.1152/ajpheart.00552.2003.
22. Zaidi D., Churchill L., Huynh H.Q., Carroll M.W., Persad R., Wine E. Capillary Flow Rates in the Duodenum of Pediatric Ulcerative Colitis Patients Are Increased and Unrelated to Inflammation. *J Pediatr Gastroenterol Nutr.* 2017;65(3):306–310. https://doi.org/10.1097/MPG.0000000000001495.
23. Nylund K., Jirik R., Mezl M., Leh S., Hausken T., Pfeffer F. et al. Quantitative contrast-enhanced ultrasound comparison between inflammatory and fibrotic lesions in patients with Crohn's disease. *Ultrasound Med Biol.* 2013;39(7):1197–1206. https://doi.org/10.1016/j.ultrasmedbio.2013.01.020.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

24. Caliskan Z., Keles N., Gokturk H.S., Ozdil K., Aksu F., Ozturk O. et al. Is activation in inflammatory bowel diseases associated with further impairment of coronary microcirculation? *Int J Cardiol.* 2016;223:176–181. https://doi.org/10.1016/j.ijcard.2016.08.141.
25. Tian Y., Zheng Y., Teng G., Li J., Wang H. Imbalanced mucosal microcirculation in the remission stage of ulcerative colitis using probe-based confocal laser endomicroscopy. *BMC Gastroenterology*. 2019;19(1):114. https://doi.org/10.1186/s12876-019-1037-6.
26. Foitzik T., Kruschewski M., Kroesen A., Buhr H.J. Does microcirculation play a role in the pathogenesis of inflammatory bowel diseases? Answers from intravital microscopic studies in animal models. *Int J Colorectal Dis*. 1999;14(1):29–34. https://doi.org/10.1007/s003840050179.
27. Zhukova N.V., Novgorodtseva T.P. Lipid composition of erythrocytes at cardiovascular and hepatobiliary diseases. Lipids: Categories, Biological functions and metabolism, nutrition and health. NY: Nova Science Publishers; 2010.
28. Miranda M., Balarini M., Caixeta D., Bouskela E. Microcirculatory dysfunction in sepsis: pathophysiology, clinical monitoring, and potential therapies. *Am J Physiol Heart Circ Physiol*. 2016;311(1):H24–35. https://doi.org/10.1152/ajpheart.00034.2016.
29. Mchedlishvili G.I. Hemorheology in the microcirculation system: its specificity and practical significance. *Thrombosis, Hemostasis and Rheology*. 2002;4(12):18–23. (In Russ.).
30. Tikhomirova I.A., Muravyev A.V. The physiological role and mechanisms of erythrocyte aggregation. *I.M. Sechenov Russian Journal of Physiology*. 2007;93(12):1382–1393. (In Russ.). EDN: JSCIWF.
31. Sokolova I.A. Erythrocyte aggregation. *Regional Blood Circulation and Microcirculation*. 2010;9(4):4–26. (In Russ.). EDN: NCRNTZ.
32. Barshtein G., Ben-Ami R., Yedgar S. Role of red blood cell flow behavior in hemodinamics and hemostasis. *Expert Rev Cardiovasc Ther*. 2007;5(4):743–752. https://doi.org/10.1586/14779072.5.4.743.
33. Baskurt O.K., Meiselman H.J. Erythrocyte aggregation: basic aspects and clinical importance. *Clin Hemorheol Microcirc*. 2013;53(1-2):23–37. https://doi.org/10.3233/CH-2012-1573.
34. Levtov V.A., Regirer S.A., Shadrina N.H. Rheology of blood. Moscow: Medicine; 1982. 272 p. (In Russ.).
35. Bishop J.J., Popel A.S., Intaglietta M., Johnson P.C. Rheological effects of red blood cell aggregation in the venous network: a review of recent studies. *Biorheology*. 2001;38(2-3):263–270. https://doi.org/10.1177/0006355X2001038002003003.
36. Reinhart W.H., Nagy C. Albumin affects erythrocyte aggregation and sedimentation. *Eur J Clin Invest*. 1995;25(7):523–528. https://doi.org/10.1111/j.1365-2362.1995.tb01739.x.
37. Lominadze D., Dean W.L. Involvement of fibrinogen specific binding in erythrocyte aggregation. *FEBS Lett*. 2002;517(1-3):41–44. https://doi.org/10.1016/s0014-5793(02)02575-9.
38. Ben-Ami R., Barshtein G., Mardi T., Deutch V., Elkayam O., Yedgar S., Berliner S. A synergistic effect of albumin and fibrinogen on immunoglobulin-induced red blood cell aggregation. *Am J Physiol Heart Circ Physiol*. 2003;285(6):H2663–H2669. https://doi.org/10.1152/ajpheart.00128.2003.
39. Barshtein G., Tamir I., Yedgar S. Red blood cell rouleaux formation in dextran solution: dependence on polymer conformation. *Eur Biophys J*. 1998;27(2):177–181. https://doi.org/10.1007/s002490050124.
40. Chien S., Sung L.A. Physicochemical basis and clinical implications of red cell aggregation. *Clin Hemorheol Microcirc*. 1987;7(1):71–91. https://doi.org/10.3233/CH-1987-7108.
41. Neu B., Meiselman H.J. Depletion-mediated red blood cell aggregation in polymer solutions. *Biophys J*. 2002;83(5):2482–2490. https://doi.org/10.1016/S0006-3495(02)75259-4.
42. Rampling M.W., Meiselman H.J., Neu B., Baskurt O.K. Influence of cell-specific factors on red blood cell aggregation. *Biorheology*. 2004;41(2):91–112.
43. Shiga T., Maeda N., Kon K. Erythrocyte rheology. *Crit Rev Oncol Hematol*. 1990;10(1):9–48. https://doi.org/10.1016/1040-8428(90)90020-s.
44. Martínez M., Vayá A., Gil L., Martí R., Dalmau J., Aznar J. The cholesterol/phospholipid ratio of the erythrocyte membrane in children with familial hypercholesterolemia. Its relationship with plasma lipids and red blood cell aggregability. *Clin Hemorheol Microcirc*. 1998;18(4):259–263.
45. Ryazantseva N.V, Novitskii V.V., Stepovaya E.A., Bulavina Y.V., Fokin V.A. Typical changes of reversible erythrocyte aggregation in various pathological processes. *Bull Exp Biol Med*. 2003;135(1):26–28. https://doi.org/10.1023/a:1023429409048.
46. Ugurlu E., Kilic-Toprak E., Altinisik G., Kilic-Erkek O., Cengiz B., Kucukatay V. et al. Increased erythrocyte aggregation and oxidative stress in patients with idiopathic interstitial pneumonia. *Sarcoidosis Vasc Diffuse Lung Dis*. 2016;33(4):308–316.
47. Cho Y.I., Mooney M.P., Cho D.J. Hemorheological disorders in diabetes mellitus. *J Diabetes Sci Technol*. 2008;2(6):1130–1138. https://doi.org/10.1177/193229680800200622.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

48. Vicaut E. Opposite effects of red blood cell aggregation on resistance to blood flow. *J Cardiovasc Surg*. 1995;36(4):361–368.
49. Bishop J.J., Nance P.R., Popel A.S., Marcos I., Johnson P.C. Relationship between erythrocyte aggregate size and flow rate in skeletal muscle venules. *Am J Physiol Heart Circ Physiol*. 2004;286(1):H113–H120. https://doi.org/10.1152/ajpheart.00587.2003.
50. Meiselman H.J. In vivo circulatory correlates of altered RBC aggregation. *Biorheology*. 2002;39(5):636.
51. Popel S., Johnson P.C. Microcirculation and hemorheology. *Annu Rev Fluid Mech*. 2005;(37):43–69. https://doi.org/10.1146/annurev.fluid.37.042604.133933.
52. Mokken F.C., Kedaria M., Henny C.P., Hardeman M.R., Gelb A.W. The clinical importance of erythrocyte deformability, a hemorrheological parameter. *Ann Hematol*. 1992;64(3):113–122. https://doi.org/10.1007/BF01697397.
53. Zinchuk V.V. Deformability of erythrocytes: physiological aspects. *Progress in Physiological Science*. 2001;32(3):64–76. (In Russ.). EDN: OBUHAU.
54. Nakache M., Caprani A., Dimicoli J., Massonnet S., Peronneau P., Jaulmes B. Relationship between deformability of red blood cells and oxygen transfer: a modelized investigation. *Clin Hemoheol*. 1983;3(2):177–189.
55. Kikuchi Y., Da Q.W., Fujino T. Variation in red blood cell deformability and possible consequences for oxygen transport to tissue. *Microvasc Res*. 1994;47(2):222–231. https://doi.org/10.1006/mvre.1994.1017.
56. Cicco G., Pirreli A. Red blood cell (RBC) deformability, RBC aggregability and tissue oxygenation in hypertension. *Clin Hemorheol Microcirc*. 1999;21(3-4):169–177.
57. Novacek G., Vogelsang H., Genser D., Moser G., Gangl A., Ehringer H., Koppensteiner R. Changes in blood rheology caused by Crohn's disease. *Eur J Gastroenterol Hepatol*. 1996;8(11):1089–1093. https://doi.org/10.1097/00042737-199611000-00011.
58. Maharshak N., Arbel Y., Shapira I., Berliner S., Ben-Ami R., Yedgar S. et al. Increased strength of erythrocyte aggregates in blood of patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2009;15(5):707–713. https://doi.org/10.1002/ibd.20838.
59. Akman T., Akarsu M., Akpinar H., Resmi H., Taylan E. Erythrocyte deformability and oxidative stress in inflammatory bowel disease. *Dig Dis Sci*. 2012;57(2):458–464. https://doi.org/10.1007/s10620-011-1882-9.
60. Yakar T., Cosar A.M., Gokturk H.S., Kanat U.G., Parlakgumus A., Kozanoglu I., Serin E. Plasma viscosity: a potential predictor of both medical treatment response and clinical stage of ulcerative colitis. *Ann Ital Chir*. 2016;87:531–543.

ЛИТЕРАТУРА

1. Grover Z., De Nardi A., Lewindon P.J. Inflammatory bowel disease in adolescents. *Aust Fam Physician*. 2017;46(8):565–571.
2. Тяжева А.А., Печкуров Д.В., Романова А.А., Стрепнёв Б.Б., Козарез Е.В. Случай диагностики болезни Крона у ребенка раннего возраста. *Практическая медицина*. 2018;2 (113):74–76. EDN: YXORSP.
3. Хавкин А.И., Богданова Н.М., Налетов А.В., Мацынина М.А., Ерохина М.И. Воспалительные заболевания кишечника и молочные продукты. *Педиатрическая фармакология*. 2024;21(5):455–461. https://doi.org/10.15690/pf.v21i5.2800.
4. Ивашкин В.Т., Шептулина А.Ф., Райхельсон К.Л., Лосик Е.А., Ивашкин К.В., Охлобыстин А.В. и др. Аутоиммунные заболевания органов пищеварительной системы. *Вестник РАМН*. 2015;70(2):139–151. https://doi.org/10.15690/vramn.v70i2.1306.
5. Хавкин А.И., Налётов А.В., Богданова Н.М., Мацынин А.Н. Этиологические предикторы в развитии воспалительных заболеваний кишечника. *Вопросы диетологии*. 2024;14(4):28–34. https://doi.org/10.20953/2224-5448-2024-4-28-34.
6. Золотова Н.А., Архиева Х.М., Зайратьянц О.В. Эпителиальный барьер толстой кишки в норме и при язвенном колите. *Экспериментальная и клиническая гастроэнтерология*. 2019;162(2):4–13. https://doi.org/10.31146/1682-8658-ecg-162-2-4-13. EDN: SUBULS.
7. Федорова О.В., Федулова Э.Н., Тутина О.А. Эндогенная интоксикация при хронических воспалительных заболеваниях толстой кишки у детей: от патогенеза к лечению. *Медицинский альманах*. 2008;(3):84–88. EDN: JTXKCB.
8. Федорова О.В., Федулова Э.Н., Тутина О.А., Копейкин В.Н., Коркоташвили Л.В. Патогенетическая сорбционная терапия эндогенной интоксикации воспалительных заболеваний кишечника у детей. *Педиатрическая фармакология*. 2009;6(5):34–37. EDN: KYLVFN.
9. Румянцев В.Г. Язвенный колит: руководство для врачей. М.: Медицинское информационное агентство; 2009. 424 с.
10. Danese S. Inflammation and the mucosal microcirculation in inflammatory bowel disease: the ebb and flow. *Curr Opin Gastroenterol*. 2007;23(4):384–389. https://doi.org/10.1097/MOG.0b013e32810c8de3.
11. Deban L., Correale C., Vetrano S., Malesci A., Danese S. Multiple pathogenic roles of microvasculature in inflammatory bowel disease: a Jack of all trades. *Am J Pathol*. 2008;172(6):1457–1466. https://doi.org/10.2353/ajpath.2008.070593.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

12. Kono T., Omiya Y., Hira Y., Kaneko A., Chiba S., Suzuki T., Noguchi M., Watanabe T. Daikenchuto (TU-100) ameliorates colon microvascular dysfunction via endogenous adrenomedullin in Crohn's disease rat model. *J Gastroenterol*. 2011;46(10):1187–1196. https://doi.org/10.1007/s00535-011-0438-2.
13. Cibor D., Domagala-Rodacka R., Rodacki T., Jurczyszyn A., Mach T., Owczarek D. Endothelial dysfunction in inflammatory bowel diseases: Pathogenesis, assessment and implications. *World J Gastroenterol.* 2016;22(3):1067–1077. https://doi.org/10.3748/wjg.v22.i3.1067.
14. Hagel S., Bruns T., Stallmach A., Schmidt C. A confocal view of the intestinal microcirculation in a patient with Crohn disease and portal vein thrombosis. *Endoscopy*. 2011;43(Suppl 2 UCTN):E126–E127. https://doi.org/10.1055/s-0030-1256161.
15. Harris N.R., Carter P.R., Yadav A.S., Watts M.N., Zhang S., Kosloski-Davidson M., Grisham M.B. Relationship between Inflammation and Tissue Hypoxia in a Mouse Model of Chronic Colitis. *Inflamm Bowel Dis.* 2011;17(3):742–746. https://doi.org/10.1002/ibd.21423.
16. Тытюк С.Ю., Пихур О.Л., Тишков Д.С., Иорданишвили А.К. Морфофункциональные особенности слизистой оболочки полости рта лиц, страдающих хроническими воспалительными заболеваниями кишечника. *Курский научно-практический вестник «Человек и его здоровье»*. 2016;(3):49–55. https://doi.org/10.21626/vestnik/2016-3/08.
17. Danese S., Fiorino G., Angelucci E., Vetrano S., Pagano N., Rando G. et al. Narrow-band imaging endoscopy to assess mucosal angiogenesis in inflammatory bowel disease: a pilot study. *World J Gastroenterol.* 2010;16(19):2396–2400. https://doi.org/10.3748/wjg.v16.i19.2396.
18. Рахметов Н.Р., Рахметова К.У., Давилова Ж.А., Каржауов А.Н. Показатели эндотелиальной дисфункции при воспалительных заболеваниях кишечника. *Вестник КазНМУ*. 2016;(4):7–11. EDN: YOEUEG.
19. Хлынова О.В., Степина Е.А. Особенности состояния сосудистого эндотелия у лиц с тяжелыми формами воспалительных заболеваний кишечника. *Российский журнал гастроэнтерологии, гепатологии, колопроктологии*. 2018;28(5):98–104. https://doi.org/10.22416/1382-4376-2018-28-5-98-104. EDN: YOCIWD.
20. Winderman R., Rabinowitz S.S., Vaidy K., Schwarz S.M. Measurement of Microvascular Function in Pediatric Inflammatory Bowel Disease. *J Pediatr Gastroenterol Nutr.* 2019;68(5):662–668. https://doi.org/10.1097/MPG.0000000000002252.
21. Hatoum O.A., Miura H., Binion D.G. The vascular contribution in the pathogenesis of inflammatory bowel disease. *Am J Physiol Heart Circ Physiol.* 2003;285(5):H1791–1796. https://doi.org/10.1152/ajpheart.00552.2003.
22. Zaidi D., Churchill L., Huynh H.Q., Carroll M.W., Persad R., Wine E. Capillary Flow Rates in the Duodenum of Pediatric Ulcerative Colitis Patients Are Increased and Unrelated to Inflammation. *J Pediatr Gastroenterol Nutr.* 2017;65(3):306–310. https://doi.org/10.1097/MPG.0000000000001495.
23. Nylund K., Jirik R., Mezl M., Leh S., Hausken T., Pfeffer F. et al. Quantitative contrast-enhanced ultrasound comparison between inflammatory and fibrotic lesions in patients with Crohn's disease. *Ultrasound Med Biol.* 2013;39(7):1197–1206. https://doi.org/10.1016/j.ultrasmedbio.2013.01.020.
24. Caliskan Z., Keles N., Gokturk H.S., Ozdil K., Aksu F., Ozturk O. et al. Is activation in inflammatory bowel diseases associated with further impairment of coronary microcirculation? *Int J Cardiol.* 2016;223:176–181. https://doi.org/10.1016/j.ijcard.2016.08.141.
25. Tian Y., Zheng Y., Teng G., Li J., Wang H. Imbalanced mucosal microcirculation in the remission stage of ulcerative colitis using probe-based confocal laser endomicroscopy. *BMC Gastroenterology*. 2019;19(1):114. https://doi.org/10.1186/s12876-019-1037-6.
26. Foitzik T., Kruschewski M., Kroesen A., Buhr H.J. Does microcirculation play a role in the pathogenesis of inflammatory bowel diseases? Answers from intravital microscopic studies in animal models. *Int J Colorectal Dis*. 1999;14(1):29–34. https://doi.org/10.1007/s003840050179.
27. Zhukova N.V., Novgorodtseva T.P. Lipid composition of erythrocytes at cardiovascular and hepatobiliary diseases. Lipids: Categories, Biological functions and metabolism, nutrition and health. NY: Nova Science Publishers; 2010.
28. Miranda M., Balarini M., Caixeta D., Bouskela E. Microcirculatory dysfunction in sepsis: pathophysiology, clinical monitoring, and potential therapies. *Am J Physiol Heart Circ Physiol.* 2016;311(1):H24–35. https://doi.org/10.1152/ajpheart.00034.2016.
29. Мчедлишвили Г.И. Гемореология в системе микроциркуляции: ее специфика и практическое значение. *Тромбоз, гемостаз и реология.* 2002;4(12):18–23.
30. Тихомирова И.А., Муравьев А.В. Физиологическая роль и механизмы объединения эритроцитов в агрегаты. *Российский физиологический журнал им. И.М. Сеченова.* 2007;93(12):1382–1393. EDN: JSCIWF.
31. Соколова И.А. Агрегация эритроцитов. *Регионарное кровообращение и микроциркуляция.* 2010;9(4):4–26. EDN: NCRNTZ.
32. Barshtein G., Ben-Ami R., Yedgar S. Role of red blood cell flow behavior in hemodinamics and hemostasis. *Expert*

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

Rev Cardiovasc Ther. 2007;5(4):743–752. https://doi.org/10.1586/14779072.5.4.743.
33. Baskurt O.K., Meiselman H.J. Erythrocyte aggregation: basic aspects and clinical importance. *Clin Hemorheol Microcirc*. 2013;53(1-2):23–37. https://doi.org/10.3233/CH-2012-1573.
34. Левтов В.А., Регирер С.А., Шадрина Н.Х. Реология крови. М.: Медицина; 1982. 272 с.
35. Bishop J.J., Popel A.S., Intaglietta M., Johnson P.C. Rheological effects of red blood cell aggregation in the venous network: a review of recent studies. *Biorheology*. 2001;38(2-3):263–270. https://doi.org/10.1177/0006355X2001038002003003.
36. Reinhart W.H., Nagy C. Albumin affects erythrocyte aggregation and sedimentation. *Eur J Clin Invest*. 1995;25(7):523–528. https://doi.org/10.1111/j.1365-2362.1995.tb01739.x.
37. Lominadze D., Dean W.L. Involvement of fibrinogen specific binding in erythrocyte aggregation. *FEBS Lett*. 2002;517(1-3):41–44. https://doi.org/10.1016/s0014-5793(02)02575-9.
38. Ben-Ami R., Barshtein G., Mardi T., Deutch V., Elkayam O., Yedgar S., Berliner S. A synergistic effect of albumin and fibrinogen on immunoglobulin-induced red blood cell aggregation. *Am J Physiol Heart Circ Physiol*. 2003;285(6):H2663–H2669. https://doi.org/10.1152/ajpheart.00128.2003.
39. Barshtein G., Tamir I., Yedgar S. Red blood cell rouleaux formation in dextran solution: dependence on polymer conformation. *Eur Biophys J*. 1998;27(2):177–181. https://doi.org/10.1007/s002490050124.
40. Chien S., Sung L.A. Physicochemical basis and clinical implications of red cell aggregation. *Clin Hemorheol Microcirc*. 1987;7(1):71–91. https://doi.org/10.3233/CH-1987-7108.
41. Neu B., Meiselman H.J. Depletion-mediated red blood cell aggregation in polymer solutions. *Biophys J*. 2002;83(5):2482–2490. https://doi.org/10.1016/S0006-3495(02)75259-4.
42. Rampling M.W., Meiselman H.J., Neu B., Baskurt O.K. Influence of cell-specific factors on red blood cell aggregation. *Biorheology*. 2004;41(2):91–112.
43. Shiga T., Maeda N., Kon K. Erythrocyte rheology. *Crit Rev Oncol Hematol*. 1990;10(1):9–48. https://doi.org/10.1016/1040-8428(90)90020-s.
44. Martínez M., Vayá A., Gil L., Martí R., Dalmau J., Aznar J. The cholesterol/phospholipid ratio of the erythrocyte membrane in children with familial hypercholesterolemia. Its relationship with plasma lipids and red blood cell aggregability. *Clin Hemorheol Microcirc*. 1998;18(4):259–263.
45. Ryazantseva N.V, Novitskii V.V., Stepovaya E.A., Bulavina Y.V., Fokin V.A. Typical changes of reversible erythrocyte aggregation in various pathological processes. *Bull Exp Biol Med*. 2003;135(1):26–28. https://doi.org/10.1023/a:1023429409048.
46. Ugurlu E., Kilic-Toprak E., Altinisik G., Kilic-Erkek O., Cengiz B., Kucukatay V. et al. Increased erythrocyte aggregation and oxidative stress in patients with idiopathic interstitial pneumonia. *Sarcoidosis Vasc Diffuse Lung Dis*. 2016;33(4):308–316.
47. Cho Y.I., Mooney M.P., Cho D.J. Hemorheological disorders in diabetes mellitus. *J Diabetes Sci Technol*. 2008;2(6):1130–1138. https://doi.org/10.1177/193229680800200622.
48. Vicaut E. Opposite effects of red blood cell aggregation on resistance to blood flow. *J Cardiovasc Surg*. 1995;36(4):361–368.
49. Bishop J.J., Nance P.R., Popel A.S., Marcos I., Johnson P.C. Relationship between erythrocyte aggregate size and flow rate in skeletal muscle venules. *Am J Physiol Heart Circ Physiol*. 2004;286(1):H113–H120. https://doi.org/10.1152/ajpheart.00587.2003.
50. Meiselman H.J. In vivo circulatory correlates of altered RBC aggregation. *Biorheology*. 2002;39(5):636.
51. Popel S., Johnson P.C. Microcirculation and hemorheology. *Annu Rev Fluid Mech*. 2005;(37):43–69. https://doi.org/10.1146/annurev.fluid.37.042604.133933.
52. Mokken F.C., Kedaria M., Henny C.P., Hardeman M.R., Gelb A.W. The clinical importance of erythrocyte deformability, a hemorrheological parameter. *Ann Hematol*. 1992;64(3):113–122. https://doi.org/10.1007/BF01697397.
53. Зинчук В.В. Деформируемость эритроцитов: физиологические аспекты. *Успехи физиологических наук*. 2001;32(3):64–76. EDN: OBUHAU.
54. Nakache M., Caprani A., Dimicoli J., Massonnet S., Peronneau P., Jaulmes B. Relationship between deformability of red blood cells and oxygen transfer: a modelized investigation. *Clin Hemoheol*. 1983;3(2):177–189.
55. Kikuchi Y., Da Q.W., Fujino T. Variation in red blood cell deformability and possible consequences for oxygen transport to tissue. *Microvasc Res*. 1994;47(2):222–231. https://doi.org/10.1006/mvre.1994.1017.
56. Cicco G., Pirreli A. Red blood cell (RBC) deformability, RBC aggregability and tissue oxygenation in hypertension. *Clin Hemorheol Microcirc*. 1999;21(3-4):169–177.
57. Novacek G., Vogelsang H., Genser D., Moser G., Gangl A., Ehringer H., Koppensteiner R. Changes in blood rheology caused by Crohn's disease. *Eur J Gastroenterol Hepatol*. 1996;8(11):1089–1093. https://doi.org/10.1097/00042737-199611000-00011.
58. Maharshak N., Arbel Y., Shapira I., Berliner S., Ben-Ami R., Yedgar S. et al. Increased strength of erythrocyte aggregates in blood of patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2009;15(5):707–713. https://doi.org/10.1002/ibd.20838.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

59. Akman T., Akarsu M., Akpinar H., Resmi H., Taylan E. Erythrocyte deformability and oxidative stress in inflammatory bowel disease. *Dig Dis Sci*. 2012;57(2):458–464. https://doi.org/10.1007/s10620-011-1882-9.

60. Yakar T., Cosar A.M., Gokturk H.S., Kanat U.G., Parlakgumus A., Kozanoglu I., Serin E. Plasma viscosity: a potential predictor of both medical treatment response and clinical stage of ulcerative colitis. *Ann Ital Chir*. 2016;87:531–543.

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Type 1 diabetes mellitus in children at the prehospital stage. The difficulties of diagnosis

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ABSTRACT. ***Introduction.*** The total number of patients with type 1 diabetes (T1D) under the age of 18 in the Russian Federation as of December 31, 2023, was 61,318 (208 per 100,000 child population), with an incidence of 8,009 (28 per 100,000 child population). In most countries, including Russia, the incidence of type 1 diabetes in childhood is increasing. Given the epidemiological indicators and social significance of this disease, as well as the importance of timely diagnosis of diabetes in children, an analysis was conducted of the difficulties at the prehospital stage in diagnosing type 1 diabetes onset. ***The aim of the study*** – to analyze complex cases in the diagnosis and management of children with new-onset type 1 diabetes at the prehospital stage of emergency and urgent medical care. ***Materials and methods.*** We analyzed 121 medical records of children with clinical and/or laboratory-confirmed type 1 diabetes onset who were emergently hospitalized via emergency and urgent medical care at the Clinic of St. Petersburg State Pediatric Medical University in 2022–2023. Blood glucose levels at the time of admission and clinical manifestations of the disease were assessed. ***Results.*** The highest blood glucose levels were found in children aged 1–3 years (27.9±2.6 mmol/L); however, glycemia levels did not correlate with the presence of "major symptoms" of type 1 diabetes, which is attributed to the polymorphic clinical presentation. It was revealed that the mean age of type 1 diabetes onset in children with a history of perinatal hypoxia was earlier (6.98±0.47 years), compared to those without such history (8.98±0.5 years). ***Conclusions.*** Type 1 diabetes in children often presents under the "masks" of acute respiratory viral infections, intestinal or genitourinary infections, leading to delayed diagnosis and the development of ketoacidosis. Adolescents have the longest period from first symptoms to laboratory confirmation of type 1 diabetes. Systematic training of outpatient physicians on the clinical and diagnostic criteria of type 1 diabetes needs to be improved.

KEYWORDS: *diabetes mellitus, children, pre-hospital stag, tactical and diagnostic measures*

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Сахарный диабет 1-го типа у детей на догоспитальном этапе. Сложности диагностики

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РЕЗЮМЕ. ***Введение.*** Общая численность пациентов с сахарным диабетом 1-го типа в возрасте до 18 лет в Российской Федерации на 31.12.2023 года составляла 61 318 человек (208 на 100 тыс. детского населения), заболеваемость — 8009 (28 на 100 тыс. детского населения). В большинстве стран, включая Россию, регистрируется нарастание заболеваемости сахарным диабетом 1-го типа в детском возрасте. Учитывая эпидемиологические показатели и социальную значимость данного заболевания, а также важность своевременной диагностики сахарного диабета у детей, проведен анализ сложностей догоспитального этапа в диагностике дебюта сахарного диабета 1-го типа. ***Цель исследования*** — провести анализ сложных случаев диагностики и тактики ведения детей с дебютом сахарного диабета на догоспитальном этапе оказания скорой и неотложной медицинской помощи. ***Материалы и методы.*** Проанализирована 121 медицинская карта детей за 2022–2023 гг. с клиническим и/или лабораторным дебютом сахарного диабета 1-го типа, госпитализированных в экстренном порядке по скорой и неотложной медицинской помощи в Клинику Санкт-Петербургского государственного педиатрического медицинского университета. Проведен анализ показателей гликемии на этапе поступления ребенка с дебютом сахарного диабета 1-го типа в стационар, рассмотрены клинические проявления заболевания. ***Результаты.*** Самый высокий уровень глюкозы крови выявлен у детей 1–3 лет (27,9±2,6 ммоль/л), при этом уровень гликемии не соотносится с наличием «больших симптомов» сахарного диабета 1-го типа, что связано с полиморфизмом клинических проявлений. Выявлено, что средний возраст дебюта сахарного диабета 1-го типа у детей с отягощенным анамнезом по перинатальной гипоксии наступал в более ранние сроки и составил 6,98±0,47 года, возраст дебюта у детей с неотягощенным анамнезом составил 8,98±0,5 года. ***Выводы.*** Сахарный диабет 1-го типа у детей часто дебютирует под «масками» ОРВИ, кишечной или мочеполовой инфекции, что приводит к поздней диагностике и развитию кетоацидоза. У подростков самый длительный период от первых симптомов до лабораторного подтверждения сахарного диабета 1-го типа. Необходимо улучшить систематическое обучение врачей амбулаторного звена клиническим и диагностическим критериям сахарного диабета 1-го типа.

КЛЮЧЕВЫЕ СЛОВА: *сахарный диабет, дети, догоспитальный этап, тактико-диагностические мероприятия*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a disease resulting from autoimmune destruction of insulin-producing β-cells of the pancreas, leading to the development of absolute insulin deficiency.

According to the International Diabetes Federation (IDF) data for 2021, the total number of children and adolescents (under 19 years of age) with type 1 diabetes worldwide exceeds 1.2 million people. The total number of patients with T1DM under the age of 18 in the Russian Federation as of December 31, 2023, was 61,318 (208 per 100,000 pediatric population) [1].

Type 1 diabetes mellitus is a multifactorial disease; however, the specific mechanisms of interaction between genetic predisposition, environmental factors, and the state of the immune system underlying T1DM remain unclear. Environmental triggers (infectious, dietary, or chemical) that initiate β-cell destruction are still unknown.

Typical complaints of type 1 diabetes mellitus (T1DM) at disease onset include thirst, frequent urination with nocturnal and daytime urinary incontinence in young children, weight loss or unexplained failure to gain weight (in infants), weakness, fatigue, and recurrent skin infections, as well as inflammatory diseases of the external genital organs.

With the development of ketoacidosis, the above complaints are accompanied by dry skin and mucous membranes, the smell of acetone in the exhaled air, vomiting, impaired consciousness up to coma, and regular deep breathing with a loud inspiration and forceful expiration (Kussmaul breathing) [2, 3]. It should be noted that from the appearance of autoantibodies to the onset of clinical manifestations, several years may pass, and the symptoms are highly heterogeneous, which may lead to delayed diagnosis of T1DM at the stage of ketoacidosis development [4–6].

AIM

To analyze complex cases involving the diagnosis and management of children with newly diagnosed type 1 diabetes mellitus during the prehospital phase of emergency and urgent medical care.

Research objectives

1. To study the age structure of children at the onset of diabetes mellitus.

2. To assess the level of newly diagnosed hyperglycemia in children at the onset of diabetes mellitus depending on age.

3. To identify diagnostic difficulties in providing medical care to children with newly diagnosed diabetes mellitus at the prehospital stage.

MATERIALS AND METHODS

An analysis was performed of 121 medical records of children for the years 2022–2023 with a clinical and/or laboratory onset of type 1 diabetes mellitus (T1DM), who were urgently admitted via emergency medical services to the Clinic of the Federal State Budgetary Educational Institution of Higher Education “Saint Petersburg State Pediatric Medical University” of the Ministry of Health of the Russian Federation (SPbSPMU).

The retrospective analysis of medical histories included the assessment of initial and final diagnoses, the age of hospitalized children, the duration from the detection of clinical and/or laboratory signs of T1DM to hospitalization, as well as the level of hyperglycemia, and the nature of diagnostic and therapeutic measures at the prehospital stage.

For statistical processing, mean values and standard deviations of quantitative indicators were calculated (M±m), intergroup differences were assessed using Student’s t-test, and a probability of error of less than 5% ($p \leq 0.05$) was considered statistically significant.

RESULTS AND DISCUSSION

All patients were divided into groups according to age: from 1 to 3 years (n=17), from 4 to 7 years (n=33), from 8 to 12 years (n=41), from 13 to 17 years (n=30). The mean age of the children was 8.93±0.39 years, including 62 boys and 59 girls (Fig. 1).

When analyzing differences between age groups in relation to sex distribution, no statistically significant differences were found ($p > 0.05$).

The reasons for emergency hospitalization at the onset of type 1 diabetes mellitus in children were clinical manifestations and/or detected laboratory abnormalities — hyperglycemia and/or glucosuria.

Complaints of children and/or parents regarding the child’s health were classified as follows: “major symptoms of diabetes mellitus” — polyuria, polydipsia, and weight loss — in 85.9% of cases (n=104), as well as dry mouth, lethargy, and

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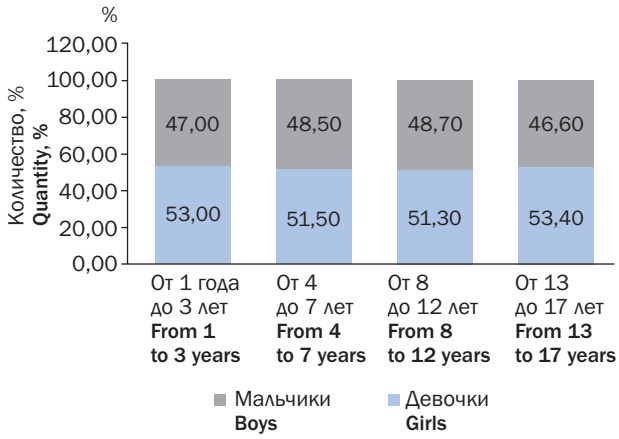

Fig. 1. The ratio of boys and girls with type I diabetes onset in different age groups in the study (the figure is prepared by the authors using their own data)

Рис. 1. Соотношение мальчиков и девочек с дебютом сахарного диабета 1-го типа в различных возрастных группах (рисунок подготовлен авторами по собственным данным)

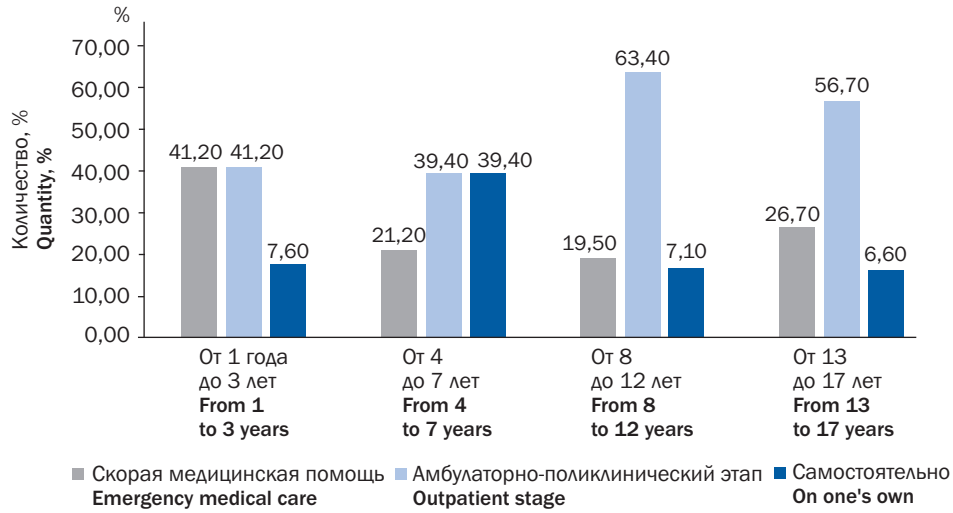

Fig. 2. The number of cases of hyperglycemia detection during the onset of type I diabetes in children at various stages of medical care and during self-admission to the hospital (the figure is prepared by the authors using their own data)

Рис. 2. Количество случаев выявления гипергликемии при дебюте сахарного диабета 1-го типа у детей на различных этапах оказания медицинской помощи и при самостоятельном обращении в стационар (рисунок подготовлен авторами по собственным данным)

drowsiness in 14.8% (n=18), nausea and vomiting in 12.4% (n=15), urinary disturbances (dysuria, nocturia, enuresis) in 6.7% of cases (n=8), abdominal pain in 5.8% (n=7), and less frequently headache and dizziness (n=3), acetone odor from the mouth (n=2), and oral candidiasis (n=1).

Hyperglycemia was initially detected at the primary care setting, at the stage of emergency medical care, and during self-referral (Fig. 2).

In children aged 1 to 3 years, hyperglycemia was more often detected during emergency medical care or at the primary care setting. In the group of children aged 4 to 7 years, hyperglycemia was also predominantly detected at the primary care setting or by parents themselves. Among children aged 8 years and older, hyperglycemia was most frequently detected at the primary care setting.

It was found that blood glucose levels at the onset of type 1 diabetes mellitus in children varied depending on age: in the 1–3 years group, higher values were observed — 27.9±2.6 mmol/L; in older age groups, lower values were recorded: in children aged 4–7 years — 19.77±1.65 mmol/L, 8–12 years — 21.34±1.53 mmol/L, and 13–17 years — 20.3±1.44 mmol/L ($p \leq 0.05$). This is most likely related to the absence of specific complaints in the child, as well as the inability to clearly articulate them due to younger age.

The duration from the onset of initial symptoms to laboratory confirmation of existing hyperglycemia or glucosuria was 16.5±3.78 days in the 1–3 years group, 16.53±2.9 days in the 4–7 years group, 19.05±2.37 days in the 8–12 years group, and 28.29±5.2 days in the 13–17 years group ($p > 0.05$).

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Table 1. Analysis of blood glucose levels in children with various clinical manifestations at the onset of diabetes mellitus

Таблица 1. Анализ уровня глюкозы крови у детей с различными клиническими проявлениями при дебюте сахарного диабета

Уровень глюкозы крови, ммоль/л Blood glucose level, mmol/l	Возраст детей Age of children			
	1–3 года 1–3 years	4–7 лет 4–7 years	8–12 лет 8–12 years	13–17 лет 13–17 years
Имели «большие симптомы сахарного диабета», уровень гликемии Had “major symptoms of diabetes mellitus”, glycemic level	27,50±2,84	19,84±1,67	22,72±1,75	20,28±6,43
Не имели «больших симптомов сахарного диабета», уровень гликемии Did not have “major symptoms of diabetes mellitus”, glycemic levels	29,93±6,43	10,85±1,70	14,13±2,99	12,56±4,37

The table is based on data from the authors' own research
Таблица составлена по данным собственного исследования авторов

A comparative analysis of glycemia levels was performed in children with “major symptoms of diabetes mellitus” and in children without corresponding specific symptoms of T1DM (Table 1).

The results show that in children under 3 years of age, glycemia levels do not correlate with the presence of “major symptoms” of T1DM, which is associated with difficulties in timely diagnosis of diabetes mellitus in this age group.

Among all analyzed medical records of children with newly diagnosed type 1 diabetes mellitus, half had a complicated medical history in the form of perinatal hypoxia during the prenatal development period. It was found that the mean age of T1DM onset in children with a history of perinatal hypoxia occurred earlier and was 6.98±0.47 years, whereas in children without such a history the age of onset was 8.98±0.5 years ($p \leq 0.05$).

Notably, 74% of children were admitted to the hospital in a state of diabetic ketoacidosis (mild or moderate severity) (mild – 15%). Such a high rate of ketoacidosis, according to the analysis of medical documentation, was associated with several reasons.

1. Lack of clinical suspicion for T1DM due to the polymorphism of clinical manifestations (differential diagnosis of the causes of existing complaints was performed, including infectious causes in cases of abdominal pain, vomiting, weakness, and headache in the child; urinary tract infection was also excluded).

2. Delayed presentation of the child’s legal guardians for medical care (attempts at self-treatment).

3. In many cases, at the outpatient stage, after detection of glucosuria or moderate hyperglycemia, further confirmatory investigations were performed in the outpatient setting instead of hospitalizing the child.

CONCLUSION

Currently, it is known that several years may pass from the appearance of autoantibodies to the clinical manifestation of type 1 diabetes mellitus. At the same time, the symptoms of the disease are highly heterogeneous and may be masked by different “clinical disguises”: from signs of acute respiratory or intestinal infection to manifestations of the genitourinary system, which at the initial diagnostic stage may lead to delayed verification of T1DM at the stage of developing ketoacidosis. In addition, a trend toward a younger age of diabetes onset is observed, including the first years of life. Infants and preschool children are unable to clearly formulate their complaints due to age-related features (emotional lability, difficulties in verbal communication, use of diapers), and their apparent well-being may mislead both parents and outpatient clinicians, preventing adequate and timely assessment of the child’s condition severity. All these factors lead to delayed diagnosis of T1DM in this group of children, with pronounced hyperglycemia and ketoacidosis. Adolescents, in turn, often conceal their complaints from relatives, which is associated with the longest interval between the onset of initial symptoms and laboratory confirmation of T1DM in this age group.

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Considering all of the above, in order to ensure timely diagnosis of diabetes mellitus, systematic training of outpatient healthcare personnel is required regarding the clinical presentation and diagnosis of diabetes mellitus. It is necessary to consider expanding the indications for emergency bedside glucometry at the prehospital stage in a number of cases, in addition to the detection of typical clinical symptoms of diabetes mellitus, in diagnostically unclear or doubtful situations: fever without obvious catarrhal symptoms, emotional lability in young children, sudden or progressive lethargy, altered level of consciousness, seizure syndrome, abdominal pain, vomiting, candidal lesions of the oral mucosa, pruritus of the skin or mucous membranes, complaints of headache, presence of dysuria/nocturia/enuresis, as well as in cases of dyspnea or noisy breathing. If laboratory abnormalities are detected — hyperglycemia, glucosuria, or ketonuria — hospital admission of the child to an endocrinology department is recommended.

It is also necessary to inform the population about socially significant diseases, including type 1 diabetes mellitus, through the placement of public awareness campaigns. A high level of awareness regarding this disease will help reduce the rate of complications, including severe ketoacidosis at the stage of T1DM diagnosis.

ADDITIONAL INFORMATION

Authors' contribution. I.Yu. Melnikova — analysis and writing of the article; D.I. Shaytor, A.V. Emelyanova, O.L. Yezhova, Yu.A. Demchuk — collection of material for writing the article, V.M. Shaytor — analysis and writing of the article; K.V. Skobeleva — preparation of graphic materials; A.V. Yakovlev — analysis of the material.

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REFERENCES

1. Dedov I.I., Shestakova M.V., Galstyan G.R. The prevalence of type 2 diabetes mellitus in the adult population of Russia (NATION study). *Diabetes Mellitus*. 2016;19(2):104–112. (In Russ.). https://doi.org/10.14341/DM2004116-17.
2. Writing Team for the DCCT/EDIC Research Group; Gubitosi-Klug R.A., Sun W., Cleary P.A. et al. Effects of Prior Intensive Insulin Therapy and Risk Factors on Patient-Reported Visual Function Outcomes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Cohort. *JAMA Ophthalmology*. 2016;134(2):137–145. https://doi.org/10.1001/jamaophthalmol.2015.4606.
3. Shaitor V.M. Emergency and urgent medical care for children. 3rd ed., corrected and supplemented. Moscow: GEOTAR-Media; 2024. 672 p. (In Russ.).
4. Type 1 Diabetes Mellitus in Children. Clinical Guidelines. Russian Association of Endocrinologists; 2025. URL: https://diseases.medelement.com/disease/сахарный-диабет-1-типа-у-детей-кп-рф-2025/18747 (accessed: 03.02.2026).
5. Hospital pediatrics. S.V. Belmer, L.I. Ilyenko, ed. Moscow: GEOTAR-Media; 2022. 1072 p. (In Russ.).
6. Writing Group for the DCCT/EDIC Research Group; Orchard T.J., Nathan D.M., Zinman B. et al. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. *JAMA*. 2015;313(1):45–53. https://doi.org/10.1001/jama.2014.16107.

ЛИТЕРАТУРА

1. Дедов И.И., Шестакова М.В., Галстян Г.Р. Распространенность сахарного диабета 2 типа у взрослого населения России (исследование NATION). *Сахарный*

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диабет. 2016;19(2):104–112. https://doi.org/10.14341/DM2004116-17.
2. Writing Team for the DCCT/EDIC Research Group; Gubitosi-Klug R.A., Sun W., Cleary P.A. et al. Effects of Prior Intensive Insulin Therapy and Risk Factors on Patient-Reported Visual Function Outcomes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Cohort. *JAMA Ophthalmology*. 2016;134(2):137–145. https://doi.org/10.1001/jamaophthalmol.2015.4606.
3. Шайтор В.М. Скорая и неотложная медицинская помощь детям. 3-е изд., испр. и доп. М.: ГЭОТАР-Медиа; 2024. 672 с.
4. Сахарный диабет 1 типа у детей. Клинические рекомендации. Российская ассоциация эндокринологов; 2025. URL: https://diseases.medelement.com/disease/сахарный-диабет-1-типа-у-детей-кп-рф-2025/18747 (дата обращения: 03.02.2026).
5. Госпитальная педиатрия. С.В. Бельмер, Л.И. Ильенко, ред. М.: ГЭОТАР-Медиа; 2022. 1072 с.
6. Writing Group for the DCCT/EDIC Research Group; Orchard T.J., Nathan D.M., Zinman B. et al. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. *JAMA*. 2015;313(1):45–53. https://doi.org/10.1001/jama.2014.16107.

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Clinical and immunological aspects of metapneumovirus infection in children

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ABSTRACT. ***Introduction.*** Metapneumovirus infection is one of the leading causes of lower respiratory tract infection in children. ***The aim of the study*** – to identify the features of immunopathogenesis and clinical course of metapneumovirus infection in children to predict the severity of the disease and optimize therapeutic approaches. ***Materials and methods.*** A retrospective analysis of the medical records of 210 children aged 1 month to 14 years hospitalized in infectious disease hospitals in St. Petersburg from 2019 to 2025 was conducted. Etiological identification was performed using PCR in nasopharyngeal swabs. Cytokine status (IL-1β, -6, -8, -10, -17, IFN-α and -γ levels) was determined using ELISA in serum. ***Results.*** Metapneumovirus infection in children was detected in 6.6% of acute respiratory viral infections. Patients with mono-metapneumovirus infection under 3 years of age accounted for 72%, of which 53% had lower respiratory tract lesions. Acute obstructive laryngitis was most often observed in children aged 1–3 years (23.4%). Children with grade I laryngeal stenosis accounted for 64.3%. Acute bronchitis/BOS was more often recorded in children under 1 year (48.8%) and 1-3 years (46.7%). Grade I–II respiratory failure was observed mainly in young patients (85.7%). Pneumonia was diagnosed in 21.5% of children under 1 year of age. Activation of cellular immunity was accompanied by an increase in proinflammatory cytokines (IL-1β, -6, -8, -17) and an anti-inflammatory cytokine (IL-10), which plays a role in limiting excessive inflammation. A simultaneous decrease in interferon levels (IFN-α and -γ) was observed. ***Conclusions.*** Metapneumovirus infection in young children primarily affects the lower respiratory tract and is associated with a high rate of complications. The immunopathogenesis of this infection is characterized by increased production of proinflammatory and anti-inflammatory cytokines, coupled with decreased interferon levels, reflecting an imbalance in the immune response that contributes to the severity of clinical manifestations.

KEYWORDS: *metapneumovirus infection, children, interferons, interleukins*

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Клинико-иммунологические аспекты метапневмовирусной инфекции у детей

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РЕЗЮМЕ. ***Введение.*** Метапневмовирусная инфекция – одна из лидирующих в поражении нижних отделов респираторного тракта у детей. ***Цель исследования*** – выявить особенности клинического течения и иммунопатогенеза метапневмовирусной инфекции у детей для прогнозирования тяжести болезни и оптимизации терапевтических подходов. ***Материалы и методы.*** Проведен ретроспективный анализ медицинских карт 210 детей в возрасте от 1 месяца до 14 лет, госпитализированных в инфекционные стационары Санкт-Петербурга в 2019–2025 гг. Этиологическая расшифровка проводилась методом полимеразной цепной реакции в носоглоточных смывах. Цитокиновый статус (содержание ИЛ-1β, -6, -8, -10, -17, ИФН-α и -γ) определяли методом иммуноферментного анализа в сыворотке крови. ***Результаты.*** Метапневмовирусная инфекция у детей выявлена в 6,6% случаев острой респираторной вирусной инфекции. Пациенты с монометапневмовирусной инфекцией в возрасте до 3 лет составили 72%, из которых 53% имели поражение нижних отделов респираторного тракта. Острый обструктивный ларингит чаще наблюдался у детей в возрасте 1–3 лет (23,4%). Дети со стенозом гортани I степени составили 64,3%. Острый бронхит/бронхообструктивный синдром чаще регистрировался у детей в возрасте до 1 года (48,8%) и 1–3 лет (46,7%). Дыхательная недостаточность I–II степени отмечалась преимущественно у пациентов раннего возраста (85,7%). Пневмония диагностирована у 21,5% детей до 1 года. Активация клеточного иммунитета сопровождалась повышением провоспалительных цитокинов (ИЛ-1β, -6, -8, -17) и противовоспалительного цитокина (ИЛ-10), играющего роль в ограничении чрезмерного воспаления. Одновременно отмечалось снижение уровня интерферонов (ИФН-α и -γ). ***Выводы.*** Метапневмовирусная инфекция у детей преимущественно поражает нижние дыхательные пути и сопровождается высокой частотой осложнений. Иммунопатогенез данной инфекции характеризуется усиленной продукцией провоспалительных и противовоспалительных цитокинов на фоне снижения уровня интерферонов, что отражает дисбаланс иммунного ответа, способствующего тяжести клинических проявлений.

КЛЮЧЕВЫЕ СЛОВА: *метапневмовирусная инфекция, дети, интерфероны, интерлейкины*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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INTRODUCTION

Acute respiratory viral infections (ARVI) continue to be the leading cause of infectious diseases in children. The incidence of ARVI remains consistently high, primarily due to the lack of specific immunoprophylaxis, the instability of the immune response, the ability of some viruses to persist latently, and chronic sensitization of the body. Young children, particularly those under three years of age, remain particularly vulnerable, with ARVI being one of the leading causes of hospitalization in this age group [1, 2]. More than 200 viruses are known to cause respiratory tract infections. The most common pathogens are: influenza viruses, parainfluenza viruses, respiratory syncytial (RS) virus, and adenoviruses, rhinoviruses, bocaviruses, metapneumoviruses, coronaviruses, and enteroviruses. The listed agents do not exhaust the etiological spectrum of ARVI in children, since currently, even with the help of modern laboratory diagnostic methods, it is possible to identify no more than 70% of all acute respiratory tract infections recorded in childhood [3, 4].

In recent years, there has been an increase in the prevalence of metapneumovirus infection, which is a cause for particular concern in pediatrics and virology. The role of metapneumovirus as a trigger for the development of chronic diseases and complications requires a more in-depth study of pathogenetic and immunological mechanisms. Metapneumovirus is capable of persisting in the respiratory tract for long periods with possible reactivation upon a decline in immunity, which contributes to the chronicity of the infection. Clinical manifestations range from mild respiratory symptoms to severe conditions: bronchiolitis, bronchial obstructive syndrome, and pneumonia, particularly in immunocompromised children [5, 6].

Metapneumovirus belongs to the family *Pneumoviridae* (formerly *Paramyxoviridae*) and is a single-stranded RNA virus. It was first identified in 2001 in the Netherlands. Analysis of serum samples from patients showed that it had been circulating in the human population since the mid-20th century. Metapneumovirus has two main genotypes — A and B — each of which includes several subtypes that determine the severity of the disease and the spread of the infection. There is evidence of a new variant of metapneumovirus unrelated to genotypes A and B, suggesting its potentially broader heterogeneity [7, 8].

The immaturity of the immune system in young children and the ability of respiratory pathogens to suppress interferon production reduce the body's antiviral defense, leading to the development of the disease. Interferons (IF) block the synthesis of viral proteins, preventing further viral replication and the spread of infection. Suppression of IF production leads to an imbalance between pro-inflammatory and anti-inflammatory cytokines, particularly interleukins (ILs), which exacerbates inflammation, triggers the development of allergic reactions, and causes airway obstruction syndrome [9, 10].

In young patients with acute respiratory infections, including metapneumovirus infection, reduced functional activity of immunocompetent cells and inadequate regulation of Th-1 interferons in the cellular immune response are observed, leading to a more severe course of the disease with predominant involvement of the lower respiratory tract [11, 12].

A comprehensive analysis of the clinical and immunological characteristics of metapneumovirus infection in children is a key prerequisite for elucidating pathogenetic mechanisms, improving methods of early diagnosis, predicting disease severity, and optimizing therapeutic strategies.

AIM

To identify the characteristics of the clinical course and immunopathogenesis of metapneumovirus infection in children in order to predict disease severity and optimize treatment.

MATERIALS AND METHODS

A retrospective analysis was conducted of the medical records of 210 children aged 1 month to 14 years with metapneumovirus infection who were treated at pediatric infectious disease hospitals in St. Petersburg (N.F. Filatov Children's City Clinical Hospital No. 5, St. Olga Children's City Clinical Hospital No. 4) between 2019 and 2025. Monoinfection was observed in 164 patients (78.1%), and co-infections with other respiratory viruses were observed in 46 children (21.9%).

This study presents an analysis of the clinical and immunological characteristics of patients with monometapneumovirus infection, whose age distribution is as follows: 1 month to 1 year — 41 (25.0%), 1 to 3 years — 77 (47.0%), 3 to 7 years — 34 (20.7%), 7 to 14 years — 12 (7.3%).

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Inclusion criteria for the study: seeking medical care within the first three days of symptom onset, no use of antiviral or topical antiseptic therapy prior to laboratory testing, and no comorbidities that could interfere with an objective assessment of the results (diabetes mellitus, tuberculosis, chronic liver and kidney diseases, cancer at any stage, HIV infection).

The diagnosis of metapneumovirus infection was based on clinical signs, including fever, redness of the oropharyngeal mucosa, nasal congestion, rhinitis, cough, shortness of breath, as well as percussion and auscultatory changes in the lungs. The patients' condition was monitored daily. Chest X-rays were performed when there were clinical and laboratory indications to detect pneumonia and other complications.

During the first day of the patient's hospitalization, a nasopharyngeal specimen was tested for respiratory viral antigens using real-time reverse transcription polymerase chain reaction (RT-PCR) with the "AmpliPrime® ARVI-Complex" and "AmpliPrime® SARS-CoV-2 / Flu (A/B/H1pdm09)" (NextBio LLC, Moscow). Cytokine status (levels of IFN-α and IFN-γ, IL-1β, -6, -8, -10, and IL-17) was assessed in blood serum by enzyme-linked immunosorbent assay (ELISA) during the acute phase of the disease. The assays were performed using commercial kits (Cytokine LLC, St. Petersburg) in the laboratory of the State Scientific Research Institute of Ultra-Pure Biopreparations.

Statistical analysis was performed using the STATISTICA 13.0 software package. Quantitative results are presented as absolute values with the percentage (%) and a confidence interval (CI) calculated using the Klopper–Pearson method. The Pearson's χ^2 test was used to assess differences between groups. Differences were considered statistically significant at a p-value <0.05. To identify cytokine markers, we used the binary logistic regression method with stepwise inclusion of variables (p <0.05).

RESULTS

An analysis of laboratory test results for patients with acute respiratory infections observed between 2019 and 2025 showed that a viral cause was identified in 84.9% (n=3,181) of cases, while in 15.1% (n=565) of cases, test results for the respiratory virus group were negative. Metapneumovirus infection was confirmed in 210 patients, accounting for 6.6% of all confirmed cases of ARVI. Monoinfection was observed in 164 patients (5.2%), and mixed infection in 46 (1.4%).

Mixed infection included various combinations, predominantly of two viral genomes (Fig. 1). An association between metapneumovirus and RSV was detected in the overwhelming majority of cases (26.1%), which is explained by the coincidence of the peaks in the circulation of these viruses [1]. Co-infection of metapneumovirus with coronaviruses was recorded in 21.7% of cases, which is associated with the high prevalence of SARS-CoV-2 during the pandemic [3]. Co-infection of metapneumovirus with rhinovirus (17.4%) and influenza virus (13.0%) was detected less frequently. According to the literature, influenza viruses and rhinoviruses are among the leading causative agents of ARVI and remain relevant pathogens to this day [4]. Less frequently, cases of viral-viral coinfections involving metapneumovirus with adenovirus (10.9%), bocavirus (6.5%), and parainfluenza virus (4.4%) were recorded.

An analysis of gender characteristics reveals a higher prevalence among boys compared to girls [2]. A similar trend was observed among patients with monometapneumovirus infection: among the 164 patients examined, boys accounted for 73.2% (n=120) and girls for 26.8% (n=44) (p <0.05). Among those hospitalized, the majority of patients were under

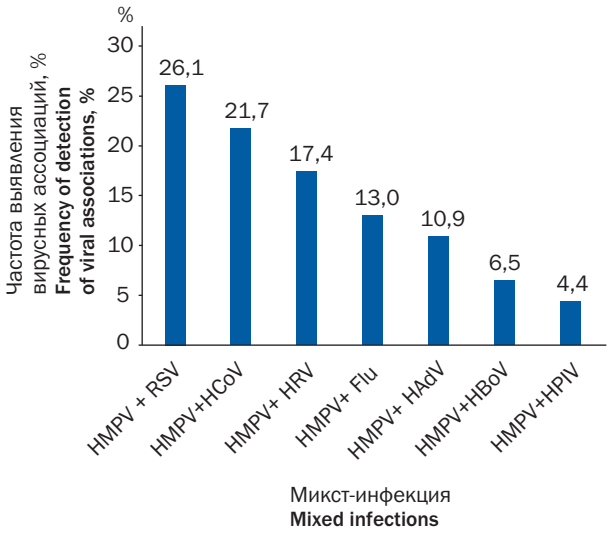

Fig. 1. Structure of viral associations in children examined in 2019–2025 (n=46): HAdV — adenovirus; HBoV — bocavirus; HCoV — coronavirus; HMPV — metapneumovirus; HPIV — parainfluenza; HRV — rhinovirus; Flu — influenza; RSV — respiratory syncytial virus (the figure is prepared by the authors)

Рис. 1. Структура вирусных ассоциаций у обследованных детей в 2019–2025 гг. (n=46): HAdV — аденовирус; HBoV — бокавирус; HCoV — коронавирус; HMPV — метапневмовирус; HPIV — парагрипп; HRV — риновирус; Flu — вирусы гриппа; RSV — респираторно-синцитиальный вирус (рисунок подготовлен авторами)

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three years of age (n=118/72.0%), which is explained by the immaturity of the immune system and the high susceptibility of children in this age group to viral infections [7].

The rate of hospitalization of children with monometapneumovirus infection was significantly higher when the lower respiratory tract was involved (n=112/68.3%) compared to the upper respiratory tract (n=52/31.7%) (p <0.05). A high incidence of lower respiratory tract involvement was observed across various age groups: 1 month to 1 year — 87.8%, 1–3 years — 66.2%, and 3–7 years — 61.8%. In children aged 7–14 years, upper respiratory tract involvement was recorded in the majority of cases (66.7%) (Table 1). Young children with lower respiratory tract involvement (n=87/53.0%) accounted for more than half of those hospitalized with monometapneumovirus infection.

Upper respiratory tract involvement in the form of rhinopharyngitis was detected in 24 children (14.6%) (Table 2). The course of metapneumovirus infection involving exclusively the upper respiratory tract was characterized by an acute onset. Hospitalization of patients was due to hyperthermia reaching 38.5–39.0 °C, which was difficult to control in an outpatient setting and persisted in the hospital for 3–5 days from the onset of symptoms. The intoxication syndrome manifested as a deterioration in general condition, lethargy, headache, and loss of appetite. The catarrhal syndrome was moderately pronounced from the first days of the illness, manifesting as serous rhinorrhea, nasal congestion, oropharyngeal hyperemia, and a persistent, non-productive cough.

Acute obstructive laryngitis was observed in 28 patients, predominantly in children aged 1–3 years (n=18/23.4%). With increasing age, the frequency of clinical manifestations of laryngeal stenosis decreased: in the 3–7-year-old group — 6 children; in the 7–14-year-old group — 2 patients. Croup more often complicated the course of the underlying disease on the second (n=15/53.6%) and third day (n=9/32.1%) from the onset of respiratory symptoms; it was less common on the first day of the illness (n=4/14.3%). At the same time, grade I laryngeal stenosis was diagnosed significantly more often (n=18/64.3%) than grade II (n=10/35.7%) (p <0.05). No cases of grade III laryngeal stenosis were observed. In 60.7% (n=17) of patients, the symptoms of stenosis were completely resolved within the first day of hospitalization; in

Table 1. Levels of respiratory tract damage in hospitalized children of different ages with mono-metapneumovirus infection in 2019–2025 (n=164)

Таблица 1. Уровни поражения респираторного тракта при монометапневмовирусной инфекции у госпитализированных детей различного возраста в 2019–2025 гг. (n=164)

Возраст Age	Уровень поражения респираторного тракта Respiratory tract lesion level	
	верхние дыхательные пути upper respiratory tract n/%	нижние дыхательные пути lower respiratory tract n/%
1 месяц — 1 год 1 month — 1 year (n=41)	5/12,2	36/87,8*
1–3 года 1–3 years (n=77)	26/33,8	51/66,2*
3–7 лет 3–7 years (n=34)	13/38,2	21/61,8*
7–14 лет 7–14 years (n=12)	8/66,7*	4/33,3
Всего детей Total children (n=164)	52/31,7	112/68,3*

The table is prepared by the authors using their own data

Таблица составлена авторами по собственным данным

Note: n — the number of patients; * — p <0.05 in relation to the corresponding indicator between the levels of respiratory tract damage.

Примечание: n — число пациентов; * — p <0,05 по отношению к соответствующему показателю между уровнями поражения респираторного тракта.

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Table 2. The nature of respiratory tract damage in hospitalized children of various ages with confirmed monometapneumovirus infection in 2019–2025 (n=164)

Таблица 2. Характер поражения респираторного тракта у госпитализированных детей различного возраста с подтвержденной монометапневмовирусной инфекцией в 2019–2025 гг. (n=164)

Возраст Age	Характер поражения респираторного тракта The nature of the respiratory tract lesion				
	острый ринофарингит acute rhinopharyngitis (n/%)	острый обструктивный ларингит acute obstructive laryngitis (n/%)	острый трахеит acute tracheitis (n/%)	острый бронхит/БОС acute bronchitis/BOS (n/%)	вирусная пневмония viral pneumonia (n/%)
1 месяц — 1 год 1 month — 1 year (n=41)	3/7,7	2/4,9	7/17,1	20/48,8*	9/21,5
1–3 года 1–3 years (n=77)	8/10,4	18/23,4	9/11,7	36/46,7*	6/7,8
3–7 лет 3–7 years (n=34)	7/20,6	6/17,6	3/8,8	14/41,2*	4/11,8
7–14 лет 7–14 year (n=12)	6/50,0	2/16,7	1/8,3	2/16,7	1/8,3
Всего детей Total children (n=164)	24/14,6	28/17,1	20/12,2	72/43,9*	20/12,2

The table is prepared by the authors using their own data

Таблица составлена авторами по собственным данным

Note: BOS — bronchial obstruction syndrome; n — number of patients, * — p <0.05 in relation to the corresponding indicator for acute rhinopharyngitis.

Примечание: БОС — бронхообструктивный синдром; n — число пациентов; * — p <0,05 по отношению к соответствующему показателю при остром ринофарингите.

28.6% (n=8) of patients, they resolved on the second day; and in only 10.7% (n=3) did croup symptoms persist for three days. Twenty patients (12.2%) were diagnosed with acute tracheitis, which manifested as a dry cough that progressed to a productive wet cough as the disease advanced.

In 72 children (43.9%), monometapneumovirus infection presented with symptoms of acute bronchitis, and 72.2% (n=52) of them exhibited bronchial obstructive syndrome (BOS) of varying severity. The age distribution of acute bronchitis/BOS was characterized by a predominance of young children: 1 month to 1 year — 48.8%, 1 to 3 years — 46.7%, with a tendency toward a decrease in frequency in older age groups: 3–7 years — 41.2%, 7–14 years — 16.7%. The complication developed in the majority of patients within the first three days — in 64.4%, and from the 4th to the 5th day — in 35.6% of children (p <0.05). The leading components of the clinical symptom complex were signs of respiratory failure (RF) against a background of obstructive syndrome, severe intoxication, and fever persisting for several days. Clinical signs of grade I–II RI were observed in 35 (21.3%) patients, with infants accounting for 85.7% (n=30) compared to children in older age groups — 14.3% (n=5) of cases (p <0.05).

In 20 (12.2%) patients with monometapneumovirus infection, pneumonia developed, more frequently in children aged 1 month to 1 year (21.5%). In other age groups, pneumonia was recorded with varying frequency: from 1 to 3 years of age — 7.8%, from 3 to 7 years of age — 11.8%, and from 7 to 14 years of age — 8.3%. In 75.0% of cases, pneumonia was detected within the first three days of the illness; in 25.0% of patients, it was diagnosed on the 4th–5th day of the illness. Radiographic examination revealed infiltrative changes predominantly in the VIII and IX segments of the right and/or left lung. In all children, the disease was accompanied by an elevated body temperature, with half of the children experiencing febrile temperatures (38.1–38.9 °C) for 3–7 days, and was accompanied by a pronounced intoxication syndrome.

We analyzed the results of a study examining serum levels of IFN-α and -γ and cytokines (IL-1β, -8,

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Table 3. Serum cytokine levels in healthy children and patients with mono-metapneumovirus infection, depending on the severity of respiratory tract damage

Таблица 3. Содержание цитокинов в сыворотке крови у пациентов с монометапневмовирусной инфекцией в зависимости от уровня поражения респираторного тракта

Цитокины Cytokines	Норма, пг/мл Standard, pg/ml (M±m)	Характер поражения респираторного тракта The nature of the respiratory tract lesion			
		острый ринофарингит, пг/мл acute rhinopharyngitis, pg/ml (M±m) (n=28)	острый обструктивный ларингит, пг/мл acute obstructive laryngitis, pg/ml (M±m) (n=20)	острый бронхит/БОС, пг/мл acute bronchitis / BOS pg/ml (M±m) (n=26)	вирусная пневмония, пг/мл viral pneumonia, pg/ml (M±m) (n=20)
ИЛ-1β	15,6±2,4	28,2±4,1	31,0±5,4	41,2±4,2*	44,7±5,1*
ИЛ-8	25,1±3,5	68,4±23,4	72,3±24,7	239,3±26,8*	326,4±27,9*
ИЛ-10	15,6±2,4	26,0±3,5	32,4±4,3	63,6±5,9*	81,0±4,6*
ИЛ-17	21,0±3,1	41,3±11,4	175,6±47,6*	267,6±39,5*	245,2±41,3*
ИФН-α	23,3±3,8	48,5±1,6	26,4±1,3	20,1±1,2*	15,4±1,1*
ИФН-γ	25,6±2,7	52,2±3,2	45,4±3,6	16,4±1,3*	10,4±1,2*

The table is prepared by the authors using their own data

Таблица составлена авторами по собственным данным

Note: BOS — bronchial obstruction syndrome; * — p<0,05 in relation to the corresponding indicator for acute rhinopharyngitis.

Примечание: БОС — бронхообструктивный синдром; * — p <0,05 по отношению к соответствующему показателю при остром ринофарингите.

-10, and -17) in patients with varying degrees of respiratory tract involvement due to mono-metapneumovirus infection (Table 3).

The study found that in children with viral pneumonia, the level of the pro-inflammatory cytokine IL-1β increases significantly, reaching 44.7±5.1 pg/mL, which is 1.6 times higher than the levels observed in acute rhinopharyngitis (28.2±4.1 pg/mL) (p <0.05). The increase in IL-8 is particularly pronounced, with its concentration rising more than fourfold, from 68.4±23.4 to 326.4±27.9 pg/mL, reflecting the intensity of the inflammatory response in the airways. The increase in IL-10 levels from 26.0±3.5 to 81.0±4.6 pg/mL indicates the activation of compensatory anti-inflammatory mechanisms aimed at limiting inflammation and protecting tissues from damage. The more than sixfold increase in IL-17, from 41.3±11.4 to 267.6±39.5 pg/ml, indicates the key role of this cytokine in the pathogenesis of obstructive inflammatory processes in the lower respiratory tract, which contributes to the recruitment and activation of neutrophils and other inflammatory cells [12]. Concurrently, a significant decrease in interferon levels is observed: IFN-α decreases from 48.5±1.6 pg/mL in acute rhinopharyngitis to 15.4±1.1 pg/mL in viral pneumonia, and IFN-γ from 52.2±3.2 to 10.4±1.2 pg/mL, respectively, indicating a substantial suppression of the antiviral interferon response [10], particularly in cases of lower respiratory tract involvement.

DISCUSSION

The analysis showed that, between 2019 and 2025, metapneumovirus infection accounted for 6.6% of confirmed cases of ARVI in children, of which 5.2% were monoinfections and 1.4% were mixed infections. The demographic profile of patients with monometapneumovirus infection was characterized by a predominance of young children (under 3 years of age) (72%), of whom 53% had inflammatory changes in the lower respiratory tract. Boys predominated among those examined (73.2%).

Acute obstructive laryngitis was most common in children aged 1–3 years (23.4%), and first-degree laryngeal stenosis was diagnosed in 64.3% of cases. Croup developed predominantly on the 2nd–3rd day of the illness (53.6% and 32.1%, respectively).

Acute bronchitis/bronchopneumonia was more frequently recorded in children aged 1 month to 1 year (48.8%) and 1–3 years (46.7%), with this complication occurring within the first three days of the illness in 64.4% of cases. Clinical signs of grade I–II respiratory distress syndrome were observed in 85.7% of young children.

Viral pneumonia was diagnosed predominantly in infants under 1 year of age (21.5%), with 75% of cases occurring within the first three days, indicating rapid progression of the inflammatory process in the lower respiratory tract. Consequently,

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acute bronchitis/BRD and pneumonia developed predominantly in the early stages of the illness.

The cytokine profile of patients was characterized by a significant increase in pro-inflammatory cytokines IL-1β (up to 44.7±5.1 pg/mL), IL-8 (up to 326.4±27.9 pg/mL), IL-17 (up to 267.6±39.5 pg/mL), as well as the anti-inflammatory cytokine IL-10 (up to 81.0±4.6 pg/mL), particularly in cases of lower respiratory tract involvement. At the same time, a decrease in IFN-α and -γ levels (to 15.4 and 10.4 pg/mL, respectively) was observed, reflecting a weakened antiviral immune response.

CONCLUSION

Metapneumovirus infection in children is characterized by predominant involvement of the lower respiratory tract and a high incidence of complications, such as acute obstructive laryngitis, bronchial obstruction syndrome, and pneumonia, which leads to a severe course of the disease and necessitates a comprehensive approach to diagnosis and treatment. Immune dysregulation in the form of an imbalance between pro- and anti-inflammatory cytokines, as well as a reduced interferon response, can serve as markers for monitoring the course of the disease and form the basis for optimizing therapy aimed at restoring antiviral immunity.

ADDITIONAL INFORMATION

Authors' contribution. Concept of the article — V.F. Sukhovetskaya, T.A. Kaplina, V.N. Timchenko, T.M. Chernova, E.V. Barakina, O.V. Bulina, E.G. Golovacheva, V.S. Timonina, O.P. Gurina, A.E. Blinov, O.N. Varlamova; text development — V.F. Sukhovetskaya, T.A. Kaplina, V.N. Timchenko, T.M. Chernova, E.V. Barakina, O.V. Bulina, E.G. Golovacheva, V.S. Timonina, O.P. Gurina, A.E. Blinov, O.N. Varlamova; editing — V.F. Sukhovetskaya, T.A. Kaplina, V.N. Timchenko; approval of the final version of the article — V.F. Sukhovetskaya, V.N. Timchenko.

All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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REFERENCES

1. Sharipova E.V., Orlova E.D., Babachenko I.V., Kozyrev E.A., Tyan N.S. Clinical and laboratory features of acute respiratory viral infections in hospitalized children. *Children's Infections*. 2022;21(2):5–10. (In Russ.). https://doi.org/10.22627/2072-8107-2022-21-2-5-10.
2. Kaluzhsky T.I., Savinykh N.A., Savinykh M.V., Utenkova E.O. Features of metapneumovirus and bocavirus infection in children. *Children's Infections*. 2020;19(3):12–14. (In Russ.). https://doi.org/10.22627/2072-8107-2020-19-3-12-14.
3. Burtseva E.I., Kolobukhina L.V., Voronina O.L., Ignatieva A.V., Mukasheva E.A., Panova A.D. et al. Features of the circulation of ARVI pathogens against the background of the emergence and widespread distribution of SARS-CoV-2 in 2018–2021. *Epidemiology and Vaccinal Prevention*. 2022;21(4):16–26. (In Russ.). https://doi.org/10.31631/2073-3046-2022-21-4-16-26.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

4. Sominina A.A., Danilenko D.M., Stolyarov K.A., Karpova L.S., Bakaev M.I., Levanyuk T.P. et al. Interference of SARS-CoV-2 with other pathogens of respiratory viral infections during the pandemic. *Epidemiology and Vaccinal Prevention*. 2021;20(4):28–39. (In Russ.). https://doi.org/10.31631/2073-3046-2021-20-4-28-39.
5. Popova O.P., Trushakova S.V., Fedorova I.M., Koteleva S.I., Bunin S.V., Shvetsova Yu.V. et al. Metapneumovirus infection in children in modern conditions: clinical and immunological parallels. *Children's Infections*. 2024;23(1):12–17. (In Russ.). https://doi.org/10.22627/2072-8107-2024-23-1-12-17.
6. Russel C.J., Penkert R.R., Kim S., Hurwitz J.L. Human metapneumovirus: a largely unrecognized threat tohuman health. *Pathogens*. 2020;9(2):109. https://doi.org/10.3390/pathogens9020109.
7. Sharipova E.V., Babachenko I.V., Orlova E.D. Metapneumovirus infection in children. *Pediatrician*. 2020;11(5):15–19. (In Russ.). https://doi.org/10.17816/PED11513-19.
8. Holzemer N., Hasvold J.J., Pohl K.J. et al. Human metapneumovirus infection in hospitalized children. *Respir Care*. 2020;65(5):650–657. https://doi.org/10.4187/respcare.07156.
9. Hadjadj J., Yatim N., Barnabei L., Corneau A., Boussier J., Smith N. et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science*. 2020;369(6504):718–724. https://doi.org/10.1126/science.abc6027.
10. Afanasyeva O.I., Golovacheva E.G., Timonina V.S. et al. Clinical and immunological assessment of the effectiveness of recombinant interferon alpha-2b intranasal preparation in children with obstructive laryngitis associated with epidemiologically significant respiratory infections. *Infectious Diseases: News, Opinions, Training*. 2024;13(3):29–36. (In Russ.). https://doi.org/10.33029/2305-3496-2024-13-3-29-36.
11. Delyagin V.M. Formation of immunity and development of anti-infectious protection in infants and young children. *Effective Pharmacotherapy*. 2024;20(11):32–36. (In Russ.). https://doi.org/10.33978/2307-3586-2024-20-11-32-36.
12. Simbirtsev A.S. Cytokines and their role in immune pathogenesis of allergy. *Russian Medical Inquiry*. 2021;5(1):32–37. https://doi.org/ 10.32364/2587-6821-2021-5-1-32-37.

ЛИТЕРАТУРА

1. Шарипова Е.В., Орлова Е.Д., Бабаченко И.В., Козырев Е.А., Тян Н.С. Клинико-лабораторные особенности острых респираторных вирусных инфекций у госпитализированных детей. *Детские инфекции*. 2022;21(2):5–10. https://doi.org/10.22627/2072-8107-2022-21-2-5-10.
2. Калужский Т.И., Савиных Н.А., Савиных М.В., Утенкова Е.О. Особенности метапневмовирусной и бокавирусной инфекции у детей. *Детские инфекции*. 2020;19(3):12–14. https://doi.org/10.22627/2072-8107-2020-19-3-12-14.
3. Бурцева Е.И., Колобухина Л.В., Воронина О.Л., Игнатьева А.В., Мукашева Е.А., Панова А.Д. и др. Особенности циркуляции возбудителей ОРВИ на фоне появления и широкого распространения SARS-CoV-2 в 2018–2021 годы. *Эпидемиология и вакцинопрофилактика*. 2022;21(4):16–26. https://doi.org/10.31631/2073-3046-2022-21-4-16-26.
4. Соминина А.А., Даниленко Д.М., Столяров К.А., Карпова Л.С., Бакаев М.И., Леванюк Т.П. и др. Интерференция SARS-CoV-2 с другими возбудителями респираторных вирусных инфекций в период пандемии. *Эпидемиология и вакцинопрофилактика*. 2021;20(4):28–39. https://doi.org/10.31631/2073-3046-2021-20-4-28-39.
5. Попова О.П., Трушакова С.В., Федорова И.М., Котелева С.И., Бунин С.В., Швецова Ю.В. и др. Метапневмовирусная инфекция у детей в современных условиях: клинико-иммунологические параллели. *Детские инфекции*. 2024;23(1):12–17. https://doi.org/10.22627/2072-8107-2024-23-1-12-17.
6. Russel C.J., Penkert R.R., Kim S., Hurwitz J.L. Human metapneumovirus: a largely unrecognized threat tohuman health. *Pathogens*. 2020;9(2):109. https://doi.org/10.3390/pathogens9020109.
7. Шарипова Е.В., Бабаченко И.В., Орлова Е.Д. Метапневмовирусная инфекция у детей. *Педиатр*. 2020;11(5):15–19. https://doi.org/10.17816/PED11513-19.
8. Holzemer N., Hasvold J.J., Pohl K.J. et al. Human metapneumovirus infection in hospitalized children. *Respir Care*. 2020;65(5):650–657. https://doi.org/10.4187/respcare.07156.
9. Hadjadj J., Yatim N., Barnabei L., Corneau A., Boussier J., Smith N. et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science*. 2020;369(6504):718–724. https://doi.org/10.1126/science.abc6027.
10. Афанасьева О.И., Головачева Е.Г., Тимонина В.С. и др. Клинико-иммунологическая оценка эффективности интраназального препарата рекомбинантного интерферона альфа-2b у детей с обструктивным ларингитом, ассоциированным с эпидемически значимыми респираторными инфекциями. *Инфекционные болезни: новости, мнения, обучение*. 2024;13(3):29–36. https://doi.org/10.33029/2305-3496-2024-13-3-29-36.
11. Делягин В.М. Формирование иммунитета и становление противоинфекционной защиты у детей раннего и младшего возраста. *Эффективная фармакотерапия*. 2024;20(11):32–36. https://doi.org/10.33978/2307-3586-2024-20-11-32-36.
12. Simbirtsev A.S. Cytokines and their role in immune pathogenesis of allergy. *Russian Medical Inquiry*. 2021;5(1):32–37. https://doi.org/10.32364/2587-6821-2021-5-1-32-37.

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Mechanisms of cognitive impairment in children after coronavirus infection

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ABSTRACT. ***Introduction.*** Identification of the causes of cognitive impairment, early diagnosis, prediction, and rehabilitation remain important tasks in pediatric practice. ***The aim*** — to investigate the mechanisms underlying the development of cognitive impairment and to identify risk factors in children who have had mild to moderate COVID-19. ***Materials and methods.*** The study included 147 children aged 7–18 years who had SARS-CoV-2 infection. Group 1 comprised 22 children with cognitive impairment, while Group 2 included 125 children without impairment. The groups were comparable in terms of age and sex. Cognitive impairment was assessed using the syndrome-based factor analysis of higher cortical functions proposed by A.R. Luria. The frequency and severity of asthenic syndrome were evaluated using the Malkova–Chertova scale (modified for adolescents). Transcranial duplex ultrasound of cerebral vessels was performed. Statistical analysis was conducted using IBM SPSS Statistics 23. Differences were considered statistically significant at $p < 0.05$. ***Results.*** Cognitive impairment was detected in 13.6% of children from the early stages of SARS-CoV-2 infection and persisted for up to three years. Moderate and severe asthenia were associated with an increased risk of cognitive deficit. The likelihood of cognitive impairment was also influenced by the severity of infection symptoms, the presence of neurological manifestations, as well as the child's sex and age.

KEYWORDS: *cognitive impairment, children, COVID-19, SARS-CoV-2, asthenic syndrome, risk factors*

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Механизмы формирования когнитивных нарушений у детей, перенесших коронавирусную инфекцию

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РЕЗЮМЕ. ***Введение.*** Выявление причин формирования когнитивных нарушений, их ранняя диагностика, прогнозирование и реабилитация пациентов остаются актуальными задачами педиатрической практики. ***Цель исследования*** — изучить механизмы формирования и определить факторы риска развития когнитивных нарушений у детей, перенесших легкую и среднетяжелую формы COVID-19. ***Материалы и методы.*** Под наблюдением находились 147 детей в возрасте от 7 до 18 лет, перенесших инфекцию SARS-CoV-2. В 1-ю группу вошли 22 ребенка с когнитивными нарушениями, во 2-ю — 125 детей без нарушений. Группы были сопоставимы по полу и возрасту. Когнитивные нарушения оценивали с помощью синдромного факторного анализа нарушений высших корковых функций человека, предложенного А.Р. Лурией. Частоту и тяжесть астенического синдрома определяли по шкале Л.Д. Малковой и Т.Г. Чертовой в модификации для подростков (Шкала астенического состояния). Проводилось транскраниальное дуплексное сканирование сосудов головного мозга. Статистическая обработка осуществлялась с использованием IBM SPSS Statistics 23. Значимость принимали при $p < 0,05$. ***Результаты.*** Когнитивные нарушения выявлены у 13,6% детей с первых дней заболевания SARS-CoV-2 и сохранялись до трех лет. Установлено, что умеренная и тяжелая астения повышает риск когнитивного дефицита. На вероятность развития нарушений также влияют выраженность симптомов инфекции, наличие неврологических проявлений, а также пол и возраст ребенка.

КЛЮЧЕВЫЕ СЛОВА: *когнитивные нарушения, дети, COVID-19, SARS-CoV-2, астенический синдром, факторы риска*

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INTRODUCTION

Children's health is one of the priority issues of medicine in the Russian Federation. At the same time, the state of physical and mental health largely depends on the body's ability to adapt to changing environmental conditions [1, 2].

Adaptation to environmental factors is ensured by the autonomic nervous system (ANS) through the coordinated activity of the sympathetic and parasympathetic divisions [3]. Exposure to adverse factors exceeding the body's reserve capacities leads to tension of adaptive mechanisms. Researchers attribute the novel coronavirus infection (SARS-CoV-2), COVID-19, to the causes of reduced quality of life and deterioration of physical and mental health in children and adolescents [4–7].

It is known that since the onset of the COVID-19 pandemic, an increase in neurological disorders has been observed worldwide, the genesis of which may be associated with damage to nervous system cells following the passage of the SARS-CoV-2 virus through the blood-brain barrier. Children of this age are particularly vulnerable in this regard, since it is during this period of life that active development of environmental perception, memory, speech, and psychomotor coordination occurs [4, 8]. Disruption of adaptive mechanisms may affect the intellectual development of the child, cause a decline in cognitive abilities, and, as a consequence, lead to difficulties in learning educational material, among other effects [2, 9].

For a comprehensive assessment of higher mental functions (HMF) and the emotional-personal sphere, it is recommended to study cerebral hemodynamics with determination of the state of adaptive and compensatory mechanisms of cerebral blood flow autoregulation [10]. For this purpose, transcranial duplex scanning (TCDS) of cerebral vessels is performed, which makes it possible to study baseline blood flow characteristics and cerebrovascular reactivity (the ability of cerebral vessels to change their diameter in response to various specific stimuli) in real time [11].

In this regard, the issues of early detection of cognitive disorders, identification of risk factors for their development, and development of prognostic models allowing timely implementation of preventive and rehabilitation measures are relevant [12, 13]. All of the above determined the purpose of the present study.

AIM

The aim is to investigate the mechanisms underlying the development of cognitive impairments and identify risk factors for their onset in children who have had mild or moderate COVID-19.

MATERIALS AND METHODS

The present cohort study was conducted from 2020 to 2024 at Children's Polyclinic No. 1 of the Krasnogorsk City Hospital. A total of 147 patients who had experienced outpatient SARS-CoV-2 infection were observed. There were 54 boys and 93 girls. The age of the participants ranged from 7 to 18 years, with a median age of 13 (10; 15) years. The children were divided into two groups: Group 1 included 22 children (6 boys and 16 girls) with identified cognitive impairment, and Group 2 included 125 children (48 boys and 77 girls) without cognitive impairment. Both groups were comparable in terms of sex and age (Table 1).

Inclusion criteria: children aged 7 to 18 years, belonging to health groups I–II, with laboratory-confirmed mild to moderate coronavirus infection.

Exclusion criteria: patients younger than 7 years or older than 18 years; children belonging to health groups III–IV (chronic somatic and neurological diseases, including autism spectrum disorders, intellectual disability of any etiology, and organic psychosomatic disorders); children who had or had not experienced coronavirus infection.

Higher mental function (HMF) impairments (memory, thinking, speech, perception, and attention) were identified using the syndrome-based factor analysis of HMF disorders proposed by Alexander Romanovich Luria, which enables assessment of working memory and attention processes, including memorization, retention, and recall of information. Intellectual activity and mnemonic performance of the child were analyzed; the speed of auditory-verbal memorization of a list of 10 words was calculated; visual memory and voluntary attention were also assessed, and the capacities of memorization and delayed text recall were determined [14].

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Table 1. Distribution of study participants by sex and age, n/%*

Таблица 1. Распределение наблюдаемых детей по полу и возрасту, n/%*

Возраст Age	1-я группа 1st group n=22		2-я группа 2nd group n=125		Итого Total n=147	
	пол sex		пол sex		пол sex	
	мальчики boys	девочки girls	мальчики boys	девочки girls	мальчики boys	д девочки girls
7–11 лет 7–11 years	3/13,6	8/36,4	18/14,4	20/16,0	21/14,3	28/19,0
12–15 лет 12–15 years	2/9,1	8/36,4	17/13,6	41/32,8	19/12,9	49/33,3
16–18 лет 16–18 years	1/4,5	–	13/10,4	16/12,8	14/9,5	16/10,9
Итого Total	6/27,3	16/72,7	48/38,4	77/61,6	54/36,7	93/63,3

The table is based on the authors' original data

Таблица составлена по данным авторского исследования

* p >0,05.

To assess the frequency and severity of asthenic syndrome, an express test for asthenic manifestations was performed using the Asthenic State Scale (developed by L.D. Malkova and T.G. Chertova in a modified version for adolescents) [15]. Manifestations of asthenic syndrome included general weakness, rapid fatigability (reduced tolerance to physical and academic activities), decreased appetite, and emotional lability (EL).

In the framework of a comprehensive assessment of higher mental functions (HMF) and the emotional-personal sphere, transcranial duplex scanning (TCDS) of cerebral vessels with functional tests was performed. The key measured parameter was the reactivity index (RI), calculated using the formula:

$$RI = V_{sys} / V_{base},$$

where V_{sys} is the linear blood flow velocity after the test; V_{base} is the baseline velocity (before the test).

An RI value ranging from 1.1 to 1.4 was interpreted as a positive response, corresponding to minimal activity of autoregulatory mechanisms (normal); an RI value exceeding 1.4 was considered an enhanced positive response (in cases of pre-existing vascular tone disturbances); RI values of 0.9–1.1 were interpreted as a negative response to hypercapnia (exhaustion of the regulatory system due to structural changes in the vascular wall caused by endothelial damage); RI values below 0.9 were regarded as a paradoxical response, indicating failure of autoregulatory mechanisms [16].

A comprehensive examination was performed in all children at baseline (within the first 48 hours of illness) and dynamically (at 1, 12, 24, and 36 months).

For statistical processing of the results, IBM SPSS Statistics 23 software was used. The Shapiro–Wilk test was applied to assess data normality. Data with non-normal distribution were presented as median and first and third quartiles Me (Q_1–Q_3); comparisons were performed using the Mann–Whitney U test. Categorical data were presented as absolute values (n) and percentages (%), and compared using Fisher's exact test.

The strength of association between binary dependent variables and binary or quantitative predictors was assessed using odds ratios (OR) obtained from univariate logistic regression models. Results were considered statistically significant at $p < 0.05$. Predictive modeling of cognitive disorder risk was performed using logistic regression with the Akaike information criterion. The informativeness of the models was evaluated using Nagelkerke's pseudo-R^2, ROC curve analysis, and AUC (area under the curve). For all models, sensitivity, specificity, predictive accuracy, and 95% confidence intervals (CI) were calculated.

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RESULTS

At the early stage of coronavirus infection in children, the following complaints were reported (n=147): elevated body temperature (117 – 79.6%), myalgia (23 – 15.6%), arthralgia (13 – 8.8%), abdominal pain (12 – 8.2%), nausea (11 – 7.5%), general weakness (142 – 96.6%), headache (125 – 85.0%), dizziness (56 – 38.1%), sweating (117 – 79.6%), and tachycardia (68 – 46.3%).

Intergroup analysis showed that in the acute phase of the disease these symptoms were more frequent in patients with cognitive impairment than in children without it: emotional lability (EL) – 19/20 (95%) and 73/127 (57.5%); dizziness – 13/20 (65%) and 43/127 (33.9%); sleep disturbances – 13/20 (65%) and 21/127 (16.5%), respectively (p <0.05). At the same time, most clinical symptoms in Group 1 persisted throughout the entire follow-up period (Table 2).

Conversely, in the group of patients without cognitive impairment, by the end of the 36th month a statistically significant (p <0.05) decrease in the frequency of all studied symptoms was recorded compared with the beginning of the disease. A positive trend toward a reduction in the frequency of several symptoms was already observed from the first month (Table 3).

Table 2. Neurological symptoms and findings in children of Group 1 during follow-up, n/%*

Таблица 2. Симптомы и показатели неврологического статуса детей 1-й группы в динамике, n/%*

Симптомы и неврологический статус Symptoms and neurological status	Исходно Initially n=20	Через 1 месяц At 1 month n=18	Через 12 месяцев At 12 months n=16	Через 24 месяца At 24 months n=13	Через 36 месяцев At 36 months n=12
Слабость Weakness	20/100,0	17/94,4	16/100,0	11/84,6	11/91,7
Утомляемость Fatigue	20/100,0	16/88,9	15/93,8	11/84,6	11/91,7
Эмоциональная лабильность Emotional lability	19/95,0	14/77,8	13/81,3	11/84,6	10/83,3
Нарушение аппетита Loss of appetite	16/80,0	12/66,7	11/68,8	9/69,2	8/66,7
Нарушение вкуса Taste impairment	14/70,0	12/66,7	11/68,8	9/69,2	8/66,7
Головная боль Headache	18/90,0	15/83,3	14/87,5	11/84,6	10/83,3
Нарушения обоняния Olfactory impairment	14/70,0	12/66,7	11/68,8	9/69,2	8/66,7
Потливость Hyperhidrosis	18/90,0	14/77,8	14/87,5	11/84,6	9/75,0
Тахикардия Tachycardia	11/55,0	9/50,0	8/50,0	7/53,8	6/50,0
Головокружение Dizziness	13/65,0	11/61,1	12/75	9/69,2	8/66,7
Лабильность артериального давления Blood pressure lability	9/45,0	7/38,9	6/37,5	5/35,5	4/33,3
Нарушения сна Sleep disorders	13/65,0	7/38,9	12/75	9/69,2	8/66,7
Дизосмия Dysosmia	14/70,0	10/55,6	12/75	10/76,9	8/66,7
Дисгевзия Dysgeusia	15/75,0	11/61,1	13/81,3	11/84,6	9/75,0

The table is based on the authors' original data

Таблица составлена по данным авторского исследования

* p >0,05.

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Table 3. Neurological symptoms and findings in children of Group 2 during follow-up, n/%

Таблица 3. Симптомы и показатели неврологического статуса детей 2-й группы в динамике, n/%

Симптомы и неврологический статус Symptoms and neurological status	Исходно Initially n=127	Через 1 месяц At 1 month n=118	Через 12 месяцев At 12 months n=85	Через 24 месяца At 24 months n=74	Через 36 месяцев At 36 months n=79
Слабость Weakness	122/96,1	108/91,5	80/94,1	63/85,1*	44/55,7*
Утомляемость Fatigue	113/89	105/89,0	76/89,4	60/81,1	44/55,7*
Эмоциональная лабильность Emotional lability	73/57,5	63/53,4	43/50,6	37/50,0	32/40,5*
Нарушение аппетита Loss of appetite	94/74,0	63/53,4*	40/47,1*	30/40,5*	29/36,7*
Нарушение вкуса Taste impairment	70/55,1	45/38,1*	28/32,9*	24/32,4*	19/24,1*
Головная боль Headache	107/84,3	80/67,8*	61/71,8*	53/71,6*	52/65,8*
Нарушения обоняния Olfactory impairment	64/50,4	47/39,8	29/34,1*	30/40,5*	20/25,3*
Потливость Sweating	99/78,0	93/78,8	51/60*	40/54,1*	37/46,8*
Тахикардия Tachycardia	57/44,9	44/37,3	22/25,9*	21/28,4*	15/19,0*
Головокружение Dizziness	43/33,9	39/33,1	27/31,8	25/33,8	16/20,3*
Лабильность артериального давления Arterial pressure lability	45/35,4	36/30,5	22/25,9	22/29,7	14/17,7*
Нарушения сна Sleep disorders	21/16,5	16/13,6	12/14,1	10/13,5	5/6,3*
Дизосмия Dysosmia	70/55,1	34/28,8*	34/40*	29/39,2*	26/32,9*
Дисгевзия Dysgeusia	67/52,8	31/26,2*	30/35,3*	27/36,5*	23/29,1*

The table is based on the authors' original data

Таблица составлена по данным авторского исследования

* Values are statistically significantly different from baseline (p <0.05).

* Значения статистически значимо отличаются от исходных (p <0,05).

As shown in Table 3, appetite disturbances decreased from 94 (74%) to 29 (36.7%), headache from 107 (84.3%) to 52 (65.8%). By the 36th month, dysosmia and dysgeusia were also less frequent than at baseline, decreasing from 70 (55.1%) to 26 (32.9%) and from 67 (52.8%) to 23 (29.1%) of children, respectively. At the same time, throughout the entire follow-up period, children with cognitive impairment had significantly higher rates of almost all post-COVID symptoms (emotional lability, appetite disturbances, smell and taste disorders, sleep disturbances, dizziness, sweating, tachycardia, as well as dysosmia and dysgeusia) compared with Group 2 (p <0.05).

Interesting data were obtained when analyzing the dynamics of clinical manifestations of cognitive impairment in children of Group 1. Thus, 30 days after COVID-19, two children showed no problems with memory, attention, or thinking, whereas 18 children with cognitive impairment continued to report reduced academic performance. Examination of schoolchildren revealed working memory deficits (17/94.4%) as well as impaired distribution and switching of attention (16/88.9%). By the end of the first year, cognitive

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disorders had resolved in four children, attention concentration had improved, and academic performance had normalized. Thus, one year after COVID-19, cognitive deficits persisted in 16 of 20 children, accounting for 88.9%.

Twenty-four months after COVID-19, transient post-COVID cognitive impairments resolved in another three children from Group 1; however, they persisted in 13 children in the form of impaired attention concentration and cognitive flexibility, short-term memory deficits, impaired encoding, and reduced verbal fluency.

By the end of the third year of follow-up, cognitive functions had normalized in one more

Table 4. Transcranial duplex ultrasound findings of cerebral vessels in children of Group 1 during follow-up, n/%

Таблица 4. Результаты транскраниального дуплексного сканирования сосудов головного мозга у детей 1-й группы в динамике, n/%

Параметры цереброваскулярной реактивности **Cerebrovascular reactivity parameters**	**Исходно** **Initially** **n=20**	**Через 1 месяц** **At 1 month** **n=18**	**Через 12 месяцев** **At 12 months** **n=16**	**Через 24 месяца** **At 24 months** **n=13**	**Через 36 месяцев** **At 36 months** **n=12**
ИР усиленно + RI enhanced + n/%	0/0	0/0	0/0,0	0/0	0/0
ИР+ RI+ n/%	9/45	9/50	8/50	7/53,8	10/83,3
ИР (–) RI (–) n/%	10/50	8/44,4	8/50	6/46,1	4/33,3
ИР <1,1 RI <1,1 n/%	11 / 55	9 / 50	8 / 50	6 / 46,1	4 / 33,3
ИР RI Me (Q_1; Q_3)	1,08 (1; 1,12)	1,09 (1; 1,12)	1,10 (1,05; 1,12)	1,10 (1,09; 1,13)	1,18* (1,1; 1,2)
ИР парадоксальный RI paradoxical n/%	1/5	1/5,6	0/0,0	0/0	0/0
Повышение линейной скорости кровотока в артериях каротидного бассейна Increased linear blood flow velocity in the carotid circulation n/%	12/60	11/61,1	11/68,8%	8/61,5	8/66,7
Повышение линейной скорости кровотока в артериях вертебробазилярного бассейна Increased linear blood flow velocity in the arteries of the vertebrobasilar basin n/%	11/55	10/55,6	10/62,6%	7/53,8	8/66,7
Повышение линейной скорости кровотока в глубоких венах мозга Increased linear blood flow velocity in the deep cerebral veins n/%	15/75	13/72,2	14/87,5	9/69,2	8/66,7

The table is based on the authors' original data

Таблица составлена по данным авторского исследования

Note: * — values are statistically significantly different from baseline (p <0.05). RI+ — positive reactivity index; RI(–) — negative reactivity index.

Примечание: * — значения статистически значимо отличаются от исходных (p <0,05); ИР+ — положительный индекс реактивности; ИР (–) — отрицательный индекс реактивности.

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child from Group 1. At the same time, 12 (60.0%) patients still exhibited impairments in memory, attention, cognitive switching skills, visual gnosia, and visuospatial function. Such abnormalities significantly reduced the cognitive and adaptive capacities of the children, diminished their ability to acquire new experience, caused distortions in behavioral and psycho-emotional domains, and often led to certain changes in personality development and socialization difficulties.

Analysis of TCDS data of cerebral vessels during COVID-19 and in the follow-up period confirmed the possibility of the infection affecting the

Table 5. Transcranial duplex ultrasound findings of cerebral vessels in children of Group 2 during follow-up, n/%

Таблица 5. Результаты транскраниального дуплексного сканирования сосудов головного мозга у детей 2-й группы в динамике, n/%

Параметры цереброваскулярной **реактивности** **Cerebrovascular reactivity parameters**	**Исходно** **Baseline** **n=127**	**Через 1 месяц** **At 1 month** **n=118**	**Через 12 месяцев** **At 12 months** **n=85**	**Через 24 месяца** **At 24 months** **n=74**	**Через 36 месяцев** **At 36 months** **n=79**
ИР усиленно + RI enhanced + n/%	1/0,8	2/1,7	0/0,0	3/4,1	8/10,1*
ИР+ RI+ n/%	48/37,8	56/47,5	44/51,8*	50/67,6*	60/75,9*
ИР (–) RI (–) n/%	73/57,5	56/47,5	37/43,5	13/17,6*	6/7,6*
ИР <1,1 RI <1,1 n/%	75/59,1	59/50	37/43,5*	16/21,6*	8/10,1*
ИР RI Me (Q_1; Q_3)	1,07 (1; 1,14)	1,09 (1,02;1,18)	1,1* (1,07; 1;16)	1,16* (1,1; 1,23)	1,2* (1,15; 1,3)
ИР парадоксальный RI paradoxical n/%	3/2,4	4/3,4	0/0,0	2/2,7	1/1,3
Повышение линейной скорости кровотока в артериях каротидного бассейна Increased blood flow velocity in the carotid circulation n/%	94/74	89/75,4	55/64,7	45/60,8	49/62,0
Повышение линейной скорости кровотока в артериях вертебро-базилярного бассейна Increased linear blood flow velocity in the arteries of the vertebrobasilar basin n/%	77/60,6	74/62,7	46/54,1	40/54,1	40/0,6
Повышение линейной скорости кровотока в глубоких венах мозга Increased blood flow velocity in the deep cerebral veins n/%	103/81,1	95/80,5	63/74,1	55/74,3	59/74,7

The table is based on the authors' original data

Таблица составлена по данным авторского исследования

Note: * — values are statistically significantly different from baseline (p <0.05). RI+ — positive reactivity index; RI(–) — negative reactivity index..

Примечание: * — значения статистически значимо отличаются от исходных (p <0,05); ИР+ — положительный индекс реактивности; ИР (–) — отрицательный индекс реактивности.

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regulatory system of cerebral blood flow. The results showed that disturbances of cerebral blood flow regulation were initially observed with equal frequency in both groups of children (p >0.05). Thus, a positive RI, indicating minimal activity of autoregulatory mechanisms, was detected in 9 (45%) children of Group 1 and in 48 (37.8%) patients of Group 2; a negative RI, indicating impaired autoregulation, was found in 10 (50%) and 73 (57.5%), respectively. In most patients in the first days of infection, regardless of the presence or absence of cognitive impairment, a similar increase (p > 0.05) in linear blood flow velocity was observed in the carotid artery system: 12 (60%) and 94 (74%), in the vertebrobasilar system: 11 (55%) and 77 (60.6%), as well as in the cerebral venous system: 15 (75%) and 103 (81.1%), respectively.

However, TCDS data obtained during follow-up showed that persistent cognitive deficit may also be associated with disturbances in cerebrovascular reactivity, which, after arising in the acute phase of infection, remained in patients of Group 1 throughout the entire observation period (Table 4), whereas in children of Group 2 cerebrovascular reactivity parameters returned to normal by the end of the third year (p <0.05). At the same time, most children in Group 2 demonstrated persistently increased blood flow velocity in the carotid and vertebrobasilar arteries (VBA), as well as in cerebral veins, throughout the observation period (Table 5).

A reduced reactivity index was significantly more frequently recorded in Group 1 than in Group 2 across all follow-up periods, being observed by the end of the second year in 6 (46.1%) and

Table 6. Predictive models for cognitive impairment in children after COVID-19 at different follow-up time points (odds ratio, 95% CI)

Таблица 6. Модели прогнозирования развития когнитивных нарушений у детей после COVID-19 в различные периоды наблюдения (отношение шансов (доверительный интервал 95%))

Предиктор **Predictor**	**Для 1-го месяца** **At 1 month**	**Для 12-го месяца** **At 12 months**	**Для 24-го месяца** **At 24 months**	**Для 36-го месяца** **At 36 months**
Возраст Age	0,63 (0,43–0,95) p=0,028	0,62 (0,43–0,89) p=0,011	0,47 (0,25–0,86) p=0,015	–
Женский пол Female sex	13,65 (2,12–88,39) p=0,006	–	–	–
Головная боль Headache	11,50 (1,5-88,13) p=0,019	–	–	–
Нарушения обоняния Olfactory impairment	–	–	–	4,49 (1,03–19,52) p=0,045
Нарушение сна Sleep disturbance	–	7,67 (1,43–41,09) p=0,017	27,07 (1,87–392,57) p=0,016	27,24 (5,01–148,18) p <0,001
Выраженность астенического состояния, баллы Severity of asthenic condition, points	–	1,10 (1,02–1,20) p=0,012	1,33 (1,11–1,59) p=0,002	1,11 (1,03–1,19) p=0,004
Повышение линейной скорости кровотока в артериях каротидного бассейна Increased blood flow velocity in the carotid circulation	11,33 (1,47–87,20) p=0,020	0,16 (0,03–0,96) p=0,046	–	–
Индекс реактивности <1,1 Reactivity index <1.1	16,13 (1,21–215,49) p=0,035	–	–	–

The table is based on the authors' original data

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Table 7. Informativeness of forecasting models

Таблица 7. Информативность моделей прогнозирования

Информативность **Informativeness**	**1-й месяц** **At 1 month**	**12-й месяц** **At 12 months**	**24-й месяц** **At 24 months**	**36-й месяц** **At 36 months**
Чувствительность Sensitivity	99,1%	66,7%	88,2%	57,9%
Специфичность Specificity	63,6%	93,8%	94,4%	96,6%
Точность Accuracy	95,9%	86,4%	92,5%	87,2%
AUC	0,929	0,904	0,980	0,876
Псевдо-R^2 Найджелкерке Nagelkerke's pseudo-R^2	0,585	0,584	0,672	0,521

The table is based on the authors' original data

Таблица составлена по данным авторского исследования

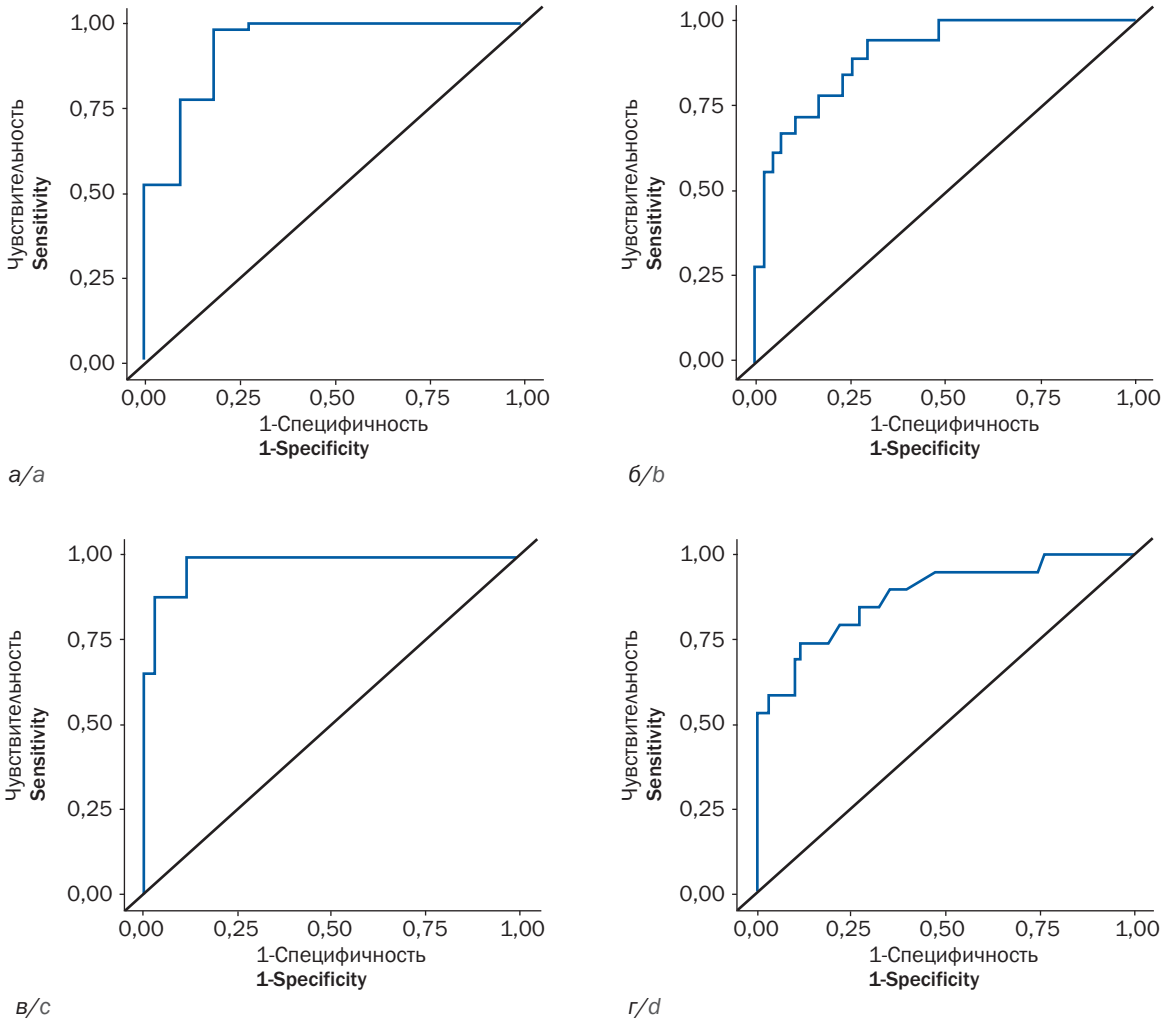

Fig. 1. ROC curves for predicting cognitive impairment at 1 (*a*), 12 (*b*), 24 (*c*), and 36 (*d*) months after COVID-19 using the developed model (the figure is prepared by the authors using their own data)

Рис. 1. ROC-кривые для прогноза развития когнитивных нарушений через 1 (*а*), 12 (*б*), 24 (*в*), 36 (*г*) месяцев после COVID-19 с использованием разработанной модели (рисунок подготовлен авторами по собственным данным)

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13 (17.6%) children, respectively (p=0.031); and by the end of the third year in 4 (33.3%) and 6 (7.6%) children, respectively (p=0.024). Quantitative RI values also differed: at 24 months of follow-up, RI values in patients with cognitive impairment were lower than in children without cognitive impairment: 1.10 (1.09; 1.13) versus 1.16 (1.1; 1.23), respectively (p=0.011). By 36 months, RI values <1.1 were more frequently observed in Group 1 than in Group 2: 4 (33.3%) and 13 (10.1%), respectively (p=0.049). These findings indicate an association between persistent cerebrovascular reactivity disturbances and the persistence of cognitive deficits over three years after COVID-19 infection.

Using logistic regression, the most effective predictors of cognitive impairment development were identified for each follow-up period. Cerebral vessel TCDS parameters and the child's age played the most significant role in predicting cognitive deficits (Table 6).

All developed predictive models for cognitive impairment demonstrated high informativeness (Table 7).

ROC curves for the prediction of cognitive impairment in children who had undergone coronavirus infection at different follow-up periods, using the developed models, are presented in Figure 1.

We also demonstrated a correlation between the probability of developing cognitive impairment and the severity of asthenia. Thus, univariate analysis showed that the presence of grade I asthenic syndrome reduced the likelihood of developing cognitive impairment by 21% at the end of the first month after COVID-19 (95% CI 0.064–0.67; p=0.009). At the same time, grade II–III asthenia, conversely, increased the risk of cognitive impairment by 3.9-fold in children one year after coronavirus infection (95% CI 1.17–13.02; p=0.026), by 23.5-fold after two years (95% CI 2.55–217.12; p=0.005), and by 13-fold at the end of the third year (95% CI 1.28–134.75; p=0.030). This relationship was confirmed by analysis of asthenic syndrome scores using the Asthenic State Scale (ASS) in the two patient groups across different follow-up periods (Table 8).

As shown in Table 8, despite initially similar asthenic manifestations in both groups of children (84 (79; 98) and 78.5 (64; 90) points, respectively), in the subsequent period the severity of asthenia scores was significantly higher in Group 1 than in Group 2. The severity of asthenia in points was also included in the predictive models for cognitive impairment for the 1st, 2nd, and 3rd years of follow-up (p <0.05).

DISCUSSION

Studies by a number of authors have shown that post-COVID syndrome in 11–53% of children may be accompanied by cognitive impairment

Table 8. Cognitive impairment severity in two patient groups at different follow-up time points (L.D. Malkova scale, Me (Q_1–Q_3))

Таблица 8. Выраженность когнитивных нарушений у пациентов двух групп в различные периоды наблюдения в баллах по шкале Л.Д. Малковой, Me (Q_1–Q_3)

Период наблюдения Observation period	Количество пациентов Number of patients, n	1-я группа (с когнитивными нарушениями) Group 1 (with cognitive impairments)	2-я группа (без когнитивных нарушений) Group 2 (without cognitive impairment)	p-value
Начало болезни Disease onset	147	84 (79–98)	78,5 (64–90)	0,034
1-й месяц At 1 month	136	79 (69–96)	69,5 (59–81)	0,043
12-й месяц At 12 months	101	69 (64–81)	61 (53–69)	0,003
24-й месяц At 24 months	87	68 (62–77)	55 (51–61)	<0,001
36-й месяц At 36 months	91	61 (52–67)	51 (46–60)	0,007

The table is based on the authors' original data

Таблица составлена по данным авторского исследования

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[17–19]. In the present study, a decline in cognitive functions after SARS-CoV-2 infection was detected both at disease onset (13.6%) and subsequently, persisting after 36 months in the majority of children (12 (60.0%)) with initially identified cognitive impairment, which is likely due to two factors:

1) direct damage to neurons and glial cells of the brain through interaction of the coronavirus with angiotensin-converting enzyme type 2 on the surface of neurons;
2) degradation of endothelial cell protein by the viral enzyme Mpro [20, 21].

The present study confirms the previously described in the literature [22, 23] stable association between cognitive impairment and asthenic syndrome in children who have had SARS-CoV-2 infection. Unlike previous publications, we have shown and scientifically substantiated that a statistically significant relationship between cognitive impairment and asthenic syndrome not only persists over a three-year period but also depends on the severity of asthenization. Thus, grade II–III asthenia increased the risk of cognitive impairment by 3.9-fold one year after COVID-19, by 23.5-fold after two years, and by 13-fold at the end of the third year ($p < 0.05$). These findings were obtained for the first time.

The study clearly demonstrates that disturbances in cerebral hemodynamics may contribute to reduced cognitive functions and the development of asthenic syndrome [11]. This assumption was confirmed by our TCDS findings, which allowed an objective assessment of the degree of intracranial blood flow disturbances in children throughout the entire clinical follow-up period (from the first month to 36 months after COVID-19). These results were also obtained for the first time.

CONCLUSION

Cognitive impairment is detected in 13.6% of children from the first days of coronavirus infection, even in cases of mild and moderate disease, and persists for up to three years.

Children who have had coronavirus infection should be followed up by a pediatrician, a neurologist, and a psychotherapist for at least three years to ensure timely correction of cognitive impairment.

During follow-up of a child with or after COVID-19, it is important to take into account age, the severity of asthenic syndrome and TCDS parameters, which are prognostically significant early markers of cognitive dysfunction.

ADDITIONAL INFORMATION

Authors' contribution. L.A. Kharitonova contributed to the study concept and design, formulation of research objectives, literature review, interpretation of the data, and drafting of the manuscript; S.N. Novoselova was responsible for data collection, instrumental examinations (transcranial duplex ultrasound of cerebral vessels), statistical analysis, development of predictive models, and critical revision of the manuscript.

Both authors made substantial contributions to the study, approved the final version of the manuscript, and take responsibility for all aspects of the work.

Competing interests. The authors declare that they have no competing interests.

Consent for publication. Written consent was obtained from legal representatives of the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Л.А. Харитонова — разработка концепции и дизайна исследования, формулировка целей и задач, анализ научной литературы, интерпретация полученных данных, подготовка и написание рукописи; С.Н. Новоселова — сбор клинического материала, проведение инструментальных исследований (транскраниального дуплексного сканирования сосудов головного мозга), статистическая обработка данных, участие в построении прогностических моделей, редактирование и критический пересмотр содержания статьи.

Авторы внесли существенный вклад в проведение исследования, согласовали окончательный вариант рукописи и несут ответственность за все аспекты работы.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Информированное согласие на публикацию. Авторы получили письменное согласие законных представителей пациентов на публикацию медицинских данных.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

REFERENCES

1. Kolodyazhnaya T.A., Zaitzeva O.I., Zaitzeva Gh.G., Ignatova I.A. Syndrome of autonomic dysfunction in children of young school age: risk factors and structural and functional state of erythrocyte membranes. *Siberian Journal of Life Sciences and Agriculture*. 2021;4(13):15–130. (In Russ.). https://doi.org/10.12731/2658-6649-2021-13-4-115-130.
2. Smirnova O.V., Ovcharenko E.S., Kasparov E.V., Fefelova V.V. Reactivity of the autonomic nervous system in children of younger school with mental retardation. *Gigiena i Sanitariya (Hygiene and Sanitation, Russian Journal)*. 2023;102(2):169–174. (In Russ.). https://doi.org/10.47470/0016-9900-2023-102-2-169-174.
3. Harteveld L.M., Nederend I., Ten Harkel A.D.J., Schutte N.M., de Rooij S.R., Vrijkotte T.G.M. et al. Maturation of the Cardiac autonomic nervous system activity in children and adolescents. *J Am Heart Assoc*. 2021;10(4): e017405. https://doi.org/10.1161/JAHA.120.017405.
4. Sorg A.L., Becht S., Jank M., Armann J., von Both U., Hufnagel M. et al. Association of SARS-CoV-2 Seropositivity with myalgic encephalomyelitis and/or chronic fatigue syndrome among children and adolescents in Germany. *JAMA Netw Open*. 2022;5(9):e2233454. https://doi.org/10.1001/jamanetworkopen.2022.33454
5. Potupchik T.V., Evert L.S., Veselova O.F., Krysenko L.V., Kostyuchenko Yu.R. Pharmacotherapy of asthenic syndrome in children. *Doctor.Ru*. 2022;21(3):66–71. (In Russ.). https://doi.org/10.31550/1727-2378-2022-21-3-66-71.
6. Zawilska J.B., Kuczyńska K. Psychiatric and neurological complications of long COVID. *J Psychiatr Res*. 2022;156:349–360. https://doi.org/10.1016/j.jpsychires.2022.10.045.
7. Troitskaya L.A., Plotnikova I.A., Avakyan G.G., Erokhina V.A., Badalyan O.L., Muraveva A.V. et al. Neuropsychological evaluation of cognitive disorders in children after COVID-19. *Eur J Transl Myol*. 2022;32(3):10685. https://doi.org/10.4081/ejtm.2022.10685.
8. Serebryakova E.N., Zhmaeva L.I. The issue of post-COVID syndrome in children and adolescents: approaches to terminology, pathogenesis, clinical manifestations, diagnosis, and treatment. *Antibiotics and Chemotherapy*. 2022;11-12(67):51–55. (In Russ.). https://doi.org/10.37489/0235-2990-2022-67-11-12-51-55.
9. Gullett N., Zajkowska Z., Walsh A., Harper R., Mondelli V. Heart rate variability (HRV) as a way to understand associations between the autonomic nervous system (ANS) and affective states: A critical review of the literature. *Int J Psychophysiol*. 2023;192:35–42. https://doi.org/10.1016/j.ijpsycho.2023.08.001.
10. Voitenkov V.B., Ekusheva E.V. Concerning the Neurotropy and neuroinvasiveness of coronaviruses. *Journal of Clinical Practice*. 2020;11(2):81–86. (In Russ.). https://doi.org/10.17816/clinpract34890.
11. Abramova M.F., Stepanova I.A., Abramov K.V., Kazykina T.N., Vasilyeva T.M. Cerebrovascular disorders and autonomic dystonia syndrome in children (adolescents) and young patients. Clinical diagnostic therapy algorithms. *Medical Alphabet*. 2019;3(24):23–27. (In Russ.). https://doi.org/10.33667/2078-5631-2019-3-24(399)-23-27.
12. Aleksandrova G.A., Akhmetzyanova R.R., Golubev N.A., Kirillova G.N., Ogryzko E.V., Oskov Yu.I. et al. Healthcare in Russia: statistical collection. 2021. Moscow: Rosstat; 2021. 179 p. (In Russ.).
13. Zavadenko N.N., Zykov V.P., Gaynetdinova D.D., Agranovich O.V., Chutko L.S., Kovalev G.I. et al. Multidisciplinary consensus on the use of Cereton drug in treatment of central nervous system diseases with cognitive impairments of congenital and acquired origin in children. Resolution of the multidisciplinary panel of experts. *S.S. Korsakov Journal of Neurology and Psychiatry*. 2024;124(7):145–153. (In Russ.). https://doi.org/10.17116/jnevro2024124071145.
14. Luria A.R. Fundamentals of Neuropsychology. Moscow: Moscow University Publishing House; 1973. 374 p. (In Russ.).
15. Zakharova I.N., Tvorogova T.M., Pshenichnikova I.I., Sgibneva A.I. Asthenic syndrome in schoolchildren: from the risk of development to diagnosis and treatment. *Pediatrics. Consilium Medicum*. 2021;(1):76–83. (In Russ.). https://doi.org/10.26442/26586630.2021.1.200713.
16. Degtyareva E.A., Gorelov A.V., Simonovskaya H.Yu., Isaeva E.P., Kufa M.A., Kantemirova M.G. et al. Cardiac and vegetative manifestations of long-COVID in children. *Clinical Practice in Pediatrics*. 2022;17(5):75–82. (In Russ.). https://doi.org/10.20953/1817-7646-2022-5-75-82.
17. Tsarkova S.A., Zaytseva O.V., Lokshina E.E., Zaytseva S.V., Isaeva E.P., Murtazaeva O.A. et al. Post-COVID syndrome in children: the results of a retrospective multicenter cross-sectional study. *Pediatrics. Consilium Medicum*. 2024;(1):55–63. (In Russ.). https://doi.org/10.26442/26586630.2024.1.202688.
18. Balykova L.A., Shirmankina M.V., Vladimirov D.O., Naumenko E.I., Samoshkina E.S., Chernyshova R.A. Post-COVID syndrome in children and adolescents: a literature review and clinical case. *Russian Journal of Woman and Child Health*. 2022;5(4):366–372. (In Russ.). https://doi.org/10.32364/2618-8430-2022-5-4-366-372.
19. Nemkova S.A. Neurological aspects of the consequences of COVID-19 in children. S.S. *Korsakov Journal of Neurology and Psychiatry*. 2022;122(4):23-30. (In Russ.). https://doi.org/10.17116/jnevro202212204123.
20. Gugliandolo A., Chiricosta L., Calcaterra V., Biasin M., Cappelletti G., Carelli S. et al. SARS-CoV-2 Infected pediatric cerebral cortical neurons: transcriptomic analysis and potential role of Toll-like Receptors in pathogenesis.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

Int J Mol Sci. 2021;22(15):8059. https://doi.org/10.3390/ijms22158059.
21. Bryce C., Grimes Z., Pujadas E., Ahuja S., Beasley M.B., Albrecht R. et al. Pathophysiology of SARS-CoV-2: the Mount Sinai COVID-19 autopsy experience. *Mod Pathol*. 2021;34(8):1456–1467. https://doi.org/ 10.1038/s41379-021-00793-y.
22. Chutko L.S., Surushkina S.Yu., Yakovenko E.A., Anisimova T.I., Cherednichenko D.V., Didur M.D. et al. Cognitive impairment in children with organic asthenic disorder. S.S. *Korsakov Journal of Neurology and Psychiatry*. 2023;123(9 vyp 2):92–99. (In Russ.). https://doi.org/10.17116/jnevro202312309292
23. Katunova V.V. Biological background of cognitive disorders in early childhood and methods for their detection. *Medical Almanac*. 2018; 5(56):158–164. (In Russ.).

ЛИТЕРАТУРА

1. Колодяжная Т.А., Зайцева О.И., Зайцева Ж.Г., Игнатова И.А. Синдром вегетативной дисфункции у детей младшего школьного возраста: факторы риска и структурно-функциональное состояние мембран эритроцитов. *Siberian Journal of Life Sciences and Agriculture*. 2021;4(13):15–130. https://doi.org/10.12731/2658-6649-2021-13-4-115-130.
2. Смирнова О.В., Овчаренко Е.С., Каспаров Э.В., Фефелова В.В. Реактивность вегетативной нервной системы у детей младшего школьного возраста с умственной отсталостью. *Гигиена и санитария*. 2023;102(2):169–174. https://doi.org/10.47470/0016-9900-2023-102-2-169-174.
3. Harteveld L.M., Nederend I., Ten Harkel A.D.J., Schutte N.M., de Rooij S.R., Vrijkotte T.G.M. et al. Maturation of the Cardiac autonomic nervous system activity in children and adolescents. *J Am Heart Assoc*. 2021;10(4):e017405. https://doi.org/10.1161/JAHA.120.017405.
4. Sorg A.L., Becht S., Jank M., Armann J., von Both U., Hufnagel M. et al. Association of SARS-CoV-2 Seropositivity with myalgic encephalomyelitis and/or chronic fatigue syndrome among children and adolescents in Germany. *JAMA Netw Open*. 2022;5(9):e2233454. https://doi.org/10.1001/jamanetworkopen.2022.33454.
5. Потупчик Т.В., Эверт Л.С., Веселова О.Ф., Крысенко Л.В., Костюченко Ю.Р. Фармакотерапия и комплементарное лечение астенического синдрома у детей. *Доктор.Ру*. 2022;21(3):66–71. https://doi.org/10.31550/1727-2378-2022-21-3-66-71.
6. Zawilska J.B., Kuczyńska K. Psychiatric and neurological complications of long COVID. *J Psychiatr Res*. 2022;156:349–360. https://doi.org/10.1016/j.jpsychires.2022.10.045.
7. Troitskaya L.A., Plotnikova I.A., Avakyan G.G., Erokhina V.A., Badalyan O.L., Muraveva A.V. et al. Neuropsychological evaluation of cognitive disorders in children after COVID-19. *Eur J Transl Myol*. 2022;32(3):10685. https://doi.org/10.4081/ejtm.2022.10685.
8. Серебрякова Е.Н., Жмаева Л.И. К вопросу о постковидном синдроме у детей и подростков: подходы к терминологии, патогенезу, клинике, диагностике и лечению. *Антибиотики и химиотерапия*. 2022;11-12(67):51–55. https://doi.org/10.37489/0235-2990-2022-67-11-12-51-55.
9. Gullett N., Zajkowska Z., Walsh A., Harper R., Mondelli V. Heart rate variability (HRV) as a way to understand associations between the autonomic nervous system (ANS) and affective states: A critical review of the literature. *Int J Psychophysiol*. 2023;192:35–42. https://doi.org/10.1016/j.ijpsycho.2023.08.001.
10. Войтенков В.Б., Екушева Е.В. К вопросу о нейротропности и нейроинвазивности коронавирусов. *Клиническая практика*. 2020;11(2):81–86. https://doi.org/10.17816/clinpract34890.
11. Абрамова М.Ф., Степанова И.А., Абрамов К.В., Казыкина Т.Н., Васильева Т.М. Цереброваскулярные нарушения и синдром вегетативной дистонии у детей (подростков) и пациентов молодого возраста. Клинико-диагностические алгоритмы терапии. *Медицинский алфавит*. 2019;3(24):23–27. https://doi.org/10.33667/2078-5631-2019-3-24(399)-23-27.
12. Александрова Г.А., Ахметзянова Р.Р., Голубев Н.А., Кириллова Г.Н., Огрызко Е.В., Оськов Ю.И. и др. Здравоохранение в России: статитический сборник. 2021. М.: Росстат; 2021. 179 с.
13. Заваденко Н.Н., Зыков В.П., Гайнетдинова Д.Д., Агранович О.В., Чутко Л.С., Ковалев Г.И. и др. Междисциплинарный консенсус по применению препарата Церетон в терапии заболеваний центральной нервной системы с когнитивными нарушениями врожденного и приобретенного генеза у детей. Резолюция междисциплинарного совета экспертов. *Журнал неврологии и психиатрии им. С.С. Корсакова*. 2024;124(7):145–153. https://doi.org/10.17116/jnevro2024124071145
14. Лурия А.Р. Основы нейропсихологии. М.: Изд-во Московского университета; 1973. 374 с.
15. Захарова И.Н., Творогова Т.М., Пшеничникова И.И., Сгибнева А.И. Астенический синдром у школьников: от риска развития до диагностики и лечения. *Педиатрия. Consilium Medicum*. 2021;(1):76–83. https://doi.org/10.26442/26586630.2021.1.200713.
16. Дегтярева Е.А., Горелов А.В., Симоновская Х.Ю., Исаева Е.П., Куфа М.А., Кантемирова М.Г. и др.

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Кардиальные и вегетативные проявления long-COVID у детей. *Вопросы практической педиатрии*. 2022;17(5):75–82. https://doi.org/10.20953/1817-7646-2022-5-75-82.
17. Царькова С.А., Зайцева О.В., Локшина Э.Э., Зайцева С.В., Исаева Е.П., Муртазаева О.А. и др. Постковидный синдром у детей: результаты ретроспективного мультицентрового одномоментного исследования. *Педиатрия. Consilium Medicum*. 2024;(1):55–63. https://doi.org/10.26442/26586630.2024.1.202688.
18. Балыкова Л.А., Ширманкина М.В., Владимиров Д.О., Науменко Е.И., Самошкина Е.С., Чернышова Р.А. Постковидный синдром у детей и подростков: обзор литературы и описание клинического наблюдения. *РМЖ. Мать и дитя*. 2022;5(4):366–372. https://doi.org/10.32364/2618-8430-2022-5-4-366-372.
19. Немкова С.А. Неврологические аспекты последствий COVID-19 у детей. *Журнал неврологии и психиатрии им. С.С. Корсакова*. 2022;122(4):23–30. https://doi.org/10.17116/jnevro202212204123.
20. Gugliandolo A., Chiricosta L., Calcaterra V., Biasin M., Cappelletti G., Carelli S. et al. SARS-CoV-2 Infected pediatric cerebral cortical neurons: transcriptomic analysis and potential role of Toll-like Receptors in pathogenesis. *Int J Mol Sci*. 2021;22(15):8059. https://doi.org/10.3390/ijms22158059.
21. Bryce C., Grimes Z., Pujadas E., Ahuja S., Beasley M.B., Albrecht R. et al. Pathophysiology of SARS-CoV-2: the Mount Sinai COVID-19 autopsy experience. *Mod Pathol*. 2021;34(8):1456–1467. https://doi.org/ 10.1038/s41379-021-00793-y.
22. Чутко Л.С., Сурушкина С.Ю., Яковенко Е.А., Анисимова Т.И., Чередниченко Д.В., Дидур М.Д. и др. Когнитивные нарушения у детей с органическим астеническим расстройством. *Журнал неврологии и психиатрии им. С.С. Корсакова*. 2023;123(9 вып. 2):92–99. https://doi.org/10.17116/jnevro202312309292.
23. Катунова В.В. Биологические предпосылки когнитивных расстройств в раннем детском возрасте и методы их выявления. *Медицинский альманах*. 2018;5(56):158–164.

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A model for predicting the absence of post-COVID gastrointestinal disorders in children who have had COVID-19 infection

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ABSTRACT. ***Introduction.*** After recovery from COVID-19, many patients experience long-term sequelae known as post-COVID syndrome. The role of changes in the gut microbiota, particularly in relation to gastrointestinal symptoms following COVID-19, is of growing interest, although data on these changes in the post-COVID period remain controversial. ***Aim*** — to identify the main predictors of the absence of gastrointestinal symptoms in the post-COVID period in children using clinical, anamnestic, molecular biological, and immunological methods. ***Materials and methods.*** A database was created that included over 400 characteristics characterizing general information, clinical presentation, laboratory data, including procalcitonin and CRP levels, 16S microbiota sequencing, zonulin determination, stool PCR for SARS-CoV-2, and analysis of antibiotic and synbiotic prescriptions. The analysis was conducted in two groups of patients. Group 1 included 24 children who developed gastrointestinal symptoms one month after recovery, while Group 2 consisted of 23 patients who had no gastrointestinal symptoms. ***Results.*** Using a neural network, five features were identified that predict the absence of post-COVID gastrointestinal symptoms in children one month after recovery from novel coronavirus infection. The sensitivity of the neural network was 95.0%, specificity 87.5%, and accuracy 91.0%. ***Conclusion.*** The main predictors of the absence of gastrointestinal symptoms in the post-COVID period in children are the relative proportion of Actinobacteriota less than 0.24 in stool by 16S sequencing one month after recovery, the presence of Actinobacteria species less than 0.1 in stool by 16S sequencing one month after recovery, treatment with a synbiotic for 30 days, normal zonulin levels in stool, and the absence of a history of food allergies.

KEYWORDS: *COVID-19, children, post-covid period, functional gastrointestinal disorders, prognosis*

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Модель прогноза отсутствия постковидных гастроинтестинальных нарушений у детей, перенесших инфекцию COVID-19

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РЕЗЮМЕ. ***Введение.*** После выздоровления от COVID-19 у многих пациентов наблюдаются долгосрочные последствия, известные как постковидный синдром. Растущий интерес вызывает роль изменений микробиоты кишечника, особенно в связи с желудочно-кишечными симптомами после COVID-19, хотя данные об этих изменениях в постковидный период остаются противоречивыми. ***Цель*** — на основании клинико-анамнестических, молекулярно-биологических и иммунологических методов выявить основные предикторы отсутствия гастроинтестинальных симптомов в постковидный период у детей. ***Материалы и методы.*** Создана база данных, которая включала более 400 признаков, характеризующих общие сведения, клиническую картину, лабораторные данные, в том числе уровень прокальцитонина и С-реактивного белка, 16S секвенирование микробиоты, определение зонулина, ПЦР кала на вирус SARS-CoV-2, анализ назначения антибиотиков и синбиотика. Анализ проводился в двух группах пациентов. Группа 1 — 24 ребенка, у которых через месяц после выздоровления появились желудочно-кишечные симптомы, группа 2 состояла из 23 пациентов, не имевших никаких гастроэнтерологических симптомов. ***Результаты.*** С помощью нейронной сети выделены пять признаков, сопровождающих отсутствие постковидных гастроинтестинальных симптомов у детей через месяц после выздоровления от новой коронавирусной инфекции. Чувствительность нейронной сети составила 95,0%, специфичность — 87,5%, точность — 91,0%. ***Заключение.*** Основные предикторы отсутствия гастроинтестинальных симптомов в постковидный период у детей — это относительная доля *Actinobacteriota* менее 0,24 в стуле методом 16S секвенирования через месяц после выздоровления, наличие вида *Actinobacteria* менее 0,1 в стуле методом 16S секвенирования через месяц после выздоровления, лечение синбиотиком в течение 30 дней, нормальный уровень зонулина в стуле, отсутствие пищевой аллергии в анамнезе.

КЛЮЧЕВЫЕ СЛОВА: *COVID-19, дети, постковидный период, функциональные расстройства ЖКТ, прогноз*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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INTRODUCTION

Although the acute phase of the COVID-19 pandemic has ended, its long-term consequences remain a major healthcare concern [1]. At present, more than 1000 different genetic lines of the SARS-CoV-2 virus have been registered, possessing unique characteristics and different degrees of resistance to the immune response [2]. It has been established that even after recovery from various variants of COVID-19 infection, patients reveal signs and symptoms that persist after the disease or appear again, which is interpreted as post-COVID syndrome [3, 4]. Symptoms may be associated with chronic inflammation, autoimmune diseases, chronic endotheliopathy, microthrombosis or persistence of the virus [3]. Changes in the composition of the microbiota may also play a role in long COVID, however data on the intestinal microbiota in the post-COVID period are contradictory [5, 6]. Recently, researchers' attention has been attracted by the relationship between changes in the intestinal microbiota and the presence of gastrointestinal manifestations after COVID-19-infection [7–11]. The characteristics of gastrointestinal symptoms in children and adults after new coronavirus infection are presented in Table 1.

In the study of A.A. Karasev (2023) it is stated that the total frequency of disorders of intestinal motor function (diarrhea/constipation) varies from 3.6 to 48%, abdominal pain of any localization — from 9 to 32% [12].

In another domestic observation, 25% of children complained of abdominal pain after COVID-19 infection [4].

In the work of A.V. Naletov et al. (2021) a predominance of diarrhea and abdominal pain in 76% of the studied patients after infection was noted [13].

One of the variants of gastrointestinal tract (GIT) damage after coronavirus infection is irritable bowel syndrome (IBS) [14, 15]. Its frequency, studied in several studies, varied from 0.6 to 11.6% [14, 15]. Prognostic factors for the development of IBS in the post-COVID period are insufficiently studied. In one study it was shown that in patients with acute gastrointestinal symptoms during COVID-19 the probability of developing persistent gastrointestinal symptoms is four times higher than in patients without acute gastrointestinal symptoms [16]. In three other studies [17–19] the presence of gastrointestinal symptoms in the acute phase was named a precursor of IBS, whereas in other studies [20, 21] no correlation between gastroenterological symptoms during illness and symptoms in the post-COVID period was found. It is considered that the pathogenesis of IBS in the post-COVID period is mainly associated with dysfunction of the "gut–brain" axis [22, 23].

Currently, the role of prebiotics and probiotics in the restoration of normal intestinal microbiota

Table 1. Characteristics of gastrointestinal symptoms in children and adults after a new coronavirus infection (in absolute numbers)

Таблица 1. Характеристика гастроинтестинальных симптомов у детей и взрослых после перенесенной новой коронавирусной инфекции (в абс. числах)

Исследователи Researchers	Страна Country	Год Year	Количество больных Number of patients	Тошнота Nausea	Рвота Vomit	Диарея Diarrhea	Боли в животе Stomach ache
Obleagă et al. [7] (дети / children)	Румыния Romania	2023	21	21	4	21	21
D. Noviello et al. [8] (взрослые / adults)	Италия Italy	2021	164	–	–	–	16
J. Weng et al. [9] (взрослые / adults)	Китай China	2021	117	–	11	17	8
Huang et al. [10] (взрослые / adults)	Китай China	2021	1655	–	80	80	–
Anaya et al. [11] (взрослые / adults)	Колумбия Colombia		100	–	4	9	8

The table was compiled by the authors
Таблица составлена авторами

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and reduction of the severity of both gastrointestinal and respiratory symptoms in patients with COVID-19 is actively being studied [24, 25]. Data have been published on successful correction of dysbiosis in patients infected with COVID-19, which reveals the role of probiotics in the treatment of this new coronavirus infection [26]. The intake of certain prebiotics and probiotics may minimize gastrointestinal symptoms of COVID-19 and the consequences of antibiotic use, which aggravate these symptoms [27, 28]. However, factors contributing to the prevention of post-COVID gastrointestinal disorders in children have not been studied.

AIM

Based on clinical-anamnestic, molecular-biological and immunological methods, to identify the main predictors of absence of gastrointestinal symptoms in the post-COVID period in children.

MATERIALS AND METHODS

The calculation of the main predictors of the absence of gastrointestinal symptoms after coronavirus infection was based on the results of a clinical post-registration open observational prospective single-center study with minimal intervention. It was approved by the local ethics committee of the Federal State Budgetary Educational Institution of Higher Education "Saint Petersburg State Pediatric Medical University" of the Ministry of Health of the Russian Federation. Children with COVID-19 infection aged from 3 to 17 years were included in the study. The diagnosis of the new coronavirus infection and the severity of the disease were established according to methodological recommendations [29].

The children were examined in dynamics: at the beginning of the disease, after two weeks, upon resolution of the main symptoms of COVID-19 infection, and four weeks after recovery. Data collection was performed: complaints, medical history, clinical status, presence of complications, routine laboratory data and C-reactive protein (CRP) testing, 16S microbiota sequencing, stool zonulin testing, polymerase chain reaction (PCR) of stool for SARS-CoV-2 virus, analysis of prescribed medications, including antibacterial therapy and synbiotic (a synbiotic containing ≥1×10^9 CFU probiotic microorganisms, including *lactobacilli* — 6.6×10^8 CFU, *Lactobacillus acidophilus* LA-14 — 1.11×10^8 CFU, *Lactobacillus rhamnosus* GG — 1.11×10^8 CFU, *Lactobacillus casei* LC-11 — 1.11×10^8 CFU, *Lactobacillus paracasei* Lpc-37 — 1.11×10^8 CFU, *Lactobacillus plantarum* Lp-115 — 1.11×10^8 CFU, *Lactobacillus salivarius* Ls-33 — 1.11×10^8 CFU, including *bifidobacteria* — 3.3×10^8 CFU, *Bifidobacterium longum* Bl-05 — 1.11×10^8 CFU, *Bifidobacterium lactis* Bl-04 — 1.11×10^8 CFU, *Bifidobacterium bifidum* Bb-02/lactis — 1.11×10^8 CFU and the prebiotic component fructooligosaccharides — 0.538 g, hereinafter referred to as synbiotic at a dose of 1 capsule per day, treatment course — 30 days).

SARS-CoV-2 virus identification by PCR and 16S microbiota sequencing were performed in the laboratory "SERBALAB", Saint Petersburg (head — geneticist V.V. Dudurich). 16S DNA libraries were prepared in accordance with the Illumina protocol "16S Metagenomic Sequencing Library Preparation" (Part # 15044223 Rev. B). 5 ng of total DNA was used for amplification of the target fragment of the 16S rRNA gene using recommended primers for the V3 and V4 region. 25 PCR cycles were performed using KAPA HiFi HotStart ReadyMix (2X) (Roche Diagnostics, Switzerland). After purification of PCR products using SPRI beads, 5 ng of obtained amplicons were indexed using KAPA HiFi HotStart ReadyMix (2X) (Roche Diagnostics, Switzerland) and Nextera XT Index Kit (Illumina, USA). 8 cycles of index PCR were performed following the Illumina protocol. Libraries were sequenced on an Illumina MiSeq System. Stool zonulin testing was performed by enzyme-linked immunosorbent assay using the IDK Zonulin ELISA test system (Immundiagnostik AG, Germany). The mean value of the indicator declared by the manufacturer of the test system, according to examination of 40 practically healthy individuals, was 61±46 ng/ml. At values less than 83.15 ng/ml the result was considered normal, at 83.15–110.0 ng/ml — as increased concentration, more than 110 ng/ml — as high concentration.

The patient database included more than 400 features characterizing general information, clinical presentation, laboratory data, including procalcitonin and CRP levels, presence of symptoms, including gastrointestinal symptoms and their dynamics, disease severity, temperature response, presence of complications and comorbidities, microbiota composition by genus and species and diversity index, fecal zonulin level,

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presence of SARS-CoV-2 virus in stool, treatment with antibiotics and synbiotic. All variable features were assessed three times: at the beginning of the disease, two weeks after their resolution, and one month after recovery.

Analysis of all features was performed in two patient groups. The first group consisted of 24 children who developed symptoms such as abdominal pain and diarrhea one month after recovery. The duration of these symptoms within one month did not allow diagnosis of IBS, therefore we designated them as a group of children with post-COVID gastrointestinal symptoms. The second group consisted of 23 patients without any gastroenterological symptoms.

Checking the obtained data for compliance with a normal distribution law was performed using the Shapiro–Wilk test. If the data corresponded to the Gauss–Laplace distribution, typical values were presented as mean and standard deviation; if not corresponding – as median and first and third quartiles. Comparison of typical values between groups was performed using Student's t-test and Mann–Whitney test. The null hypothesis was rejected at a significance level of $p < 0.05$. A 95% confidence interval was calculated by Poisson distribution approximation via χ^2.

For determining predictors of absence of gastrointestinal symptoms after coronavirus infection using a neural network, a combined method of global optimization, random search, inertial and genetic algorithms was used.

RESULTS AND DISCUSSION

Using a neural network, five features accompanying the absence of post-COVID gastrointestinal symptoms in children one month after recovery from a novel coronavirus infection were identified. The data are presented in Table 2.

The sensitivity of individual variables in the neural network model was defined as the ratio of neural network errors without the factor feature of interest to the errors of the network with the factor feature of interest. The higher the sensitivity, the greater the importance of the studied feature, and the lower the prediction error of the neural network. The neural network sensitivity was 95.0%, specificity – 87.5%, accuracy – 91.0%.

Thus, the data obtained using the neural network indicate that the leading role in the development of gastrointestinal symptoms one month after recovery from a novel coronavirus infection is played by disturbances of the intestinal microbiota, namely the detection of the phylum *Actinobacteriota* and the species *Actinobacteria* in stool by 16S sequencing.

The results of the study are consistent with several studies in which significant groups of microor-

Table 2. Signs accompanying the absence of post-COVID gastrointestinal symptoms in children one month after recovery from novel coronavirus infection

Таблица 2. Признаки, сопровождающие отсутствие постковидных гастроинтестинальных симптомов у детей через месяц после выздоровления от новой коронавирусной инфекции

Признак **Sign**	**Чувствительность** **Sensitivity**	**Ранг** **Rank**
Относительная доля *Actinobacteriota* менее 0,24 в стуле методом 16S секвенирования через месяц после выздоровления Relative proportion of Actinobacteriota less than 0.24 in stool by 16S sequencing one month after recovery	6,8	1
Вид *Actinobacteria* менее 0,1 в стуле методом 16S секвенирования через месяц после выздоровления Actinobacteria species less than 0.1 in the stool by 16S sequencing one month after recovery	5,3	2
Лечение синбиотиком в течение 30 дней в возрастной дозе 1 капсула в сутки Treatment with a synbiotic for 30 days at an age-appropriate dosage of 1 capsule per day	3,6	3
Нормальный уровень зонулина в стуле Normal zonulin levels in the stool	2,3	4
Отсутствие пищевой аллергии в анамнезе No history of food allergies	1,8	5

The table was compiled by the authors

Таблица составлена авторами

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ganisms acting as predictors of disease severity in novel coronavirus infection were identified [30, 31]. In a study comparing the microbiome of patients with H1N1 virus and another group of patients with SARS-CoV-2 virus, five groups of microorganisms typical of the microbiota of COVID-19 patients were noted, including *Actinobacteriota*. The obtained data confirm the necessity of synbiotic treatment for the prevention of gastrointestinal disorders.

Recent studies have shown that food allergy in the medical history and increased intestinal permeability are pathogenetically related [32]. The influence of these features on the development of gastrointestinal disorders is confirmed by a number of publications dedicated to functional disorders of IBS [33, 34].

CONCLUSION

The main predictors of absence of gastrointestinal symptoms in the post-COVID period in children are: a relative proportion of *Actinobacteriota* less than 0.24 in stool by 16S sequencing one month after recovery, the presence of the species *Actinobacteria* less than 0.1 in stool by 16S sequencing one month after recovery, treatment with a synbiotic containing ≥1×10^9 CFU probiotic microorganisms, including *lactobacilli* — 6.6×10^8 CFU, *Lactobacillus acidophilus* LA-14 — 1.11×10^8 CFU, *Lactobacillus rhamnosus GG* — 1.11×10^8 CFU, *Lactobacillus casei* LC-11 — 1.11×10^8 CFU, *Lactobacillus paracasei* Lpc-37 — 1.11×10^8 CFU, *Lactobacillus plantarum* Lp-115 — 1.11×10^8 CFU, *Lactobacillus salivarius* Ls-33 — 1.11×10^8 CFU, including *bifidobacteria* — 3.3×10^8 CFU, *Bifidobacterium longum* Bl-05 — 1.11×10^8 CFU, *Bifidobacterium lactis* Bl-04 — 1.11×10^8 CFU, *Bifidobacterium bifidum* Bb-02/*lactis* — 1.11×10^8 CFU and the prebiotic component fructooligosaccharides — 0.538 g, for 30 days in age-appropriate dosage of 1 capsule per day, normal stool zonulin level, absence of food allergy in medical history.

ADDITIONAL INFORMATION

Authors' contribution. A.V. Polunina — article writing; V.P. Novikova — author of the concept and study design; S.L. Bannova — clinical data collection; V.V. Dudurich — genetic studies; A.E. Blinov — zonulin ELISA testing; O.N. Varlamova — biobank creation; M.A. Dokhov — predictive model calculation; A.A. Tikhomirova — article design; N.A. Dementyev — statistical database creation; A.L. Balashov — article editing and proofreading.

All authors read and approved the final version before publication.

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Consent for publication. Written consent was obtained from legal representatives of the patients for publication of relevant medical information within the manuscript.

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REFERENCES

1. Kosenkova T.V., Timchenko V.N., Bannova S.L., Chernova T.M., Shakmaeva M.A., Bulina O.V., Egorova I.A. Coronavirus infection and COVID-19 in children. Part 1. Epidemiology, etiology, and pathogenesis. *Children's Medicine of the North-West*. 2024;12(4):21–38. (In Russ.). https://doi.org/10.56871/CmN-W.2024.86.55.002.
2. Jin X., Lian J.S., Hu J.H., Gao J., Zheng L., Zhang Y.M. et al. Epidemiological, clinical and virological characteristics of

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut*. 2020;69(6):1002–1009. https://doi.org/10.1136/gutjnl-2020-320926.
3. Lippi G., Sanchis-Gomar F., Henry B.M. COVID-19 and its long-term sequelae: what do we know in 2023? *Pol Arch Intern Med*. 2023;133(4):16402. https://doi.org/10.20452/pamw.16402.
4. Sidorova I.V., Simahodskij A.S., Leonova I.A., Pen'kov D.G. Clinical manifestations of the consequences of the new coronavirus infection COVID-19 in children. *Profilakticheskaya i Klinicheskaya Meditsina*. 2021;4(81):41–48. (In Russ.). https://doi.org/10.47843/2074-9120_2021_4_41.
5. Newsome R.C., Gauthier J., Hernandez M.C., Abraham G.E., Robinson T.O., Williams H.B. et al. The gut microbiome of COVID-19 recovered patients returns to uninfected status in a minority-dominated United States cohort. *Gut Microbes*. 2021;13(1):1–15. https://doi.org/10.1080/19490976.2021.1926840.
6. Yeoh Y.K., Zuo T., Lui G.C., Zhang F., Liu Q., Li A.Y. et al. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. *Gut*. 2021;70(4):698–706. https://doi.org/10.1136/gutjnl-2020-323020.
7. Obleagă C.V., Ahmet R.A.M., Florescu D.N. Post-COVID-19 enterocolitis — a cause of rebellious diarrhea, acute abdomen and liver failure. *Rom J Morphol Embryol*. 2023;64(4):527–533. https://doi.org/10.47162/RJME.64.4.09.
8. Noviello D., Costantino A., Muscatello A. Functional gastrointestinal and somatoform symptoms five months after SARS CoV-2 infection: A controlled cohort study. *Neurogastroenterol Motil*. 2022;34(2):e14187. https://doi.org/10.1111/nmo.14187.
9. Weng J., Li Y., Li J. Gastrointestinal sequelae 90 days after discharge for COVID-19. *Lancet Gastroenterol Hepatol*. 2021;6(5):344–346. https://doi.org/10.1016/S2468-1253(21)00076-5.
10. Huang C., Huang L., Wang Y. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397(10270):220–232. https://doi.org/10.1016/S0140-6736(20)32656-8.
11. Anaya J.M., Rojas M., Salinas M.L. Post-COVID syndrome. A case series and comprehensive review. *Autoimmun Rev*. 2021;20(11):102947. https://doi.org/10.1016/j.autrev.2021.102947.
12. Karaseva A.A., Khudiakova A.D., Garbuzova E.V., Ragino Yu.I., Logvinenko I.I. Severity of Postcovid Syndrome: A Systematic Review. *The Russian Archives of Internal Medicine*. 2023;13(6):422–435. (In Russ.). https://doi.org/10.20514/2226-6704-2023-13-6-422-435. EDN: RLJOEE.
13. Naletov A.V., Kaspir D.V., Guz N.P., Boraeva T.T. Optimization of treatment for irritable bowel syndrome in patients who have recovered from COVID-19. *Arkhiv Klinicheskoi i Ehksperimental'noi Meditsiny*. 2021;30(4):314–316. (In Russ.).
14. Marasco G., Cremon C., Barbaro M.R. Post COVID-19 irritable bowel syndrome. *Gut*. 2022:gutjnl-2022-328483. https://doi.org/10.1136/gutjnl-2022-328483.
15. Farsi F., Zonooz S.R., Ebrahimi Z. The Incidence of Post-infectious Irritable Bowel Syndrome, Anxiety, and Depression in Iranian Patients with Coronavirus Disease 2019 Pandemic: A Cross-Sectional Study. *Turk J. Gastroenterol*. 2022;33(12):1033–1042. https://doi.org/10.5152/tjg.2022.21651.
16. Austhof E., Bell M.L., Riddle M.S. Persisting gastrointestinal symptoms and post-infectious irritable bowel syndrome following SARS-CoV-2 infection results from the Arizona CoVHORT. *Epidemiol Infect*. 2022;150:e136. https://doi.org/10.1017/S0950268822001200.
17. Siyal M., Abbas Z., Ashraf J. Incidence and predisposing factors for de novo post-COVID-19 irritable bowel syndrome. *Eur J Gastroenterol Hepatol*. 2023;35:(1):59–63. https://doi.org/10.1097/MEG.0000000000002475.
18. Golla R., Vuyyuru S., Kante B. Long-term gastrointestinal sequelae following COVID-19: a prospective follow up cohort study. *Clin Gastroenterol Hepatol*. 2023;21(3):789–796.e1. https://doi.org/10.1016/j.cgh.2022.10.015.
19. Ghoshal U.C., Ghoshal U., Rahman M.M. Post-infection functional gastrointestinal disorders following coronavirus disease-19: a case-control study. *J Gastroenterol Hepatol*. 2022;37(3):489–498. https://doi.org/10.1111/jgh.15717.
20. Vélez C., Paz M., Silvernale C. Factors Associated with chronic de novo post-coronavirus disease gastrointestinal disorders in a metropolitan US County. *Clin Gastroenterol Hepatol*. 2022;20(6):e1488–e1492. https://doi.org/10.1016/j.cgh.2021.10.020.
21. Nazarewska A., Lewandowski K., Kaniewska M. Irritable bowel syndrome following COVID-19 an underestimated consequence of SARS-CoV-2 infection. *Pol Arch Intern Med*. 2022;132(11):16323. https://doi.org/10.20452/PAMW.16323.
22. Chan W.W., Grover M. The COVID-19 Pandemic and Post-Infection Irritable Bowel Syndrome: What Lies Ahead for Gastroenterologists. *Clin Gastroenterol Hepatol*. 2022;20(10):2195–2197. https://doi.org/10.1016/j.cgh.2022.05.044.
23. Settanni C.R., Ianiro G., Ponziani F.R. COVID-19 as a trigger of irritable bowel syndrome: a review of potential mechanisms. *World J Gastroenterol*. 2021;27(43):7433–7445. https://doi.org/10.3748/wjg.v27.i43.7433.
24. Malik J.A., Ahmed S., Yaseen Z. Association of SARS-CoV-2 and Polypharmacy with Gut-Lung Axis: From Pathogenesis to Treatment. *ACS Omega*. 2022;7(38):33651–33665. https://doi.org/10.1021/acsomega.2c02524.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

25. Gutiérrez-Castrellón P., Gandara-Martí T., Abreu A.T., Abreu Y. Probiotic improves symptomatic and viral clearance in Covid19 outpatients: a randomized, quadruple-blinded, placebo-controlled trial. *Gut Microbes*. 2022;14(1):2018899. https://doi.org/10.1080/19490976.2021.2018899.
26. Tiwari S.K., Dicks L.M.T., Popov I.V. Probiotics at war against viruses: what is missing from the picture? *Front Microbiol*. 2020;11:1877. https://doi.org/10.3389/fmicb.2020.01877.
27. Guo Q., Goldenberg J.Z., Humphrey C. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Cochrane Database Syst Rev*. 2019;4(4):CD004827. https://doi.org/10.1002/14651858.CD004827.pub5.
28. Kazemi A., Soltani S., Ghorabi S. Is probiotic and synbiotic supplementation effective on immune cells? A systematic review and meta-analysis of clinical trials. *Food Rev Int*. 2020;37(5):491–537. https://doi.org/10.1080/87559129.2019.1710748.
29. Methodological recommendations. Clinical manifestations and treatment of the disease caused by the novel coronavirus infection (COVID-19) in children (version 2, approved by the Ministry of Health of the Russian Federation). URL: https://www.garant.ru/products/ipo/prime/doc/74232682/ (accessed: 15.12.2025).
30. Song J., Wu Y., Yin X. The causal links between gut microbiota and COVID-19: a Mendelian randomization study. *J Med Virol*. 2023;95(5):e28784. https://doi.org/10.1002/jmv.28784.
31. Zhang H., Zhou Z. Association of gut microbiota and dietary component intake with COVID-19: a mendelian randomization study. *Clin Nutr*. 2023;42(8):1308–1313. https://doi.org/10.1016/j.clnu.2023.06.017.
32. Listopadova A.P., Novikova V.P., Zamyatina Yu.E. Zonulin, a biomarker of increased intestinal permeability syndrome, in children with atopic dermatitis and chronic gastroduodenitis. *Profilakticheskaya i Klinicheskaya Meditsina*. 2024;1(90):33–36. (In Russ.).
33. Clinical guidelines for irritable bowel syndrome. URL: https://cr.minzdrav.gov.ru/preview-cr/892_1 (accessed: 31.01.2025). (In Russ.).
34. Silva J.T.C., Fonseca Neto O.C.L.D. Post-COVID-19 irritable bowel syndrome: an integrative review. *Rev Col Bras Cir*. 2023;50:e20233618. https://doi.org/10.1590/0100-6991e-20233618-en.

ЛИТЕРАТУРА

1. Косенкова Т.В., Тимченко В.Н., Баннова С.Л., Чернова Т.М., Шакмаева М.А., Булина О.В., Егорова И.А. Коронавирусная инфекция и COVID-19 у детей. Часть 1. Эпидемиология, этиология, патогенез. *Children's Medicine of the North-West*. 2024;12(4):21–38. https://doi.org/10.56871/CmN-W.2024.86.55.002.
2. Jin X., Lian J.S., Hu J.H., Gao J., Zheng L., Zhang Y.M. et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut*. 2020;69(6):1002–1009. https://doi.org/10.1136/gutjnl-2020-320926.
3. Lippi G., Sanchis-Gomar F., Henry B.M. COVID-19 and its long-term sequelae: what do we know in 2023? *Pol Arch Intern Med*. 2023;133(4):16402. https://doi.org/10.20452/pamw.16402.
4. Сидорова И.В., Симаходский А.С., Леонова И.А., Пеньков Д.Г. Клинические проявления последствий новой коронавирусной инфекции COVID-19 у детей. *Профилактическая и клиническая медицина*. 2021;4(81):41–48. https://doi.org/10.47843/2074-9120_2021_4_41.
5. Newsome R.C., Gauthier J., Hernandez M.C., Abraham G.E., Robinson T.O., Williams H.B. et al. The gut microbiome of COVID-19 recovered patients returns to uninfected status in a minority-dominated United States cohort. *Gut Microbes*. 2021;13(1):1–15. https://doi.org/10.1080/19490976.2021.1926840.
6. Yeoh Y.K., Zuo T., Lui G.C., Zhang F., Liu Q., Li A.Y. et al. *Gut* microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. *Gut*. 2021;70(4):698–706. https://doi.org/10.1136/gutjnl-2020-323020.
7. Obleagă C.V., Ahmet R.A.M., Florescu D.N. Post-COVID-19 enterocolitis — a cause of rebellious diarrhea, acute abdomen and liver failure. *Rom J Morphol Embryol*. 2023;64(4):527–533. https://doi.org/10.47162/RJME.64.4.09.
8. Noviello D., Costantino A., Muscatello A. Functional gastrointestinal and somatoform symptoms five months after SARS CoV-2 infection: A controlled cohort study. *Neurogastroenterol Motil*. 2022;34(2):e14187. https://doi.org/10.1111/nmo.14187.
9. Weng J., Li Y., Li J. Gastrointestinal sequelae 90 days after discharge for COVID-19. *Lancet Gastroenterol Hepatol*. 2021;6(5):344–346. https://doi.org/10.1016/S2468-1253(21)00076-5.
10. Huang C., Huang L., Wang Y. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397(10270):220–232. https://doi.org/10.1016/S0140-6736(20)32656-8.
11. Anaya J.M., Rojas M., Salinas M.L. Post-COVID syndrome. A case series and comprehensive review. *Autoimmun Rev*. 2021;20(11):102947. https://doi.org/10.1016/j.autrev.2021.102947.
12. Карасева А.А., Худякова А.Д., Гарбузова Е.В., Рагино Ю.И., Логвиненко И.И. Степени тяжести постковидного синдрома: систематический обзор. *Архивъ*

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

внутренней медицины. 2023;13(6):422–435. https://doi.org/10.20514/2226-6704-2023-13-6-422-435. EDN: RLJOEE.
13. Налетов А.В., Каспир Д.В., Гуз Н.П., Бораева Т.Т. Оптимизация лечения синдрома раздраженного кишечника у пациентов, перенесших COVID-19. *Архив клинической и экспериментальной медицины*. 2021;30(4):314–316.
14. Marasco G., Cremon C., Barbaro M.R. Post COVID-19 irritable bowel syndrome. *Gut*. 2022:gutjnl-2022-328483. https://doi.org/10.1136/gutjnl-2022-328483.
15. Farsi F., Zonooz S.R., Ebrahimi Z. The Incidence of Post-infectious Irritable Bowel Syndrome, Anxiety, and Depression in Iranian Patients with Coronavirus Disease 2019 Pandemic: A Cross-Sectional Study. *Turk J. Gastroenterol*. 2022;33(12):1033–1042. https://doi.org/10.5152/tjg.2022.21651.
16. Austhof E., Bell M.L., Riddle M.S. Persisting gastrointestinal symptoms and post-infectious irritable bowel syndrome following SARS-CoV-2 infection results from the Arizona CoVHORT. *Epidemiol Infect*. 2022;150:e136. https://doi.org/10.1017/S0950268822001200.
17. Siyal M., Abbas Z., Ashraf J. Incidence and predisposing factors for de novo post-COVID-19 irritable bowel syndrome. *Eur J Gastroenterol Hepatol*. 2023;35:(1):59–63. https://doi.org/10.1097/MEG.0000000000002475.
18. Golla R., Vuyyuru S., Kante B. Long-term gastrointestinal sequelae following COVID-19: a prospective follow up cohort study. *Clin Gastroenterol Hepatol*. 2023;21(3):789–796.e1. https://doi.org/10.1016/j.cgh.2022.10.015.
19. Ghoshal U.C., Ghoshal U., Rahman M.M. Post-infection functional gastrointestinal disorders following coronavirus disease-19: a case-control study. *J Gastroenterol Hepatol*. 2022;37(3):489–498. https://doi.org/10.1111/jgh.15717.
20. Vélez C., Paz M., Silvernale C. Factors Associated With Chronic De Novo Post-Coronavirus Disease Gastrointestinal Disorders in a Metropolitan US County. *Clin Gastroenterol Hepatol*. 2022;20(6):e1488–e1492. https://doi.org/10.1016/j.cgh.2021.10.020.
21. Nazarewska A., Lewandowski K., Kaniewska M. Irritable bowel syndrome following COVID-19 an underestimated consequence of SARS-CoV-2 infection. *Pol Arch Intern Med*. 2022;132(11):16323. https://doi.org/10.20452/PAMW.16323.
22. Chan W.W., Grover M. The COVID-19 Pandemic and Post-Infection Irritable Bowel Syndrome: What Lies Ahead for Gastroenterologists. *Clin Gastroenterol Hepatol*. 2022;20(10):2195–2197. https://doi.org/10.1016/j.cgh.2022.05.044.
23. Settanni C.R., Ianiro G., Ponziani F.R. COVID-19 as a trigger of irritable bowel syndrome: a review of potential mechanisms. *World J Gastroenterol*. 2021;27(43):7433–7445 https://doi.org/10.3748/wjg.v27.i43.7433.
24. Malik J.A., Ahmed S., Yaseen Z. Association of SARS-CoV-2 and Polypharmacy with Gut-Lung Axis: From Pathogenesis to Treatment. *ACS Omega*. 2022;7(38):33651–33665. https://doi.org/10.1021/acsomega.2c02524.
25. Gutiérrez-Castrellón P., Gandara-Martí T., Abreu A.T., Abreu Y. Probiotic improves symptomatic and viral clearance in Covid19 outpatients: a randomized, quadruple-blinded, placebo-controlled trial. *Gut Microbes*. 2022;14(1):2018899. https://doi.org/10.1080/19490976.2021.2018899.
26. Tiwari S.K., Dicks L.M.T., Popov I.V. Probiotics at war against viruses: what is missing from the picture? *Front Microbiol*. 2020;11:1877. https://doi.org/10.3389/fmicb.2020.01877.
27. Guo Q., Goldenberg J.Z., Humphrey C. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Cochrane Database Syst Rev*. 2019;4(4):CD004827. https://doi.org/10.1002/14651858.CD004827.pub5.
28. Kazemi A., Soltani S., Ghorabi S. Is probiotic and synbiotic supplementation effective on immune cells? A systematic review and meta-analysis of clinical trials. *Food Rev Int*. 2020;37(5):491–537. https://doi.org/10.1080/87559129.2019.1710748.
29. Методические рекомендации. Особенности клинических проявлений и лечения заболевания, вызванного новой коронавирусной инфекцией (COVID-19) у детей (версия 2, утверждено Минздравом РФ). URL: https://www.garant.ru/products/ipo/prime/doc/74232682/ (дата обращения: 15.12.2025).
30. Song J., Wu Y., Yin X. The causal links between gut microbiota and COVID-19: a Mendelian randomization study. *J Med Virol*. 2023;95(5):e28784. https://doi.org/10.1002/jmv.28784.
31. Zhang H., Zhou Z. Association of gut microbiota and dietary component intake with COVID-19: a mendelian randomization study. *Clin Nutr*. 2023;42(8):1308–1313. https://doi.org/10.1016/j.clnu.2023.06.017.
32. Листопадова А.П., Новикова В.П., Замятина Ю.Е. Биомаркер синдрома повышенной кишечной проницаемости зонулин у детей с атопическим дерматитом и хроническим гастродуоденитом. *Профилактическая и клиническая медицина*. 2024;1(90):33–36.
33. Клинические рекомендации. Синдром раздраженного кишечника. URL: https://cr.minzdrav.gov.ru/preview-cr/892_1 (дата обращения: 31.01.2025).
34. Silva J.T.C., Fonseca Neto O.C.L.D. Post-COVID-19 irritable bowel syndrome: an integrative review. *Rev Col Bras Cir*. 2023;50:e20233618. https://doi.org/10.1590/0100-6991e-20233618-en.

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Review

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Necrotizing enterocolitis in newborns: description, diagnosis, treatment, suggestions (literature review)

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ABSTRACT. This review presents current data on the diagnosis and intensive care of necrotizing enterocolitis in neonates from the perspective of an anesthesiologist-intensivist. The disease is considered a multifactorial process, most common in preterm infants. The main risk factors are described, including early antibiotic use, formula feeding, and hemodynamic disturbances. Criteria for patient transfer to the intensive care unit are systematized based on multiple organ dysfunction scores and ultrasound findings. The principles of fluid management, inotropic and respiratory support, antibiotic therapy, as well as approaches to parenteral nutrition and coagulopathy correction, are detailed. Special attention is paid to indications for surgical treatment, resection techniques, and peritoneal drainage. Practical suggestions for optimizing the management of this patient population are formulated, including the use of dalargin, prolonged epidural analgesia, and low-molecular-weight heparins.

KEYWORDS: *necrotizing enterocolitis, neonates, intensive care*

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Некротизирующий энтероколит новорожденных: описание, диагностика, лечение, предложения (обзор литературы)

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РЕЗЮМЕ. В обзорной статье представлены современные данные о диагностике и интенсивной терапии некротизирующего энтероколита у новорожденных с позиции анестезиолога-реаниматолога. Заболевание рассматривается как многофакторный процесс, чаще встречающийся у недоношенных детей. Описаны основные факторы риска, включая раннее применение антибиотиков, искусственное вскармливание и гемодинамические нарушения. Систематизированы критерии перевода пациентов в отделение реанимации на основе шкал полиорганной дисфункции и ультразвуковых данных. Детально изложены принципы инфузионной, инотропной, респираторной и антибактериальной терапии, а также подходы к парентеральному питанию и коррекции коагулопатий. Отдельное внимание уделено показаниям к хирургическому лечению, тактике резекции и дренирования брюшной полости. Сформулированы практические предложения по оптимизации ведения данной категории пациентов, включая применение даларгина, продленной эпидуральной аналгезии и низкомолекулярных гепаринов.

КЛЮЧЕВЫЕ СЛОВА: *некротизирующий энтероколит, новорожденные, интенсивная терапия*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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DEFINITION

Necrotizing enterocolitis (NEC) is a common complication of neonatal pathology; however, in extremely preterm infants, it can be regarded as a distinct clinical entity [1, 2]. It is among preterm infants that NEC occurs most consistently. For instance, NEC is reported in 7–11% of very-low-birth-weight preterm infants in the USA, in 5.1% of preterm infants born at less than 33 weeks of gestation in Canada, in 5.8% of those with a gestational age below 27 weeks in Sweden, and in 3–4% of preterm infants under 32 weeks of gestation in Switzerland [3–5]. Mortality in infants with stage I–II NEC ranges from 20% to 30%, while in surgically treated patients it reaches 50–60% [3, 6, 7].

NEC lacks a clearly defined etiology, and there is no consensus among researchers on the fundamental nature of this disease [8–11]. A broad group of conditions of both iatrogenic and non-iatrogenic origin is recognized as predisposing factors. These include birth weight below 1500 g; formula feeding or the use of cow's and goat's milk; mechanical and osmotic stressors, such as oral and enteral administration of medications and hyperosmolar formulas; diseases and conditions associated with intrapulmonary or extrapulmonary right-to-left blood shunting — for instance, respiratory distress syndrome, pneumonia, patent ductus arteriosus, pulmonary embolism, and cyanotic congenital heart defects — and intestinal capillary hypoperfusion due to low cardiac output, vasoplegic shock, or diastolic dysfunction, the latter most often caused by hypocalcemia [12–20]. It is also necessary to take into account the spasmogenic effects of opiates (morphine, fentanyl) — with the exception of trimeperidine, which acts as a spasmolytic — as well as vasoactive agents that increase oxygen demand (such as catecholamines, methylxanthines (aminophylline), corticosteroids, sildenafil, and ibuprofen) and mechanical ventilation with high positive end-expiratory pressure (PEEP). Each day of antibiotic therapy (ABT) has been shown to increase the risk of NEC by 20%, with an odds ratio (OR) of 1.2 (95% confidence interval [CI], 1–1.5); when the duration of ABT exceeds 10 days, the OR reaches 3.0 (95% CI, 1.5–3.3). A well-known adverse effect of protected semi-synthetic penicillins, and to a lesser extent cephalosporins, is the development of pseudomembranous colitis, i.e., the provocation of NEC [21, 22]. Factors that reliably reduce the risk of NEC include feeding with native human milk (both maternal and donor milk) and probiotics containing Lactobacillus and Bifidobacterium species [13, 18, 23]. Lactoferrin reduces the risk of both NEC and late-onset neonatal sepsis [2, 3, 24]. Early pharmacological closure of the ductus arteriosus with ibuprofen is traditionally regarded as beneficial; at the same time, however, the negative impact of this drug on cerebral, pulmonary, and intestinal blood flow is emphasized, and data on the long-term consequences of its use remain lacking [3, 16, 17, 25–27].

The clinical picture consists of a combination of systemic toxic symptoms (lethargy, somnolence, poikilothermia, episodes of apnea, and a tendency toward bradycardia and arterial hypotension) and gastrointestinal manifestations, including abdominal distension (70–98%), increased gastric residual volume (>70%), regurgitation, vomiting (>70%), gastrointestinal bleeding (22–59%), and diarrhea (4–26%) [28–30].

The stages of NEC are defined by Bell's classification as modified by Walsh and Kliegman [31], supplemented by the ultrasound (US) findings presented below [32–36].

Stage Ia: suspected NEC. The skin has a mottled appearance; brief episodes of apnea and temperature instability are noted. The abdomen is distended and tender to palpation. Stools are frothy and odorless. Cessation of enteral feeding leads to clinical improvement. US reveals increased intestinal echogenicity.

Stage Ib: suspected NEC. The overall clinical picture is similar to that of stage Ia. Blood may be present in the stool. Radiographic signs include intestinal distension with gas, bowel wall edema, irregularity of intestinal loops, and moderate hepatosplenomegaly. US demonstrates hyperemia, increased perfusion (on Doppler imaging), bowel wall thickening, and increased intestinal echogenicity.

Stage IIa: definite NEC (negative dynamics). Lethargy, hypothermia, muscular hypotonia, and centralization of circulation (shock) develop. Apneic episodes become more frequent and prolonged. Bradycardia is observed. Vomiting is bile-stained, and blood is present in the stool. Intra-abdominal pressure rises: the abdomen is enlarged, the skin is tense ("shiny"), and palpation is painful. Hyperemia of the abdominal wall (Besenreiser's sign) is noted. Hepatosplenomegaly is pronounced. Radiographic signs include a progressive increase in intestinal gas; paresis with fluid levels;

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worsening bowel wall edema; moderate pneumatosis; and separation of intestinal loops in the presence of free fluid in the abdominal cavity. In addition to the previously described signs, US may reveal free gas in the portal area of the liver. Thinning of the bowel wall and decreased perfusion indicate pre-perforation. In the absence of adequate intensive care, this stage progresses within several hours to stage IIb and subsequently to stage III.

Stage IIb: NEC with physiological deterioration. Bradycardia, heart failure, metabolic acidosis, thrombocytopenia, jaundice, oliguria, somnolence or stupor, and muscular atonia develop. Edema of the abdominal wall is markedly pronounced. Any touch is painful. The bowel contains frothy stool, but defecation is absent. Radiographic signs include an increase in the amount of free fluid in the abdominal cavity with separation of intestinal loops, pronounced pneumatosis, and obliteration of the preperitoneal fat line. Ultrasound (US) findings are identical. Stage IIb is rapidly progressive and requires emergency stabilization of vital functions.

Stage IIIa: advanced NEC without perforation. Peritonitis develops as a result of increased intestinal wall permeability and loss of the intestinal barrier (glycocalyx); the abdomen is extremely distended and markedly tense, with visible contours of intestinal loops, ecchymoses, and severe hyperemia of the abdominal wall. The patient's condition is critical: sepsis, vasoplegic and cardiogenic shock, and multiple organ dysfunction syndrome (MODS) are present.

Stage IIIb: advanced NEC with perforation. Pneumoperitoneum and gangrene are observed. Radiographic signs include significant hepatosplenomegaly, a reduced bladder size, a marked increase in the amount of free fluid and pneumatosis of the intestine and portal vein area, with a corresponding decrease in the amount of free gas.

DIAGNOSIS

The objective physical signs of NEC have been described above. It should be emphasized that, when NEC is suspected, palpation of the abdomen during physical examination must be avoided. Regular surgical consultations are mandatory. Other investigations include measurement of abdominal circumference every 2 hours; ultrasound (US); a complete blood count, with particular attention paid to thrombocytosis, leukocytosis, and the neutrophil-to-lymphocyte ratio (not exceeding 5.5); serum electrolytes; acute-phase proteins — C-reactive protein, fibrinogen, and transthyretin (a dynamic decrease in which indicates depletion of energy reserves required to counteract inflammation); creatinine; urea; blood gas analysis and acid – base status parameters; bacteriological studies; and a coagulation profile [37–42].

TREATMENT (NON-SURGICAL)

Intensive care includes nil per os, gastric decompression, total parenteral nutrition, antibiotic therapy, inotropic and respiratory support, correction of fluid and electrolyte balance, management of coagulopathies and thrombocytopenia, as well as infrequently used and rarely employed measures, such as the administration of lactulose and dalargin.

ELABORATION AND DISCUSSION OF THE ABOVE POINTS

1. Cessation of feeding produces a clear positive effect when NEC is suspected (stage Ia) [2, 3, 43]. As the process progresses, the beneficial role of fasting is reduced to the prevention of abdominal distension and the intra-abdominal hypertension caused by it. However, prolonged fasting (exceeding 24 hours) in a preterm newborn is a risk factor for intestinal atrophy, since the small intestine receives 50% of its nutrition from its lumen, and the large intestine receives 80% [44–46]. Atrophy of the intestinal wall leads to degradation of the glycocalyx and facilitates the translocation of intestinal flora in the setting of an immature biocenosis, i.e., it provokes septic complications [1, 24]. For this reason, some researchers, in the absence of gas in the portal area of the liver, permit trophic feeding starting with a semi-elemental formula, with subsequent transition to maternal or donor milk, up to and including the development of stage IIa [41, 46, 47]. In the parenteral nutrition program, it is essential to adhere to the following conditions. Total energy supply should not exceed 50 kcal/kg per day and should be achieved gradually (over 7–9 days), with a lipid-to-glucose ratio of 1:1.5 (40% of energy supply provided by third-generation lipid emulsions — the agent of choice being SMOFlipid — and 60% by glucose). Amino acid mixtures (Aminoven Infant, Aminoplasma-Ped) are dosed according to the principle of 100 kcal per 1 g of amino nitrogen or 6.25 g of amino acids,

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while for newborns of very low and extremely low birth weight who require increased protein supplementation, the energy supply may be reduced to 80 kcal per 1 g of amino nitrogen [48–50]. Prevention of cholestasis requires the maintenance of gastrointestinal motility: perianal mechanical stimulation; the administration of hypertonic microenemas in consultation with the surgeon; and, as a priority, continuous epidural anesthesia (the technique of choice being caudal anesthesia with 0.2% ropivacaine) [51, 52]. Gastric decompression is continuous: the tube is not clamped, it is looped, and the free end is positioned above the zero reference point (the manubrium of the sternum). The administration of probiotics containing Lactobacillus and Bifidobacterium species is always indicated.

2. Antibiotic therapy. Despite the fact that NEC begins as an aseptic process, reduced microcirculation destroys the intestinal barrier (glycocalyx), leading to the appearance of microcroses; degradation of the glycocalyx facilitates the translocation of intestinal flora; and microbial colonization of the intestine outpaces the development of primary immune responses, which dictates the need for early initiation of antibiotic therapy in stages I–II. No clear, objectively substantiated recommendations exist regarding the choice of antibiotics [3]. Traditionally, antibiotic therapy in newborns is often initiated with protected semi-synthetic penicillins as monotherapy or in combination with an aminoglycoside. However, residual clavulanic acid, sulbactam, avibactam, and cilastatin carry a risk of inducing pseudomembranous colitis and disinhibiting clostridial intestinal flora, and Clostridium difficile is recognized as an etiological factor in toxic megacolon. For this reason, a combination of an aminoglycoside with a third- or fourth-generation cephalosporin appears more justified, with metronidazole added when additional anti-anaerobic activity is required. As an alternative, carbapenem monotherapy (meropenem or doripenem) is recommended. In stage I, the course of antibiotic therapy should be short (ideally 72 hours), whereas in stages II–III it should last 10–14 days. Probiotics are not administered during antibiotic therapy. The issue of combined antibiotic therapy remains without evidence-based solutions. Two, three, and sometimes up to five agents are frequently prescribed based on the susceptibility (more precisely, the minimal inhibitory concentration) of microorganisms isolated from non-sterile sites, without consideration of pharmacological and bacteriological antagonism [53, 54].

3. Inotropic support. While the goal of inotropic support in the setting of NEC is the restoration of capillary perfusion in the gastrointestinal tract, the primary task to be accomplished in achieving this goal is an increase in cardiac stroke volume (a direct inotropic effect; if its efficacy is insufficient, a vasoconstrictor effect is additionally recruited) [55–59]. In doing so, it is important not to raise peripheral vascular resistance above a certain critical

Table 1. Effects of vasoactive drugs

Таблица 1. Эффекты вазоактивных медикаментов

Препараты (рецепторы) Drugs (receptors)	СИ CI	ЧСС HR	САД MAP	ОПСС TVR	ЛСС PVR	Потребность миокарда в O_2 Myocardial O_2 demand
Добутамин (α-1; β-1,2) Dobutamine (α-1; β-1,2)	++	++	+	–	–	++
Допамин (α-1; β-1,2; D) Dopamine (α-1; β-1,2; D)	+	+	++	++	+	+
Адреналин (α-1; β-1,2) Epinephrine (α-1; β-1,2)	++	++	++	+++	+++	+
Норадреналин (α-1; β-1) Norepinephrine (α-1; β-1)	+/–	–	++	+++	+++	++
Милринон (α-1) Milrinone (α-1)	+	+/–	+/–	–	–	+/–

The table was compiled by the authors

Таблица составлена авторами

Note: PVR — pulmonary vascular resistance; TVR — total vascular resistance; MAP — mean arterial pressure; CI — cardiac index; HR — heart rate.

Примечание: ЛСС — легочное сосудистое сопротивление; ОПСС — общее периферическое сопротивление сосудов; САД — среднее артериальное давление; СИ — сердечный индекс; ЧСС — частота сердечных сокращений.

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value, which, unfortunately, has not been precisely defined. Table 1 presents the qualitative characteristics of catecholamines and milrinone.

At the initiation of inotropic support, the oxygen extraction index (O2ER) should be quantitatively determined [60, 61]:

$$O_2ER = (SpO_2 - SvO_2)/SpO_2,$$

where SpO_2 is the oxygen saturation of hemoglobin in the pulsatile blood flow (which constitutes 97–99% of SaO_2) [62], and SvO_2 is the oxygen saturation of hemoglobin in venous blood.

The normal range of this index is from 0.22 to 0.35. Values ≤0.2 indicate an excessive oxygen supply or, less commonly, hypometabolism that reduces the efficacy of vasopressors, i.e., they reflect the need to reduce or discontinue oxygen supplementation; values above 0.4 invariably reflect hypercatabolism and may require deepening of sedation and an increase in the fraction of inspired oxygen (FiO_2). In the absence of milrinone, the agent of choice is dobutamine, which does not increase systemic vascular resistance (SVR; also referred to as total vascular resistance, TVR, in Table 1), improves perfusion of the pulmonary circulation and overall capillary perfusion, at an initial dose of 5 μg/kg/min, with possible escalation to 10–15 μg/kg/min [45, 63]. Dopamine at doses of 5 to 10 μg/kg/min acts similarly to dobutamine but increases mean arterial pressure (MAP) by raising SVR (enhancing myocardial contractility to a lesser extent), whereas dobutamine increases cardiac output with virtually no effect on SVR. The target parameter for assessing the efficacy of vasoactive agents is mean arterial pressure, which in full-term newborns should be no lower than 40 mmHg and no higher than 55 mmHg. In extremely preterm infants, the lower acceptable limit of MAP is 35 mmHg and the upper limit is 50 mmHg. If MAP remains unstable under the action of dobutamine or dopamine, the regimen is modified [1, 2, 44, 56]. Two options are possible, based on the physiological effects of vasoactive medications:

1) epinephrine from 0.05 to 1–2 μg/kg/min (does not require combination with other agents);
2) norepinephrine 0.2–2 μg/kg/min + dobutamine.

During inotropic and vasopressor support, one should aim for the gradual but earliest possible discontinuation of catecholamines.

4. Respiratory support. NEC, even at stage I, requires respiratory support, since increasing intra-abdominal pressure restricts tidal volumes and promotes atelectasis of the lower lobes of the lungs, compensatory increasing the work of breathing. The reduction in the respiratory surface area decreases the ventilation-perfusion (V/Q) ratio to <0.8, thereby increasing the shunt of deoxygenated blood into the systemic circulation. Furthermore, NEC rarely begins to develop against a background of full health but rather emerges as a complication of a wide variety of pathologies in the neonatal period. The principle that, in any neonatal pathology, the hemodynamic, external respiratory, and digestive systems are universally affected has been confirmed by the work of N.N. Volodin [64] and A.G. Antonov [65].

Non-invasive respiratory support, most commonly in the form of continuous positive airway pressure, may delay the need to transition the newborn to volume-controlled mechanical ventilation but may also serve as a factor in increasing intragastric and subsequently intra-abdominal pressure. When the latter rises above 10 mmHg, the conditions for adequate renal perfusion and capillary perfusion in the celiac trunk region deteriorate [45, 63, 66]. For this reason, early transition of patients with NEC to invasive respiratory support is considered advisable [67, 68].

High-frequency oscillatory ventilation (HFOV), which is gaining popularity, holds promise for lesions of the pulmonary parenchyma and interstitium, since active expiration guarantees the absence of auto-PEEP and reduces the risk of dysatelectasis, barotrauma, and volutrauma [30]. However, in the presence of elevated intra-abdominal pressure and reduced splanchnic blood flow, there is no physiological rationale or sufficient evidence for the superiority of HFOV over the more conventional convection (volume-controlled) ventilation [69, 70]. In particular, the effect of high oscillation frequency (≥5 Hz) on perfusion blood flow in the celiac trunk region has not been studied.

Among the specific aspects of volume-controlled ventilation in newborns with NEC, the need to overcome hypoventilation of the segments of the lower third of the lungs resulting from intra-abdominal hypertension should be noted. In these segments, the ventilation-perfusion (V/Q) ratio is substantially lower than 0.8, and during a rapid inspiration, a significant proportion of alveoli and bronchioles do not participate in gas exchange, thereby increasing the

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capacity of the functional dead space [44, 45, 67, 71]. By the term "rapid inspiration," we denote the inspiratory-to-expiratory time ratio (Ti:Te) routinely used in most neonatal intensive care units, i.e., a ratio of 1:3–1:4 [72, 73]. To counteract this effect, elevated PEEP and FiO_2 are routinely employed, which exert opposing influences on CO_2 exchange. A high FiO_2, by stimulating the Haldane effect, enhances the "washout" of CO_2 from erythrocytes in venous blood, whereas PEEP impedes its alveolar elimination [67, 68, 74]. As a result, both hypercapnia at normal or reduced respiratory rates and hypocapnia at elevated respiratory rates are frequently recorded. The PEEP level also affects the perfusion of pulmonary capillaries, the perfusion pressure in which does not exceed 5–7 mmHg (6.7–9.4 mbar) in extremely preterm infants, while an FiO_2 above 0.6 promotes cerebral vasodilation, increasing the risk of hemorrhages and periventricular leukomalacia. The Ti:Te ratio, as shown in Table 2, depends on the respiratory rate per minute [67, 68, 73]. At a fixed inspiratory time (usually 0.3±0.05 s), a respiratory rate of 40 breaths per minute yields a Ti:Te of 1:4, at 50 per minute — 1:3, at 65 per minute—1:2, and only at 80 per minute does it correspond to the physiological ratio for quiet breathing — 1:1.5 [44].

In view of the above, the initial ventilation parameters required to establish and maintain an "open lung" in a newborn with NEC (especially those weighing less than 1500 g) may be presented as follows:

- tidal volume (Vt) not exceeding 4–5 mL/kg (in the absence of signs of acute respiratory distress syndrome [ARDS], it may be gradually increased to 6–7 mL/kg);
- circuit flow (flow) 3–4 L/min (up to 5–6 L/min when a heat and moisture exchange filter is used);
- respiratory rate (RR) 45–50 breaths/min;
- inspiratory time 0.67–0.6 s (Ti:Te—1:1), with gradual reduction (as SpO_2 normalizes) to 0.53–0.48 s (Ti:Te—1:1.5);
- peak inspiratory pressure (PIP) 18–22 mbar;
- PEEP 3–5 mbar;
- FiO_2 at the minimum level required to achieve SpO_2 of 88–94%, preferably not exceeding 0.4;
- maintain the following parameters within the specified ranges: O_2ER 0.22–0.4; SpO_2 88–94%; arterial oxygen tension (PaO_2) 57–75 mmHg; venous oxygen tension (PvO_2) 35–45 mmHg; venous carbon dioxide tension ($PvCO_2$) 35–50 mmHg.

5. Correction of fluid and electrolyte balance. In the early neonatal period, by analogy with the general principles of intensive care, infusion therapy is considered a priority anti-shock measure. However, no physiologically substantiated volumes or rates of infusion solution administration

Table 2. Dependence of inhalation time on respiratory rate and the ratio of “inhalation time : exhalation time”

Таблица 2. Зависимость времени вдоха от частоты дыханий и соотношения «время вдоха : время выдоха»

Частота дыхания в минуту Respiratory rate in minute	Ti + Te (с) Ti + Te (s)	Соотношение Ti:Te Ti:Te ratio							
		1,2:1	1:1	1:1,25	1:1,5	1:2	1:2,5	1:3	1:4
20	3	1,64	1,5	1,33	1,2	1	0,86	0,75	0,6
25	2,4	1,31	1,2	1,1	0,96	0,8	0,69	0,6	0,48
30	2	1,1	1	0,89	0,8	0,67	0,57	0,5	0,4
35	1,7	0,93	0,85	0,76	0,68	0,57	0,49	0,43	0,34
40	1,5	0,82	0,75	0,67	0,6	0,5	0,43	0,38	0,3
45	1,33	0,73	0,67	0,59	0,53	0,44	0,38	0,33	0,27
50	1,2	0,65	0,6	0,53	0,48	0,4	0,34	0,3	0,24
55	1,1	0,6	0,55	0,49	0,44	0,37	0,31	0,28	0,22
60	1	0,55	0,5	0,44	0,4	0,33	0,29	0,25	0,2
65	0,92	0,5	0,46	0,41	0,37	0,31	0,26	0,23	0,18
70	0,86	0,47	0,43	0,38	0,34	0,29	0,25	0,22	0,17
80	0,75	0,41	0,38	0,33	0,3	0,25	0,21	0,19	0,15

The table was compiled by the authors

Таблица составлена авторами

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exist for the neonatal period. For example, the algorithm for resuscitation in the delivery room of a newborn with an Apgar score of 0 prescribes, after successful resuscitation, the intravenous administration of isotonic sodium chloride solution at 10 mL/kg over 10 minutes (i.e., at a rate of 60 mL/kg per hour!) [75]. In the absence of intravascular volume loss and with restored pump function of the cardiac chambers, such an emergency rehydration regimen is regarded as a risk factor for pulmonary circulatory overload and acute kidney injury [76–79]. Moreover, the absence of the newborn's first breath implies the absence of evacuation of fetal extravascular lung water, i.e., hyperhydration of the pulmonary interstitium. The combination of a high total body water content in the newborn, a large relative amount of extracellular water (40% of body weight), and rapid recirculation (at least 25 circulating blood volumes per day) gives rise to lability of the extracellular compartment. It follows that the danger of hypervolemia of the pulmonary circulation due to rapid infusion combined with pulmonary interstitial edema exceeds the danger of dehydration and hypovolemia [76, 77, 80, 81]. Hypovolemia in newborns, especially preterm infants, is, as a rule, a consequence not of blood loss but of capillary plasma leakage, and massive infusion is highly likely to exacerbate this leakage. In preterm newborns, already at the onset of NEC development, the high rate of water recirculation and the relative weakness of the left cardiac chambers create a risk of volume overload of the pulmonary circulation, intestinal edema, and acute kidney injury [82–84]. Thus, the principle of judicious restriction of infusion volumes and rates in newborns at risk of NEC, and even more so in those with an established process, appears logical.

The infusion therapy program is as follows.

1. Emergency rehydration: 10 mL/kg per hour until a mean arterial pressure of 40 mmHg is achieved (35 mmHg in newborns with a body weight less than 1500 g) and capillary refill time is ≤3 s, but for no longer than 2 hours.

2. Maintenance rehydration: the physiological requirement on the first day of life is no more than 60 mL/kg, with a gradual increase in daily volumes to 135 mL/kg (for infants with a birth weight of at least 1500 g) or to 150 mL/kg (for preterm infants with a birth weight less than 1500 g) over 12–14 days. Perspiration losses in open systems cannot be precisely determined (ranging from 1 to 2.5 mL/kg per hour); in an incubator with a relative humidity above 75%, perspiration is negligible [70].

3. Composition: isotonic Sterofundin (Plasmafusol) in a volume that supplements the deficit of oral or enteral feeding. If intravenous administration of medications is necessary, they are accounted for in the total rehydration volume.

4. Monitoring: determination of body weight at least twice daily with recording of the mean value (during the first 5–7 days, a weight loss of 1% of birth weight per day indicates a normal rate of rehydration; from the eighth day onward, a weight gain in the same order should be observed) and a urine output rate of no less than 0.5 mL/kg per hour up to two days of life, and no less than 1 mL/kg per hour thereafter. Additional monitoring criteria include the absence of signs of right heart overload on electrocardiography/echocardiography and the absence of signs of interstitial pulmonary edema, pneumatosis, and progressive thickening of the intestinal walls on ultrasound [85–88]. Along with monitoring of water balance, it is necessary to monitor the levels of major ions in the blood plasma. Heart rate variability analysis is rarely used but provides highly valuable information, reflecting the balance of the autonomic nervous system [55, 78, 89].

6. Management of coagulopathies and correction of thrombocytopenia. In the neonatal period, factors that create a risk of both thrombosis and embolism and paradoxical bleeding are combined. The most important of these are: tissue factor (thromboplastin); antithrombin III deficiency and an insufficient rate of synthesis of its cofactor, heparin; insufficient functional intensity of the cytochrome P450 system and the absence of an intestinal biocenosis, both of which are necessary for the activation of phytomenadione; a high hematocrit; and biliary system overload with a deficiency of glucuronic acid, which is engaged in the detoxification of bilirubin [90]. Microthrombosis of the capillaries of the mesentery and intestinal villi is an important factor in the progression of NEC. The generally accepted class of drugs for the prevention of thrombotic complications is low-molecular-weight heparins (LMWHs). Subcutaneous administration of these agents is unacceptable in the neonatal period; therefore, the only method of LMWH administration in newborns is continuous intravenous infusion. These drugs should preferably be used prophylactically in all newborns with manifestations of infectious processes or at risk of infectious lesions,

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harnessing the following effects. These include blockade of TNFα expression, damping of platelet adhesive function, and an increase in the optical density of lipoproteins, which collectively reduce the activity of the inflammatory cytokine cascade and the risk of cholestasis. The daily dose of nadroparin or enoxaparin (anti-Xa to anti-IIa activity ratio of 4:1) may be 150–200 IU (anti-Xa)/kg or 2000 IU/m^2; however, for preterm infants, weight-based doses are safer. For dalteparin, the dose is lower (125–150 IU/kg), since the anti-Xa to anti-IIa activity ratio for this agent is 2:1. Monitoring is performed 2–4 times per week (thrombocytosis, international normalized ratio [INR], D-dimer, bleeding time). Thrombocytopenia does not necessarily correlate with a reduction in the activity of vascular-platelet hemostasis, since platelets can break down into microvesicles whose adhesive properties exceed the activity of intact platelets [90, 91]. The administration of platelet concentrate is indicated only in cases of overt bleeding against a background of profound thrombocytopenia. The classical regimen for arresting hemorrhage in hemorrhagic disease of the newborn — transfusion of fresh citrated blood and administration of phytomenadione (konakion) — is also relevant for NEC. In cases of massive bleeding, tranexamic acid (20–100 mg/kg with a maintenance infusion of 10 mg/kg per hour), prothrombin complex concentrate (25 IU/kg), and Coagil-VII (90 μg/kg with a maintenance infusion of 20 μg/kg per hour for up to 12 hours) are additionally employed. These agents are not used prophylactically.

7. Infrequently used and rarely employed measures. The use of lactulose is theoretically promising as a choleretic agent and a factor that enhances the activity of lactic acid flora and acidifies the contents of the large intestine. This reduces the toxicity of ammonia (i.e., promotes its migration into the intestinal lumen and conversion to ammonium) and diminishes the activity of opportunistic flora, including anaerobic species. The hyperosmolarity of lactulose syrup (concentration 66.7%) must be taken into account; therefore, the daily dose (depending on the child's body weight, from 3 to 5 mL) should be divided into four administrations via a nasogastric tube, with each portion diluted 5- to 10-fold. This means the preparation can be used during trophic feeding but not in fasting patients.

The use of dalargin, a Russian-developed drug created as a stress protector for the prevention and treatment of stress ulcers of the gastrointestinal tract, is highly effective. Dalargin is a synthetic analogue of leu-enkephalin and is used in general anesthesia regimens as an opioid adjuvant, allowing a 30% reduction in opioid consumption [92, 93]; its use in the neonatal period has been described in rare publications [94–96]. Other proven properties of dalargin include antioxidant and antihypoxant effects, and it prolongs the half-life of surfactant [93]. The estimated dose is 0.2–0.4 mg/kg per day, administered as a continuous infusion over 2–4 days.

SURGICAL TREATMENT

When there is doubt as to the necessity of laparotomy, laparoscopy is performed. In the presence or with a high probability of peritonitis, a palliative intervention — laparocentesis and drainage of the abdominal cavity — is indicated. Depending on the nature of the exudate obtained, the indication for extending the surgical intervention is determined. After revision of the abdominal organs, economical (local) resection of the affected segment of the intestine with the creation of a double enterostomy or colostomy (or multiple stomas) is most expedient. The rationale for this tactic lies in preserving intestinal functional activity sufficient for growth and development [97]. Staged closure of the intestinal stomas is generally considered feasible 1–5 months after the initial operation. In the presence of isolated perforations (1–2 ulcers), suturing of the ulcerative defects with a two-layer suture is performed. Resections of necrotized intestinal segments are completed by the formation of primary anastomoses. A combined surgical tactic (laparostomy in combination with intestinal stomas) is used in the presence of multiple, mosaically distributed subserosal necroses; the use of an isolated laparostomy is also justified. The placement of a polyvinyl chloride micro-irrigator, 0.2 to 0.4 cm in diameter, through a separate skin puncture is indicated. This allows for the administration of an antibiotic and a 0.5% metronidazole solution into the area of the local purulent-inflammatory focus. This method of passive sanitation is used for 3–4 days after surgery [98, 99].

SUGGESTIONS BASED ON THE ABOVE

1. Newborns with suspected NEC (stage Ia) should be managed in the intensive care unit (ICU) when the sum of scores on the following scales increases by 2 points per day from a baseline of

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Table 3. Quantitative assessment of indications for transfer of a newborn with suspected necrotizing enterocolitis to the pediatric intensive care unit

Таблица 3. Количественная оценка показаний для перевода новорожденного с подозрением на некротический энтероколит в педиатрическое отделение реанимации и интенсивной терапии

Признаки **Signs**	**Баллы** **Points**		
	0	**1**	**2**
Кожные покровы Skin	Розовые Pink	Мраморность Mottling	Цианоз Cyanosis
Ритм дыхания, частота дыхательных движений в минуту Respiratory rate, respiratory rate per minute	40–60	61–80	>80 или апноэ >80 or apnea
Время наполнения капилляров, с Capillary refill time, s	1–3	4	4
Гепатоспленомегалия Hepatosplenomegaly	Нет No	–	Да Yes
Перистальтика желудочно-кишечного тракта Gastrointestinal peristalsis	Живая Brisk	Спорадическая Sporadic	Усиленная или отсутствует Increased or absent
Прирост окружности живота, см Abdominal circumference increase, cm	0–1	2	>2
Метеоризм Flatulence	Нет No	Умеренный Moderate	Выраженный Severe
Застой в желудке Gastric congestion	Нет No	–	Да Yes
Кал Stool	Обычный Normal	Жидкий Liquid	Пенистый или отсутствует Foamy or absent
Кровотечение из желудочно-кишечного тракта Gastrointestinal bleeding	Нет No	Скрытая кровь Occult blood	Явное Obvious
Рвота (срыгивание) Vomition (regurgitation)	Нет No	1–2 раза за сутки 1–2 times per day	>2 раз за сутки >2 times per day
Данные ультразвукового исследования Ultrasound data	Норма Normal	Повышенная эхогенность кишечника Increased intestinal echogenicity	Пневматоз, утолщение стенки кишки, билиопневматоз Pneumatosis, intestinal wall thickening, biliopneumatosis

The table was compiled by the authors

Таблица составлена авторами

Note: 0–2 points — no translation required; 3 points — translation subject to agreement with the head of the intensive care unit; 4 points — translation required.

Примечание: 0–2 балла — перевод не требуется; 3 балла — перевод по согласованию с заведующим отделением реанимации и интенсивной терапии; 4 балла — перевод обязателен.

0 points [100–105]. These scales include NEOMOD (Neonatal Multiple Organ Dysfunction Score, 1999), pSOFA (pediatric Sequential Organ Failure Assessment, 2017), and aSOFA (adaptive Sequential Organ Failure Assessment, 2007). Table 3 is proposed for the formalization of indications.

2. The following should be mandatory components of monitoring and intensive care:

- daily ultrasound of the abdominal cavity;
- continuous epidural anesthesia (alternatively, caudal anesthesia) with ropivacaine;
- the use of dalargin as a stress protector;
- prophylaxis of thromboembolic complications with low-molecular-weight heparin fractions.

3. Stratification and standardization of antibiotic therapy regimens are necessary:

- monotherapy or combination therapy with two (at most, three) agents;
- if any component of a combination is deemed ineffective, the entire combination should be replaced;

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- a judicious approach to microorganisms contaminating non-sterile body regions or isolated from non-sterile sites as potential pathogens;
- the development of and adherence to a protocol for probiotic administration.

4. If prolonged analgosedation is required, the routinely used spasmogenic opioid (fentanyl) should be replaced with an agent possessing spasmolytic properties (trimeperidine) or, by decision of the medical committee, with dexmedetomidine. The prescribing information for dexmedetomidine does not contain a formal contraindication for use in children of any age.

5. Discontinue the use of agents that remain the subject of debate in the literature — sildenafil, cholecalciferol, vikasol, and octreotide.

ADDITIONAL INFORMATION

Authors' contribution. A.N. Shmakov — article concept development, article writing; K.V. Budarova — article visualization, editing, and approval.

All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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REFERENCES

1. Aleksandrovich Yu.S., Ivanov D.O., Pshenisnov K.V. Sepsis of newborns. Saint Petersburg: SPbSPMU; 2018 176 p. (In Russ.).
2. Xiong T., Maheshwari A., Neu J., Ei-Saie A., Pammi M. An overview of systematic reviews of randomized-controlled trials for preventing necrotizing enterocolitis in preterm infants. *Neonatology*. 2020;117(1):46–56. https://doi.org/10.1159/000504371.
3. Maier R.F., Obladen M. Intensive care of newborns. Evidence and experience (translated from German). Moscow: MEDpress-inform; 2021. P. 140–231. (In Russ.).
4. Isayama T., Lee S.K., Mori R., Kusuda S., Fujimura M., Ye X.Y. et al. Comparison of mortality and morbidity of very low birth weight infants between Canada and Japan. *Pediatrics*. 2012;130(4):e957–e965. https://doi.org/10.1542/peds.2012-0336.
5. Alsaied A., Islam N., Thalib L. Global incidence of necrotizing enterocolitis: a systematic review and Meta-analysis. *BMC Pediatr*. 2020;20(1):344. https://doi.org/10.1186/s12887-020-02231-5.
6. Pankratieva L.L., Volodin N.N. Methodological problems of rehabilitation of premature children. Pediatria. 2019;98(2):14–18. (In Russ.). https://doi.org/10.24110/0031-403X-2019-98-2-14-18.
7. Jin Y.T., Duan Y., Deng X.K., Lin J. Prevention of necrotizing enterocolitis in premature infants — an updated review. *World J Clin Pediatr*. 2019;8(2):23–32. https://doi.org/10.5409/wjcp.v8.i2.23.
8. Roberts A.G., Younge N., Greenberg R.G. Neonatal necrotizing enterocolitis: an update on pathophysiology, treatment, and prevention. *Paediatr Drugs*. 2024;26(3):259–275. https://doi.org/10.1007/s40272-024-00626-w.
9. Wu S., Di S., Liu T., Shi Y. Emerging prediction methods for early diagnosis of necrotizing enterocolitis. *Front Med (Lausanne)*. 2022;9:985219. https://doi.org/10.3389/fmed.2022.985219.
10. Fundora J.B., Guha P., Shores D.R., Pammi M., Maheshwari A. Intestinal dysbiosis and necrotizing enterocolitis: assessment for causality using bradford hill criteria. *Pediatr Res*. 2020;87:235–248. https://doi.org/10.1038/s41390-019-0482-9.
11. Kim S., Oh Y., Son J. et al. Machine learning-based analysis for prediction of surgical necrotizing enterocolitis in very low birth weight infants using perinatal factors: a nationwide cohort study. *Eur J Pediatr*. 2024;183(6):2743–2751. https://doi.org/10.1007/s00431-024-05505-7.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

12. Shulhan J., Dicken B., Hartling L., Larsen B.M. Current knowledge of necrotizing enterocolitis in preterm infants and the impact of different types of enteral nutrition products. *Adv Nutr An Int Rev J*. 2017;8(1):80–91. https://doi.org/10.3945/an.116.013193.
13. AlFaleh K., Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Cochrane Database Syst Rev*. 2014;(4):CD005496. https://doi.org/10.1002/14651858.CD005496.pub4.
14. Gidrewicz D.A., Fenton T.R. A systematic review and meta-analysis of the nutrient content of preterm and term breast milk. *BMC Pediatr*. 2014;14:216. https://doi.org/10.1186/1471-2431-14-216.
15. Hartel C., Hartz A., Pagel J. et al. NOD 2 loss-of-function mutations and risk of necrotizing enterocolitis or focal intestinal perforation in very low-birth-weight infants. *Inflamm Bowel Dis*. 2016;22(2):249–256. https://doi.org/10.1097/MIB.0000000000000658.
16. Kessler U., Schulte F., Cholewa D., Nelle M., Schaefer S.C., Klimek P.M. Outcome in neonates with necrotizing enterocolitis and patent ductus arteriosus. *World J Pediatr*. 2016;12(1):55–59. https://doi.org/10.1007/s12519-015-0059-6.
17. Kort E.J. Patent Ductus arteriosus in the preterm infant: an update on morbidity and mortality. *Curr Pediatr Rev*. 2016;12(2):98–105. https://doi.org/10.2174/1573396312021605060016 21.
18. Morgan J., Young L., Mc Guire W. Slow advancement of enteral feed volumes to prevent necrotizing enterocolitis in very low birth weight infants. *Cochrane Database Syst Rew*. 2015;(10):CD001241. https://doi.org/10.1002/14651858.CD001241.pub6.
19. Hackam D.J., Sodhi C.P. Bench to bedside — new insights into the pathogenesis of necrotizing enterocolitis. *Nat Rev Gastroenterol Hepatol*. 2022;19(7):468–479. https://doi.org/10.1038/s41575-022-00594-x.
20. Mani S., Garg P.M., Pammi M. Do hematological biomarkers predict surgical necrotizing enterocolitis? *Pediatr Res*. 2024;95(7):1680–1682. https://doi.org/10.1038/s41390-024-03066-x.
21. Cuna A., Morowitz M.J., Sampath V. Early antibiotics and risk for necrotizing enterocolitis in premature infants: A narrative review. *Front Pediatr*. 2023;11:1112812. https://doi.org/10.3389/fped.2023.1112812.
22. Dierikx T.H., Deianova N., Groen J. et al. Association between duration of early empiric antibiotics and necrotizing enterocolitis and late-onset sepsis in preterm infants: a multicenter cohort study. *Eur J Pediatr*. 2022;181(10):3715–3724. https://doi.org/10.1007/s00431-022-04579-5.
23. Lau C.S., Chamberlain R.S. Probiotic administration can prevent necrotizing enterocolitis in preterm infants: a meta-analysis. *J Pediatr Surg*. 2015;50(8):1405–1412. https://doi.org/10.1016/j.jpedsurg.2015.05.008.
24. Hui Y., Smith B., Mortensen M.S., Krych L., Sørensen S.J., Greisen G., Krogfelt K.A., Nielsen D.S. The effect of early probiotic exposure on the preterm infant gut microbiome development. *Gut Microbes*. 2021;13(1):1951113. https://doi.org/10.1080/19490976.2021.1951113.
25. Havranek T., Rahimi M., Hall H., Armbrecht E. Feeding preterm neonates with patent ductus arteriosus (PDA): Intestinal blood flow characteristics and clinical outcomes. *J Matern Neonatal Med Informa Healthcare*. 2015;28(5):526–530. https://doi.org/10.3109/14767058.2014.923395.
26. Mitra S., Scrivens A., von Kursell A.M., Disher T. Early treatment versus expectant management of hemodynamically significant patent ductus arteriosus for preterm infants. *Cochrane Database Syst Rev*. 2025;6(6):CD013278. https://doi.org/10.1002/14651858.CD013278.pub3.
27. Mitra S., de Boode W.P., Weisz D.E., Shah P.S. Interventions for patent ductus arteriosus (PDA) in preterm infants: an overview of Cochrane Systematic Reviews. *Cochrane Database Syst Rev*. 2023;11;4(4):CD013588. https://doi.org/10.1002/14651858.CD013588.pub2.
28. Kaplina A.V., Petrova N.A., Pervunina T.M., Khavkin A.I., Surkov A.N., Nazarenko L.P. et al. Necrotizing enterocolitis: pathogenetic features and differential diagnosis with inflammatory bowel disease in newborns. *Current Pediatrics*. 2024;23(6):438–446. (In Russ.). https://doi.org/10.15690/vsp.v23i6.2830.
29. Zozaya C., González G., Avila-Alvarez A. et al. Incidence, treatment, and outcome trends of necrotizing enterocolitis in preterm infants: a multicenter cohort study. *Front Pediatr*. 2020;8:188. https://doi.org/10.3389/fped.2020.00188.
30. Lu P., Gong X., Gu X., Jiang S., Cao Y., Sun C. et al. Mortality and extrauterine growth restriction of necrotizing enterocolitis in very preterm infants with heart disease: a multicenter cohort study. *Eur J Pediatr*. 2024;183(8):3579–3588. https://doi.org/10.1007/s00431-024-05599-z.
31. Walsh M.C., Kliegman R.M. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatr Clin North Am.* 1986;33(1):179–201. https://doi.org/10.1016/s0031-3955(16)34975-6.
32. Jia L., Li Z., Zhu H., Ye X., Luo S., Wang Q. The diagnostic value of abdominal ultrasound in the progression of necrotizing enterocolitis in low-birth-weight neonates. *Medicine (Baltimore)*. 2025;104(43):e45427. https://doi.org/10.1097/MD.0000000000045427.
33. Chen S., Hu Y., Liu Q., Li X., Wang H., Wang K. Comparison of abdominal radiographs and sonography in prognostic prediction of infants with necrotizing enterocolitis. *Pediatr*

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

Surg Int. 2018;34(5):535–541. https://doi.org/10.1007/s00383-018-4256-y.
34. Chen J., Mu F., Gao K., Yan C., Chen G., Guo C. Value of abdominal ultrasonography in predicting intestinal resection for premature infants with necrotizing enterocolitis. *BMC Gastroenterol*. 2022;22(1):524. https://doi.org/10.1186/s12876-022-02607-0.
35. May L.A., Epelman M., Daneman A. Ultrasound for necrotizing enterocolitis: how can we optimize imaging and what are the most critical findings? *Pediatr Radiol*. 2023;53(7):1237–1247. https://doi.org/10.1007/s00247-022-05545-x.
36. Hegedus C., Essex C., Vincent K., Shiflett A., Spence L., Hill J., Chetta K.E. A standardized universal protocol for using adjunct abdominal ultrasound at the time of diagnosis for suspected necrotizing enterocolitis. *Pediatr Radiol*. 2025;55(13):2823–2831. https://doi.org/10.1007/s00247- 025-06408-x.
37. Agakidou E., Agakidis C., Gika H., Sarafidis K. Emerging biomarkers for prediction and early diagnosis of necrotizing enterocolitis in the era of metabolomics and proteomics. *Front Pediatr*. 2020;8(8):602255. https://doi.org/10.3389/fped.2020.602255.
38. ElMeneza S., Okasha A., El-Hafez M.A., Hussein N. Ischemia-modified albumin as a novel marker for diagnosis of necrotizing enterocolitis in newborn infants. *J Pediatr Neonat Individual Med*. 2021;10(2):e100205. https://doi.org/10.7363/100205.
39. Chaaban H., Shin M., Sirya E., Lim Y.-P., Caplan M., Padbury J.F. Inter-alpha inhibitor protein level in neonates predicts necrotizing enterocolitis. *J Pediatr*. 2010;157(5):757–761. https://doi.org/10.1016/j.jpeds.2010.04.075.
40. Goldstein G.P., Sylvester K.G. Biomarker discovery and utility in necrotizing enterocolitis. *Clin Perinatol*. 2019;46(1):1–17. https://doi.org/10.1016/j.clp.2018.10.001.
41. Sharif S.P., Friedmacher F., Amin A., Zaki R.A., Hird M.F., Khashu M., Phelps S.R. Low serum albumin concentration predicts the need for surgical intervention in neonates with necrotizing enterocolitis. *J Pediatr Surg*. 2020;55(12):2625–2629. https://doi.org/10.1016/j.jpedsurg.2020.07.003.
42. Palleri E., Frimmel V., Fläring U. et al. Hyponatremia at the onset of necrotizing enterocolitis is associated with intestinal surgery and higher mortality. *Eur J Pediatr*. 181(4):1557–1565. https://doi.org/10.1007/s00431-021-04339-x.
43. Arbra C.A., Oprisan A., Wilson D.A., Ryan R.M., Lesher A.P. Time to reintroduction of feeding in infants with nonsurgical necrotizing enterocolitis. *J Pediatr Surg*. 2018;53:1187–1191. https://doi.org/10.1016/j.jpedsurg.2018.02.082.
44. Guyton A.K., Hall J.E. Medical Physiology. Translate from English. Moscow: Logosfera; 2018. 1328 p. (In Russ.).
45. Vincent J.-L. Textbook of critical care (7th edit.; b II). Elsevier; 2017. P. 1192–1200.
46. Ionov O.V., Balashova E.N., Lenyushkina A.A., Kirtbaya A.R., Kuhartseva M.V., Zubkov V.V. Show vs fast advancetement of enteral feeding in very low body weight infants in neonatal intensive care unit. *Neonatology: news, opinions, training*. 2015;4(10):73–81. (In Russ.).
47. Sadrudin Premji S., Chessell L., Stewart F. Continuous nasogastric milk feeding versus intermittent bolus milk feeding for preterm infants less than 1500 grams. *Cochrane Database Syst Rev*. 2021;6(6):CD001819. https://doi.org/10.1002/14651858.CD001819.pub3.
48. Robinson D.T., Calkins K.L., Chen Y. et al. Guidelines for parenteral nutrition in preterm infants: the American society for parenteral and enteral nutrition. *JPEN J Parenter Enteral Nutr*. 2023;47(7):830–858. https://doi.org/10.1002/jpen.2550.
49. Phongpreecha T., Ghanem M., Reiss J.D. et al. AI-guided precision parenteral nutrition for neonatal intensive care units. *Nat Med*. 2025;31(6):1882–1894. https://doi.org/10.1038/s41591-025-03601-1.
50. Asfour S.S, Alshaikh B., AlMahmoud L. et al. SMOFlipid impact on growth and neonatal morbidities in very preterm infants. *Nutrients*. 2022;14(19):3952. https://doi.org/10.3390/nu14193952.
51. Hu X., Liang H., Li F., Zhang R., Zhu Y., Zhu X., Xu Y. Necrotizing enterocolitis: current understanding of the prevention and management. *Pediatr Surg Int*. 2024;10;40(1):32. https://doi.org/10.1007/s00383-023-05619-3.
52. Evidence-Based Medicine Group. Clinical guidelines for the diagnosis and treatment of neonatal necrotizing enterocolitis. *Zhongguo Dang Dai Er Ke Za Zhi*. 2021;23(1):1–11. https://doi.org/10.7499/j.issn.1008-8830.2011145.
53. Beloborodov V.B., Goloshchapov O.V., Gusarov V.G., Dekhnich A.V., Zamyatin M.N., Zolotukhin K.N. et al. Diagnosis and antimicrobial therapy of infections caused by polyresistant microorganisms (updated 2024). *Messenger of Anesthesiology and Resuscitation*. 2025;22(2):149–189. (In Russ.). https://doi.org/10.24884/2078-5658-2025-22-2-149-189.
54. Pace E., Yanowitz T.D., Waltz P., Morowitz M.J. Antibiotic therapy and necrotizing enterocolitis. *Semin Pediatr Surg*. 2023;32(3):151308. https://doi.org/10.1016/j.sempedsurg.2023.151308.
55. Janaillac M., Beausoleil T.P., Barrington K.J., Raboisson M.-J., Karam O., Dehaes M., Lapointe A. Correlations between near-infrared spectroscopy, perfusion index, and cardiac outputs in extremely preterm infants in the first 72 h of life. *Eur J Pediatr*. 2018;177(4):541–550. https://doi.org/10.1007/s00431-018-3096-z.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

56. El-Khuffash A., McNamara P.J. Hemodynamic assessment and monitoring of premature infants. *Clin Perinatol*. 2017;44(2):377–393. https://doi.org/10.1016/j.clp.2017.02.001.
57. Laan M.E., Roofthooft M.T.R., Fries M.W.A., Schat T.E., Bos A.F., Berger R.M.F., Kooi E.M.W. Multisite Tissue oxygenation monitoring indicates organ-specific flow distribution and oxygen delivery related to low cardiac output in preterm infants with clinical sepsis. *Pediatr Crit Care Med*. 2016;17(8):764–771. https://doi.org/10.1097/PCC.0000000000000833.
58. Johnston N., Waal de K. Clinical and haemodynamic characteristics of preterm infants with early onset sepsis. *J Paediatr Child Health*. 2022;58(12):2267–2272. https://doi.org/10.1111/jpc.16218.
59. Nissimov S., Joye S., Kharrat A., Zhu F., Ripstein G., Baczynski M. et al. Dopamine or norepinephrine for sepsis-related hypotension in preterm infants: a retrospective cohort study. *Eur J Pediatr*. 2023;182(3):1029–1038. https://doi.org/10.1007/s00431-022-04758-4.
60. Khalesi N., Choobdar F.A., Khorasani M. et al. Accuracy of oxygen saturation index in determining the severity of respiratory failure among preterm infants with respiratory distress syndrome. *J Matern Fetal Neonatal Med*. 2021;34(14):2334–2339. https://doi.org/10.1080/14767058.2019.1666363.
61. Rawat M., Chandrasekharan P.K., Williams A. et al. Oxygen saturation index and severity of hypoxic respiratory failure. *Neonatology*. 2015;107(3):161–166. https://doi.org/10.1159/000369774.
62. Severinghaus J.W., Kelleher J.F. Recent developments in pulse oximetry. *Anesthesiology*. 1992;76(6):1018–1038. https://doi.org/10.1097/00000542-199206000-00024.
63. Agakidou E., Chatziioannidis I., Kontou A., Stathopoulou T., Chotas W., Sarafidis K. An update on pharmacologic management of neonatal hypotension: when, why, and which medication. *Children (Basel)*. 2024;11(4):490. https://doi.org/10.3390/children11040490.
64. Clinical recommendations. Neonatology. Volodin N.N., Degtyarev D.N., Kryuchko D.S., eds. Moscow: GEOTAR-Media; 2020. 320 p. (In Russ.).
65. Antonov A.G., Avdeeva O.V., Babaka O.A. et al. Neonatology: clinical guidelines. Volodin N.N. et al., eds. Moscow: GEOTAR-Media; 2019. 319 p. (In Russ.).
66. Dini G., Ceccarelli S., Celi F. Strategies for the prevention of bronchopulmonary dysplasia. *Front Pediat*. 2024:12:1439265. https://doi.org/10.3389/fped.2024.1439265.
67. Aleksandrovich Yu.S., Pshenisnov K.V. Respiratory support in critical conditions in pediatrics and neonatology. Moscow: GEOTAR-Media; 2020. 272 p. (In Russ.).
68. Thome U.H., Genzel-Boroviczeny O., Bohnhorst B., Schmid M. et al. PHELBI Study Group Permissive hypercapnia in extremely low birthweight infants (PHELBI): a randomized controlled multicentre trial. *Lancet Respir Med*. 2015;3(7):534–543. https://doi.org/10.1016/S2213-2600(15)00204-0.
69. Ackermann B.W, Klotz D., Hentschel R., Thome U.H., Kaam A.H. High-frequency ventilation in preterm infants and neonates. *Pediatr Res*. 2023;93(7):1810–1818. https://doi.org/10.1038/s41390-021-01639-8.
70. Nof E., Heller-Algazi M., Coletti F., Waisman D., Josué S. Ventilation-induced jet suggests biotrauma in reconstructed airways of the intubated neonate. *J R Soc Interface*. 2020;17(162):20190516. https://doi.org/10.1098/rsif.2019.0516.
71. Abdel-Hady H., Shouman B. Permissive hypercapnia in extremely low-birthweight infants: how far should we go? *Acta Paediatr*. 2017;106(6):1011. https://doi.org/10.1111/apa.13727.
72. Shmakov A.N., Budarova K.V., Elizar'eva N.L., Kokhno V.N. Evaluation of deadspace effects created by heat and moisture exchange filter during artificial lung ventilation in newborns. *Siberian Scientific Medical Journal*. 2022;42(5):69–73. (In Russ.). https://doi.org/10.18699/SSMJ20220509.
73. Aleksandrovich Yu.S., Pechueva O.A., Pshenisnov K.V., Hienas V. Estimation of recruitment maneuver efficiency in premature infants with respiratory distress syndrome. *Neonatology: news, opinions, training*. 2014;4(6):87–93. (In Russ.).
74. Tsurukawa S., Zuiki M., Naito Y., Kitamura K., Matsumura U., Kanayama T. et al. Oxygenation saturation index in neonatal hypoxemic respiratory failure. *Pediatr Int*. 2024;66(1):715–753. https://doi.org/10.1111/ped.15753.
75. Neonatal resuscitation and stabilization in delivery room. Methodological letter. E.N. Baibarina, ed. (Moscow, 2020). *Neonatology: news, opinions, training*. 2020;8(1):34–52. (In Russ.).
76. Prometnoi D.V., Aleksandrovich Yu.S., Pshenisnov K.V. Fluid Overload as a predictor of lethal outcome in critically-ill children. *General Reanimatology*. 2019;15(1):12–26. (In Russ.). https://doi.org/10.15360/1813-9779-2019-1-12-26.
77. Ivanov D.O., Kozlova L.V., Derevtsov V.V., Priyma N.F. Assesssment of the cardiovascular system state in newborns with intrauterine grow threstriction. *Translational Medicine*. 2016;3(5):53–63. (In Russ.). https://doi.org/10.18705/2311-4495-2016-3-5-53-63.
78. Budarova K.V., Shmakov A.N., Elizar'eva N.L., Kokhno V.N. Reaction pattern of the autonomic nervous system to the infusion load in the intensive care in children: a prospective comparative study. *Annals of*

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

Critical Care. 2022;(3):133–144. (In Russ.). https://doi.org/10.21320/1818-474X-2022-3-133-144.
79. Li Y., Wang J., Bai Z., Chen J., Wang X., Pan J., Li X., Feng X. Early fluid overload is associated with acute kidney injury and PICU mortality in critically ill children. *Eur J Pediatr*. 2015;175(1):39–48. https://doi.org/10.1007/s00431-015-2592-7.
80. Vazemiller O.A., Vaganov A.A., Golubenko N.K., Aksanova R.Kh., Salmina A.B., Emelyanchik E.Yu. Diagnostics of myocardial damage in premature newborns with transient heart disease in the early neonatal period. *Russian Bulletin of Perinatology and Pediatrics*. 2019;64(5):38–43. (In Russ.). https://doi.org/10.21508/1027-4065-2019-64-5-38-43.
81. Irmak K., Tuten N., Karaoglu G. et al. Evaluation of cord blood creatine kinase (CK), cardiac troponin T (cTnT), N-terminal-pro-B-type natriuretic peptide (NT-proBNP), and s100B levels in nonreassuring foetal heart rate. *J Matern Fetal Neonatal Med*. 2021;34(8):1249–1254. https://doi.org/10.1080/14767058.2019.1632285.
82. Budarova K.V., Shmakov A.N. significance of markers of transient myocardial ischemia and hemodynamic overload in critically ill neonates. *Messenger of Anesthesiology and Resuscitation*. 2022;19(5):79–86. (In Russ.). https://doi.org/10.21292/2078-5658-2022-19-5-79-86.
83. Budarova K.V., Shmakov A.N., Sergeev S.A., Kokhno V.N., Elizar'eva N.L. Diagnosis and correction of cardiorenal-syndrome in neonatal surgery. *Children's Medicine of the North-West*. 2025;13(4):173–183. (In Russ.). https://doi.org/10.56871/CmN-W.2025.56.14.013.
84. Pervunina T.M., Vasichkina E.S., Erman M.V. Personalized approach in the management of children with cardiorenal syndrome (combined congenital heart and kidney defects). *Russian Journal for Personalized Medicine*. 2023;3(2):77–81. (In Russ.). https://doi.org/10.18705/2782-3806-2023-3-2-77-81.
85. Singh Y., Tissot C., Fraga M.V. International evidence-based guidelines on Point of Care Ultrasound (POCUS) for critically ill neonates and children issued by the POCUS Working Group of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC). *Crit Care*. 2020;24(1):65. https://doi.org/10.1186/s13054-020-2787-9.
86. Alyanov I.A., Budarova K.V., Sirota S.I., Shmakov A.N. Cumulative balance of infusion therapy for newborns with necrotic enterocolitis. *Siberian Scientific Medical Journal*. 2018;38(3):66–70. https://doi.org/ 10.15372/SSMJ20180310. (In Russ.).
87. Budarova K.V., Shmakov A.N., Yakovleva Yu.V. Objectification of choosing albumin transfusion regimen in newborns during intensive care. *Siberian Scientific Medical Journal*. 2025;45(2):142–150. (In Russ.). https://doi.org/10.18699/SSMJ20250215.
88. Kucherov Yu.I., Zhirkova Yu.V., Nasser M.M. Intraoperative infusion therapy in newborns. *Russian Journal of Pediatric Surgery*. 2018;22(3):130–134. (In Russ.). https://doi.org/10.18821/1560-9510-2018-22-3-130-134.
89. Budarova K.V., Shmakov A.N. Heart rate variability in newborns with cardiorespiratory failure. *Russian Journal of Anesthesiology and Reanimatology*. 2021;(1):25-31. (In Russ.). https://doi.org/10.17116/anaesthesiology202101125.
90. Kuznik B.I., Sturov V.G., Maksimova O.G. Hemorrhagic and thrombotic diseases and syndromes in children. Novosibirsk: Nauka Publ; 2012. 456 p. (In Russ.).
91. Shmakov A.N., Budarova K.V., Danchenko S.V. Dependence of newborns homeostasis on the quality composition of basic infusion therapy. *Medicine: Theory and Practice*. 2018;3(4):222–226. (In Russ.).
92. Zabolotskikh I.B., Chuprin S.V., Kurzanov A.N. Dose-dependent effects of dalargin in anesthesiology and intensive care. *Vestnik intensivnoy terapii*. 2002;(4):50–52. EDN: QBTIAZ. (In Russ.).
93. Luboshevsky P.A. General anesthesia with dalargin and tranexamic acid in microendoscopic endonasal surgeries. Abstract of a PhD Thesis. Moscow; 2003. 25 p. (In Russ.).
94. Bichenov R.G., Slepushkin V.D., Mildzikhov G.K. Effect of dalargin on gas exchange functions of the lungs in newborns with respiratory distress syndrome. Proceedings of the VI Congress of Pediatricians of Russia. Moscow; 2000. P. 61–62. (In Russ.).
95. Shmakov A.N., Danchenko S.V., Kasymov V.A. Dalargin in intensive therapy of children in critical conditions. *Children's medicine of the North-West*. 2012;3(1):41–44. (In Russ.).
96. Shmakov A.N., Kasymov V.A., Kasymov V.A., Kokhno V.N. Adjuvants to the treatment of acute cerebral insufficiency in newborns. *S.S. Korsakov Journal of Neurology and Psychiatry*. 2011;111(2):60–63. (In Russ.).
97. Brindle M.E., McDiarmid C., Short K., Miller K., MacRobie A. et al. Consensus guidelines for perioperative care in neonatal intestinal surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. *World J Surg*. 2020;44(8):2482–2492. https://doi.org/10.1007/s00268-020-05530-1.
98. Rao S.C., Basani L., Simmer K., Samnakay N., Deshpande G. Peritoneal drainage versus laparotomy as initial surgical treatment for perforated necrotizing enterocolitis of spontaneous intestinal perforation in preterm low birth weight infants. *Cochrane Database Syst Rew*. 2011;(6):CD006182. https://doi.org/10.1002/14651858.CD006182.pub2.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

99. Park J.S., Jeong S.-A., Seo J.H., Lim J.Y., Woo H.O., Youn H.S., Park C.-H. Risk factors and effects of severe late-onset hyponatremia on long-term growth of prematurely born infants. *Pediatr Gastroenterol Hepatol Nutr*. 2020;23(5):472–483. https://doi.org/10.5223/pghn.2020.23.5.472.
100. Budarova K.V., Shmakov A.N., Sirota S.I. Comparison of information value of the scale estimating multiple organ failure in newborns with necrotizin enterocolitis. *Russian Journal of Pediatric Surgery, Anesthesia and Intensive Care*. 2017;VII(3):81–85. (In Russ.). EDN: ZXHMRZ.
101. Budarova K.V., Shmakov A.N., Elizar'eva N.L., Kokhno V.N. Objectification of the prognosis of postoperative outcomes in abdominal surgery of the newborn. *Annals of Critical Care*. 2019;(3):65–68. (In Russ.). https://doi.org/10.21320/1818-474X-2019-3-65-68.
102. Budarova K.V., Shmakov A.N., Elizaryeva N.L., Kokhno V.N. Prognostic model as a method of formalization the results of the outcomes of critical conditions in newborn surgery. *Sibirskij Medicinskij Vestnik*. 2018;(3):3–8. (In Russ).
103. Janota J., Simak J., Stranak Z., Matthews T., Clarke T., Corcoran D. Critically ill newborns with multiple organ dysfunction: assessment by NEOMOD score in a tertiary NICU. *Irish J Med Sci*. 2008;177(1):11–17. https://doi.org/10.1007/s11845-008-0115-5.
104. Wynn J.L., Kelly M.S., Benjamin D.K., Clark R.H., Greenberg R., Benjamin Jr. D.K., Smith P.B. Timing of multiorgan dysfunction among hospitalized infants with fatal fulminant sepsis. *Am J Perinatol*. 2017;34(7):633–639. https://doi.org/10.1055/s-0036-1597130.
105. Matics T.J., Sanchez-Pinto L.N. Adaptation and validation of a pediatric sequential organ failure assessment score and evaluation of the Sepsis-3 definitions in critically ill children. *JAMA Pediatr*. 2017;171(10):e172352. https://doi.org/10.1001/jamapediatrics.2017.2352.

ЛИТЕРАТУРА

1. Александрович Ю.С., Иванов Д.О., Пшениснов К.В. Сепсис новорожденных. СПб.: СПбГПМУ; 2018. 176 с.
2. Xiong T., Maheshwari A., Neu J., Ei-Saie A., Pammi M. An overview of systematic reviews of randomized-controlled trials for preventing necrotizing enterocolitis in preterm infants. *Neonatology*. 2020;117(1):46–56. https://doi.org/10.1159/000504371.
3. Майер Р.Ф., Обладен М. Интенсивная терапия новорожденных. Доказательность и опыт. Пер. с нем. М.: МЕДпресс-информ; 2021. С. 140–231.
4. Isayama T., Lee S.K., Mori R., Kusuda S., Fujimura M., Ye X.Y. et al. Comparison of mortality and morbidity of very low birth weight infants between Canada and Japan. *Pediatrics*. 2012;130(4):e957–e965. https://doi.org/10.1542/peds.2012-0336.
5. Alsaied A., Islam N., Thalib L. Global incidence of necrotizing enterocolitis: a systematic review and Meta-analysis. *BMC Pediatr*. 2020;20(1):344. https://doi.org/10.1186/s12887-020-02231-5.
6. Панкратьева Л.Л., Володин Н.Н. Методологические проблемы реабилитации недоношенных детей. *Педиатрия*. 2019;98(2):14–18. https://doi.org/10.24110/0031-403X-2019-98-2-14-18.
7. Jin Y.T., Duan Y., Deng X.K., Lin J. Prevention of necrotizing enterocolitis in premature infants — an updated review. *World J Clin Pediatr*. 2019;8(2):23–32. https://doi.org/10.5409/wjcp.v8.i2.23.
8. Roberts A.G., Younge N., Greenberg R.G. Neonatal necrotizing enterocolitis: an update on pathophysiology, treatment, and prevention. *Paediatr Drugs*. 2024;26(3):259–275. https://doi.org/10.1007/s40272-024-00626-w.
9. Wu S., Di S., Liu T., Shi Y. Emerging prediction methods for early diagnosis of necrotizing enterocolitis. *Front Med (Lausanne)*. 2022;9:985219. https://doi.org/10.3389/fmed.2022.985219.
10. Fundora J.B., Guha P., Shores D.R., Pammi M., Maheshwari A. Intestinal dysbiosis and necrotizing enterocolitis: assessment for causality using bradford hill criteria. *Pediatr Res*. 2020;87:235–248. https://doi.org/10.1038/s41390-019-0482-9.
11. Kim S., Oh Y., Son J. et al. Machine learning-based analysis for prediction of surgical necrotizing enterocolitis in very low birth weight infants using perinatal factors: a nationwide cohort study. *Eur J Pediatr*. 2024;183(6):2743–2751. https://doi.org/10.1007/s00431-024-05505-7.
12. Shulhan J., Dicken B., Hartling L., Larsen B.M. Current knowledge of necrotizing enterocolitis in preterm infants and the impact of different types of enteral nutrition products. *Adv Nutr An Int Rev J*. 2017;8(1):80–91. https://doi.org/10.3945/an.116.013193.
13. AlFaleh K., Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Cochrane Database Syst Rev*. 2014;(4):CD005496. https://doi.org/10.1002/14651858.CD005496.pub4.
14. Gidrewicz D.A., Fenton T.R. A systematic review and meta-analysis of the nutrient content of preterm and term breast milk. *BMC Pediatr*. 2014;14:216. https://doi.org/10.1186/1471-2431-14-216.
15. Hartel C., Hartz A., Pagel J. et al. NOD 2 loss-of-function mutations and risk of necrotizing enterocolitis or focal intestinal perforation in very low-birth-weight infants.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

Inflamm Bowel Dis. 2016;22(2):249–256. https://doi.org/10.1097/MIB.0000000000000658.
16. Kessler U., Schulte F., Cholewa D., Nelle M., Schaefer S.C., Klimek P.M. Outcome in neonates with necrotizing enterocolitis and patent ductus arteriosus. *World J Pediatr*. 2016;12(1):55–59. https://doi.org/10.1007/s12519-015-0059-6.
17. Kort E.J. Patent Ductus arteriosus in the preterm infant: an update on morbidity and mortality. *Curr Pediatr Rev*. 2016;12(2):98–105. https://doi.org/10.2174/1573396312666160506001621.
18. Morgan J., Young L., Mc Guire W. Slow advancement of enteral feed volumes to prevent necrotizing enterocolitis in very low birth weight infants. *Cochrane Database Syst Rew*. 2015;(10):CD001241. https://doi.org/10.1002/14651858.CD001241.pub6.
19. Hackam D.J., Sodhi C.P. Bench to bedside — new insights into the pathogenesis of necrotizing enterocolitis. *Nat Rev Gastroenterol Hepatol*. 2022;19(7):468–479. https://doi.org/10.1038/s41575-022-00594-x.
20. Mani S., Garg P.M., Pammi M. Do hematological biomarkers predict surgical necrotizing enterocolitis? *Pediatr Res*. 2024;95(7):1680–1682. https://doi.org/10.1038/s41390-024-03066-x.
21. Cuna A., Morowitz M.J., Sampath V. Early antibiotics and risk for necrotizing enterocolitis in premature infants: A narrative review. *Front Pediatr*. 2023;11:1112812. https://doi.org/10.3389/fped.2023.1112812.
22. Dierikx T.H., Deianova N., Groen J. et al. Association between duration of early empiric antibiotics and necrotizing enterocolitis and late-onset sepsis in preterm infants: a multicenter cohort study. *Eur J Pediatr*. 2022;181(10):3715–3724. https://doi.org/10.1007/s00431-022-04579-5.
23. Lau C.S., Chamberlain R.S. Probiotic administration can prevent necrotizing enterocolitis in preterm infants: a meta-analysis. *J Pediatr Surg*. 2015;50(8):1405–1412. https://doi.org/10.1016/j.jpedsurg.2015.05.008.
24. Hui Y., Smith B., Mortensen M.S., Krych L., Sørensen S.J., Greisen G., Krogfelt K.A., Nielsen D.S. The effect of early probiotic exposure on the preterm infant gut microbiome development. *Gut Microbes*. 2021;13(1):1951113. https://doi.org/10.1080/19490976.2021.1951113.
25. Havranek T., Rahimi M., Hall H., Armbrecht E. Feeding preterm neonates with patent ductus arteriosus (PDA): Intestinal blood flow characteristics and clinical outcomes. *J Matern Neonatal Med Informa Healthcare*. 2015;28(5):526–530. https://doi.org/10.3109/14767058.2014.923395.
26. Mitra S., Scrivens A., von Kursell A.M., Disher T. Early treatment versus expectant management of hemodynamically significant patent ductus arteriosus for preterm infants. *Cochrane Database Syst Rev*. 2025;6(6):CD013278. https://doi.org/10.1002/14651858.CD013278.pub3.
27. Mitra S., de Boode W.P., Weisz D.E., Shah P.S. Interventions for patent ductus arteriosus (PDA) in preterm infants: an overview of Cochrane Systematic Reviews. *Cochrane Database Syst Rev*. 2023;11;4(4):CD013588. https://doi.org/10.1002/14651858.CD013588.pub2.
28. Каплина А.В., Петрова Н.А., Первунина Т.М., Хавкин А.И., Сурков А.Н., Назаренко Л.И. и др. Некротизирующий энтероколит: особенности патогенеза и дифференциальная диагностика с воспалительными заболеваниями кишечника у новорожденных. *Вопросы современной педиатрии*. 2024;23(6):438–446. https://doi.org/10.15690/vsp.v23i6.2830.
29. Zozaya C., González G., Avila-Alvarez A. et al. Incidence, treatment, and outcome trends of necrotizing enterocolitis in preterm infants: a multicenter cohort study. *Front Pediatr*. 2020;8:188. https://doi.org/10.3389/fped.2020.00188.
30. Lu P., Gong X., Gu X., Jiang S., Cao Y., Sun C. et al. Mortality and extrauterine growth restriction of necrotizing enterocolitis in very preterm infants with heart disease: a multicenter cohort study. *Eur J Pediatr*. 2024;183(8):3579–3588. https://doi.org/10.1007/s00431-024-05599-z.
31. Walsh M.C., Kliegman R.M. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatr Clin North Am.* 1986;33(1):179–201. https://doi.org/10.1016/s0031-3955(16)34975-6.
32. Jia L., Li Z., Zhu H., Ye X., Luo S., Wang Q. The diagnostic value of abdominal ultrasound in the progression of necrotizing enterocolitis in low-birth-weight neonates. *Medicine (Baltimore)*. 2025;104(43):e45427. https://doi.org/10.1097/MD.0000000000045427.
33. Chen S., Hu Y., Liu Q., Li X., Wang H., Wang K. Comparison of abdominal radiographs and sonography in prognostic prediction of infants with necrotizing enterocolitis. *Pediatr Surg Int*. 2018;34(5):535–541. https://doi.org/10.1007/s00383-018-4256-y.
34. Chen J., Mu F., Gao K., Yan C., Chen G., Guo C. Value of abdominal ultrasonography in predicting intestinal resection for premature infants with necrotizing enterocolitis. *BMC Gastroenterol*. 2022;22(1):524. https://doi.org/10.1186/s12876-022-02607-0.
35. May L.A., Epelman M., Daneman A. Ultrasound for necrotizing enterocolitis: how can we optimize imaging and what are the most critical findings? *Pediatr Radiol*. 2023;53(7):1237–1247. https://doi.org/10.1007/s00247-022-05545-x.
36. Hegedus C., Essex C., Vincent K., Shiflett A., Spence L., Hill J., Chetta K.E. A standardized universal protocol for using adjunct abdominal ultrasound at the time of diagnosis for suspected necrotizing enterocolitis. *Pediatr*

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

Radiol. 2025;55(13):2823–2831. https://doi.org/10.1007/s00247- 025-06408-x.
37. Agakidou E., Agakidis C., Gika H., Sarafidis K. Emerging biomarkers for prediction and early diagnosis of necrotizing enterocolitis in the era of metabolomics and proteomics. *Front Pediatr*. 2020;8(8):602255. https://doi.org/10.3389/fped.2020.602255.
38. ElMeneza S., Okasha A., El-Hafez M.A., Hussein N. Ischemia-modified albumin as a novel marker for diagnosis of necrotizing enterocolitis in newborn infants. *J Pediatr Neonat Individual Med*. 2021;10(2):e100205. https://doi.org/10.7363/100205.
39. Chaaban H., Shin M., Sirya E., Lim Y.-P., Caplan M., Padbury J.F. Inter-alpha inhibitor protein level in neonates predicts necrotizing enterocolitis. *J Pediatr*. 2010;157(5):757–761. https://doi.org/10.1016/j.jpeds.2010.04.075.
40. Goldstein G.P., Sylvester K.G. Biomarker discovery and utility in necrotizing enterocolitis. *Clin Perinatol*. 2019;46(1):1–17. https://doi.org/10.1016/j.clp.2018.10.001.
41. Sharif S.P., Friedmacher F., Amin A., Zaki R.A., Hird M.F., Khashu M., Phelps S.R. Low serum albumin concentration predicts the need for surgical intervention in neonates with necrotizing enterocolitis. *J Pediatr Surg*. 2020;55(12):2625–2629. https://doi.org/10.1016/j.jpedsurg.2020.07.003.
42. Palleri E., Frimmel V., Fläring U. et al. Hyponatremia at the onset of necrotizing enterocolitis is associated with intestinal surgery and higher mortality. *Eur J Pediatr*. 181(4):1557–1565. https://doi.org/10.1007/s00431-021-04339-x.
43. Arbra C.A., Oprisan A., Wilson D.A., Ryan R.M., Lesher A.P. Time to reintroduction of feeding in infants with nonsurgical necrotizing enterocolitis. *J Pediatr Surg*. 2018;53:1187–1191. https://doi.org/10.1016/j.jpedsurg.2018.02.082.
44. Гайтон А.К., Холл Дж.Э. Медицинская физиология. Пер. с англ. М.: Логосфера; 2024. 1344 с.
45. Vincent J.-L. Textbook of critical care (7th edit.; b II). Elsevier; 2017. P. 1192–1200.
46. Ионов О.В., Балашова Е.Н., Ленюшкина А.А., Киртбая А.Р., Кухарцева М.В., Зубков В.В. Сравнение двух стартовых схем — быстрого и медленного увеличения объема энтерального питания у новорожденных с очень низкой массой тела в условиях отделения реанимации и интенсивной терапии. *Неонатология: новости, мнения, обучение*. 2015;4(10):73–81.
47. Sadrudin Premji S., Chessell L., Stewart F. Continuous nasogastric milk feeding versus intermittent bolus milk feeding for preterm infants less than 1500 grams. *Cochrane Database Syst Rev*. 2021;6(6):CD001819. https://doi.org/10.1002/14651858.CD001819.pub3.
48. Robinson D.T., Calkins K.L., Chen Y. et al. Guidelines for parenteral nutrition in preterm infants: the American society for parenteral and enteral nutrition. *JPEN J Parenter Enteral Nutr*. 2023;47(7):830–858. https://doi.org/10.1002/jpen.2550.
49. Phongpreecha T., Ghanem M., Reiss J.D. et al. AI-guided precision parenteral nutrition for neonatal intensive care units. *Nat Med*. 2025;31(6):1882–1894. https://doi.org/10.1038/s41591-025-03601-1.
50. Asfour S.S, Alshaikh B., AlMahmoud L. et al. SMOFlipid impact on growth and neonatal morbidities in very preterm infants. *Nutrients*. 2022;14(19):3952. https://doi.org/10.3390/nu14193952.
51. Hu X., Liang H., Li F., Zhang R., Zhu Y., Zhu X., Xu Y. Necrotizing enterocolitis: current understanding of the prevention and management. *Pediatr Surg Int*. 2024;10;40(1):32. https://doi.org/10.1007/s00383-023-05619-3.
52. Evidence-Based Medicine Group. Clinical guidelines for the diagnosis and treatment of neonatal necrotizing enterocolitis. *Zhongguo Dang Dai Er Ke Za Zhi*. 2021;23(1):1–11. https://doi.org/10.7499/j.issn.1008-8830.2011145.
53. Белобородов В.Б., Голощапов О.В., Гусаров В.Г., Дехнич А.В., Замятин М.Н., Золотухин К.Н. и др. Диагностика и антимикробная терапия инфекций, вызванных полирезистентными микроорганизмами (обновление 2024 года). *Вестник анестезиологии и реаниматологии*. 2025;22(2):149–189. https://doi.org/10.24884/2078-5658-2025-22-2-149-189.
54. Pace E., Yanowitz T.D., Waltz P., Morowitz M.J. Antibiotic therapy and necrotizing enterocolitis. *Semin Pediatr Surg*. 2023;32(3):151308. https://doi.org/10.1016/j.sempedsurg.2023.151308.
55. Janaillac M., Beausoleil T.P., Barrington K.J., Raboisson M.-J., Karam O., Dehaes M., Lapointe A. Correlations between near-infrared spectroscopy, perfusion index, and cardiac outputs in extremely preterm infants in the first 72 h of life. *Eur J Pediatr*. 2018;177(4):541–550. https://doi.org/10.1007/s00431-018-3096-z.
56. El-Khuffash A., McNamara P.J. Hemodynamic assessment and monitoring of premature infants. *Clin Perinatol*. 2017;44(2):377–393. https://doi.org/10.1016/j.clp.2017.02.001.
57. Laan M.E., Roofthooft M.T.R., Fries M.W.A., Schat T.E., Bos A.F., Berger R.M.F., Kooi E.M.W. Multisite Tissue oxygenation monitoring indicates organ-specific flow distribution and oxygen delivery related to low cardiac output in preterm infants with clinical sepsis. *Pediatr Crit Care Med*. 2016;17(8):764–771. https://doi.org/10.1097/PCC.0000000000000833.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

58. Johnston N., Waal de K. Clinical and haemodynamic characteristics of preterm infants with early onset sepsis. *J Paediatr Child Health*. 2022;58(12):2267–2272. https://doi.org/10.1111/jpc.16218.
59. Nissimov S., Joye S., Kharrat A., Zhu F., Ripstein G., Baczynski M. et al. Dopamine or norepinephrine for sepsis-related hypotension in preterm infants: a retrospective cohort study. *Eur J Pediatr.* 2023;182(3):1029–1038. https://doi.org/10.1007/s00431-022-04758-4.
60. Khalesi N., Choobdar F.A., Khorasani M. et al. Accuracy of oxygen saturation index in determining the severity of respiratory failure among preterm infants with respiratory distress syndrome. *J Matern Fetal Neonatal Med*. 2021;34(14):2334–2339. https://doi.org/10.1080/14767058.2019.1666363.
61. Rawat M., Chandrasekharan P.K., Williams A. et al. Oxygen saturation index and severity of hypoxic respiratory failure. *Neonatology*. 2015;107(3):161–166. https://doi.org/10.1159/000369774.
62. Severinghaus J.W., Kelleher J.F. Recent developments in pulse oximetry. *Anesthesiology*. 1992;76(6):1018–1038. https://doi.org/10.1097/00000542-199206000-00024.
63. Agakidou E., Chatziioannidis I., Kontou A., Stathopoulou T., Chotas W., Sarafidis K. An update on pharmacologic management of neonatal hypotension: when, why, and which medication. *Children (Basel)*. 2024;11(4):490. https://doi.org/10.3390/children11040490.
64. Клинические рекомендации. Неонатология. Володин Н.Н., Дегтярев Д.Н., Крючко Д.С., ред. М.: ГЭОТАР-Медиа; 2020. 320 с.
65. Антонов А.Г., Авдеева О.В., Бабака О.А. и др. Неонатология: клинические рекомендации. Володин Н.Н. и др., ред. М.: ГЭОТАР-Медиа; 2019. 319 с.
66. Dini G., Ceccarelli S., Celi F. Strategies for the prevention of bronchopulmonary dysplasia. *Front Pediat*. 2024:12:1439265. https://doi.org/10.3389/fped.2024.1439265.
67. Александрович Ю.С., Пшениснов К.В. Респираторная поддержка при критических состояниях в педиатрии и неонатологии. М.: ГЭОТАР-Медиа; 2020. 288 с.
68. Thome U.H., Genzel-Boroviczeny O., Bohnhorst B., Schmid M. et al. PHELBI Study Group Permissive hypercapnia in extremely low birthweight infants (PHELBI): a randomized controlled multicentre trial. *Lancet Respir Med*. 2015;3(7):534–543. https://doi.org/10.1016/S2213-2600(15)00204-0.
69. Ackermann B.W, Klotz D., Hentschel R., Thome U.H., Kaam A.H. High-frequency ventilation in preterm infants and neonates. *Pediatr Res*. 2023;93(7):1810–1818. https://doi.org/10.1038/s41390-021-01639-8.
70. Nof E., Heller-Algazi M., Coletti F., Waisman D., Josué S. Ventilation-induced jet suggests biotrauma in reconstructed airways of the intubated neonate. *J R Soc Interface*. 2020;17(162):20190516. https://doi.org/10.1098/rsif.2019.0516.
71. Abdel-Hady H., Shouman B. Permissive hypercapnia in extremely low-birthweight infants: how far should we go? *Acta Paediatr*. 2017;106(6):1011. https://doi.org/10.1111/apa.13727.
72. Шмаков А.Н., Бударова К.В., Елизарьева Н.Л., Кохно В.Н. Оценка эффектов аппаратного мертвого пространства, создаваемого тепловлагосберегающим фильтром, при искусственной вентиляции легких у новорожденных. *Сибирский научный медицинский журнал*. 2022;42(5):69–72. https://doi.org/10.18699/SSMJ20220509.
73. Александрович Ю.С., Печуева О.А., Пшениснов К.В., Хиенас В. Оценка эффективности маневра рекруитмента при респираторном дистресс-синдроме у недоношенных новорожденных. *Неонатология: новости, мнения, обучение*. 2014;4(6):87–93.
74. Tsurukawa S., Zuiki M., Naito Y., Kitamura K., Matsumura U., Kanayama T. et al. Oxygenation saturation index in neonatal hypoxemic respiratory failure. *Pediatr Int*. 2024;66(1):715–753. https://doi.org/10.1111/ped.15753.
75. Реанимация и стабилизация состояния новорожденных детей в родильном зале. Методическое письмо. Е.Н. Байбарина, ред. (М.; 2020). *Неонатология: новости, мнения, обучение*. 2020;8(1):34–52.
76. Прометной Д.В., Александрович Ю.С., Пшениснов К.В. Перегрузка жидкостью как предиктор летального исхода у детей в критическом состоянии. *Общая реаниматология*. 2019;15(1):12–26. https://doi.org/10.15360/1813-9779-2019-1-12-26.
77. Иванов Д.О., Козлова Л.В., Деревцов В.В., Прийма Н.Ф. Оценка состояния сердечно-сосудистой системы у новорожденных, рожденных с внутриутробной задержкой роста. *Трансляционная медицина*. 2016;3(5):53–63. https://doi.org/10.18705/2311-4495-2016-3-5-53-63.
78. Бударова К.В., Шмаков А.Н., Елизарьева Н.Л., Кохно В.Н. Закономерности реакции автономной нервной системы на инфузионную нагрузку в комплексе интенсивной терапии у детей: проспективное сравнительное исследование. *Вестник интенсивной терапии им. А.И. Салтанова*. 2022;(3):133–144. https://doi.org/10.21320/1818-474X-2022-3-133-144.
79. Li Y., Wang J., Bai Z., Chen J., Wang X., Pan J., Li X., Feng X. Early fluid overload is associated with acute kidney injury and PICU mortality in critically ill children. *Eur J Pediatr*. 2015;175(1):39–48. https://doi.org/10.1007/s00431-015-2592-7.
80. Ваземиллер О.А., Ваганов А.А., Голубенко Н.К. и др. Диагностика повреждения миокарда у недоношенных детей с транзиторной ишемией сердца в раннем

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

неонатальном периоде. *Российский вестник перинатологии и педиатрии*. 2019;64(5):38–43. https://doi.org/10.21508/1027-4065-2019-64-5-38-43.
81. Irmak K., Tuten N., Karaoglu G. et al. Evaluation of cord blood creatine kinase (CK), cardiac troponin T (cTnT), N-terminal-pro-B-type natriuretic peptide (NT-proBNP), and s100B levels in nonreassuring foetal heart rate. *J Matern Fetal Neonatal Med*. 2021;34(8):1249–1254. https://doi.org/10.1080/14767058.2019.1632285.
82. Бударова К.В., Шмаков А.Н. Значимость маркеров транзиторной ишемии миокарда и гемодинамической перегрузки у новорожденных в критическом состоянии. *Вестник анестезиологии и реаниматологии*. 2022;19(5):79–86. https://doi.org/10.21292/2078-5658-2022-19-5-79-86.
83. Бударова К.В., Шмаков А.Н., Сергеев С.А., Кохно В.Н., Елизарьева Н.Л. Диагностика и коррекция кардиоренального синдрома в неонатальной хирургии. *Children's Medicine of the North-West*. 2025;13(4):173–183. https://doi.org/10.56871/CmN-W.2025.56.14.013.
84. Первунина Т.М., Васичкина Е.С., Эрман М.В. Персонифицированный подход в ведении детей с кардиоренальным синдромом (сочетанные врожденные пороки сердца и почек). *Российский журнал персонализированной медицины*. 2023;3(2):77–81. https://doi.org/10.18705/2782-3806-2023-3-2-77-81.
85. Singh Y., Tissot C., Fraga M.V. International evidence-based guidelines on Point of Care Ultrasound (POCUS) for critically ill neonates and children issued by the POCUS Working Group of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC). *Crit Care*. 2020;24(1):65. https://doi.org/10.1186/s13054-020-2787-9.
86. Альянов И.А., Бударова К.В., Сирота С.И., Шмаков А.Н. Кумулятивный баланс инфузионной терапии новорожденных с некротическим энтероколитом. *Сибирский научный медицинский журнал*. 2018;38(3):66–70. https://doi.org/10.15372/SSMJ20180310.
87. Бударова К.В., Шмаков А.Н., Яковлева Ю.В. Объективизация выбора режима трансфузии альбумина у новорожденных при проведении интенсивной терапии. *Сибирский научный медицинский журнал*. 2025;45(2):142–150. https://doi.org/10.18699/SSMJ20250215.
88. Кучеров Ю.И., Жиркова Ю.В., Нассер М.М. Интраоперационная инфузионная терапия у новорожденных детей. *Детская хирургия*. 2018;22(3):130–134. https://doi.org/10.18821/1560-9510-2018-22-3-130-134.
89. Бударова К.В., Шмаков А.Н. Вариабельность ритма сердца при сердечно-легочной недостаточности у новорожденных. *Анестезиология и реаниматология*. 2021;(1):25–31. https://doi.org/10.17116/anaesthesiology202101125.
90. Кузник Б.И., Стуров В.Г., Максимова О.Г. Геморрагические и тромботические заболевания и синдромы у детей. Новосибирск: Наука; 2012. 456 с.
91. Шмаков А.Н., Бударова К.В., Данченко С.В. Зависимость гомеостаза новорожденных от качественного состава плановой инфузии. *Медицина: теория и практика.* 2018;3(4):222–226.
92. Заболотских И.Б., Чуприн С.В., Курзанов А.Н. Дозозависимые эффекты даларгина в анестезиологии и интенсивной терапии. *Вестник интенсивной терапии*. 2002;(4):50–52. EDN: QBTIAZ.
93. Любошевский П.А. Общая анестезия с применением даларгина и транексамовой кислоты при микроэндоскопических эндоназальных операциях. Автореф. … дис. канд. мед. наук. М.; 2003. 25 с.
94. Биченов Р.Г., Слепушкин В.Д., Мильдзихов Г.К. Влияние даларгина на газообменные функции легких у новорожденных с респираторным дистресс-синдромом. Материалы VI Конгресса педиатров России. М.; 2000. С. 61–62.
95. Шмаков А.Н., Данченко С.В., Касымов В.А. Даларгин в интенсивной терапии детей в критических состояниях. *Детская медицина Северо-Запада*. 2012;3(1):41–44.
96. Шмаков А.Н., Касымов В.А., Касымов В.А., Кохно В.Н. Адъюванты интенсивной терапии острой церебральной недостаточности новорожденных. *Журнал неврологии и психиатрии им. С.С. Корсакова*. 2011;111(2):60–63.
97. Brindle M.E., McDiarmid C., Short K., Miller K., MacRobie A. et al. Consensus guidelines for perioperative care in neonatal intestinal surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. *World J Surg*. 2020;44(8):2482–2492. https://doi.org/10.1007/s00268-020-05530-1.
98. Rao S.C., Basani L., Simmer K., Samnakay N., Deshpande G. Peritoneal drainage versus laparotomy as initial surgical treatment for perforated necrotizing enterocolitis of spontaneous intestinal perforation in preterm low birth weight infants. *Cochrane Database Syst Rew*. 2011;(6):CD006182. https://doi.org/10.1002/14651858.CD006182.pub2.
99. Park J.S., Jeong S.-A., Seo J.H., Lim J.Y., Woo H.O., Youn H.S., Park C.-H. Risk factors and effects of severe late-onset hyponatremia on long-term growth of prematurely born infants. *Pediatr Gastroenterol Hepatol Nutr*. 2020;23(5):472–483. https://doi.org/10.5223/pghn.2020.23.5.472.
100. Бударова К.В., Шмаков А.Н., Сирота С.И. Сравнительная оценка информативности шкал полиорганной недостаточности у новорожденных с некротизирующим энтероколитом. *Российский вестник детской хирургии,*

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

анестезиологии реаниматологии. 2017;VII(3):81–85. EDN: ZXHMRZ.
101. Бударова К.В., Шмаков А.Н., Елизарьева Н.Л., Кохно В.Н. Объективизация прогноза исходов послеоперационного периода в абдоминальной хирургии новорожденных. *Вестник интенсивной терапии имени А.И. Салтанова*. 2019;(3):65–68. https://doi.org/10.21320/1818-474X-2019-3-65-68.
102. Бударова К.В., Шмаков А.Н., Елизарьева Н.Л., Кохно В.Н. Прогностическая модель как способ формализации результатов исхода критических состояний в хирургии новорожденных. *Сибирский медицинский вестник*. 2018;(3):3–8.
103. Janota J., Simak J., Stranak Z., Matthews T., Clarke T., Corcoran D. Critically ill newborns with multiple organ dysfunction: assessment by NEOMOD score in a tertiary NICU. *Irish J Med Sci*. 2008;177(1):11–17. https://doi.org/10.1007/s11845-008-0115-5.
104. Wynn J.L., Kelly M.S., Benjamin D.K., Clark R.H., Greenberg R., Benjamin Jr. D.K., Smith P.B. Timing of multiorgan dysfunction among hospitalized infants with fatal fulminant sepsis. *Am J Perinatol*. 2017;34(7):633–639. https://doi.org/10.1055/s-0036-1597130.
105. Matics T.J., Sanchez-Pinto L.N. Adaptation and validation of a pediatric sequential organ failure assessment score and evaluation of the Sepsis-3 definitions in critically ill children. *JAMA Pediatr*. 2017;171(10):e172352. https://doi.org/10.1001/ jamapediatrics.2017.2352.

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Review

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Bronchopulmonary dysplasia: inflammation induced by exogenous factors and myeloid cells

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ABSTRACT. Inflammation in the immature lung, triggered by oxygen toxicity and the formation of reactive oxygen species early on, is the primary cause of bronchopulmonary dysplasia in premature infants. Inflammation is characterized by activation of the innate immune response, with migration of predominantly macrophages and neutrophils and the release of proinflammatory cytokines. The degree of damage and disruption of subsequent lung development determine the severity of bronchopulmonary dysplasia, which leads to limited lung function. Based on observational studies of premature infants and experimental work in preclinical models, it has been demonstrated that excessive stimulation of proinflammatory signaling pathways leads to lung injury, but at the same time, the physiological activation of these pathways underlies physiological lung growth. This pathophysiological concept explains why suppression of individual pathways leads to an imbalance in the complex signaling network in the immature lung, with more severe inflammation and lung injury affecting the alveolar, mesenchymal, and vascular compartments. Therefore, the number of available drugs with proven efficacy for the prevention of bronchopulmonary dysplasia is currently limited. Evidence is accumulating that global suppression of the inflammatory response with corticosteroids leads to more severe limitations in lung function later in life, despite its high short-term effectiveness in improving gas exchange. Therefore, a detailed analysis of the immunophenotypes of myeloid cells and their associated gene and immune signatures will be useful for understanding the cellular and molecular genetic mechanisms of disease development and progression.

KEYWORDS: *bronchopulmonary dysplasia, preterm infant, inflammation, differential gene expression, monocytes, macrophages, gene signatures, immune signatures, M1/M2 macrophages*

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Обзор

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Бронхолегочная дисплазия: воспаление, индуцированное экзогенными факторами и миелоидными клетками

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РЕЗЮМЕ. Воспаление в незрелых легких, спровоцированное кислородной токсичностью и образованием активных форм кислорода на начальном этапе, является основной причиной бронхолегочной дисплазии у недоношенных детей. Воспаление характеризуется активацией врожденного иммунного ответа с миграцией преимущественно макрофагов и нейтрофилов и высвобождением провоспалительных цитокинов. Степень повреждения и нарушение дальнейшего развития легких определяют тяжесть бронхолегочной дисплазии, которая приводит к ограничению функции легких. Основываясь на наблюдательных исследованиях недоношенных детей и экспериментальных работах на доклинических моделях, доказано, что чрезмерная стимуляция провоспалительных сигнальных путей приводит к повреждению легких, но в то же время физиологический статус активации этих путей является основой физиологического роста легких. Эта патофизиологическая концепция объясняет, почему подавление отдельных путей приводит к дисбалансу сложной сигнальной сети в незрелом легком с более тяжелым воспалением и повреждением легких, затрагивающим альвеолярные, мезенхимальные и сосудистые отделы. Именно поэтому количество доступных препаратов с подтвержденной эффективностью для профилактики бронхолегочной дисплазии пока ограничено. В настоящее время накапливаются доказательства того, что глобальное подавление воспалительной реакции кортикостероидами приводит к более серьезным ограничениям функции легких в дальнейшем, несмотря на высокую краткосрочную эффективность в улучшении газообмена. И поэтому детальный анализ особенностей иммунофенотипов миелоидных клеток и ассоциированных с ними генных и иммунных сигнатур будет полезен для понимания клеточных и молекулярно-генетических механизмов развития и прогрессирования заболевания.

КЛЮЧЕВЫЕ СЛОВА: *бронхолегочная дисплазия, недоношенный ребенок, воспаление, дифференциальная экспрессия генов, моноциты, макрофаги, генные сигнатуры, иммунные сигнатуры, M1/M2 макрофаги*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that develops in preterm infants [1–5]. BPD affects up to 70% of children born extremely preterm and represents the second most common chronic lung disease in children after bronchial asthma (BA) [4, 6]. Our understanding of BPD pathophysiology has evolved continuously since the condition was first described as pulmonary fibrosis and emphysema by W.H. Northway in 1967 [5–8]. The consequences of BPD can be long-lasting and severe. In childhood, they include susceptibility to respiratory infections, an elevated risk of BA, and delayed physical and neurodevelopmental growth. In adolescence and adulthood, BPD is associated with diminished lung function and physical working capacity, as well as chronic non-communicable diseases [4, 5, 8–13]. Given the growing number of surviving preterm infants and the stable incidence of BPD with no downward trend, improving the monitoring and prognostication of this disease is critically important [14–18]. Identifying targets that minimize primary lung injury in preterm infants and restrain the damaging immune response, thereby promoting early repair, constitutes a critically important and unresolved clinical challenge. Myeloid cells, acting as immunoregulators, can fulfill these functions in the developing lung [19–21].

This literature review provides a detailed analysis of the mechanisms of lung injury, starting with hyperoxia as a factor that triggers inflammation. It also examines the phenotypic diversity of monocytes and macrophages migrating to the focus of pulmonary inflammation and thoroughly characterizes the differential gene expression and gene and immune signatures underlying BPD development. The literature search was performed in the Medline, PubMed, PubMed Central, and ClinicalTrials.gov databases using keywords that included the following search strings: "bronchopulmonary dysplasia is inflammation of the lungs," "bronchopulmonary dysplasia, monocyte inflammation in the lungs," "bronchopulmonary dysplasia, macrophages, inflammation in the lungs," "bronchopulmonary dysplasia is an inflammation of the lungs and myeloid cells," "bronchopulmonary dysplasia, inflammation, hyperoxia," "bronchopulmonary dysplasia inflammation immune signatures," and "bronchopulmonary dysplasia inflammation gene signatures." The search in international databases was focused on the period from 2019 to 2025.

FROM HYPEROXIA TO INFLAMMATION

Bronchopulmonary dysplasia is a multifactorial disease, and exposure to hyperoxia in the lungs of preterm infants contributes to immune response dysregulation, impaired alveolarization, and abnormal vascular development [22–28]. The adverse effects of hyperoxia include the generation of reactive oxygen species (ROS), which negatively affect the immature lung. These ROS-induced effects lead to mitochondrial dysfunction, alterations in gene expression, and an inflammatory response with the migration of myeloid cells into the pulmonary parenchyma (Fig. 1).

Numerous studies demonstrate the effect of hyperoxia on gene expression. In a hyperoxic mouse model of BPD, the expression levels of the angiogenic markers *FOXF1* and *c-KIT* were reduced. *FOXF1* is a forkhead family transcription factor important for the development of lung and gastrointestinal tract mesenchyme, while *c-KIT* encodes a receptor tyrosine kinase that plays an important role in hematopoiesis. Hyperoxia exposure during the first seven days of life decreased the number of *c-KIT* endothelial progenitor cells. Adoptive transfer of *c-KIT* endothelial cells improved angiogenesis and alveolarization [29].

Substantial changes in expression across all cellular compartments were observed in the largest study to date of developing mice exposed to hyperoxia, conducted by M. Hurskainen et al. [20]. In the lung parenchyma, the authors identified transcriptomic shifts in myofibroblasts, pericytes, and *Col13a1* fibroblasts. Col13a1 encodes the alpha chain of one of the non-fibrillar collagens, and these fibroblasts were among the most active cells in the hyperoxic lung model. The study further revealed a significant depletion of endothelial cells and an increase in alveolar type 1 cells following hyperoxia exposure [20, 21].

C. Revhaug et al. identified changes in gene methylation and transcriptome regulation in the lungs of mice ventilated with 85% oxygen from birth for 14 days. The PI3K-AKT pathway (an intracellular signaling pathway important in cell cycle regulation), associated with the immune system and the inflammatory response, was identified as a major target. Suppression of this pathway

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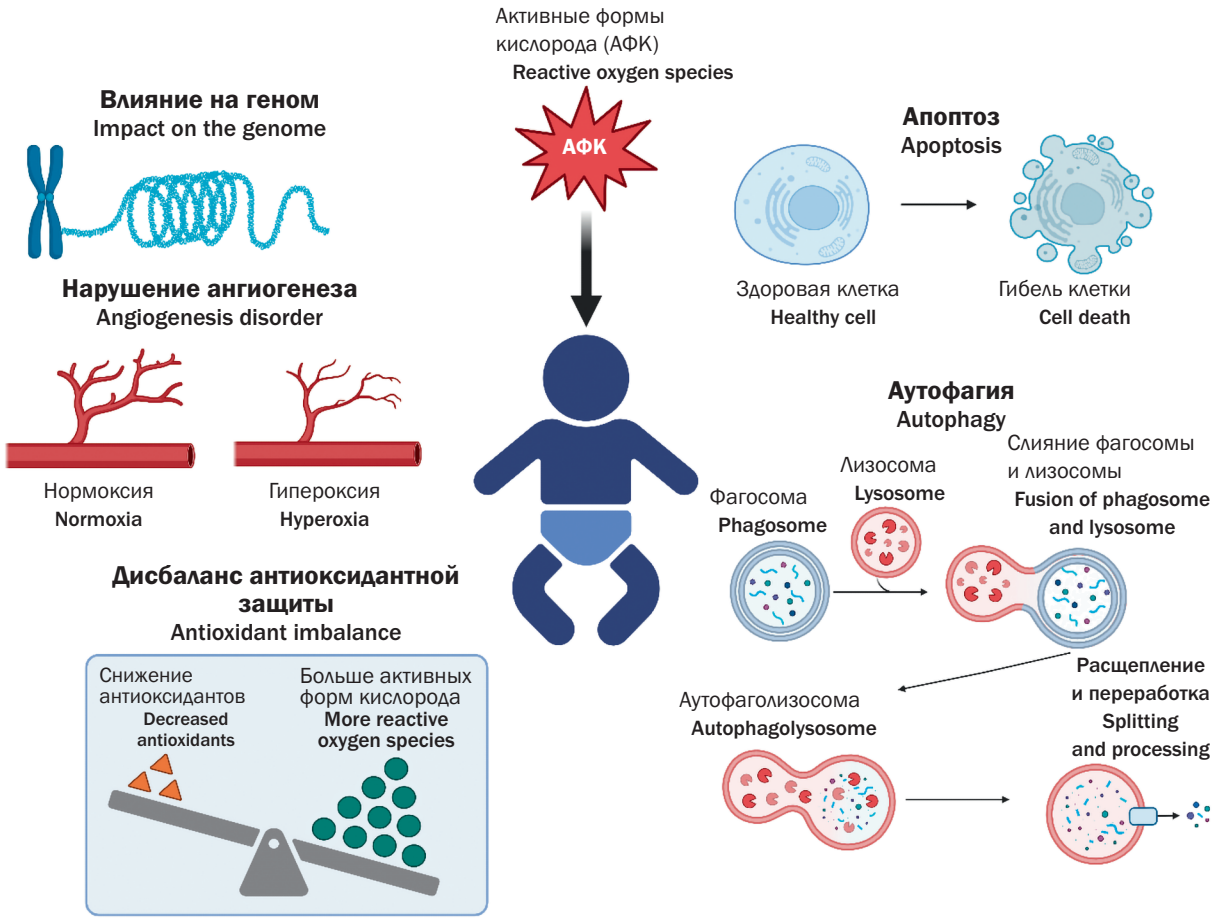

Fig. 1. The contribution of oxygen toxicity to the pathogenesis of bronchopulmonary dysplasia (created by I. Doroshenko, 2024)

Рис. 1. Вклад кислородной токсичности в патогенез бронхолегочной дисплазии (составлено И. Дорошенко, 2024)

contributed to increased susceptibility and an abnormal response to respiratory viruses [30].

In another experimental study conducted in 2017, the process of DNA methylation in genes involved in lung tissue growth and differentiation was analyzed. The researchers divided rat pups into two groups: group 1 was raised in room air (n=24), and group 2 was raised in an atmosphere containing 85% O_2 (n=26) from postnatal day 1 to 14. The rat pups exposed to hyperoxia had larger airspaces and thinner septa than those maintained in room air [31]. Further analysis revealed activation of the TGF-β signaling pathway involving key genes such as *TGFBR1, CREBBP,* and *CREB-1*. *CREBBP* functions as a transcriptional coactivator, linking various protein transactivators of transcription to the core transcriptional complex through protein–protein interactions, while *CREB-1* binds cyclic adenosine monophosphate (cAMP) and the DNA nucleotide sequence present in many viral and cellular promoters [31]. Overexpression of TGF-β1 during postnatal alveolarization in rat lungs leads to morphological, pathological, and biochemical changes corresponding to those observed in BPD in children.

IMBALANCE OF ANTIOXIDANT DEFENSE

When the balance between ROS production and antioxidant capacity is disrupted, oxidative reactions progress, ultimately resulting in cell and tissue damage through lipid peroxidation, DNA damage, and protein oxidation. The toxic effect of oxygen leads to the death of alveolar epithelium and capillary endothelium, the development of capillary dysplasia, impaired alveolarization, fibrosis, and pulmonary hypertension. It should be noted that the development of the antioxidant system occurs in parallel with surfactant synthesis during the third trimester of pregnancy; therefore,

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the lung cellular structures of preterm infants remain insufficiently protected against peroxidation processes [1–5].

Inadequate activity of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase) and endogenous antioxidants (vitamin E, glutathione, ceruloplasmin) has been reported [32]. Within the framework of antioxidant defense mechanisms, the transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2) represents a critical regulator of cellular defense mechanisms against xenobiotic and oxidative stress. However, studies show that the levels of antioxidants (vitamin A, vitamin E, and catalase) in preterm infants with BPD are significantly lower, whereas the level of malondialdehyde (a marker of lipid peroxidation), by contrast, is higher compared with term infants [8, 9, 32].

Research into the role of antioxidant enzymes such as SOD3 (superoxide dismutase 3) is ongoing. Notably, serum SOD3 levels are reduced in infants with extremely low birth weight, and the loss of SOD3 leads to dysregulation of gene expression involved in lung development [32].

Thus, at present, neonatal diseases can be classified as belonging to the spectrum of "oxygen radical diseases." Extremely preterm infants constitute a high-risk group due to the immaturity of their antioxidant system. Currently, active research continues not only into the role of the latter in the development of perinatal diseases but also into the design of therapeutic interventions [33].

IMPAIRED ANGIOGENESIS

Hypoxia-inducible factor HIF-1α is one of the principal transcription factors governing the expression of a number of genes required for cellular adaptation to hypoxia [34]. This factor regulates fetal growth and development under hypoxic conditions and is, therefore, rapidly degraded under hyperoxia or normoxia. Loss of HIF-1α in mice leads to embryonic lethality; the surviving embryos exhibit multiple cardiac malformations and abnormally dilated blood vessels.

VEGFA (vascular endothelial growth factor A) is a key factor in vascular development and a mediator of endothelial NO synthesis. Vascular growth encompasses two main processes: vasculogenesis, the formation of new blood vessels from endothelial cells in the mesenchyme, and angiogenesis, the formation of new blood vessels from sprouts of pre-existing vessels [15, 35]. Both hyperoxia and mechanical ventilation inhibit pro-angiogenic VEGF signaling in rodents and rabbits, and the inhibition of VEGF signaling is accompanied by reduced alveologenesis and angiogenesis in many animal species [35]. For example, the expression of VEGF and one of its receptors (VEGF-R1) is decreased in a BPD model in preterm baboons. Ventilation of two-day-old mice with 40% O_2 reduces the expression of VEGF-A and VEGF-R2 genes and proteins in the lungs and leads to structural lung abnormalities corresponding to BPD [35].

A number of studies demonstrate reduced levels of additional pro-angiogenic factors. Specifically, NO acts downstream of HIF and VEGFA in the signaling cascade and is suppressed by ROS-induced injury; ROS attenuate NO signaling and stimulate the growth and phenotypic modulation of smooth muscle cells, as well as pulmonary vascular remodeling. eNOS expression levels are decreased in lambs exposed to hyperoxia [23].

Reduced levels of Tie-2 (the angiopoietin receptor, expressed exclusively in endothelial cells of mice, rats, and humans) and Ang-1 (a member of the family of vascular growth factors that play a role in embryonic and postnatal angiogenesis) have been detected in preterm infants on mechanical ventilation. Moreover, Ang-1 expression is decreased in mouse pups exposed to hyperoxia [21, 23].

MYELOID CELL DYSFUNCTION

It has been shown that macrophage activation in mice with hyperoxia-induced BPD leads not only to epithelial cell apoptosis and pulmonary parenchymal injury but also affects fibroblasts and endothelial cells, causing matrix remodeling and impaired pulmonary vascularization [23]. The transcription factor Klf4 is known to participate in transcriptional regulation in many diseases, including BPD, and Klf4 can induce macrophage polarization by interacting with Stat6. Klf4 can influence not only monocyte differentiation but also the expression of genes characteristic of M1 and M2 macrophages, such as iNOS and Arg1 [36]. In a study by Y. He et al., increased M1 macrophage infiltration and decreased Klf4 expression were detected in the lungs of mice with BPD [24].

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C. Leek et al. found that immediately after birth and on day 7 of hyperoxia exposure, a significant reduction in the total number of alveolar macrophages (AMs) was observed in the hyperoxia-exposed lung compared with the normoxic control. This reduction was observed in both male and female mice. SiglecF-low AMs (SiglecF, sialic acid-binding Ig-like lectin F) represent monocyte-derived macrophages that exhibit an intermediate phenotype along the continuum of differentiation into AMs [37]. Siglecs (sialic acid-binding immunoglobulin-type lectins) are sialic acid-specific lectins with an immunoglobulin-like structure that interact with sialic acid on the cell surface. They are expressed predominantly by immune cells and regulate cell proliferation, differentiation, apoptosis, and intercellular interactions. Interestingly, the number of SiglecF-high AMs decreased following hyperoxia exposure, and this was followed by a corresponding increase in the number of SiglecF-low AMs. No depletion of AMs was observed by day 14 or day 21 in either female or male mice. On day 21, the number of interstitial macrophages in the hyperoxia-exposed lungs was reduced compared with the control group. Overall, neonatal hyperoxia exerts differential effects on the abundance of myeloid cell subpopulations, with the most marked changes observed in AMs [37].

MONOCYTES AND MACROPHAGES IN THE MECHANISMS OF BRONCHOPULMONARY DYSPLASIA DEVELOPMENT

To understand the early changes in the neonatal immune response that give rise to the persistent inflammation associated with BPD development at the cellular level and beyond, research attention has been focused on one of the inflammatory mechanisms — the characterization of monocyte subtypes at birth and throughout the neonatal period. Pulmonary monocytes and macrophages are key players in innate immunity that undergo a complex maturation process and, in newborns, perform diverse functions, including lipopolysaccharide (LPS)-induced activation, IFN-γ-mediated and IL-10-mediated responses, and Fc receptor-dependent phagocytosis [28, 38, 39]. Several macrophage immunophenotypes are distinguished. Thus, M1 macrophages represent a pro-inflammatory macrophage phenotype (classically activated), the key cells of innate immunity responsible for host defense. They are activated by interferon gamma (IFNγ) and lipopolysaccharides, eliminate pathogens (bacteria and viruses) and tumor cells, and produce reactive oxygen species and pro-inflammatory cytokines (TNF-α, IL-12). M2 macrophages represent a functional macrophage phenotype that mediates an anti-inflammatory response, tissue repair (regeneration), and the suppression of immune reactions. They are activated by IL-4 and IL-13, promote wound healing, tissue remodeling, and the clearance of apoptotic cells, and can also stimulate tumor growth.

A.C. Windhorst et al. established that monocyte subtypes differ between preterm and term neonates. Specifically, CD14++CD16+ (intermediate) monocytes were more frequently present in term infants, whereas elevated levels of non-classical monocytes (CD14+CD16++) were characteristic of preterm infants developing BPD. Both monocyte subtypes were the main source of intracellular TNF-α expression. Multifactorial modeling of protein profiles identified FGF2, sIL-2Rα, MCP-1, MIP-1a, and TNF-α as predictors of BPD. It has been confirmed that TNF-α, IL-6, and IFN-α are the most highly activated cytokines in severe BPD [40].

L.C. Eldredge et al. identified a predominance of CD14+CD16+ and CD14+CD16– monocytes in tracheal aspirates from ventilated patients with a gestational age of less than 29 weeks and aged less than 30 days. Moreover, the mRNA expression of IL-1A, IL-1B, and IL-1 receptor antagonist genes was elevated in monocytes obtained from tracheal aspirates on days 7, 14, and 28 of life compared with monocytes obtained on day 3 of life. This study confirms that early alterations in monocyte-specific pathways of the IL-1 cytokine family — a potent pro-inflammatory cytokine — may be associated with the development of BPD [41]. In contrast, low production of anti-inflammatory cytokines, particularly IL-10, is observed in the setting of BPD [42]. Comparable cytokine profiles can also be observed in animals (mice, sheep) receiving mechanical ventilation (hyperoxia).

It has been demonstrated that the development of BPD is associated with an increase in intermediate monocytes and the persistence of high levels of non-classical monocytes, as well as with high expression of TNF-α, IL-6, IL-8, MCP-1, MIP-1a, IL-1Rα, sIL-2Rα, EGF, and FGF2. The described signature (a unique molecular profile) is associated with monocyte activation, proliferation, chemotaxis, and myeloid cell

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recruitment [40]. These findings are consistent with transcriptome analysis, which revealed that TNF-α, IL-2, IL-6, IL-10, and interferons are the most highly activated cytokines in patients with moderate and severe BPD. With regard to the functional significance for BPD development, TNF-α and IFN-γ signaling are known to drive polarization of the pro-inflammatory monocyte and macrophage phenotype, enhancing the extravasation of these cells and the accumulation of AMs. Moreover, these cytokines exhibit considerable pro-fibrotic potential [43].

The picture of monocyte and granulocyte activation revealed by protein and transcriptome analyses is further illustrated by the activation network of genes involved in immune cell regulation, cell-matrix interactions, and remodeling (IL-6, TNF-α, CXCL9, LGALS3, MMP7, TLR3, IL-10, TCR, LAT) in BPD. The differential expression of genes involved in leukocyte chemotaxis and eosinophil accumulation (*CAT, CDH13, IL-10, LGALS3, TNFRSF1A, BID, TF, ZFP36)* was regulated by TNF-α [39]. Mild BPD manifestations were associated with the involvement of the Wnt1 pathway and increased IL-5 expression [44].

The predominance of non-classical and intermediate monocyte subtypes, confirmed by a characteristic transcriptome and protein signature, reflects processes critical for BPD development. The identification of distinct developmental pathways from circulating monocytes to lung macrophages highlights the potential of specific monocyte subtypes to make differential contributions to the populations of alveolar, interstitial, and pulmonary intravascular macrophages [45]. Whereas non-classical blood monocytes give rise to intravascular macrophages in the lungs, classical monocytes have been associated with interstitial and alveolar macrophages. Intermediate CD14+ monocytes expressing macrophage markers represent transitional stages of monocyte-to-macrophage differentiation. The role of macrophages, including their influence on growth factor production and their association with a pro-fibrotic phenotype, underscores their potential as critical regulators of BPD development [46].

INTERCELLULAR INTERACTIONS BETWEEN MACROPHAGES, ALVEOLAR EPITHELIAL CELLS, AND ENDOTHELIAL CELLS IN BRONCHOPULMONARY DYSPLASIA

Y. He et al. assessed intercellular communication and found that, among signal-sending cells, alveolar epithelial type I cells (AT1) exhibited the greatest number and strength of interactions with other cell types. In contrast, among signal-receiving cells, CAR4+ endothelial cells displayed the greatest interaction strength. It is known that pulmonary endothelial cells (ECs) are essential participants in gas exchange. Despite this, the extent and function of EC heterogeneity in the lungs remain incompletely understood. To date, several EC populations have been identified, including macrovascular endothelium (maEC), microvascular endothelium (miEC), and a novel population of Car4-high ECs. Car4-high ECs express a unique gene signature, and ligand–receptor analysis indicates that they are poised to receive reparative signals from AT1 cells. Following acute injury, they are predominantly localized to regenerating regions of the alveoli [24].

A close relationship exists between macrophages and alveolar epithelial cells. Macrophages participate in the following signaling pathways as signal-receiving cells.

- SEMA3 (the semaphorin-plexin signaling pathway, Sema3/Plexin) represents a series of molecular interactions initiated by the binding of semaphorin receptors (including plexins and neuropilins) to their ligands. This pathway plays a key role in the development of the nervous system, in particular by guiding axonal growth and contributing to the formation of neural connections. Beyond nervous system development, the semaphorin-plexin pathway is involved in the regulation of cell migration and angiogenesis, as well as in immune responses. For example, Sema3A, a member of the semaphorin family, has been studied for its effects on thymocyte (thymus cell) functions, including proliferation, migration, and adhesion.
- MIF (macrophage migration inhibitory factor) activates various signaling pathways that influence cell growth, survival, and the immune response. Key signaling pathways engaged by MIF include MAPK (ERK1/2) and NF-κB, as well as interactions with Toll-like receptor 4 (TLR4) and chemokine receptors. MIF can activate MAPK pathways such as ERK1/2, thereby promoting cell proliferation, including that of tumor cells. MIF activates the NF-κB pathway, leading to increased production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-8. MIF upregulates TLR4 expres-

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sion, which enhances the immune response to Gram-negative bacteria. MIF can interact with chemokine receptors (e.g., CXCR2 and CXCR4), thereby influencing cell migration. MIF can inhibit apoptosis (programmed cell death), which is important for maintaining cell survival under conditions of inflammation and tumor growth.

- GALECTINS (galectins) are a family of carbohydrate-binding proteins involved in various cellular processes, including adhesion, migration, proliferation, and apoptosis. Galectin signaling pathways, such as galectin-3/SMAD and galectin-9/Tim-3, play an important role in the development of diseases, including fibrosis and the immune response. *Galectin-3* and *the TGF-β/SMAD* signaling pathway — galectin-3 can activate this pathway, leading to fibrosis and scar tissue formation, and also promotes the translocation of transcription factors into the nucleus for collagen synthesis. The galectin-9/Tim-3 signaling pathway is an important regulatory mechanism for immune cells such as natural killer (NK) cells. Galectins, including galectin-1, galectin-3, galectin-9, and galectin-12, are involved in the development of leukemia by influencing the growth, differentiation, and survival of cancer cells.
- CXCL (chemokine (C-X-C motif) ligand) is a family of chemokines, proteins involved in the recruitment and activation of leukocytes (immune cells). They play an important role in inflammation, the immune response, the development of lymphoid organs, and other biological processes.
- CCL (C-C motif ligand, chemokines with a C-C motif) represents a subfamily of chemokines. The CCL subfamily, in particular, plays an important role in inflammatory processes, during infection, organ and tissue injury, and in lymphocyte migration. The CCL subfamily is characterized by the presence of two adjacent cysteines (without an intervening amino acid) in the amino acid sequence of the chemokines. CCL chemokines primarily attract monocytes, macrophages, eosinophils, and lymphocytes, thereby regulating the immune response to various pathological processes.

At the same time, macrophages act as signal senders, participating in GRN (Gene Regulatory Network) signaling pathways. These pathways represent a cascade of intracellular reactions initiated by the binding of a growth factor to its receptor on the cell surface. This pathway plays a key role in the regulation of cell growth, differentiation, survival, and many other cellular processes, as well as in CCL signaling.

MIF is a pleiotropic cytokine and one of the key factors in intercellular communication. MIF is antagonistic to glucocorticoids and prolongs the survival of inflammatory cells [47]. It should be noted that adequate MIF levels are required for lung development, since both MIF deficiency and overexpression in neonatal mice have been shown to cause alveolar and vascular abnormalities. It has been established that MIF signaling involves two pathways. MIF signaling between AT2 cells and endothelial cells may be required for alveolarization and angiogenesis, whereas the involvement of macrophages in MIF signaling following hyperoxia may promote inflammation and impair lung maturation [24].

In the control group, among all pro-inflammatory macrophages (CD86+), the Cybb protein was expressed in 60.1% of cells, whereas in patients with BPD it was expressed in only 4.6% ($p < 0.05$). Thus, Cybb expression in M1 macrophages is significantly reduced in BPD.

It was also established that in the control group, 86.5% of all Cybb-expressing cells simultaneously co-expressed the pro-inflammatory macrophage marker CD86. In BPD, this proportion was only 7.3% ($p < 0.05$). This indicates that the co-expression of Cybb and CD86, a marker of pro-inflammatory macrophages, is impaired in BPD [24].

It has been shown that alveolar epithelial cells actively interacted with macrophages via MIF-(CD74+CD44) signaling pathways. Macrophages were more active and engaged in more extensive interactions with alveolar epithelial cells in mice with BPD through MIF-(CD74+CD44) signaling. It should be noted that M1 macrophages play an important role in the development of lung injury in BPD. This role correlates with a specific reduction in Cybb gene expression and its end product in macrophages, as well as with the potential activation of MIF signaling pathways.

FEATURES OF THE GENETIC REGULATION OF INTERCELLULAR INTERACTIONS

It has been established that differentially expressed genes in mice with BPD are enriched for leukocyte migration and M1 macrophage infil-

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tration of the lungs. The influence of hub genes (*Cybb, Papss2, F7, Fpr2*) has been confirmed at the single-cell level. Specifically, reduced *Cybb* expression is associated with M1 macrophage infiltration. In an experimental study, Yi He et al. from China identified 16 hub genes associated with immune system function. Subsequently, single-cell identification analysis was performed using data from 65,733 cells (38,223 cells from the BPD group and 27,510 cells from the control group). It was shown that, of the 65,733 single cells, 2,492 were classified as alveolar macrophages and 5,447 as other macrophage types. Cell source analysis revealed that the *Cybb, Fpr2,* and *F7* genes were highly expressed in macrophages in both the BPD group and the control group. Among the total number of single cells, 12,615 cells expressed the *Cybb* gene (19.19%), representing the highest percentage among the three genes. At the next stage, to assess the functional role of the identified genes, the researchers evaluated hub gene expression between the BPD group and the control group using scRNA-seq data and demonstrated that *Cybb* gene expression was reduced in the BPD mouse group. Comparison of *Cybb* gene expression at the single-cell level between BPD mice and wild-type mice also showed that this reduction was primarily attributable to lower mean expression and a lower percentage of *Cybb*-positive cells in macrophages in BPD mice compared with wild-type mice. These results indicate that *Cybb* expression was predominantly reduced in macrophages under hyperoxic conditions [24]. It should be noted that hub genes are genes that play a key role in metabolic pathways, possess a large number of connections with other genes, and exert a significant influence on cell function. Alterations in the expression or activity of hub genes may be associated with specific diseases and conditions, making them useful for the diagnosis and monitoring of various diseases.

The CYBB protein, also known as NOX2 or gp91phox, is a transmembrane subunit of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, also referred to as cytochrome b-245 [48]. CYBB is a key component of NADPH oxidase, an enzyme complex that generates superoxide, a reactive oxygen species. CYBB is a transmembrane protein composed of two subunits: alpha and beta. Mutations in the *CYBB* gene lead to chronic granulomatous disease, since a deficiency of functional CYBB protein impairs the ability of immune cells to effectively combat infections. The CYBB protein is localized to cellular membranes, primarily within phagosomes (intracellular compartments where pathogen degradation takes place).

Cybb is a gene associated with enhanced inflammatory infiltration of lung tissue by macrophages. It encodes gp91phox (NOX2), a component of the phagocytic NADPH oxidase (NOX) family, which primarily generates ROS. *Cybb* is required not only for microbial killing and host defense but also for immune and inflammatory regulation. Studies have demonstrated an important role for *Cybb* in LPS-induced lung injury [24, 48, 49]. In particular, *Cybb* expression in macrophages appears to play a protective role in the aseptic inflammatory response. Germ-free *Cybb*-deficient mice developed spontaneous lung inflammation independently of the microbiota composition. Moreover, *Cybb*-deficient alveolar macrophages tended toward pro-inflammatory responses with an enhanced cytokine response and gave rise to an immunoactivated CD11bhigh subpopulation following sterile stimulation, such as with Toll-like receptor agonists [49]. In a mouse model of zymosan-induced systemic inflammatory response syndrome, *Cybb* deficiency in mice was associated with elevated chemokine levels, neutrophil infiltration, platelet activation, and thrombosis, suggesting an anti-inflammatory role for *Cybb*, particularly alveolar macrophage-derived *Cybb* [50]. Furthermore, *Cybb*-deficient macrophages exhibited enhanced transcriptional priming of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome. In addition, they triggered post-translational activation of NLRP3 through increased K^+ efflux and mitochondrial damage [51]. In a study by Y. He et al., a specific reduction in *Cybb* expression was detected in lung macrophages under hyperoxic conditions [24]. Such an abnormal pattern of *Cybb* expression under hyperoxia may adversely affect lung development and homeostasis. Interestingly, the *Cybb* gene, which is located on the X chromosome, may be responsible for sex-dependent BPD phenotypes.

INFLUENCE OF SEX ON THE TRANSCRIPTOME, DIFFERENTIATION, AND FUNCTIONS OF MACROPHAGES

Sex-dependent differences in macrophage diversity and function have been identified in many

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diseases [37, 52, 53]. In an experimental study, C. Leek et al. detected sex-specific differences in the differential gene expression (DGE) of macrophages. In female mice, 132 DEGs were identified (71 upregulated, 61 downregulated) compared with the normoxic control. In contrast, in male AMs, 58 DEGs were identified (26 upregulated, 32 downregulated) [37]. One of the highly expressed genes in hyperoxia-exposed AMs was the gene encoding extracellular matrix protein 1 (*ECM1*), which plays an important role in macrophage polarization. *ECM1* is actively expressed in macrophages, particularly in those infiltrating tissues under inflammatory conditions. Macrophage-specific knockout of *ECM1* increases the expression of arginase 1 (ARG1) and impairs polarization toward the M1 macrophage phenotype. Macrophage-specific knockout of *ECM1* ameliorates pathological changes in a mouse model of inflammatory bowel disease, highlighting the importance of *ECM1* in M1 macrophage polarization. The expression of the *Fcna* gene (Ficolin A) is also increased in hyperoxia-exposed AMs; it mediates complement activation and enhances pro-inflammatory responses in the lungs [37].

The gene encoding fatty acid-binding protein 4 (Fabp4) is an adipokine and one of the most strongly suppressed genes; it regulates inflammation and angiogenesis. Interestingly, Fabp4 expression was increased in peribronchial vessels of neonates with BPD and enhanced angiogenesis [54]. The gene encoding pyruvate dehydrogenase kinase 4 (Pdk4) was also suppressed in hyperoxia-exposed AMs. Pdk4 plays an important role in the metabolic reprogramming of macrophages [55, 56]. The DEGs identified in the study by C. Leek et al. were associated with the cell cycle, DNA integrity and apoptosis, myeloid cell differentiation, leukocyte migration, and interferon-beta production. Macrophages play a key role in interferon signaling owing to their dual function: they serve as important producers of interferon and exhibit high sensitivity to it [37].

In the study by C. Leek et al., one of the unique genes with increased expression in female AMs was the prolactin receptor gene *Prlr* (prolactin receptor), which is expressed in macrophages and modulates local inflammatory responses, angiogenesis, phagocytosis of apoptotic cells, and cytokine production [37]. Prolactin has been shown to increase heme oxygenase-1 expression and vascular endothelial growth factor production in human macrophages, indicating its potential role in angiogenesis. In males, AMs exhibited increased expression of the gene encoding secreted phosphoprotein 1 (*Spp1*). *Spp1*, or osteopontin, is an arginine-glycine-aspartate-containing adhesive glycoprotein produced by AMs [57]. *Spp1* plays an important role in the recruitment and accumulation of myeloid cells at sites of injury. *Spp1* in lung macrophages stimulates fibrotic processes and macrophage polarization toward a pro-fibrotic phenotype [57].

In the study by C. Leek et al., it was found that pathways associated with DNA damage and IFN-β, glucose and carbohydrate metabolism, ossification, and aging were positively enriched in AMs from female mice. In contrast, oxidative phosphorylation and the tricarboxylic acid cycle were negatively enriched in AMs from male mice [37]. Loss of Klf4 increased macrophage polarization similarly to that observed with LPS or IFN-γ stimulation, and hyperoxia reduced Klf4 expression in macrophages *in vitro*. Interferon regulatory factors play a crucial role in macrophage function and differentiation. *Irf1* plays an important role in enhancing the myeloid cell response to IFN-γ and in myeloid cell development. *Irf2* inhibits the expression of glycolytic genes and pro-inflammatory responses. *Irf4* is critically important for the synergistic macrophage response induced by IL-4. Runx2, a transcription factor known primarily for its role in bone metabolism, also substantially influences macrophage function, particularly during inflammation and tissue remodeling. The expression levels of these transcription factors in male and female AMs did not differ according to sex or treatment, suggesting that transcription factors may bind differently to chromatin in male and female AMs under hyperoxic conditions.

Furthermore, C. Leek et al. assessed the influence of sex on AM gene activity across all developmental periods. They found that three genes exhibited high expression in hyperoxia-exposed females: integrin subunit alpha M (*ITGAM*, the gene encoding CD11b protein), C-type lectin domain family 5 member A (Clec5a), and guanylate binding protein 3 (*Gbp3)* [37]. *ITGAM* and CD11b play an important role in macrophage functions, including adhesion, migration, and phagocytosis. Guanylate binding protein 3 (Gbp3) is a member of the guanylate binding protein (GBP) family, a group of intracellular guanosine triphosphatases

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induced by IFN-γ. It also plays a role in macrophage activation and the immune response [58]. *Clec5a* modulates macrophage function and contributes to the pathophysiology of chronic lung diseases, including chronic obstructive pulmonary disease [59, 60]. No differentially expressed genes were detected in male AMs in response to hyperoxia.

Chromatin remodeling was more pronounced in female prenatal myeloid cells, whereas the Wnt signaling pathway was more pronounced in males. Postnatal female myeloid cells were enriched for pathways associated with leukocyte migration, whereas male cells were enriched for pathways associated with the cellular response to TGF-β [37].

Furthermore, the expression of sex-specific genes was higher in pro-inflammatory CD14+CD16– monocytes (279 genes) than in double-positive non-classical (or patrolling) CD14+CD16+ monocytes (33 genes). Male CD14+CD16– monocytes were enriched for inflammatory pathways associated with IL-1, TNF, and neutrophil degranulation. Female monocytes were enriched for genes related to oxidative stress-induced senescence, chromatin remodeling, oxidative phosphorylation, and the response to IFN-α in both monocyte classes. Metabolic pathways differed markedly according to sex in both CD14+CD16– and CD14+CD16+ monocytes. Carbohydrate metabolism and glycolysis were enriched in male cells, whereas oxidative phosphorylation and associated pathways were enriched in female cells [37]. D. Sahoo et al. showed that apoptosis and cell death were more pronounced in female AMs. Male AMs were positively enriched for pro-inflammatory pathways, nitric oxide generation, and T-cell activation, and negatively enriched for the aerobic electron transport chain and oxidative phosphorylation [61].

Thus, sex influences AM function and polarization. The balance between the pro-inflammatory and anti-inflammatory roles of macrophages is critically important in the progression of lung injury. *In vitro*, classically activated macrophages (M1) secrete pro-inflammatory mediators such as TNF-α and ROS in the acute phase, whereas alternatively activated macrophages (M2) participate in the resolution of inflammation and tissue repair at a later phase. Studies have shown that alveolar macrophages from female mice express higher levels of M2 genes, indicating sex-dependent differences in macrophage polarization.

CONCLUSION

Elucidating the patterns of immune cell infiltration of the pulmonary parenchyma and the key immunomodulators involved may facilitate targeted therapeutic interventions directed at inflammation, which is of vital importance for improving the treatment of BPD. The study of immune signatures represents a promising avenue toward the development of anti-inflammatory therapeutic approaches.

Based on the results of published studies, distinct immune and gene signatures have been successfully identified in monocyte and macrophage samples from preterm infants with BPD at various time points after birth, complemented by comprehensive protein and transcriptome profiling. The immune response identified in preterm infants with BPD holds immense potential for the development of diagnostic and therapeutic strategies. However, future studies with larger patient cohorts are required to determine the differential impact of prenatal complications and genetic background on disease characteristics.

Thus, the diversity of pathophysiological mechanisms leading to the development and progression of bronchopulmonary dysplasia warrants in-depth investigation in experimental and clinical studies. With each passing year, our understanding of the pathogenesis of this chronic lung disease, which manifests in infancy, continues to expand. This will ultimately enable the delineation of the phenotypic heterogeneity of the disease and the implementation of a personalized approach to the prevention and treatment of bronchopulmonary dysplasia.

ADDITIONAL INFORMATION

Authors' contribution. E.V. Loshkova — scientific concept of the publication, structure, research and data analysis, writing, discussion of the manuscript and verification of the content, final approval of the manuscript for publication; T.S. Liulka — research and data analysis, structure, writing, technical editing; I.V. Doroshenko — research and data analysis, structure, writing, drawing preparation, technical editing; A.V. Budkin, Yu.S. Rafikova A.A. Terentieva, G.N. Yankina, E.V. Mikhalev, M.V. Rebrienko, A.D. Popova — discussion of the manuscript; V.A. Zhelev — control of deadlines; M.V. Fedosova — discussion

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of the manuscript, stylistic editing of text and technical editing.

All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Вклад авторов. Е.В. Лошкова — научная концепция публикации, структурирование материала, поиск и анализ источников литературы, написание статьи, обсуждение рукописи и проверка содержания, окончательное утверждение рукописи для публикации; Т.С. Люлька — поиск и анализ литературы, структурирование материала, написание статьи, техническое редактирование; И.В. Дорошенко — поиск и анализ литературы, структурирование материала, написание статьи, подготовка рисунков, техническое редактирование; А.В. Будкин, Ю.С. Рафикова, А.А. Терентьева, Г.Н. Янкина, Е.В. Михалев, М.В. Ребриенко, А.Д. Попова — обсуждение рукописи; В.А. Желев — контроль сроков выполнения; М.В. Федосова — обсуждение рукописи, стилистическое редактирование текста и техническое редактирование.

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REFERENCES

1. Bronchopulmonary dysplasia. Ovsyannikov D.Yu., Geppe N.A., Malakhov A.B., Degtyarev D.N., eds. Moscow; 2020. URL: https://pulmodeti.ru/wp-content/uploads/BLD-Klin_Rukovod_2020_Nestle_BLOK_NEW.pdf (accessed: 05.12.2025). (In Russ.).
2. Ovsyannikov D.Yu. Bronchopulmonary dysplasia: natural development, outcomes and control. *Pediatriya*. 2011;90(1):141–150. (In Russ.).
3. Davydova I.V., Fisenko A.P., Pozharischenskaya V.K., Kazakova K.A., Basargina E.Yu., Bondar V.A. A new form of bronchopulmonary dysplasia: current realias. *Doctor.Ru*. 2020;19(10):6–9. (In Russ.). https://doi.org/10.31550/1727-2378-2020-19-10-6-9. EDN: ISJJZW.
4. Harris C., Greenough A. The prevention and management strategies for neonatal chronic lung disease. *Expert Rev Respir Med*. 2023;17(2):143–154. https://doi.org/10.1080/17476348.2023.2183842.
5. Sillers L., Alexiou S., Jensen E.A. Lifelong pulmonary sequelae of bronchopulmonary dysplasia. *Curr Opin Pediatr*. 2020;32(2):252–260. https://doi.org/10.1097/MOP.0000000000000884.
6. Ovsyannikov D.Yu., Keshishyan E.S., Krsheminskaya I.V., Bystrova O.V. Prevalence of bronchopulmonary dysplasia in the Russian Federation. Are the data real? *Russian Bulletin of Perinatology and Pediatrics*. 2022;67(3):34–38. (In Russ.). https://doi.org/10.21508/1027-4065-2022-67-3-34-38. EDN: TKYCMI.
7. Northway W.H.Jr., Rosan R.C., Porter D.Y. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. *N Engl J Med*. 1967;276(7):357–368. https://doi.org/10.1056/NEJM196702162760701.
8. Humayun J., Löfqvist C., Ley D., Hellström A., Gyllensten H. Systematic review of the healthcare cost of bronchopulmonary dysplasia. *BMJ Open*. 2021;11(8):e045729. https://doi.org/10.1136/bmjopen-2020-045729.
9. Boitsova E.V., Ovsyannikov D.Y. Clinical and structural-functional respiratory consequences of a bronchopulmonary dysplasia at children, adolescents and young adults. *Therapy*. 2019;(5):86–96. (In Russ.). https://doi.org/10.18565/therapy.2019.5.86-96.
10. DeMauro S.B. Neurodevelopmental outcomes of infants with bronchopulmonary dysplasia. *Pediatr Pulmonol*. 2021;56(11):3509–3517. https://doi.org/10.1002/ppul.25381.
11. Harris C., Morris S., Lunt A., Peacock J., Greenough A. Influence of bronchopulmonary dysplasia on lung function in adolescents who were born extremely prematurely. *Pediatr Pulmonol*. 2022;57(12):3151–3157. https://doi.org/10.1002/ppul.26151.
12. Harris C., Lunt A., Bisquera A., Peacock J., Greenough A. Lung function and exercise capacity in prematurely born

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

young people. *Pediatr Pulmonol*. 2020;55(9):2289–2295. https://doi.org/10.1002/ppul.24918.
13. Yallapragada S.G., Savani R.C., Goss K.N. Cardiovascular impact and sequelae of bronchopulmonary dysplasia. *Pediatr Pulmonol*. 2021;56(11):3453–3463. https://doi.org/10.1002/ppul.25370.
14. Ovsyannikov D.Yu., Krsheminskaya I.V., Daniel-Abu M.I., Karpenko M.A. Radiodiagnosis in bronchopulmonary dysplasia: projection radiograph of the chest. *Neonatology: News, Opinions, Training*. 2020;8(3):39–49. (In Russ.). https://doi.org/10.33029/2308-2402-2020-8-3-39-49.
15. Davydova I.V. Current possibilities of predicting the development of bronchopulmonary dysplasia in premature infants. *Doctor.Ru*. 2025;24(3):76–79. (In Russ.). https://doi.org/10.31550/1727-2378-2025-24-3-76-79.
16. Shestak E.V., Starkov V.Y., Makarov V.S., Dodrov D.S., Svetlakova D.V., Adylov T.S., Evdokimova M.V. Analysis of the dynamics of the ultrasound picture of the lungs of newborns during inhalation prophylaxis of bronchopulmonary dysplasia with the surfactant drug: Pilot prospective clinical study. *Medical Council*. 2025;(4):124–134. (In Russ.). https://doi.org/10.21518/ms2025-090.
17. Chistyakova G.N., Ustyantseva L.S., Remizova I.I., Ryumin V.E.. Clinical and immunological risk factors for the formation of severe broncho-pulmonary dysplasia in children with extremely low body weight. *Russian Journal of Human Reproduction*. 2022;28(1):106–114. (In Russ.). https://doi.org/10.17116/repro202228011106.
18. Khishtilova P.B., Sergienko D.F. Influence of various factors on the formation of outcomes of bronchopulmonary dysplasia in children. *Farmateka*. 2021;(1):86–90. (In Russ.). https://doi.org/10.18565/pharmateca.
19. Savchenko O.A., Pavlinova E.B., Mingairova A.G., Vlasenko N.Yu., Polyanskaya H.A., Demchenko V.I., Kirshina I.A. Polymorphism of genes of antioxidatic enzymes as a risk factor of development of the radical induced damages in premature newborns. *Modern Problems of Science and Education*. 2016;(6). URL: https://science-education.ru/ru/article/view?id=25732 (accessed: 05.12.2025). (In Russ.).
20. Hurskainen M., Mižíková I., Cook D.P., Andersson N., Cyr-Depauw C., Lesage F. et al. Single cell transcriptomic analysis of murine lung development on hyperoxia-induced damage. *Nat Commun*. 2021;12(1):1565. https://doi.org/10.1038/s41467-021-21865-2.
21. Cyr-Depauw C., Hurskainen M., Vadivel A., Mižíková I., Lesage F., Thébaud B. Characterization of the innate immune response in a novel murine model mimicking bronchopulmonary dysplasia. *Pediatr Res*. 2021;89(4):803–813. https://doi.org/10.1038/s41390-020-0967-6.
22. Heydarian M., Schulz C., Stoeger T., Hilgendorff A. Association of immune cell recruitment and BPD development. *Mol Cell Pediatr*. 2022;9(1):16. https://doi.org/10.1186/s40348-022-00148-w.
23. Riccetti M.R., Ushakumary M.G., Waltamath M. et al. Maladaptive functional changes in alveolar fibroblasts due to perinatal hyperoxia impair epithelial differentiation. *JCI Insight*. 2022;7(5):e152404. https://doi.org/10.1172/jci.insight.152404.
24. He Y., Li D., Zhang M. et al. Bioinformatic analysis reveals the relationship between macrophage infiltration and Cybb downregulation in hyperoxia-induced bronchopulmonary dysplasia. *Sci Rep*. 2024;14(1):20089. https://doi.org/10.1038/s41598-024-70877-7.
25. Aslan M., Gokce I.K., Turgut H., Tekin S., Cetin Taslidere A., Deveci M.F. et al. Molsidomine decreases hyperoxia-induced lung injury in neonatal rats. *Pediatr Res*. 2023;94(4):1341–1348. https://doi.org/10.1038/s41390-023-02643-w.
26. Weng W., Wang X., Cui Y. Artesunate alleviates chronic hyperoxia-induced bronchopulmonary dysplasia by suppressing NF-κB pathway in neonatal mice. *Comb Chem High Throughput Screen*. 2024;27(18):2681-2690. https://doi.org/10.2174/0113862073246710231002042239.
27. Xiong J., Ai Q., Bao L., Gan Y., Dai X., Han M., Shi Y. Dose-dependent effects of human umbilical cord-derived mesenchymal stem cell treatment in hyperoxia-induced lung injury of neonatal rats. *Front Pediatr*. 2023;11:1111829. https://doi.org/10.3389/fped.2023.1111829.
28. Twisselmann N., Pagel J., Künstner A., Weckmann M., Hartz A., Glaser K. et al. Hyperoxia/Hypoxia exposure primes a sustained pro-inflammatory profile of preterm infant macrophages upon LPS stimulation. *Front Immunol*. 2021;12:762789. https://doi.org/10.3389/fimmu.2021.762789.
29. Ren X., Ustiyan V., Guo M., Wang G., Bolte C., Zhang Y. et al. Postnatal alveologenesis depends on FOXF1 signaling in c-KIT+ endothelial progenitor cells. *Am J Respir Crit Care Med*. 2019;200(9):1164–1176. https://doi.org/10.1164/rccm.201812-2312OC.
30. Revhaug C., Bik-Multanowski M., Zasada M., Rognlien A.G.W., Günther C.C., Książek T. et al. Immune system regulation affected by a murine experimental model of bronchopulmonary dysplasia: genomic and epigenetic findings. *Neonatology*. 2019;116(3):269–277. https://doi.org/10.1159/000501461.
31. Chen C.M., Liu Y.C., Chen Y.J., Chou H.C. Genome-wide analysis of DNA methylation in hyperoxia-exposed newborn rat lung. *Lung*. 2017;195(5):661–669. https://doi.org/10.1007/s00408-017-0036-z.
32. Kicinski P., Malachowska B., Wyka K., Gach A., Jakubowski L., Gulczynska E. The level of extracellular superoxide dismutase in the first week of life in very and extremely low birth weight infants and the risk of developing bron-

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

chopulmonary dysplasia. *J Perinat Med*. 2019;47(6):671–676. https://doi.org/10.1515/jpm-2018-0418.
33. Shahzad T., Dong Y., Behnke N.K., Brandner J., Hilgendorff A., Chao C.M. et al. Anti-CCL2 therapy reduces oxygen toxicity to the immature lung. *Cell Death Discov*. 2024;10(1):311. https://doi.org/10.1038/s41420-024-02073-5.
34. Troise D., Infante B., Mercuri S., Netti G.S., Ranieri E., Gesualdo L., Stallone G., Pontrelli P. Hypoxic state of cells and immunosenescence: a focus on the role of the HIF signaling pathway. *Biomedicines*. 2023;11(8):2163. https://doi.org/10.3390/biomedicines11082163.
35. Mathew R. Signaling pathways involved in the development of bronchopulmonary dysplasia and pulmonary hypertension. *Children (Basel)*. 2020;7(8):100. https://doi.org/10.3390/children7080100.
36. Hirani D., Alvira C.M., Danopoulos S., Milla C., Donato M., Tian L. et al. Macrophage-derived IL-6 trans-signalling as a novel target in the pathogenesis of bronchopulmonary dysplasia. *Eur Respir J*. 2022;59(2):2002248. https://doi.org/10.1183/13993003.02248-2020.
37. Leek C., Cantu A., Sonti S., Gutierrez M.C., Eldredge L., Sajti E. et al. Role of sex as a biological variable in neonatal alveolar macrophages. *Redox Biol*. 2024;75:103296. https://doi.org/10.1016/j.redox.2024.103296.
38. Aegerter H., Lambrecht B.N., Jakubzick C.V. Biology of lung macrophages in health and disease. *Immunity*. 2022;55(9):1564–1580. https://doi.org/10.1016/j.immuni.2022.08.010.
39. Dreschers S., Ohl K., Schulte N., Tenbrock K., Orlikowsky T.W. Impaired functional capacity of polarised neonatal macrophages. *Sci Rep*. 2020;10(1):1–12. https://doi.org/10.1038/s41598-019-56928-4.
40. Windhorst A.C., Heydarian M., Schwarz M., Oak P., Förster K., Frankenberger M. et al. Monocyte signature as a predictor of chronic lung disease in the preterm infant. *Front Immunol*. 2023;14:1112608. https://doi.org/10.3389/fimmu.2023.1112608. Erratum in: *Front Immunol*. 2023;14:1209992. https://doi.org/10.3389/fimmu.2023.1209992.
41. Eldredge L.C., Creasy R.S., Presnell S., Debley J.S., Juul S.E., Mayock D.E., Ziegler S.F. Infants with evolving bronchopulmonary dysplasia demonstrate monocyte-specific expression of IL-1 in tracheal aspirates. *Am J Physiol Lung Cell Mol Physiol*. 2019;317(1):L49–L56. https://doi.org/10.1152/ajplung.00060.2019.
42. Eldredge L.C., Creasy R.S., Tanaka S., Lai J.-F., Ziegler S.F. Imbalance of Ly-6C(hi) and Ly-6C(lo) monocytes/macrophages worsens hyperoxia-induced lung injury and is rescued by IFN-γ. *J Immunol*. 2019;202(9):2772–2781. https://doi.org/10.4049/jimmunol.1801374.
43. Misharin A.V., Morales-Nebreda L., Reyfman P.A., Cuda C.M., Walter J.M., McQuattie-Pimentel A.C. et al. Monocyte-derived alveolar macrophages drive lung fibrosis and persist in the lung over the life span. *J Exp Med*. 2017;214(8):2387–2404. https://doi.org/10.1084/jem.20162152.
44. Lingappan K., Savani R.C. The Wnt signaling pathway and the development of bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2020;201(10):1174–1176. https://doi.org/10.1164/rccm.202002-0277ED.
45. Yao H., Wallace J., Peterson A.L., Scaffa A., Rizal S., Hegarty K. et al. Timing and cell specificity of senescence drives postnatal lung development and injury. *Nat Commun*. 2023;14(1):273. https://doi.org/10.1038/s41467-023-35985-4.
46. Travaglini K.J., Nabhan A.N., Penland L., Sinha R., Gillich A., Sit R.V. et al. A molecular cell atlas of the human lung from single-cell RNA sequencing. *Nature*. 2020;587:619–625. https://doi.org/10.1038/s41586-020-2922-4.
47. Kang I., Bucala R. The immunobiology of MIF: Function, genetics and prospects for precision medicine. *Nat Rev Rheumatol*. 2019;15(7):427–437. https://doi.org/10.1038/s41584-019-0238-2.
48. Kračun D., Lopes L.R., Cifuentes-Pagano E., Pagano P.J. NADPH oxidases: redox regulation of cell homeostasis and disease. *Physiol Rev*. 2025;105(3):1291–1428. https://doi.org/10.1152/physrev.00034.2023.
49. Bhattacharya S., Idol R.A., Yang W. et al. Macrophage NOX2 NADPH oxidase maintains alveolar homeostasis in mice. *Blood*. 2022;139(19):2855–2870. https://doi.org/10.1182/blood.2021015365.
50. Potera R.M., Cao M., Jordan L.F. et al. Alveolar macrophage chemokine secretion mediates neutrophilic lung injury in Nox2-deficient mice. *Inflammation*. 2019;42(1):185–198. https://doi.org/10.1007/s10753-018-0883-7.
51. Monjarret B., Shour S., Benyoucef A. et al. NOX2 deficiency enhances priming and activation of the NLRP3 inflammasome. *J Allergy Clin Immunol*. 2023;S0091-6749(23)01242-3. https://doi.org/10.1016/j.jaci.2023.09.030.
52. Bain C.C., Gibson D.A., Steers N.J., Boufea K., Louwe P.A., Doherty C. et al. Rate of replenishment and microenvironment contribute to the sexually dimorphic phenotype and function of peritoneal macrophages. *Sci Immunol*. 2020;5(48):eabc4466. https://doi.org/10.1126/sciimmunol.abc4466.
53. Dolfi B., Gallerand A., Firulyova M.M., Xu Y., Merlin J., Dumont A. et al. Unravelling the sex-specific diversity and functions of adrenal gland macrophages. *Cell Rep*. 2022;39(11):110949 https://doi.org/10.1016/j.celrep.2022.110949.
54. Ghelfi E., Karaaslan C., Berkelhamer S., Akar S., Kozakewich H., Cataltepe S. Fatty acid-binding proteins and peribronchial angiogenesis in bronchopulmonary dysplasia. *Am J Respir Cell Mol Biol*. 2011;45(3):550–556. https://doi.org/10.1165/rcmb.2010-0376OC.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

55. Meyers A.K., Wang Z., Han W., Zhao Q., Zabalawi M., Duan L. et al. Pyruvate dehydrogenase kinase supports macrophage NLRP3 inflammasome activation during acute inflammation. *Cell Rep*. 2023;42(11):111941. https://doi.org/10.1016/j.celrep.2022.111941.
56. Li C., Liu C., Zhang J., Lu Y., Jiang B., Xiong H., Li C. Pyruvate dehydrogenase kinase regulates macrophage polarization in metabolic and inflammatory diseases. *Front Immunol*. 2023;14:1296687. https://doi.org/10.3389/fimmu.2023.1296687.
57. Morse C., Tabib T., Sembrat J., Buschur K.L., Bittar H.T., Valenzi E. et al. Proliferating SPP1/MERTK-expressing macrophages in idiopathic pulmonary fibrosis. *Eur Respir J*. 2019;54(2):1802441. https://doi.org/10.1183/13993003.02441-2018.
58. Kirkby M., Enosi Tuipulotu D., Feng S., Lo Pilato J., Man S.M. Guanylate-binding proteins: mechanisms of pattern recognition and antimicrobial functions. *Trends Biochem Sci*. 2023;48(10):883–893. https://doi.org/10.1016/j.tibs.2023.07.002.
59. Zhang Z., Yu H., Wang Q., Ding Y., Wang Z., Zhao S., Bian T. A macrophage-related gene signature for identifying COPD based on bioinformatics and ex vivo experiments. *J Inflamm Res*. 2023;16:5647–5665. https://doi.org/10.2147/JIR.S438308.
60. Tosiek M.J., Groesser K., Pekcec A., Zwirek M., Murugesan G., Borges E. Activation of the innate immune checkpoint CLEC5A on myeloid cells in the absence of danger signals modulates macrophages' function but does not trigger the adaptive T cell immune response. *J Immunol Res*. 2022;2022:9926305. https://doi.org/10.1155/2022/9926305.
61. Sahoo D., Zaramela L.S., Hernandez G.E., Mai U., Taheri S., Dang D. et al. Transcriptional profiling of lung macrophages identifies a predictive signature for inflammatory lung disease in preterm infants. *Commun Biol*. 2020;3(1):259. https://doi.org/10.1038/s42003-020-0985-2.

ЛИТЕРАТУРА

1. Бронхолегочная дисплазия. Овсянников Д.Ю., Геппе Н.А., Малахов А.Б., Дегтярев Д.Н., ред. М.; 2020. URL: https://pulmodeti.ru/wp-content/uploads/BLD-Klin_Rukovod_2020_Nestle_BLOK_NEW.pdf (дата обращения: 05.12.2025).
2. Овсянников Д.Ю. Бронхолегочная дисплазия: естественное развитие, исходы и контроль. *Педиатрия*. 2011;90(1):141–150.
3. Давыдова И.В., Фисенко А.П., Пожарищенская В.К., Казакова К.А., Басаргина Е.Ю., Бондарь В.А. Новая форма бронхолегочной дисплазии: реалии сегодняшнего дня. *Доктор.Ру*. 2020;19(10):6–9. https://doi.org/10.31550/1727-2378-2020-19-10-6-9. EDN: ISJJZW.
4. Harris C., Greenough A. The prevention and management strategies for neonatal chronic lung disease. *Expert Rev Respir Med*. 2023;17(2):143–154. https://doi.org/10.1080/17476348.2023.2183842.
5. Sillers L., Alexiou S., Jensen E.A. Lifelong pulmonary sequelae of bronchopulmonary dysplasia. *Curr Opin Pediatr*. 2020;32(2):252–260. https://doi.org/10.1097/MOP.0000000000000884.
6. Овсянников Д.Ю., Кешишян Е.С., Кршеминская И.В., Быстрова О.В. Распространенность бронхолегочной дисплазии в Российской Федерации. Реальны ли получаемые данные? *Российский вестник перинатологии и педиатрии*. 2022;67(3):34–38. https://doi.org/10.21508/1027-4065-2022-67-3-34-38. EDN: TKYCMI.
7. Northway W.H.Jr., Rosan R.C., Porter D.Y. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. *N Engl J Med*. 1967;276(7):357–368. https://doi.org/10.1056/NEJM196702162760701.
8. Humayun J., Löfqvist C., Ley D., Hellström A., Gyllensten H. Systematic review of the healthcare cost of bronchopulmonary dysplasia. *BMJ Open*. 2021;11(8):e045729. https://doi.org/10.1136/bmjopen-2020-045729.
9. Бойцова Е.В., Овсянников Д.Ю. Клинические и структурно-функциональные респираторные последствия бронхолегочной дисплазии у детей, подростков и молодых взрослых. *Терапия*. 2019;(5):86–96. https://doi.org/10.18565/therapy.2019.5.86-96.
10. DeMauro S.B. Neurodevelopmental outcomes of infants with bronchopulmonary dysplasia. *Pediatr Pulmonol*. 2021;56(11):3509–3517. https://doi.org/10.1002/ppul.25381.
11. Harris C., Morris S., Lunt A., Peacock J., Greenough A. Influence of bronchopulmonary dysplasia on lung function in adolescents who were born extremely prematurely. *Pediatr Pulmonol*. 2022;57(12):3151–3157. https://doi.org/10.1002/ppul.26151.
12. Harris C., Lunt A., Bisquera A., Peacock J., Greenough A. Lung function and exercise capacity in prematurely born young people. *Pediatr Pulmonol*. 2020;55(9):2289–2295. https://doi.org/10.1002/ppul.24918.
13. Yallapragada S.G., Savani R.C., Goss K.N. Cardiovascular impact and sequelae of bronchopulmonary dysplasia. *Pediatr Pulmonol*. 2021;56(11):3453–3463. https://doi.org/10.1002/ppul.25370.
14. Овсянников Д.Ю., Кршеминская И.В., Даниэл-Абу М.И., Карпенко М.А. Рентгенодиагностика бронхолегочной дисплазии: обзорная рентгенография грудной клетки. *Неонатология: новости, мнения, обу-*

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

чение. 2020;8(3):39–49. https://doi.org/10.33029/2308-2402-2020-8-3-39-49.
15. Давыдова И.В. Современные возможности прогнозирования формирования бронхолегочной дисплазии у недоношенных детей. *Доктор.Ру*. 2025;24(3):76–79. https://doi.org/10.31550/1727-2378-2025-24-3-76-79.
16. Шестак Е.В., Старков В.Ю., Макаров В.С., Додров Д.С., Светлакова Д.В., Адылов Т.С., Евдокимова М.В. Анализ динамики ультразвуковой картины легких новорожденных в ходе ингаляционной профилактики бронхолегочной дисплазии препаратом сурфактанта: пилотное проспективное клиническое исследование. *Медицинский совет*. 2025;(4):124–134. https://doi.org/10.21518/ms2025-090.
17. Чистякова Г.Н., Устьянцева Л.С., Ремизова И.И., Рюмин В.Е. Клинико-иммунологические факторы риска формирования бронхолегочной дисплазии тяжелой степени у детей с экстремально низкой массой тела. *Проблемы репродукции*. 2022;28(1):106–114. https://doi.org/10.17116/repro202228011106.
18. Хиштилова П.Б., Сергиенко Д.Ф. Влияние различных факторов на формирование исходов бронхолегочной дисплазии у детей. *Фарматека*. 2021;(1):86–90. https://doi.org/10.18565/pharmateca.
19. Савченко О.А., Павлинова Е.Б., Мингаирова А.Г., Власенко Н.Ю., Полянская Н.А., Демченко В.И., Киршина И.А. Полиморфизм генов антиоксидантных ферментов как фактор риска развития радикально-индуцированных повреждений у недоношенных новорожденных. *Современные проблемы науки и образования*. 2016;(6). URL: https://science-education.ru/ru/article/view?id=25732 (дата обращения: 05.12.2025).
20. Hurskainen M., Mižíková I., Cook D.P., Andersson N., Cyr-Depauw C., Lesage F. et al. Single cell transcriptomic analysis of murine lung development on hyperoxia-induced damage. *Nat Commun*. 2021;12(1):1565. https://doi.org/10.1038/s41467-021-21865-2.
21. Cyr-Depauw C., Hurskainen M., Vadivel A., Mižíková I., Lesage F., Thébaud B. Characterization of the innate immune response in a novel murine model mimicking bronchopulmonary dysplasia. *Pediatr Res.* 2021;89(4):803–813. https://doi.org/10.1038/s41390-020-0967-6.
22. Heydarian M., Schulz C., Stoeger T., Hilgendorff A. Association of immune cell recruitment and BPD development. *Mol Cell Pediatr.* 2022;9(1):16. https://doi.org/10.1186/s40348-022-00148-w.
23. Riccetti M.R., Ushakumary M.G., Waltamath M. et al. Maladaptive functional changes in alveolar fibroblasts due to perinatal hyperoxia impair epithelial differentiation. *JCI Insight*. 2022;7(5):e152404. https://doi.org/10.1172/jci.insight.152404.
24. He Y., Li D., Zhang M. et al. Bioinformatic analysis reveals the relationship between macrophage infiltration and Cybb downregulation in hyperoxia-induced bronchopulmonary dysplasia. *Sci Rep*. 2024;14(1):20089. https://doi.org/10.1038/s41598-024-70877-7.
25. Aslan M., Gokce I.K., Turgut H., Tekin S., Cetin Taslidere A., Deveci M.F. et al. Molsidomine decreases hyperoxia-induced lung injury in neonatal rats. *Pediatr Res*. 2023;94(4):1341–1348. https://doi.org/10.1038/s41390-023-02643-w.
26. Weng W., Wang X., Cui Y. Artesunate alleviates chronic hyperoxia-induced bronchopulmonary dysplasia by suppressing NF-κB pathway in neonatal mice. *Comb Chem High Throughput Screen*. 2024;27(18):2681–2690. https://doi.org/10.2174/0113862073246710231002042239.
27. Xiong J., Ai Q., Bao L., Gan Y., Dai X., Han M., Shi Y. Dose-dependent effects of human umbilical cord-derived mesenchymal stem cell treatment in hyperoxia-induced lung injury of neonatal rats. *Front Pediatr*. 2023;11:1111829. https://doi.org/10.3389/fped.2023.1111829.
28. Twisselmann N., Pagel J., Künstner A., Weckmann M., Hartz A., Glaser K. et al. Hyperoxia/Hypoxia exposure primes a sustained pro-inflammatory profile of preterm infant macrophages upon LPS stimulation. *Front Immunol*. 2021;12:762789. https://doi.org/10.3389/fimmu.2021.762789.
29. Ren X., Ustiyan V., Guo M., Wang G., Bolte C., Zhang Y. et al. Postnatal alveologenesis depends on FOXF1 signaling in c-KIT+ endothelial progenitor cells. *Am J Respir Crit Care Med*. 2019;200(9):1164–1176. https://doi.org/10.1164/rccm.201812-2312OC.
30. Revhaug C., Bik-Multanowski M., Zasada M., Rognlien A.G.W., Günther C.C., Książek T. et al. Immune system regulation affected by a murine experimental model of bronchopulmonary dysplasia: genomic and epigenetic findings. *Neonatology*. 2019;116(3):269–277. https://doi.org/10.1159/000501461.
31. Chen C.M., Liu Y.C., Chen Y.J., Chou H.C. Genome-wide analysis of DNA methylation in hyperoxia-exposed newborn rat lung. *Lung*. 2017;195(5):661–669. https://doi.org/10.1007/s00408-017-0036-z.
32. Kicinski P., Malachowska B., Wyka K., Gach A., Jakubowski L., Gulczynska E. The level of extracellular superoxide dismutase in the first week of life in very and extremely low birth weight infants and the risk of developing bronchopulmonary dysplasia. *J Perinat Med*. 2019;47(6):671–676. https://doi.org/10.1515/jpm-2018-0418.
33. Shahzad T., Dong Y., Behnke N.K., Brandner J., Hilgendorff A., Chao C.M. et al. Anti-CCL2 therapy reduces oxygen toxicity to the immature lung. *Cell Death Discov*. 2024;10(1):311. https://doi.org/10.1038/s41420-024-02073-5.
34. Troise D., Infante B., Mercuri S., Netti G.S., Ranieri E., Gesualdo L., Stallone G., Pontrelli P. Hypoxic state of

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

cells and immunosenescence: a focus on the role of the HIF signaling pathway. *Biomedicines*. 2023;11(8):2163. https://doi.org/10.3390/biomedicines11082163.
35. Mathew R. Signaling pathways involved in the development of bronchopulmonary dysplasia and pulmonary hypertension. *Children (Basel)*. 2020;7(8):100. https://doi.org/10.3390/children7080100.
36. Hirani D., Alvira C.M., Danopoulos S., Milla C., Donato M., Tian L. et al. Macrophage-derived IL-6 trans-signalling as a novel target in the pathogenesis of bronchopulmonary dysplasia. *Eur Respir J*. 2022;59(2):2002248. https://doi.org/10.1183/13993003.02248-2020.
37. Leek C., Cantu A., Sonti S., Gutierrez M.C., Eldredge L., Sajti E. et al. Role of sex as a biological variable in neonatal alveolar macrophages. *Redox Biol*. 2024;75:103296. https://doi.org/10.1016/j.redox.2024.103296.
38. Aegerter H., Lambrecht B.N., Jakubzick C.V. Biology of lung macrophages in health and disease. *Immunity*. 2022;55(9):1564–1580. https://doi.org/10.1016/j.immuni.2022.08.010.
39. Dreschers S., Ohl K., Schulte N., Tenbrock K., Orlikowsky T.W. Impaired functional capacity of polarised neonatal macrophages. *Sci Rep*. 2020;10(1):1–12. https://doi.org/10.1038/s41598-019-56928-4.
40. Windhorst A.C., Heydarian M., Schwarz M., Oak P., Förster K., Frankenberger M. et al. Monocyte signature as a predictor of chronic lung disease in the preterm infant. *Front Immunol*. 2023;14:1112608. https://doi.org/10.3389/fimmu.2023.1112608. Erratum in: *Front Immunol*. 2023;14:1209992. https://doi.org/10.3389/fimmu.2023.1209992.
41. Eldredge L.C., Creasy R.S., Presnell S., Debley J.S., Juul S.E., Mayock D.E., Ziegler S.F. Infants with evolving bronchopulmonary dysplasia demonstrate monocyte-specific expression of IL-1 in tracheal aspirates. *Am J Physiol Lung Cell Mol Physiol*. 2019;317(1):L49–L56. https://doi.org/10.1152/ajplung.00060.2019.
42. Eldredge L.C., Creasy R.S., Tanaka S., Lai J.-F., Ziegler S.F. Imbalance of Ly-6C(hi) and Ly-6C(lo) monocytes/macrophages worsens hyperoxia-induced lung injury and is rescued by IFN-γ. *J Immunol*. 2019;202(9):2772–2781. https://doi.org/10.4049/jimmunol.1801374.
43. Misharin A.V., Morales-Nebreda L., Reyfman P.A., Cuda C.M., Walter J.M., McQuattie-Pimentel A.C. et al. Monocyte-derived alveolar macrophages drive lung fibrosis and persist in the lung over the life span. *J Exp Med*. 2017;214(8):2387–404. https://doi.org/10.1084/jem.20162152.
44. Lingappan K., Savani R.C. The Wnt signaling pathway and the development of bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2020;201(10):1174–1176. https://doi.org/10.1164/rccm.202002-0277ED.
45. Yao H., Wallace J., Peterson A.L., Scaffa A., Rizal S., Hegarty K. et al. Timing and cell specificity of senescence drives postnatal lung development and injury. *Nat Commun*. 2023;14(1):273. https://doi.org/10.1038/s41467-023-35985-4.
46. Travaglini K.J., Nabhan A.N., Penland L., Sinha R., Gillich A., Sit R.V. et al. A molecular cell atlas of the human lung from single-cell RNA sequencing. *Nature*. 2020;587:619–25. https://doi.org/10.1038/s41586-020-2922-4.
47. Kang I., Bucala R. The immunobiology of MIF: Function, genetics and prospects for precision medicine. *Nat Rev Rheumatol*. 2019;15(7):427–437. https://doi.org/10.1038/s41584-019-0238-2.
48. Kračun D., Lopes L.R., Cifuentes-Pagano E., Pagano P.J. NADPH oxidases: redox regulation of cell homeostasis and disease. *Physiol Rev*. 2025;105(3):1291–1428. https://doi.org/10.1152/physrev.00034.2023.
49. Bhattacharya S., Idol R.A., Yang W. et al. Macrophage NOX2 NADPH oxidase maintains alveolar homeostasis in mice. *Blood*. 2022;139(19):2855–2870. https://doi.org/10.1182/blood.2021015365.
50. Potera R.M., Cao M., Jordan L.F. et al. Alveolar macrophage chemokine secretion mediates neutrophilic lung injury in Nox2-deficient mice. *Inflammation*. 2019;42(1):185–198. https://doi.org/10.1007/s10753-018-0883-7.
51. Monjarret B., Shour S., Benyoucef A. et al. NOX2 deficiency enhances priming and activation of the NLRP3 inflammasome. *J Allergy Clin Immunol*. 2023;S0091-6749(23)01242-3. https://doi.org/10.1016/j.jaci.2023.09.030.
52. Bain C.C., Gibson D.A., Steers N.J., Boufea K., Louwe P.A., Doherty C. et al. Rate of replenishment and microenvironment contribute to the sexually dimorphic phenotype and function of peritoneal macrophages. *Sci Immunol*. 2020;5(48):eabc4466. https://doi.org/10.1126/sciimmunol.abc4466.
53. Dolfi B., Gallerand A., Firulyova M.M., Xu Y., Merlin J., Dumont A. et al. Unravelling the sex-specific diversity and functions of adrenal gland macrophages. *Cell Rep*. 2022;39(11):110949 https://doi.org/10.1016/j.celrep.2022.110949.
54. Ghelfi E., Karaaslan C., Berkelhamer S., Akar S., Kozakewich H., Cataltepe S. Fatty acid-binding proteins and peribronchial angiogenesis in bronchopulmonary dysplasia. *Am J Respir Cell Mol Biol*. 2011;45(3):550–556. https://doi.org/10.1165/rcmb.2010-0376OC.
55. Meyers A.K., Wang Z., Han W., Zhao Q., Zabalawi M., Duan L. et al. Pyruvate dehydrogenase kinase supports macrophage NLRP3 inflammasome activation during acute inflammation. *Cell Rep*. 2023;42(11):111941. https://doi.org/10.1016/j.celrep.2022.111941.
56. Li C., Liu C., Zhang J., Lu Y., Jiang B., Xiong H., Li C. Pyruvate dehydrogenase kinase regulates macrophage pola-

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

rization in metabolic and inflammatory diseases. *Front Immunol*. 2023;14:1296687. https://doi.org/10.3389/fimmu.2023.1296687.
57. Morse C., Tabib T., Sembrat J., Buschur K.L., Bittar H.T., Valenzi E. et al. Proliferating SPP1/MERTK-expressing macrophages in idiopathic pulmonary fibrosis. *Eur Respir J.* 2019;54(2):1802441. https://doi.org/10.1183/13993003.02441-2018.
58. Kirkby M., Enosi Tuipulotu D., Feng S., Lo Pilato J., Man S.M. Guanylate-binding proteins: mechanisms of pattern recognition and antimicrobial functions. *Trends Biochem Sci.* 2023;48(10):883–893. https://doi.org/10.1016/j.tibs.2023.07.002.
59. Zhang Z., Yu H., Wang Q., Ding Y., Wang Z., Zhao S., Bian T. A macrophage-related gene signature for identifying COPD based on bioinformatics and ex vivo experiments. *J Inflamm Res.* 2023;16:5647–5665. https://doi.org/10.2147/JIR.S438308.
60. Tosiek M.J., Groesser K., Pekcec A., Zwirek M., Murugesan G., Borges E. Activation of the innate immune checkpoint CLEC5A on myeloid cells in the absence of danger signals modulates macrophages' function but does not trigger the adaptive T cell immune response. *J Immunol Res.* 2022;2022:9926305. https://doi.org/10.1155/2022/9926305.
61. Sahoo D., Zaramela L.S., Hernandez G.E., Mai U., Taheri S., Dang D. et al. Transcriptional profiling of lung macrophages identifies a predictive signature for inflammatory lung disease in preterm infants. *Commun Biol.* 2020;3(1):259. https://doi.org/10.1038/s42003-020-0985-2.

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Review

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Hyperhomocysteinemia syndrome in children with various diseases

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ABSTRACT. ***Introduction.*** The problem of the relationship of homocysteine level with the development of pathological conditions is becoming more and more relevant every year. The article presents a literature review of works devoted to the study of this issue. ***Aim*** – to study the role of homocysteine in the development of various diseases in children using literary sources. ***Materials and methods.*** Using keywords (homocysteine, hyperhomocysteinemia, adolescents, children) we searched for papers published from 1969 to 2025 in PubMed, World Wide Science and eLIBRARY databases. 1200 studies were found, and 42 were selected for review, including 5 systematic reviews and meta-analyses. ***Results.*** Hyperhomocysteinemia initiates activation of the unified cellular-humoral defense system of the organism, manifested in the development of hypercoagulation, increase in the number of leukocyte-platelet coaggregates, increase in the level of autoantibodies, cytokines, adhesion molecules, change in the phenotype of lymphocytes, which has a damaging effect on organs and systems, causing their damage. ***Conclusions.*** Domestic and foreign studies of homocysteine, in healthy and sick children show the association of homocysteine, with various pathologies in children and adolescents. First of all, they confirm the significance of this indicator as a diagnostic biomarker. Further in-depth and large-scale study of this issue is necessary.

KEYWORDS: *homocysteine, hyperhomocysteinemia, adolescents*

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Синдром гипергомоцистеинемии у детей при различных заболеваниях

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РЕЗЮМЕ. ***Введение.*** Проблема взаимосвязи уровня гомоцистеина с развитием патологических состояний с каждым годом становится все более актуальной. В статье представлен литературный обзор работ, посвященных изучению данного вопроса. ***Цель*** — используя литературные источники, изучить роль гомоцистеина в развитии различных заболеваний у детей. ***Материалы и методы.*** Благодаря использованию ключевых слов (гомоцистеин, гипергомоцистеинемия, дети) был проведен поиск работ, опубликованных с 1969 по 2025 год в базах данных PubMed, World Wide Science и eLIBRARY. Найдено 1200 исследований, отобрано для обзора 42, в том числе 5 систематических обзоров и метаанализов. ***Результаты.*** Гипергомоцистеинемия инициирует активацию единой клеточно-гуморальной системы защиты организма, проявляющуюся в развитии гиперкоагуляции, росте числа лейкоцитарно-тромбоцитарных коагрегатов, увеличении уровня аутоантител, цитокинов, молекул адгезии, изменении фенотипа лимфоцитов, что оказывает повреждающее действие на органы и системы. ***Выводы.*** Отечественные и зарубежные исследования гомоцистеина у здоровых и больных детей показывают связь гипергомоцистеинемии с различными патологиями у детей и подростков. В первую очередь, они подтверждают значимость этого показателя как диагностического биомаркера. Необходимо дальнейшее углубленное и масштабное изучение данного вопроса.

КЛЮЧЕВЫЕ СЛОВА: *гомоцистеин, гипергомоцистеинемия, подростки*

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INTRODUCTION

In recent years, the correlation between elevated plasma homocysteine (Hcy) concentrations and the development of a range of childhood disorders has attracted considerable research attention in the fields of pediatrics and biochemistry. Published epidemiological data indicate that homocysteine levels exceeding 15 μmol/L — a condition referred to as hyperhomocysteinemia (HHCy) — are found in approximately 5–7% of the general population [1–6].

More than half a century ago, Kilmer S. McCully proposed the hypothesis that elevated Hcy concentrations exert pathogenic effects on the human body. This supposition was grounded in clinical observations of children with inborn errors of methionine metabolism. In these patients, HHCy was accompanied by severe cardiovascular damage. In the absence of treatment, the disease typically had a fatal outcome: the children died at a young age from myocardial infarction or stroke. Postmortem examination consistently revealed the presence of atherosclerotic plaques in muscular arteries [1].

The development of HHCy is attributable to several factors. These include a metabolic factor — the level and activity of enzymes responsible for Hcy metabolism; the functional state of the kidneys, which governs homocysteine elimination; and a deficiency of vitamins B_6, B_{12}, and folic acid, which serve as cofactors (B_6, B_{12}) or substrates (folic acid). Early manifestation of HHCy is of particular interest, as it is associated in most cases with inherited defects in the genes encoding enzymes of the methylation and transsulfuration cycles [7, 8].

The universality of homocysteine's cytotoxic effects on cellular structures throughout the body is beyond dispute [9–15]. In this context, HHCy is gaining recognition as a potential risk marker for the onset and exacerbation of a broad spectrum of childhood diseases. Nevertheless, the pathogenetic role of this metabolic disturbance in pediatric practice remains controversial and warrants more detailed investigation.

The present review aims to systematize current evidence regarding the involvement of HHCy in the pathogenesis of various nosological entities in pediatric patients.

AIM

This review aims to evaluate the role of HHCy in the pathogenesis of various pediatric diseases.

MATERIALS AND METHODS

A search of PubMed, WorldWideScience, and eLIBRARY was conducted for studies published between 1969 and 2025 using the keywords "homocysteine," "hyperhomocysteinemia," and "children."

HOMOCYSTEINE: PHYSIOLOGICAL ROLE AND PLASMA CONCENTRATIONS IN CHILDREN

Homocysteine is a non-proteinogenic sulfhydryl amino acid synthesized endogenously via the intracellular demethylation of methionine; it is not obtained from dietary sources. Intracellular Hcy metabolism proceeds through two principal pathways: remethylation, regenerating methionine, and transsulfuration, producing cysteine. Remethylation represents the predominant cycle, its key cofactors being folate derivatives and cobalamin (vitamin B_{12}). The irreversible conversion of Hcy to cysteine takes place via the transsulfuration reaction, catalyzed by pyridoxal phosphate-dependent enzymes (Fig. 1) [16–19].

The physiological role of Hcy lies in maintaining stable methionine concentrations required for methylation reactions, as well as for the biosynthesis of cysteine — a structural component of glutathione and a source of sulfides. Additionally, Hcy participates in the synthesis of α-ketobutyrate, the immediate precursor of succinyl-CoA, an intermediate of the Krebs cycle [20].

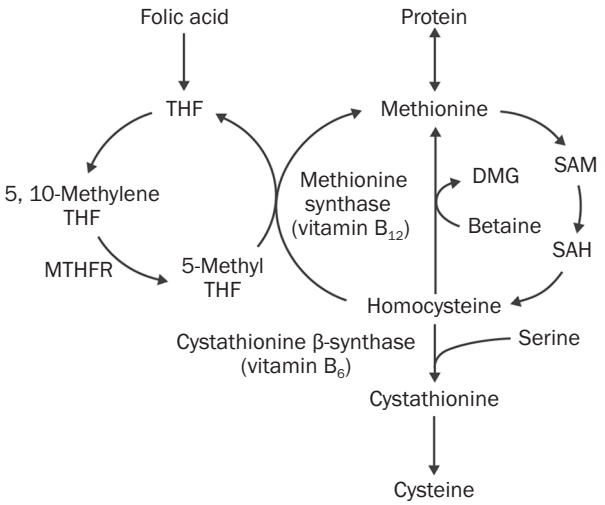

Fig. 1. Homocysteine metabolism [20]

Рис. 1. Метаболизм гомоцистеина [20]

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Fasting plasma homocysteine is generally considered normal within the range of 5 to 15 μmol/L. In children and adolescents, levels approximate 5 μmol/L; over the lifespan, mean Hcy concentrations increase by 3–5 μmol/L and are consistently higher in males than in females. Age-dependent changes are attributable to declining renal function, whereas higher baseline values in males reflect greater muscle mass. Plasma homocysteine concentrations of 15–30 μmol/L define moderate hyperhomocysteinemia, 30–100 μmol/L intermediate hyperhomocysteinemia, and >100 μmol/L severe hyperhomocysteinemia [21–25].

HYPERHOMOCYSTEINEMIA AND CARDIOVASCULAR DISEASE

A growing body of evidence identifies homocysteine (Hcy) as a significant contributor to cardiovascular pathology in children and adolescents. The pathogenesis is mediated by several interrelated mechanisms. The first is downregulation of adenosine receptors and upregulation of proinflammatory cytokines, which jointly impair myocardial perfusion. The second is oxidative stress resulting from the accumulation of reactive oxygen species. The third is elevated levels of asymmetric dimethylarginine — an endogenous inhibitor of nitric oxide synthase, a pivotal mediator of vasodilation. The combined influence of elevated Hcy and its metabolites on the vascular wall promotes endothelial dysfunction and vascular remodeling, thus establishing a substrate for the early onset of arterial hypertension in childhood. Of particular concern is the proatherosclerotic potential of HHCy, which may be amplified by genetic variants (polymorphisms) in genes encoding key enzymes of the folate cycle, including *MTHFR*, *MTRR*, and *MTR*. Collectively, these observations argue for the implementation of rigorous screening and preventive measures in patients with documented hyperhomocysteinemia [26–29].

HYPERHOMOCYSTEINEMIA AND OBESITY

To date, original studies that could definitively establish the relationship between these two pathologies remain limited. Nevertheless, available data point to an association between elevated homocysteine concentrations and an increased risk of cardiovascular complications in children with obesity relative to their normal-weight peers. A study conducted at Kemerovo Medical University included 81 adolescents, 65 of whom had a body mass index (BMI) above the 95th percentile. The results demonstrated that structural myocardial changes were detected 2.2 times more frequently in patients with a BMI above the 95th percentile and hyperhomocysteinemia exceeding 210 μmol/L than in children with normal Hcy levels. The risk of cardiac remodeling was statistically significantly higher in children with hyperhomocysteinemia [30–32].

HYPERHOMOCYSTEINEMIA AND UNDIFFERENTIATED CONNECTIVE TISSUE DYSPLASIA SYNDROME

Undifferentiated connective tissue dysplasia (UCTD) is a genetically determined condition characterized by defects in the fibrous structures and ground substance of connective tissue, resulting in multiorgan damage that shapes the profile of associated comorbidities and drug responses. Studies investigating the link between hyperhomocysteinemia and UCTD in children and adolescents are scarce. Yu.I. Rovda et al. examined 210 children aged 1 to 17 years, 58 of whom carried a clinically established diagnosis of UCTD. The aim of the study was to determine Hcy levels in patients with HHCy. The authors found that homocysteine levels were elevated both in patients with UCTD and in healthy children. However, the majority of patients with UCTD and HHCy reported an increased bleeding tendency, which may point to an association between hemorrhagic syndrome and homocysteine levels. A direct correlation was also observed between blood homocysteine levels and von Willebrand factor. This finding suggests a greater damaging effect of homocysteine on the endothelium in patients with UCTD, which may predispose to earlier development of thrombotic complications [33].

HYPERHOMOCYSTEINEMIA AND MIGRAINE

Several published studies point to an association between elevated homocysteine concentrations and migraine in children. From a pathogenetic standpoint, endothelial dysfunction occurring in the context of HHCy contributes to the development of this pathology. Elevated blood homocysteine promotes the accumulation of proinflammatory cytokines, including IL-6, IL-8, and TNF-α, increases reactive oxygen species, and diminishes vasodilatory components. Collectively, these effects play an important role in the cerebrovascular regulation of

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migraine, and intracranial arterial vasoconstriction may intensify pain. A neurogenic theory has also been advanced, according to which the release of neurotransmitters from trigeminal nerve neurons triggers marked vasodilation and edema. In genetically determined HHCy due to the *C677T* mutation in the gene, migraine attacks are provoked by the excessive accumulation of excitotoxic amino acids exerting a direct toxic effect on the brain. Elevated blood Hcy has been documented in children with migraine in several studies. These observations warrant consideration both in patients with newly diagnosed migraine — to address all components of pathogenesis — and in individuals with HHCy, to prevent the development of migraine [34–36].

HYPERHOMOCYSTEINEMIA AND DISEASES OF THE URINARY SYSTEM

The kidneys play a well-established central role in homocysteine metabolism, as the greater part of Hcy undergoes a series of metabolic transformations within the renal tubules. Accordingly, when Hcy levels rise, the kidneys are the first organs to sustain damage. O.V. Nesterenko et al. demonstrated that in children with chronic pyelonephritis, the development of nephrosclerosis was associated with elevated blood homocysteine. Patients with this diagnosis should therefore be regarded as being at risk for nephrosclerosis. Moreover, the detection of HHCy in a patient with renal disease may provide a rationale for initiating homocysteine-lowering therapy [36, 37].

HYPERHOMOCYSTEINEMIA AND THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The interrelationship between HHCy and the renin-angiotensin-aldosterone system (RAAS) continues to be debated. Nevertheless, given the established role of hyperhomocysteinemia in promoting arterial hypertension and renal pathology, it is reasonable to hypothesize that HHCy may adversely affect the RAAS and thereby further drive the development of arterial hypertension, including in children [38].

HYPERHOMOCYSTEINEMIA AND NEUROINFECTIONS

Neuroinfections remain a significant clinical challenge across multiple medical disciplines due to the high risk of severe complications. The outcome of infectious central nervous system involvement depends on a constellation of factors, most notably the magnitude of the inflammatory response and the functional integrity of the vascular endothelium. Plasma homocysteine concentration is recognized as an important laboratory marker of endothelial dysfunction. T.S. Berezovskaya and N.A. Mironova analyzed blood samples from 60 patients, 30 of whom formed a group with neuroinfections of diverse etiology and severity. Their findings revealed a statistically significant elevation of Hcy levels in patients with neuroinfections — an elevation that was universal in character and independent of the specific pathogen [19, 39–42].

HYPERHOMOCYSTEINEMIA AND THE DEVELOPMENT OF NEUROLOGICAL DISORDERS

S. Yoganathan et al. and B. Li et al. have reported clinical cases in which HHCy presented with a spectrum of neurological manifestations, including epileptic seizures, autism spectrum disorder, hyporeflexia, atonia, and encephalopathy. In each of these cases, screening of blood homocysteine and methionine levels was undertaken, and disturbances in the metabolism of this amino acid were confirmed in all instances. The initiation of appropriate pharmacological therapy aimed at reducing blood homocysteine was followed by clinical improvement [22, 30, 31, 37, 40].

CONCLUSION

Hyperhomocysteinemia sets in motion a complex cellular and humoral defense response. The clinical and laboratory hallmarks of this process include the development of hypercoagulation, an increase in leukocyte-platelet aggregates, and rising concentrations of autoantibodies, proinflammatory cytokines, and adhesion molecules. Alterations in the phenotypic profile of leukocytes are also observed. Together, these factors drive endothelial dysfunction and tissue injury [26, 39].

Studies of Hcy in healthy children and those with various diseases, conducted both nationally and internationally, point to an association between HHCy and a range of pediatric and adolescent pathologies. Importantly, they affirm the value of this parameter as a diagnostic biomarker. Further in-depth, large-scale investigation of this subject is warranted.

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ADDITIONAL INFORMATION

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All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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REFERENCES

1. McCully K.S. Vascular pathology of homocysteinemia: implications for the pathogenesis of arteriosclerosis. *Am J Pathol*. 1969;56(1):111–128.
2. Hermann A., Sitdikova G. Homocysteine: biochemistry, molecular biology and role in disease. *Biomolecules*. 2021;11(5):737. https://doi.org/10.3390/biom11050737.
3. Selhub J., Jacques P.F., Wilson P.W., Rush D., Rosenberg I.H. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. *JAMA*. 1993;270(22):2693–2698. https://doi.org/10.1001/jama.1993.03510220049033.
4. Esnafoglu E., Ozturan D.D. The relationship of severity of depression with homocysteine, folate, vitamin B_{12}, and vitamin D levels in children and adolescents. *Child Adolesc Ment Health*. 2020;25(4):249–255. https://doi.org/10.1111/camh.12387.
5. Ozkarakaya I.S., Celik B., Karakukcu C., Torun Y.A. Effect of zinc supplementation on hemogram parameters and circulating concentrations of homocysteine, vitamin B_{12}, and folate in zinc-deficient children and adolescents. *J Trace Elem Med Biol*. 2021;65:126724. https://doi.org/10.1016/j.jtemb.2021.126724.
6. Caleyachetty R., Echouffo-Tcheugui J.B., Tait C.A., Schilsky S., Forrester T., Kengne A.P. Prevalence of behavioural risk factors for cardiovascular disease in adolescents in low-income and middle-income countries: an individual participant data meta-analysis. *Lancet Diabetes Endocrinol*. 2015;3(7):535–544. https://doi.org/10.1016/S2213-8587(15)00076-5.
7. Morris A.A., Kožich V., Santra S., Andria G., Ben-Omran T.I., Chakrapani A.B., Chapman K.A. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. *J Inherit Metab Dis*. 2017;40:49–74. https://doi.org/10.1007/s10545-016-9979-0.
8. Luksha A.V., Naumov A.V., Maksimovich N.A. Functional state of vascular endothelium in hyperhomocysteinemia in children with arterial hypertension. *Journal of the Grodno State Medical University*. 2023;21(1):40–45. (In Russ.). https://doi.org/10.25298/2221-8785-2023-21-1-40-45.
9. Paganelli F., Mottola G., Fromonot J., Marlinge M., Deharo P., Guieu R., Ruf J. Hyperhomocysteinemia and cardiovascular disease. *Int J Mol Sci*. 2021;22(4):1690. https://doi.org/10.3390/ijms22041690.
10. Lonn E. Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease. *Nat Clin Pract Cardiovasc Med*. 2006;354(15):414–415. https://doi.org/110.1056/NEJMoa060900.
11. Miniyailova N.N., Shishkova Y.N., Rovda Y.I. Hyperhomocysteinemia in children with excessive fat deposition as a factor associated with insulin resistance and cardiac risk. Pediatria. 2017;96(3):39–47. (In Russ.). https://doi.org/10.24110/0031-403X-2017-96-3-39-47.
12. Miao L., Deng G. X., Yin R. X., Nie R. J., Yang S., Wang Y., Li H. No causal effects of plasma homocysteine levels on the risk of coronary heart disease or acute myocardial infarction: A Mendelian randomization study. *European journal of preventive cardiology*. 2021;28(2):227-234. https://doi.org/ 10.1177/2047487319894679.
13. Asmae T., Cito M., Gaouzi A., Chabraoui L. Hyperhomocysteinemia and risk factors of metabolic syndrome in obese children. *Open access journal article*. 2022;1(1):1–4. https://doi.org/10.35702/cases.10004.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

14. Rovda Yu.I., Dorokhov N.A., Skudarnov E.V., Strozenko L.A., Malyuga O.M., Zenchenko O.A. et al. Changes in the level of blood homocystein on the background of connective tissue dysplasia in children. *Bulletin of Medical Science*. 2022;(4):5–12. (In Russ.). https://doi.org/10.31684/25418475-2022-4-5.
15. Kambarova D., Usmanova D. Laboratory diagnostics of genetic predictors of homocysteine in the development of migraine. *Medical Sciene of Uzbekistan*. 2023;(1):19–20. (In Russ.). https://doi.org/10.56121/2181-3612-2023-1-19-20.
16. Söbü E., Düzkalır H.G., Özcabı B., Kaya Özçora G.D. The association between vitamin B12, folate, homocysteine levels, and carotid intima-media thickness in children with obesity: a cross-sectional study. *J Pediatr Endocrinol Metab*. 2022;35(8):1051–1058. https://doi.org/10.1515/jpem-2022-0250.
17. Tadtaeva Z.G., Yakovleva E.E., Amelin A.V. Polymorphism of methylenetetrahydrofolate reductase (MTHFR) folate metabolism gene and hyperhomocysteinemia in migraine. *Physiology and Experimental Therapy*. 2021;65(4):109–115. (In Russ.). https://doi.org/10.25557/0031-2991.2021.04.109-115.
18. Berezovskaya T.S., Miromanova N.A. Diagnostic meaning of determination of homocystein in the blood serum in children with neuroinfections. *Journal Infectology*. 2018;10(1):42–46. (In Russ.). https://doi.org/10.22625/2072-6732-2018-10-1-42-46.
19. Nesterenko O.V., Utts S.R., Borodulin V.B., Goremykin V.I., Elizarova S.Yu., Bobyleva E.V. et al. Hyperhomocysteinemia in children with pyelonephritis. *Russian Bulletin of Perinatology and Pediatrics*. 2016;61(4):88–92. (In Russ.). https://doi.org/10.21508/1027-4065-2016-61-4-88-92.
20. Cordaro M., Siracusa R., Fusco R., Cuzzocrea S., Di Paola R., Impellizzeri D. Involvements of hyperhomocysteinemia in neurological disorders. *Metabolites*. 2021;11(1):37. https://doi.org/10.3390/metabo11010037.
21. Chien S.J., Lin I.C., Hsu C.N., Lo M.H., Tain Y.L. Homocysteine and arginine to asymmetric dimethylarginine ratio associated with blood pressure abnormalities in children with early cronic kidney disease. *Circ J*. 2015;79(9):2031–2037. https://doi.org/10.1253/circj.CJ-15-0412.
22. Li B., Xu Y., Pang D., Zhao Q., Zhang L., Li M., Zhu C. Interrelation between homocysteine metabolism and the development of autism spectrum disorder in children. *Front Mol Neurosci*. 2022;15:947513. https://doi.org/10.3389/fnmol.2022.947513.
23. Godfrey K.M., Titcombe P., El-Heis S., Albert B.B., Tham E.H., Barton S.J. NiPPeR Study Group. Maternal B-vitamin and vitamin D status before, during, and after pregnancy and the influence of supplementation preconception and during pregnancy: Prespecified secondary analysis of the NiPPeR double-blind randomized controlled trial. *PLoS Med*. 2023;20(12):e1004260. https://doi.org/10.1371/journal.pmed.1004260.
24. Naumov A.V. Homocysteine. Medical and biological problems. Minsk: Professional Publishing; 2013. 311 p. (In Russ.).
25. Chirkova N.N., Kislyak O.A. Hyperhomocysteinemia as a risk factor for cardiovascular diseases. *Lechebnoe Delo*. 2006;(2):48–52. (In Russ.). EDN: MSYPSH.
26. Fefelova E.V. Pathogenetic effects of hyperhomocysteinemia in experiment and clinic. MD thesis. Chita: 2021. (In Russ.).
27. Zhang Z., Wei C., Zhou Y., Yan T., Wang Z., Li W., Zhao L. Homocysteine induces apoptosis of human umbilical vein endothelial cells via mitochondrial dysfunction and endoplasmic reticulum stress. *Oxid Med Cell Longev*. 2017;2017:5736506. https://doi.org/10.1155/2017/5736506.
28. Martseva E.M., Evdokimova N.V., Prokopyeva N.E. The role of homocystein in the pathogenesis of arterial hypertension in obesity and comorbid diseases. *Children's Medicine of the North-West*. 2023;11(4):39–46. (In Russ.). https://doi.org/10.56871/CmN-W.2023.18.64.004.
29. Butenko A.V. Homocysteine: influence on biochemical processes in the human body. *Molodoi uchenyi*. 2016;(1):78–82. (In Russ.). EDN: VIIUKR.
30. Yoganathan S., Bhasin H., Garg D., Malik P., Saini A.G., Chandran M. Childhood neurological disorders with hyperhomocystinemia: a case-based review. *Pediatr Neurol*. 2023;146:26–30. https://doi.org/10.1016/j.pediatrneurol.2023.06.003.
31. Liampas I.N., Siokas V., Aloizou A.M., Tsouris Z., Dastamani M., Aslanidou P., Brotis A., Dardiotis E. Pyridoxine, folate and cobalamin for migraine: A systematic review. *Acta Neurol Scand*. 2020;42(2):108–120. https://doi.org/10.1111/ane.13251.
32. Habib S.S., Al-Khlaiwi T., Almushawah A., Alsomali A., Habib S.A. Homocysteine as a predictor and prognostic marker of atherosclerotic cardiovascular disease: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci*. 2023;27(18):8598–8608. https://doi.org/ 10.26355/eurrev_202309_33784.
33. Ding N., Ma S., Chang Q., Xie L., Li G., Hao Y. et al. Novel long noncoding lncARF mediated hyperhomocysteinemia-induced atherosclerosis via autophagy inhibition in foam cells. *J Adv Res*. 2025;73:311–328. https://doi.org/10.1016/j.jare.2024.08.030.
34. Qu R., Han A., Zhao Y., Qu X., Zhu Y. Characteristics of clinical manifestations and molecular genetics of inherited hyperhomocysteinemia in children and adolescents: a single center experience from China. *Front Neurol*. 2025;9(16):1588273. https://doi.org/10.3389/fneur.2025.1588273.
35. Chen W., Liang X., Liang G., Zhao X., Wang J., Jiang Q. Hyperhomocysteinemia and its association with de-

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

creased glomerular filtration rate in patients with chronic kidney disease: a comprehensive meta-analysis. *PeerJ*. 2025;15:13:e20064. https://doi.org/10.7717/peerj.20064.
36. Bai B., Liu L., Liu Y., Yang S., Wu H., Zhang K., Shi L., Zhang Q. High Hcy regulates fluid shear stress pathway activity through histone H3K79 homocysteinylation in hyperhomocysteinemia-related child hypertension. *J Transl Med*. 2025;23(1):525. https://doi.org/10.1186/s12967-025-06483-6.
37. Orimadegun B.E., Ademola A.A., Asinobi A.O. Vitamin B supplementation and homocysteine reduction in nigerian children with nephrotic syndrome: a randomized controlled trial. *World J Nutr Health*. 2025;12(1):8–15. https://doi.org/10.12691/jnh-12-1-2.
38. Zhang Q., Ma S., Kang X., Liu Y., Ma F., Yu F. et al. A dual-targeting bio-liposomes nanodrug repair endothelial cell dysfunction and restore macrophage cholesterol flow homeostasis to treat early atherosclerosis. *J Nanobiotechnology*. 2025;23(1):365. https://doi.org/10.1186/s12951-025-03436-5.
39. Rouphael M., Bitar T., Alarcan H., Gerges P., Sacre Y., Andres C.R., Hleihel W. Exploration of homocysteine metabolism and genetics in autism spectrum disorder. *Nutrients*. 2025;17(23):3761. https://doi.org/10.3390/nu17233761.
40. Al-Tai M.R., Kareem A.A., Saadi N.W., Omran T.B., Abdul Majeed B.A., Ibrahim I.F., Alattar L.A. A study of Iraqi patients with homocysteine remethylation disorders in a tertiary pediatric centre. *Mol Genet Metab Rep*. 2025;11(43):101217. https://doi.org/10.1016/j.ymgmr.2025.101217.
41. Rumińska M., Witkowska-Sędek E., Krajewska M., Stelmaszczyk-Emmel A., Sobol M., Pyrżak B. Evaluation of total homocysteine levels in relation to abdominal fat mass and traditional cardiovascular risk factors in overweight and obese adolescents. *Life (Basel)*. 2025;15(8):1329. https://doi.org/10.3390/life15081329.
42. Zhao W., Zhang Y., Pi Y., Li Y., Zhang H. Clinical and molecular spectrum of patients with methylmalonic acidemia and homocysteinemia complicated by cardiovascular manifestations. *Orphanet J Rare Dis*. 2025;20(1):443. https://doi.org/10.1186/s13023-025-03907-w.

ЛИТЕРАТУРА

1. McCully K.S. Vascular pathology of homocysteinemia: implications for the pathogenesis of arteriosclerosis. *Am J Pathol*. 1969;56(1):111–128.
2. Hermann A., Sitdikova G. Homocysteine: biochemistry, molecular biology and role in disease. *Biomolecules*. 2021;11(5):737. https://doi.org/10.3390/biom11050737.
3. Selhub J., Jacques P.F., Wilson P.W., Rush D., Rosenberg I.H. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. *JAMA*. 1993;270(22):2693–2698. https://doi.org/10.1001/jama.1993.03510220049033.
4. Esnafoglu E., Ozturan D.D. The relationship of severity of depression with homocysteine, folate, vitamin B_{12}, and vitamin D levels in children and adolescents. *Child Adolesc Ment Health*. 2020;25(4):249–255. https://doi.org/10.1111/camh.12387.
5. Ozkarakaya I.S., Celik B., Karakukcu C., Torun Y.A. Effect of zinc supplementation on hemogram parameters and circulating concentrations of homocysteine, vitamin B_{12}, and folate in zinc-deficient children and adolescents. *J Trace Elem Med Biol*. 2021;65:126724. https://doi.org/10.1016/j.jtemb.2021.126724.
6. Caleyachetty R., Echouffo-Tcheugui J.B., Tait C.A., Schilsky S., Forrester T., Kengne A.P. Prevalence of behavioural risk factors for cardiovascular disease in adolescents in low-income and middle-income countries: an individual participant data meta-analysis. *Lancet Diabetes Endocrinol*. 2015;3(7):535–544. https://doi.org/10.1016/S2213-8587(15)00076-5.
7. Morris A.A., Kožich V., Santra S., Andria G., Ben-Omran T.I., Chakrapani A.B., Chapman K.A. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. *J Inherit Metab Dis*. 2017;40:49–74. https://doi.org/10.1007/s10545-016-9979-0.
8. Лукша А.В., Наумов А.В., Максимович Н.А. Функциональное состояние эндотелия сосудов при гипергомоцистеинемии у детей с артериальной гипертензией. *Журнал Гродненского государственного медицинского университета*. 2023;21(1):40–45. https://doi.org/10.25298/2221-8785-2023-21-1-40-45.
9. Paganelli F., Mottola G., Fromonot J., Marlinge M., Deharo P., Guieu R., Ruf J. Hyperhomocysteinemia and cardiovascular disease. *Int J Mol Sci*. 2021;22(4):1690. https://doi.org/10.3390/ijms22041690.
10. Lonn E. Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease. *Nat Clin Pract Cardiovasc Med*. 2006;354(15):414–415. https://doi.org/110.1056/NEJMoa060900.
11. Миняйлова Н.Н., Шишкова Ю.Н., Ровда Ю.И. Гипергомоцистеинемия у детей с избыточным жироотложением как фактор, сопряженный с инсулинорезистентностью и кардиальным риском. *Педиатрия*. 2017;96(3):39. https://doi.org/10.24110/0031-403X-2017-96-3-39-47.
12. Miao L., Deng G.X., Yin R.X., Nie R.J., Yang S., Wang Y., Li H. No causal effects of plasma homocysteine levels on the risk of coronary heart disease or acute myocardial infarction: A Mendelian randomization study. *Eur J Prev Cardiol*. 2021;28(2):227–234. https://doi.org/10.1177/2047487319894679.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

13. Asmae T., Cito M., Gaouzi A., Chabraoui L. Hyperhomocysteinemia and risk factors of metabolic syndrome in obese children. *Open access journal article.* 2022;1(1):1–4. https://doi.org/10.35702/cases.10004.
14. Ровда Ю.И., Дорохов Н.А., Скударнов Е.В., Строзенко Л.А., Малюга О.М., Зенченко О.А. и др. Изменение уровня гомоцистеина крови на фоне дисплазии соединительной ткани у детей. *Бюллетень медицинской науки.* 2022;(4):5–12. https://doi.org/10.31684/25418475-2022-4-5.
15. Кабурова Д.Н., Усманова Д.Д. Лабораторная диагностика генетических предикторов гомоцистеина в развитии мигрени. *Medical Sciene of Uzbekistan.* 2023;(1):19–20. https://doi.org/10.56121/2181-3612-2023-1-19-20.
16. Söbü E., Düzkalır H.G., Özcabı B., Kaya Özçora G.D. The association between vitamin B12, folate, homocysteine levels, and carotid intima-media thickness in children with obesity: a cross-sectional study. *J Pediatr Endocrinol Metab.* 2022;35(8):1051–1058. https://doi.org/10.1515/jpem-2022-0250.
17. Тадтаева З.Г., Яковлева Е.Е., Амелин А.В. Полиморфизм гена фолатного обмена метилентетранидрофолат-редуктазы (MTHFR) и гипергомоцистеинемия при мигрени. *Патологическая физиология и экспериментальная терапия.* 2021;65(4):109–115. https://doi.org/10.25557/0031-2991.2021.04.109-115.
18. Березовская Т.С., Мироманова Н.А. Диагностическое значение определения гомоцистеина в сыворотке крови у детей при нейроинфекциях. *Журнал инфектологии*. 2018;10(1):42–46. https://doi.org/10.22625/2072-6732-2018-10-1-42-46.
19. Нестеренко О.В., Утц С.В., Бородулин В.Б., Горемыкин В.И., Елизарова С.Ю., Бобылева Е.В. и др. Гипергомоцистеинемия у детей с пиелонефритом. *Российский вестник перинатологии и педиатрии.* 2016;61(4):88–92. https://doi.org/10.21508/1027-4065-2016-61-4-88-92.
20. Cordaro M., Siracusa R., Fusco R., Cuzzocrea S., Di Paola R., Impellizzeri D. Involvements of hyperhomocysteinemia in neurological disorders. *Metabolites.* 2021;11(1):37. https://doi.org/10.3390/metabo11010037.
21. Chien S.J., Lin I.C., Hsu C.N., Lo M.H., Tain Y.L. Homocysteine and arginine to asymmetric dimethylarginine ratio associated with blood pressure abnormalities in children with early cronic kidney disease. *Circ J.* 2015;79(9):2031–2037. https://doi.org/10.1253/circj.CJ-15-0412.
22. Li B., Xu Y., Pang D., Zhao Q., Zhang L., Li M., Zhu C. Interrelation between homocysteine metabolism and the development of autism spectrum disorder in children. *Front Mol Neurosci.* 2022;15:947513. https://doi.org/10.3389/fnmol.2022.947513.
23. Godfrey K.M., Titcombe P., El-Heis S., Albert B.B., Tham E.H., Barton S.J. NiPPeR Study Group. Maternal B-vitamin and vitamin D status before, during, and after pregnancy and the influence of supplementation preconception and during pregnancy: Prespecified secondary analysis of the NiPPeR double-blind randomized controlled trial. *PLoS Med.* 2023;20(12):e1004260. https://doi.org/10.1371/journal.pmed.1004260.
24. Наумов А.В. Гомоцистеин. Медико-биологические проблемы. Минск: Профессиональные издания; 2013. 311 с.
25. Чиркова Н.Н., Кисляк О.А. Гипергомоцистеинемия как фактор риска сердечно-сосудистых заболеваний. *Лечебное дело.* 2006;(2):48–52. EDN: MSYPSH.
26. Фефелова Е.В. Патогенетические эффекты гипергомоцистеинемии в эксперименте и клинике. Автореф. … дис. д-ра мед. наук. Чита; 2021.
27. Zhang Z., Wei C., Zhou Y., Yan T., Wang Z., Li W., Zhao L. Homocysteine induces apoptosis of human umbilical vein endothelial cells via mitochondrial dysfunction and endoplasmic reticulum stress. *Oxid Med Cell Longev.* 2017;2017:5736506. https://doi.org/10.1155/2017/5736506.
28. Марцева Е.М., Евдокимова Н.В., Прокопьева Н.Э. Роль гомоцистеина в патогенезе артериальной гипертензии при ожирении и коморбидных заболеваниях. *Children's Medicine of the North-West.* 2023;11(4):39–46. https://doi.org/10.56871/CmN-W.2023.18.64.004.
29. Бутенко А.В. Гомоцистеин: влияние на биохимические процессы в организме человека. *Молодой ученый.* 2016;105(1):78–82. EDN: VIIUKR.
30. Yoganathan S., Bhasin H., Garg D., Malik P., Saini A.G., Chandran M. Childhood neurological disorders with hyperhomocystinemia: a case-based review. *Pediatr Neurol.* 2023;146:26–30. https://doi.org/10.1016/j.pediatrneurol.2023.06.003.
31. Liampas I.N., Siokas V., Aloizou A.M., Tsouris Z., Dastamani M., Aslanidou P., Brotis A., Dardiotis E. Pyridoxine, folate and cobalamin for migraine: A systematic review. *Acta Neurol Scand.* 2020;42(2):108–120. https://doi.org/10.1111/ane.13251.
32. Habib S.S., Al-Khlaiwi T., Almushawah A., Alsomali A., Habib S.A. Homocysteine as a predictor and prognostic marker of atherosclerotic cardiovascular disease: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci.* 2023;27(18):8598–8608. https://doi.org/10.26355/eurrev_202309_33784.
33. Ding N., Ma S., Chang Q., Xie L., Li G., Hao Y. et al. Novel long noncoding lncARF mediated hyperhomocysteinemia-induced atherosclerosis via autophagy inhibition in foam cells. *J Adv Res.* 2025;73:311–328. https://doi.org/10.1016/j.jare.2024.08.030.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

34. Qu R., Han A., Zhao Y., Qu X., Zhu Y. Characteristics of clinical manifestations and molecular genetics of inherited hyperhomocysteinemia in children and adolescents: a single center experience from China. *Front Neurol.* 2025;9(16):1588273. https://doi.org/10.3389/fneur.2025.1588273.
35. Chen W., Liang X., Liang G., Zhao X., Wang J., Jiang Q. Hyperhomocysteinemia and its association with decreased glomerular filtration rate in patients with chronic kidney disease: a comprehensive meta-analysis. *PeerJ.* 2025;15:13:e20064. https://doi.org/10.7717/peerj.20064.
36. Bai B., Liu L., Liu Y., Yang S., Wu H., Zhang K., Shi L., Zhang Q. High Hcy regulates fluid shear stress pathway activity through histone H3K79 homocysteinylation in hyperhomocysteinemia-related child hypertension. *J Transl Med.* 2025;23(1):525. https://doi.org/10.1186/s12967-025-06483-6.
37. Orimadegun B.E., Ademola A.A., Asinobi A.O. Vitamin B supplementation and homocysteine reduction in nigerian children with nephrotic syndrome: a randomized controlled trial. *World J Nutr Health.* 2025;12(1):8–15. https://doi.org/10.12691/jnh-12-1-2.
38. Zhang Q., Ma S., Kang X., Liu Y., Ma F., Yu F. et al. A dual-targeting bio-liposomes nanodrug repair endothelial cell dysfunction and restore macrophage cholesterol flow homeostasis to treat early atherosclerosis. *J Nanobiotechnology.* 2025;23(1):365. https://doi.org/10.1186/s12951-025-03436-5.
39. Rouphael M., Bitar T., Alarcan H., Gerges P., Sacre Y., Andres C.R., Hleihel W. Exploration of homocysteine metabolism and genetics in autism spectrum disorder. *Nutrients.* 2025;17(23):3761. https://doi.org/10.3390/nu17233761.
40. Al-Tai M.R., Kareem A.A., Saadi N.W., Omran T.B., Abdul Majeed B.A., Ibrahim I.F., Alattar L.A. A study of Iraqi patients with homocysteine remethylation disorders in a tertiary pediatric centre. *Mol Genet Metab Rep.* 2025;11(43):101217. https://doi.org/10.1016/j.ymgmr.2025.101217.
41. Rumińska M., Witkowska-Sędek E., Krajewska M., Stelmaszczyk-Emmel A., Sobol M., Pyrżak B. Evaluation of total homocysteine levels in relation to abdominal fat mass and traditional cardiovascular risk factors in overweight and obese adolescents. *Life (Basel).* 2025;15(8):1329. https://doi.org/10.3390/life15081329.
42. Zhao W., Zhang Y., Pi Y., Li Y., Zhang H. Clinical and molecular spectrum of patients with methylmalonic acidemia and homocysteinemia complicated by cardiovascular manifestations. *Orphanet J Rare Dis.* 2025;20(1):443. https://doi.org/10.1186/s13023-025-03907-w.

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Features of body composition in children with atopic dermatitis and different physical development

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ABSTRACT. ***Introduction.*** Atopic dermatitis is one of the most common dermatological diseases in children and adolescents. Like any chronic disease requiring dietary restrictions, it can affect physical development and nutritional status. ***Aim*** – to identify features of body composition in children with atopic dermatitis and different nutritional status based on the body mass index (BMI) Z-score. ***Materials and methods.*** This single-center, cross-sectional cohort study included 74 patients with atopic dermatitis aged 6 to 17 years 11 months (mean age 13.6 years), comprising 40 (54%) boys and 34 (46%) girls. Physical development was assessed using Z-scores. Nutritional status was initially evaluated using the BMI Z-score. Body composition was subsequently determined using bioimpedance analysis. ***Results.*** According to the SCORAD index, a moderate disease course was observed in 59 patients (78%; more frequently in the second childhood and adolescent periods), and a severe course in 15 patients (22%). Satisfactory nutritional status was found in 48 children (66%), obesity in 3 (4%), and overweight in 10 (14%). Undernutrition of varying degrees was detected in 12 patients (16%). In the group with undernutrition, body composition was characterized by a deficit in active cell mass (%ACM) in 66.7%, adequate fat mass (%FM), and a moderate excess of skeletal muscle mass (%SMM) in all children with a BMI Z-score <–1. Among overweight patients, %FM exceeded the norms in 20% and was sharply exceeded in 60%, while %ACM was within age norms in 70%, as was %SMM in 50%. All obese patients had a sharp excess of %FM; among them, 25% had a deficit in both %ACM and %SMM against the background of this excess. Notably, one-third (27%) of children with satisfactory nutritional status according to BMI Z-score had a sharp excess of %FM, and another 18% had an excess relative to sex- and age-specific norms. Only one-third of children with average BMI Z-score values demonstrated normal levels of %ACM, %SMM, and %FM. ***Conclusions.*** Based on the BMI Z-score, satisfactory nutritional status was observed in two-thirds of children with atopic dermatitis (66%), while 13% had deficient and 21% had excess nutritional status or obesity. In each nutritional status group, patients were identified with excessive fat accumulation accompanied by reduced active cellular and skeletal muscle mass. These alterations in body composition began even with satisfactory nutritional status and were more frequent among adolescents and young adults with severe skin lesions according to the SCORAD index.

KEYWORDS: *atopic dermatitis, nutritional status, body composition, bioimpedance analysis, sarcopenia*

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Особенности компонентного состава тела у детей с атопическим дерматитом при разном физическом развитии

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РЕЗЮМЕ. ***Введение.*** Атопический дерматит является одним из самых часто встречающихся дерматологических заболеваний у детей и подростков. Как любое хроническое заболевание, требующее ограничений в питании, может влиять на физическое развитие и нутритивный статус детей. ***Цель*** — выявить нарушения в компонентном составе тела у детей при разном нутритивном статусе по показателю Z-score индекса массы тела (ИМТ) у детей с атопическим дерматитом. ***Материалы и методы.*** В одноцентровое одномоментное когортное исследование вошли 74 пациента с атопическим дерматитом в возрасте от 6 лет до 17 лет 11 месяцев (средний возраст 13,6 года), 40 (54%) из них — мальчики, 34 (46%) — девочки. Изучено физическое развитие по Z-score, нутритивный статус первоначально оценивали по Z-score ИМТ, на втором этапе методом биоимпедансометрии определяли компонентный состав тела. ***Результаты.*** По шкале SCORAD у 59 (78%) пациентов заболевание сопровождалось среднетяжелым течением (чаще в период второго детства и у подростков), а у остальных 15 (22%) — тяжелым течением. Удовлетворительный нутритивный статус был у 48 (66%) пациентов, ожирение — у 3 (4%), избыток массы тела — у 10 (14%) детей. Недостаточность питания разной степени выявлена у 12 (16%) пациентов. В компонентном составе тела для них характерен дефицит доли активной клеточной массы (%АКМ) — у 66,7%, удовлетворительное содержание доли жировой массы (%ЖМ) и умеренный избыток доли скелетно-мышечной массы (%СММ) — у всех детей, имеющих Z-score ИМТ менее –1. У пациентов с избыточной массой тела превышали нормативы %ЖМ — у 20%, а резко превышали у 60%. При этом %АКМ был в пределах возрастных норм у 70%, как и доля СММ — у 50%. Среди пациентов с ожирением у всех отмечено резкое превышение %ЖМ, при этом у 25% дефицит и доли %АКМ, и доли %СММ, что на фоне избытка %ЖМ *является саркопенией*. Треть (27%) детей с удовлетворительным нутритивным статусом по Z-score ИМТ имели резкое превышение %ЖМ, еще 18% — превышение нормальных для половозрастных значений доли %ЖМ, и только треть детей со средними показателями Z-score ИМТ демонстрировали средние показатели доли %АКМ, %СММ и %ЖМ. ***Выводы.*** Удовлетворительный нутритивный статус по данным Z-score ИМТ наблюдался у двух третей детей с атопическим дерматитом (66%), у 13% — дефицитный и у 21% пациентов — избыточный нутритивный статус и ожирение. В каждой группе детей с разными нутритивными статусами выявлены пациенты с избыточным накоплением жировой массы на фоне снижения активной клеточной и скелетно-мышечной массы. Старт изменений в компонентном составе тела начинается еще при удовлетворительном нутритивном статусе. Чаще это были пациенты с тяжелым поражением кожи по шкале SCORAD, подросткового и юношеского возраста.

КЛЮЧЕВЫЕ СЛОВА: *атопический дерматит, нутритивный статус, компонентный состав тела, биоимпедансометрия, саркопения*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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INTRODUCTION

The physical development of children against the background of chronic diseases has been evaluated in numerous scientific publications [1–3], and skin diseases are no exception [4, 5]. It is recognized that severe pathology of organs responsible for vital functions is typically associated with a deceleration of physical development (body mass deficit, growth stagnation) [6–8]. At the same time, the impact of chronic dermatoses on the nutritional status and physical development of children remains insufficiently studied [4, 9, 10]. This gap persists despite the considerable prevalence of atopic dermatitis in the pediatric population (15–20% according to various studies) [11, 12] and highlights the need for an in-depth investigation of this issue.

Of particular importance is the examination of the relationship between atopic dermatitis severity and physical development. Moderate-to-severe and severe disease course exerts a systemic effect on the child's body, extending beyond skin involvement [13, 14]. Sleep disturbances, dietary restrictions, skin condition (hyperemia, dryness, pruritus), and psycho-emotional stress create a vicious cycle capable of critically influencing the body's growth and developmental processes [15, 16].

Researchers note the polymorphic spectrum of this problem, ranging from deficiency to excess, which necessitates a clear differentiation by severity. On the one hand, children with mild atopic dermatitis most frequently present with excess body weight and obesity [14, 17–19]. This is attributed to the side effects of topical corticosteroids and physical inactivity due to reduced physical loads [20]. On the other hand, a number of authors report the development of deficiency states and delays in physical development in children with moderate and severe forms of atopic dermatitis [10, 21, 22]. This is linked to chronic inflammation, protein loss through damaged skin, and strict elimination diets [9, 22–25].

AIM

The aim of this study was to identify disturbances in body composition in children with atopic dermatitis and different nutritional status as defined by body mass index (BMI) Z-score.

MATERIALS AND METHODS

This single-center, cross-sectional cohort study enrolled 74 patients with atopic dermatitis aged 6 years to 17 years 11 months (mean age, 13.6 years); 40 (54%) were boys and 34 (46%) were girls.

All children underwent a unified examination protocol at the Dermatovenereology Department of a tertiary-level clinic (Saint Petersburg State Pediatric Medical University, Ministry of Health of the Russian Federation). The protocol included collection of life and disease history and assessment of skin involvement severity using the SCORAD scale. Physical development, including height and body mass, was evaluated, and BMI (kg/m²) was calculated. Physical development and nutritional status were assessed using WHO Anthro Plus reference tables with determination of Z-scores. To verify nutritional status disturbances, body composition was analyzed by bioimpedance analysis using the MEDASS system (Russia). The following key parameters were assessed in relation to sex- and age-specific reference values: fat mass (FM) and its percentage (%FM), active cell mass (ACM) and its percentage (%ACM), and skeletal muscle mass (SMM) and its percentage (%SMM). Patterns of physical development were analyzed by age, sex, and severity of skin involvement according to the SCORAD scale.

Legal representatives and children over 15 years of age provided written informed voluntary consent for the conduct / possible conduct of diagnostic and anthropometric procedures before enrollment in the study. The study was approved by the Ethics Committee of Saint Petersburg State Pediatric Medical University on 08 November 2023, Protocol No. 32/01.

Statistical analysis was performed using StatTech software, version 3.1.8. Categorical variables are presented as absolute numbers and percentages (%). Continuous variables were tested for normality of distribution using the Kolmogorov–Smirnov test and the Shapiro–Wilk test. When the distribution deviated from normal, the Kruskal–Wallis test was applied. When statistically significant differences were identified, the Mann–Whitney U test was applied. A two-tailed p-value of <0.05 was considered statistically significant.

RESULTS

The 74 patients (100%) were stratified into four age groups: first childhood (n=33, 45%), second

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childhood (n=17, 23%), adolescence (n=10, 13%), and youth (n=14, 19%). The first childhood group predominated in the study sample. Pruritus, xerosis, desquamation, lichenification, and skin infiltration were documented in 100% of the children enrolled in the study. Cutaneous hyperemia was observed in only 24% of the children. According to the SCORAD severity grading, 59 (78%) patients had moderate atopic dermatitis and the remaining 15 (22%) had severe disease. The most pronounced SCORAD changes in severe atopic dermatitis were found among adolescent boys (Fig. 2).

Assessment of physical development (body mass, height, and BMI) across the different age groups revealed a noteworthy pattern. Specifically, a leftward shift of indicators (into the deficit zone) was observed in children of first childhood, while a tendency toward a rightward shift (into the area of excess values) was noted in adolescents and youths (Fig. 1).

Nutritional status was initially assessed using BMI Z-scores. Two-thirds of the children (n=48; 66%) had a satisfactory nutritional status (corresponding to an average BMI Z-score). Obesity was diagnosed in 3 patients, and overweight in 10 children. Malnutrition of varying severity (undernutrition) was identified in 12 patients. Body mass deficit and growth retardation were diagnosed in the first and second childhood periods in the setting of moderate atopic dermatitis. Starting from adolescence, physical development indicators exhibited a rightward shift, reaching the range of high values by youth. Among children with deficient BMI Z-scores (corresponding to a low BMI Z-score), 75% had moderate atopic dermatitis according to the SCORAD scale. Overall, deficient BMI Z-scores predominated in girls across all age periods, with the exception of adolescence. Among children with excess BMI Z-scores (corresponding to overweight and obesity according to Z-score BMI), 86% also had moderate atopic dermatitis according to the SCORAD scale. This group was predominantly composed of male patients of adolescent and youth age ($p < 0.005$).

Body composition was assessed by age using qualitative indicators separately for children with satisfactory nutritional status according to BMI Z-score, for children with deficient nutritional status, and for those with excess nutritional status. The bioimpedance analysis data were scored as follows: 1 — deficient, 2 — satisfactory, and 3 — excess. A score of 4 denoted values exceeding

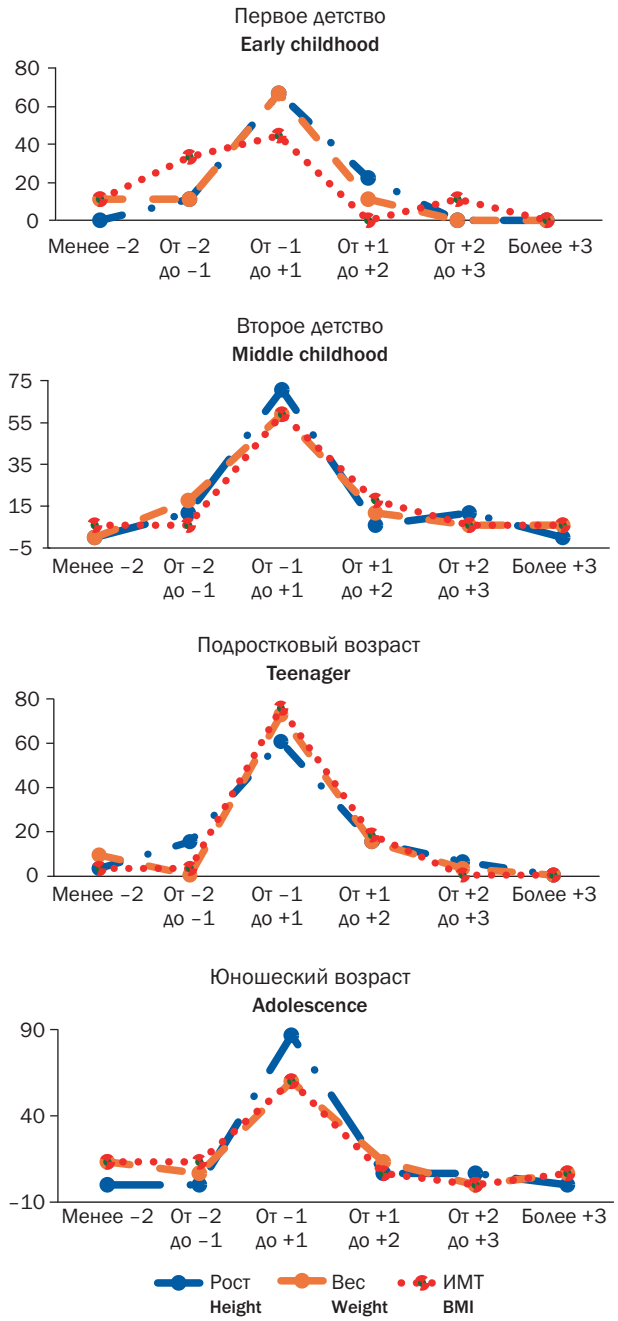

Fig. 1. The Z-score indicators of children's physical development by age (the figure is prepared by the authors using their own data)

Рис. 1. Показатели Z-score физического развития детей в зависимости от возрастного периода (рисунок подготовлен авторами по собственным данным)

100% of age-specific reference values, adjusted for height.

Among children with deficient BMI Z-scores (n=12; 16%), a deficit of active cell mass percentage (%ACM) was characteristic in 66.7%. At the same time, the percentage of fat mass (%FM) was satisfactory and the percentage of skeletal muscle mass

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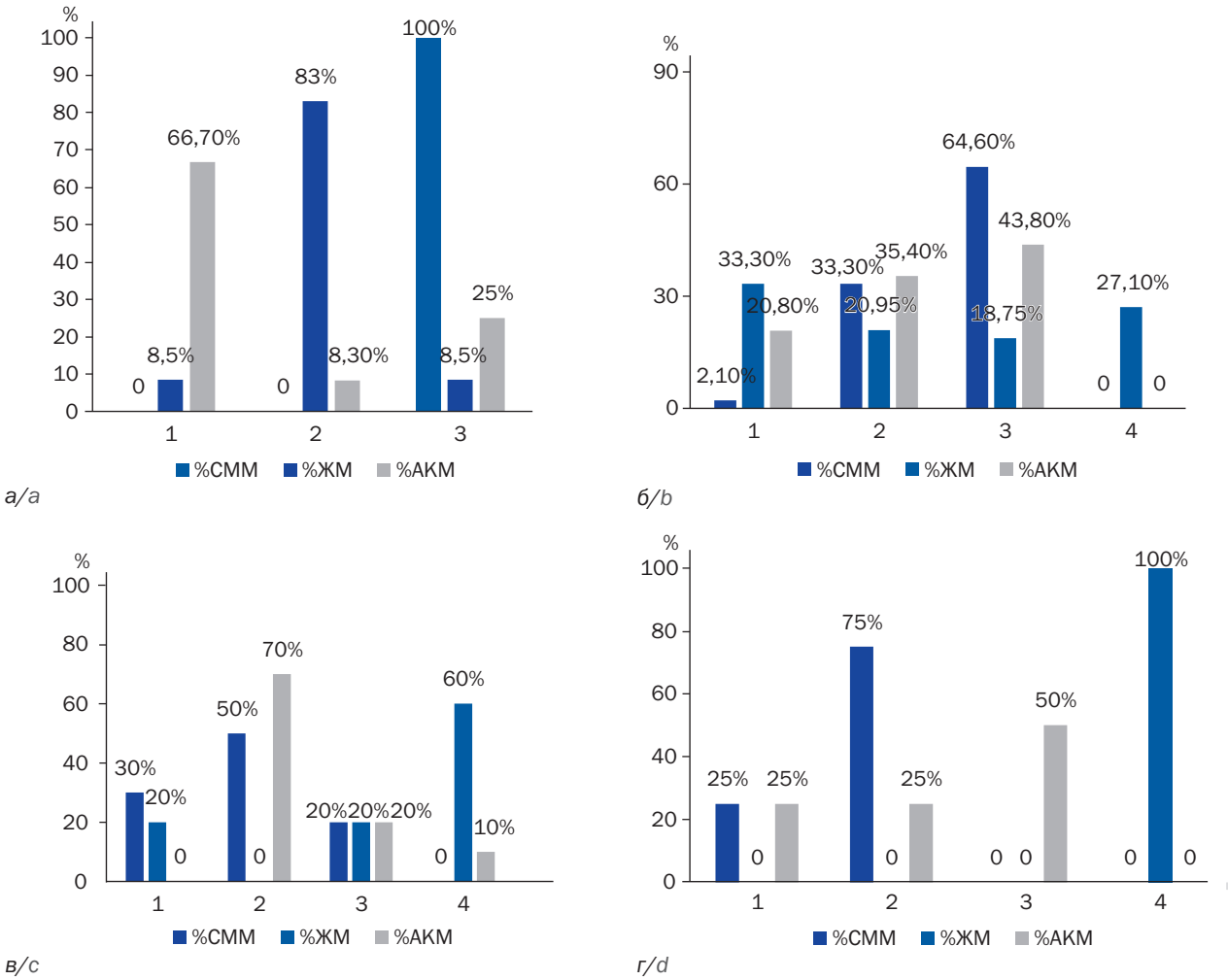

Fig. 2. Individual indicators of body composition (proportion of skeletal muscle mass (%CMM), proportion of fat mass (%ЖМ), proportion of active cell mass (%АКМ)) in children with low BMI Z-score indicators: *a* — with low BMI Z-score indicators; *b* — in children with average BMI Z-score; *c* — overweight according to the Z-score BMI; *d* — in obese children according to Z-score BMI. Columns: 1 — deficiency indicators, 2 — average values, 3 — excess indicators; 4 — excess of more than 100% depending on age standards considering growth (the figure is prepared by the authors using their own data)

Рис. 2. Отдельные показатели компонентного состава тела (доли скелетно-мышечной массы (%СММ), жировой массы (%ЖМ), активной клеточной массы (%АКМ)) у детей: *а* — дефицитный нутритивный статус; *б* — удовлетворительный нутритивный статус (Z-score ИМТ); *в* — избыточный нутритивный статус (Z-score ИМТ); *г* — ожирение (Z-score ИМТ). Столбцы: 1 — дефицитные показатели; 2 — средние значения; 3 — избыточные показатели; 4 — превышение более 100% в зависимости от возрастных нормативов с учетом роста (рисунок подготовлен авторами по собственным данным)

(%SMM) was moderately excessive in all children with a BMI Z-score below −1 (Fig. 2, *a*).

In patients with excess BMI Z-scores, the percentage of fat mass exceeded reference values in 20% of cases and was markedly excessive in 60%. Concurrently, the percentage of active cell mass fell within age-specific reference values in 70% of patients, and the percentage of skeletal muscle mass was within normal limits in 50% of those examined. Of particular note are children with a deficit of skeletal muscle mass percentage against the background of excess body mass according to BMI, a condition that may be regarded as sarcopenia (Fig. 2, *c*) [26, 27].

Among patients with obesity, a marked excess of fat mass percentage was observed in all cases, whereas 25% exhibited a deficit of both %ACM and %SMM, which, in the setting of excess %FM, is regarded as sarcopenia (Fig. 2, *d*).

Of greatest interest are patients with satisfactory BMI Z-scores. Their body composition proved to be the most heterogeneous. One-third (27%) of

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these children had a markedly excessive %FM, another 18% had an excess of %FM relative to sex- and age-specific reference values, and only one-third of children with satisfactory BMI Z-scores demonstrated average values of %ACM, %SMM, and %FM. Excess body mass and obesity were more frequently encountered among boys in the adolescent and youth age group ($p < 0.005$).

DISCUSSION

This study included predominantly children with severe atopic dermatitis. Physical development indicators varied across age periods. However, body composition data in children with satisfactory nutritional status according to BMI Z-score revealed fat mass accumulation in 18% and a marked excess relative to age- and sex-specific reference values in 27% of children. Physical development indicators in children with chronic diseases do not always reflect the true nutritional status [4]. Both satisfactory values of skeletal muscle mass, active cell mass, and fat mass, as well as various combinations of %SMM, %ACM, and %FM proportions, may be concealed behind deficient or excess body mass or BMI Z-scores [2, 24, 27, 28]. In the long-term course of chronic diseases requiring systemic therapy, the proportion of patients with excess body mass and obesity increases toward adolescence and youth [5]. Notably, the onset of changes in body composition occurs while mean BMI Z-scores still fall within the satisfactory range [29], a pattern also observed in our study. The replacement of active cell mass and skeletal muscle mass by fat mass, together with the initiation of fat mass accumulation in the setting of average body mass relative to height and satisfactory nutritional status according to BMI Z-score, may be regarded as the onset of obesity [9, 10, 18, 25]. These changes also mark the onset of metabolic risk in these patients [29].

CONCLUSIONS

Satisfactory nutritional status according to BMI Z-score was documented in two-thirds of children with atopic dermatitis (66%), whereas deficient nutritional status was identified in 13% and excess nutritional status and obesity in 21% of patients. In each nutritional status group, patients with excessive fat mass accumulation against the background of reduced active cell mass and skeletal muscle mass were detected. In patients with excess body mass and obesity, these alterations are an anticipated finding: a marked excess and predominance of fat mass percentage over active cell mass and skeletal muscle mass were observed in 100% of cases. By contrast, similar alterations were identified for the first time in the group of children with satisfactory nutritional status. Only one-third of children with satisfactory nutritional status according to BMI Z-score demonstrated average body composition values for age and physical development. Among the remaining children, one-third (33%) exhibited a fat mass deficit, 18% had an excess, and 27% had a marked excess (exceeding 100%) of fat mass percentage relative to reference values in body structure. All these patients had severe skin involvement according to the SCORAD scale and were of adolescent and youth age.

ADDITIONAL INFORMATION

Authors' contribution. Kh.Z.H. Al-Nawaiseh — examination of patients, bioimpedance measurement, anthropometric research, article preparation; E.S. Myslinchuk — analysis of anthropometric data, graphic representation of anthropometric drawings; E.S. Bolshakova — examination of patients, permission to work with patients; A.A. Sakovtseva — bioimpedance measurement, data analysis; I.N. Markovskaya — article writing, analysis of body component composition, graphic representation of body component composition; A.N. Zavyalova — article idea, article editing.

All authors read and approved the final version before publication.

Competing interests. The authors declare that they have no competing interests.

Consent for publication. Written consent was obtained from legal representatives of the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Х.З.Х. Аль-Навайсех — осмотр пациентов, биоимпедансометрия, антропометрические исследование, оформление статей; Е.С. Мыслинчук — анализ антропометрических данных, графическое изображение антропометрических рисунков; Е.С. Большакова — осмотр пациентов, разрешение на работу

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Все авторы прочли и одобрили финальную версию перед публикацией.

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REFERENCES

1. Zvonkova N.G., Borovik T.E., Chernikov V.V., Gemdzhian E.G., Yatsyk S.P., Fisenko A.P. et al. Adaptation and validation of the STRONGkids nutritional risk screening tool for the Russian language speaking audience. *Pediatria n.a. G.N. Speransky*. 2022;101(4):157–165. (In Russ.). https://doi.org/10.24110/0031-403X-2022-101-4-155-164.
2. Zavyalova A.N., Novikova V.P., Klikunova K.A. Nutritional status and feeding problems in children with dysphagia and cerebral palsy in diff erent social settings. *Experimental and Clinical Gastroenterology*. 2022;198(2):21–29. (In Russ.) https://doi.org/10.31146/1682-8658-ecg-198-2-21-29.
3. Pavlovskaya E.V., Zubovich A.I., Strokova T.V. Nutritional disorders in children with rheumatic diseases and opportunities for their correction. *Pediatric Nutrition*. 2022;20(3):40–50. (In Russ.). https://doi.org/10.20953/1727-5784-2022-3-40-50.
4. Kozlova E.V., Borovik T.E., Zvonkova N.G., Fisenko A.P., Bushueva T.V., Skvortsova V.A. et al. The nutritional status in children with atopic dermatitis caused by food allergies. *Pediatria n.a. G.N. Speransky*. 2021;100(2):119–126. (In Russ.).
5. Zavyalova A.N., Matalygina O.A., Listopadova A.P., Buzina D.V., Rusinova E.A., Yakovleva M.N., Slobodchikova M.P. Physical development of children with atopic dermatitis at diff erent age periods. *Preventive and Clinical Medicine*. 2021;2(79):31–41. (In Russ.). https://doi.org/10.47843/2074-9120_2021_2_31.
6. Firsova L.A., Zavyalova A.N., Lebedev D.A. Physical development of children with chronic kidney decease. *Nutrition*. 2020;10(2):5–11. (In Russ.). https://doi.org/10.20953/2224-5448-2020-2-5-11.
7. Zenkova K.I., Skvortsova V.A., Potapov A.S., Borovik T.E., Fisenko A.P., Sokolov I. et al. Nutritional status and the risks for its impairment in children with Crohn's disease: a crosssectional study. *Pediatria n.a. G.N. Speransky*. 2024;103(5):99–107. (In Russ.). https://doi.org/10.24110/0031-403X2024-103-5-99-107.
8. Zakharova I.N., Berezhnaya I.V., Simakova M.A. Growth retardation in children with allergies: A review. *Pediatrics. Consilium Medicum*. 2023;(1):34–41. (In Russ.). https://doi.org/10.26442/26586630.2023.1.202182.
9. Yew Y.W., Loh M., Guan Thng S.T., Chambers J.C. Investigating causal relationships between Body Mass Index and risk of atopic dermatitis: A Mendelian randomization analysis. *Sci Rep*. 2020;10(1):15279. https://doi.org/10.1038/s41598-020-72301-2.
10. Meyer R. Nutritional disorders resulting from food allergy in children. *Pediatr Allergy Immunol*. 2018;29(7):689–704. https://doi.org/10.1111/pai.12960.
11. Ramessur R., Dand N., Langan S.M., Saklatvala J., Fritzsche M.C., Holland S. et al. Defining disease severity in atopic dermatitis and psoriasis for the application to biomarker research: an interdisciplinary perspective. *Br J Dermatol*. 2024;191(1):14–23. https://doi.org/10.1093/bjd/ljae080.
12. Barinova A.N., Gelezhe K.A., Zamyatina Yu.E., Zaslavsky D.V. et al. Atopic dermatitis. An interdisciplinary approach to diagnosis and treatment. Moscow: GEOTAR-Media; 2025. 288 p. (In Russ.). https://doi.org/10.33029/9704-9070-9-ADM-2025-1-288.
13. Fishbein A.B., Silverberg J.I., Wilson E.J., Ong P.Y. Update on atopic dermatitis: diagnosis, severity assessment, and treatment selection. *J Allergy Clin Immunol Pract*. 2020;8(1):91–101. https://doi.org/10.1016/j.jaip.2019.06.044.
14. Khavkin A.I., Novikova V.P., Matalygina O.A., Zavyalova A.N. Allergy and obesity: identification of common links of pathogenesis as the basis of an adequate therapy strategy. *Clinical Practice in Pediatrics*. 2022;17(4):59–66. (In Russ.). https://doi.org/10.20953/1817-7646-2022-4-59-66.
15. Paller A.S., Rangel S.M., Chamlin S.L., Hajek A., Phan S., Hogeling M. et al.; Pediatric Dermatology Research Alliance. Stigmatization and mental health impact of chronic pediatric skin disorders. *JAMA Dermatol*. 2024;160(6):621–630. https://doi.org/10.1001/jamadermatol.2024.0594.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

16. Huang E., Ong P.Y. Severe atopic dermatitis in children. *Curr Allergy Asthma Rep*. 2018;18(6):35. https://doi.org/10.1007/s11882-018-0788-4.
17. De Simoni E., Rizzetto G., Molinelli E., Lucarini G., Mattioli-Belmonte M., Capodaglio I. et al. Metabolic comorbidities in pediatric atopic dermatitis: a narrative review. *Life (Basel)*. 2022;13(1):2. https://doi.org/10.3390/life13010002.
18. Gilaberte Y., Pérez-Gilaberte J.B., Poblador-Plou B., Bliek-Bueno K., Gimeno-Miguel A., Prados-Torres A. Prevalence and comorbidity of atopic dermatitis in children: a large-scale population study based on real-world data. *J Clin Med*. 2020;9(6):1632. https://doi.org/10.3390/jcm9061632.
19. von Stülpnagel C.C., Augustin M., Düpmann L., da Silva N., Sommer R. Mapping risk factors for cumulative life course impairment in patients with chronic skin diseases — a systematic review. *J Eur Acad Dermatol Venereol*. 2021;35(11):2166–2184. https://doi.org/10.1111/jdv.17348.
20. Elhage K.G., Kranyak A., Jin J.Q., Haran K., Spencer R.K., Smith P.L. et al. Mendelian randomization studies in atopic dermatitis: a systematic review. *J Invest Dermatol*. 2024;144(5):1022–1037. https://doi.org/10.1016/j.jid.2023.10.016.
21. Ahn K., Penn R.B., Rattan S., Panettieri R.A .Jr, Voight B.F., An S.S. Mendelian Randomization Analysis Reveals a Complex Genetic Interplay among Atopic Dermatitis, Asthma, and Gastroesophageal Reflux Disease. *Am J Respir Crit Care Med*. 2023;207(2):130–137. https://doi.org/10.1164/rccm.202205-0951OC.
22. Low D.W., Jamil A., Md Nor N., Kader Ibrahim S.B., Poh B.K. Food restriction, nutrition status, and growth in toddlers with atopic dermatitis. *Pediatr Dermatol*. 2020;37(1):69–77. https://doi.org/10.1111/pde.14004.
23. Grigorieva K.M., Sinyugina A.I., Novikova V.P., Zavyalova A.N., Klikunova K.A. Nutritional status of children suffering from allergic enteropathy. *University Therapeutic Journal*. 2023;5(1):122–129. (In Russ.). https://doi.org/10.56871/UTJ.2023.38.66.010.
24. Jung M.J., Kim H.R., Kang S.Y., Kim H.O., Chung B.Y., Park C.W. Effect of weight reduction on treatment outcomes for patients with atopic dermatitis. *Ann Dermatol*. 2020;32(4):319–326. https://doi.org/10.5021/ad.2020.32.4.319.
25. Gervazieva V.B., Mazurina S.A., Lysogora V.A. Allergic diseases in infants with increased body weight and obesity. *Clinical Practice in Pediatrics*. 2017;12(4):54–58. (In Russ.). https://doi.org/10.20953/1817-7646-2017-4-54-58.
26. Zavyalova A.N., Novikova V.P., Yakovleva M.N. Sarcopenia in children: Lecture. *Medical Council*. 2024;(1):245–253. (In Russ.). https://doi.org/10.21518/ms2023-470.
27. Zavyalova A.N., Novikova V.P., Klikunova K.S., Gavshchuk M.V., Lisovsky O.V. Method for diagnosing sarcopenia. Eurasian Patent for Invention No. 044862, October 6, 2023. URL: https://old.eapo.org/ru/patents/reestr/patent.php?id=44862 (accessed: 15.12.2025). (In Russ.).
28. Melnikova K.S., Revyakina V.A. Assessment of nutritional status in children with atopic dermatitis associated with food allergy. *Doctor.Ru*. 2024;23(6):27–31. (In Russ.). https://doi.org/10.31550/1727-2378-2024-23-6-27-31.
29. Ali Z., Ulrik C.S., Agner T., Thomsen S.F. Association between atopic dermatitis and the metabolic syndrome: a systematic review. *Dermatology*. 2018;234(3-4):79–85. https://doi.org/10.1159/000491593.

ЛИТЕРАТУРА

1. Звонкова Н.Г., Боровик Т.Э., Черников В.В., Гемджян Э.Г., Яцык С.П., Фисенко А.П. и др. Адаптация и валидация русскоязычной версии опросника STRONGkids для оценки нутритивного риска у детей. *Педиатрия им. Г.Н. Сперанского*. 2022;101(4):155–164. https://doi.org/10.24110/0031-403X-2022-101-4-155-164.
2. Завьялова А.Н., Новикова В.П., Кликунова К.А. Нутритивный статус и проблемы при кормлении у детей с дисфагией и детским церебральным параличом, находящихся в разных социальных условиях. *Экспериментальная и клиническая гастроэнтерология*. 2022;198(2):21–29. https://doi.org/10.31146/1682-8658-ecg-198-2-21-29.
3. Павловская Е.В., Зубович А.И., Строкова Т.В. Нутритивные нарушения у детей с ревматическими заболеваниями и возможности их коррекции. *Вопросы детской диетологии*. 2022;20(3):40–50. https://doi.org/10.20953/1727-5784-2022-3-40-50.
4. Козлова Е.В., Боровик Т.Э., Звонкова Н.Г., Фисенко А.П., Бушуева Т.В., Скворцова В.А. и др. Нутритивный статус у детей с атопическим дерматитом, обусловленным пищевой аллергией. *Педиатрия им. Г.Н. Сперанского*. 2021;100(2):119–126.
5. Завьялова А.Н., Маталыгина О.А., Листопадова А.П., Бузина Д.В., Русинова Е.А., Яковлева М.Н., Слободчикова М.П. Физическое развитие детей с атопическим дерматитом в разные возрастные периоды. *Профилактическая и клиническая медицина*. 2021;2(79):31–41. https://doi.org/10.47843/2074-9120_2021_2_31.
6. Фирсова Л.А., Завьялова А.Н., Лебедев Д.А. Физическое развитие детей с хронической болезнью почек. *Вопросы диетологии*. 2020;10(2):5–11. https://doi.org/10.20953/2224-5448-2020-2-5-11.
7. Зенкова К.И., Скворцова В.А., Потапов А.С., Боровик Т.Э., Фисенко А.П., Соколов И. и др. Оценка нутритивного статуса и рисков его нарушения у детей с болезнью Крона: одномоментное исследование. *Педиатрия им. Г.Н. Сперанского*. 2024;103(5):99–107. https://doi.org/10.24110/0031-403X-2024-103-5-99-107.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

8. Захарова И.Н., Бережная И.В., Симакова М.А. Задержка роста у детей с аллергией. *Педиатрия. Consilium Medicum*. 2023;(1):34–41. https://doi.org/10.26442/26586630.2023.1.202182.
9. Yew Y.W., Loh M., Guan Thng S.T., Chambers J.C. Investigating causal relationships between Body Mass Index and risk of atopic dermatitis: A Mendelian randomization analysis. *Sci Rep*. 2020;10(1):15279. https://doi.org/10.1038/s41598-020-72301-2.
10. Meyer R. Nutritional disorders resulting from food allergy in children. *Pediatr Allergy Immunol*. 2018;29(7):689–704. https://doi.org/10.1111/pai.12960.
11. Ramessur R., Dand N., Langan S.M., Saklatvala J., Fritzsche M.C., Holland S. et al. Defining disease severity in atopic dermatitis and psoriasis for the application to biomarker research: an interdisciplinary perspective. *Br J Dermatol*. 2024;191(1):14–23. https://doi.org/10.1093/bjd/ljae080.
12. Баринова А.Н., Гележе К.А., Замятина Ю.Е., Заславский Д.В. и др. Атопический дерматит. Междисциплинарный подход к диагностике и лечению. М.: ГЭОТАР-Медиа; 2025. 288 с. https://doi.org/10.33029/9704-7812-7-ADM-2024-1-288.
13. Fishbein A.B., Silverberg J.I., Wilson E.J., Ong P.Y. Update on atopic dermatitis: diagnosis, severity assessment, and treatment selection. *J Allergy Clin Immunol Pract*. 2020;8(1):91–101. https://doi.org/10.1016/j.jaip.2019.06.044.
14. Хавкин А.И., Новикова В.П., Маталыгина О.А., Завьялова А.Н. Аллергия и ожирение: выявление общих звеньев патогенеза как основа стратегии адекватной терапии. *Вопросы практической педиатрии*. 2022;17(4):59–66. https://doi.org/10.20953/1817-7646-2022-4-59-66.
15. Paller A.S., Rangel S.M., Chamlin S.L., Hajek A., Phan S., Hogeling M. et al.; Pediatric Dermatology Research Alliance. Stigmatization and mental health impact of chronic pediatric skin disorders. *JAMA Dermatol*. 2024;160(6):621–630. https://doi.org/10.1001/jamadermatol.2024.0594.
16. Huang E., Ong P.Y. Severe atopic dermatitis in children. *Curr Allergy Asthma Rep*. 2018;18(6):35. https://doi.org/10.1007/s11882-018-0788-4.
17. De Simoni E., Rizzetto G., Molinelli E., Lucarini G., Mattioli-Belmonte M., Capodaglio I. et al. Metabolic comorbidities in pediatric atopic dermatitis: a narrative review. *Life (Basel)*. 2022;13(1):2. https://doi.org/10.3390/life13010002.
18. Gilaberte Y., Pérez-Gilaberte J.B., Poblador-Plou B., Bliek-Bueno K., Gimeno-Miguel A., Prados-Torres A. Prevalence and comorbidity of atopic dermatitis in children: a large-scale population study based on real-world data. *J Clin Med*. 2020;9(6):1632. https://doi.org/10.3390/jcm9061632.
19. von Stülpnagel C.C., Augustin M., Düpmann L., da Silva N., Sommer R. Mapping risk factors for cumulative life course impairment in patients with chronic skin diseases — a systematic review. *J Eur Acad Dermatol Venereol*. 2021;35(11):2166–2184. https://doi.org/10.1111/jdv.17348.
20. Elhage K.G., Kranyak A., Jin J.Q., Haran K., Spencer R.K., Smith P.L. et al. Mendelian randomization studies in atopic dermatitis: a systematic review. *J Invest Dermatol*. 2024;144(5):1022–1037. https://doi.org/10.1016/j.jid.2023.10.016.
21. Ahn K., Penn R.B., Rattan S., Panettieri R.A .Jr, Voight B.F., An S.S. Mendelian Randomization Analysis Reveals a Complex Genetic Interplay among Atopic Dermatitis, Asthma, and Gastroesophageal Reflux Disease. *Am J Respir Crit Care Med*. 2023;207(2):130–137. https://doi.org/10.1164/rccm.202205-0951OC.
22. Low D.W., Jamil A., Md Nor N., Kader Ibrahim S.B., Poh B.K. Food restriction, nutrition status, and growth in toddlers with atopic dermatitis. *Pediatr Dermatol*. 2020;37(1):69–77. https://doi.org/10.1111/pde.14004.
23. Григорьева К.М., Синюгина А.И., Новикова В.П., Завьялова А.Н., Кликунова К.А. Нутритивный статус детей, страдающих аллергической энтеропатией. *University Therapeutic Journal*. 2023;5(1):122–129. https://doi.org/10.56871/UTJ.2023.38.66.010.
24. Jung M.J., Kim H.R., Kang S.Y., Kim H.O., Chung B.Y., Park C.W. Effect of weight reduction on treatment outcomes for patients with atopic dermatitis. *Ann Dermatol*. 2020;32(4):319–326. https://doi.org/10.5021/ad.2020.32.4.319.
25. Гервазиева В.Б., Мазурина С.А., Лысогора В.А. Аллергические заболевания у детей с повышенной массой тела и ожирением. *Вопросы практической педиатрии*. 2017;12 (4):54–58. https://doi.org/10.20953/1817-7646-2017-4-54-58.
26. Завьялова А.Н., Новикова В.П., Яковлева М.Н. Саркопения у детей: лекция. *Медицинский совет*. 2024;18(1):245–253. https://doi.org/10.21518/ms2023-470.
27. Завьялова А.Н., Новикова В.П., Кликунова К.С., Гавщук М.В., Лисовский О.В. Способ диагностики саркопении. Евразийский патент на изобретение № 044862, 06.10.2023. URL: https://old.eapo.org/ru/patents/reestr/patent.php?id=44862 (дата обращения: 15.12.2025).
28. Мельникова К.С., Ревякина В.А. Оценка пищевого статуса у детей с атопическим дерматитом, ассоциированным с пищевой аллергией. *Доктор.Ру*. 2024;23(6):27–31. https://doi.org/10.31550/1727-2378-2024-23-6-27-31.
29. Ali Z., Ulrik C.S., Agner T., Thomsen S.F. Association between atopic dermatitis and the metabolic syndrome: a systematic review. *Dermatology*. 2018;234(3-4):79–85. https://doi.org/10.1159/000491593.

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Electrocardiographic features in 6-year-old children who were born with extremely low, very low and low body weight

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ABSTRACT. ***Introduction.*** Identification of electrocardiographic markers of risk of cardiovascular diseases is an actual topic in connection with modern possibilities of nursing of children with birth weight less than 2500 grams. ***The aim of the study*** – to evaluate electrocardiographic parameters in children aged 6 years, born with extremely low, very low and low body weight. ***Materials and methods.*** An electrocardiographic analysis was performed on 6-year-old children who were born with low birth weights. ***Results.*** No significant differences were found in electrocardiographic parameters between 6-year-old children who were born small for gestational age and those who were born weighing more than 2500 g. ***Conclusion.*** Children with extremely low, very low and low body weight at birth are at risk of developing cardiovascular pathology, which requires in-depth diagnostics and further research.

KEYWORDS: *children, electrocardiography, extremely low body weight, ENBW, very low body weight, VLBW, low body weight, LBW*

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Оригинальная статья

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Электрокардиографические особенности у детей 6-летнего возраста, родившихся с экстремально низкой, очень низкой и низкой массой тела

Азалия Ирековна Мулюкова[1], Людмила Викторовна Яковлева[1], Зиля Климовна Галышева[1, 2], Гузель Наилевна Шангареева[1]

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РЕЗЮМЕ. ***Введение.*** Выявление электрокардиографических маркеров риска развития сердечно-сосудистых заболеваний является актуальной темой в связи с современными возможностями выхаживания детей с массой тела при рождении менее 2500 г. ***Цель исследования*** – оценить электрокардиографические параметры у детей в возрасте 6 лет, родившихся с экстремально низкой, очень низкой и низкой массой тела. ***Материалы и методы.*** Проведен анализ электрокардиограмм у детей шестилетнего возраста, родившихся маловесными. ***Результаты.*** Не выявлено значимых различий в электрокардиографических показателях у детей шестилетнего возраста, родившихся маловесными, и детей с массой тела более 2500 г при рождении. ***Заключение.*** Дети с экстремально низкой, очень низкой и низкой массой тела при рождении составляют группу риска по развитию сердечно-сосудистой патологии, что требует углубленной диагностики и дальнейших исследований.

КЛЮЧЕВЫЕ СЛОВА: *дети, электрокардиография, экстремально низкая масса тела, ЭНМТ, очень низкая масса тела, ОНМТ, низкая масса тела, НМТ*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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INTRODUCTION

Advances in modern medicine have been marked by substantial progress in the care of preterm infants weighing less than 2500 g. The steady improvement in survival of newborns with low birth weight (LBW), very low birth weight (VLBW), and extremely low birth weight (ELBW) has been driven by refinements in medical technology. This progress raises new scientific challenges. Particular relevance is currently attached to the evaluation of long-term sequelae involving various organs and systems in this group of children [1].

The cardiovascular system is exposed to factors related to preterm birth [2]. Accumulated scientific evidence indicates that children born with low birth weight constitute a high-risk group for the development of cardiometabolic disease in adulthood, within the framework of the so-called Developmental Origins of Health and Disease (DOHaD) concept. According to this concept, adverse intrauterine conditions program structural and functional changes in organs, including the cardiovascular system, thereby predisposing to future cardiac disease [3–5].

The cardiovascular system of children born with low birth weight undergoes a range of adaptive and remodeling processes [6]. Compensating for intrauterine hypoxia, the body redistributes cardiac output in favor of vital organs, which imposes a hemodynamic load on the right heart chambers and may lead to their dilation and hypertrophy [7]. In the postnatal period, these children may face the influence of a hemodynamically significant patent ductus arteriosus, bronchopulmonary dysplasia, and pulmonary hypertension, which exert an additional long-term impact on the myocardium and the process of electrical impulse generation within it [8].

Electrocardiography (ECG) is a routine, non-invasive, and highly informative tool for assessing myocardial status, the cardiac conduction system, and electrolyte balance. In six-year-old children who underwent intensive care management during the neonatal period, standard ECG can detect specific features that mirror prior adaptive processes and cardiac remodeling. These features may include repolarization abnormalities, electrocardiographic signs of right and left ventricular myocardial hypertrophy, as well as various rhythm and conduction disturbances. Notably, ECG is not a definitive method for the diagnosis of cardiovascular pathology. A normal ECG does not preclude the presence of current cardiovascular disease, nor does it exclude the possibility of its development in later years.

The age of six years is a critical milestone immediately preceding school entry, which entails a marked increase in physical demands and psychoemotional stress. Furthermore, by this age the principal processes of morphological maturation of the cardiac conduction system are normally completed, and "adult" ECG parameters become established.

Despite the importance of this issue, comprehensive studies specifically addressing ECG features in preschool-aged children with a burdened perinatal history of low birth weight remain scarce in the available literature. Most studies have focused on the neonatal period [9], early childhood [10], or adolescence and adulthood [11, 12]. T.S. Tumaeva and L.A. Balykova demonstrated that ST–T abnormalities, rhythm disturbances (sinus tachycardia or, less commonly, bradycardia), conduction disturbances, and QTc prolongation were more frequent in a specific group of newborns. These findings were more common in newborns who had suffered cerebral ischemia, especially those born preterm, and in children delivered by cesarean section [9]. T. Salaets et al. found no significant relationship between corrected Q–T interval and perinatal factors, including birth weight, in adolescent children [11]. Conversely, A.-S. Gervais et al. reported QTc prolongation during physical exercise among adults [12].

AIM

The aim of this study was to evaluate electrocardiographic parameters in 6-year-old children born with ELBW, VLBW, and LBW.

MATERIALS AND METHODS

A total of 173 children aged 6 years (mean age 6.1±0.24 years) were enrolled in the study, including 78 (45.1%) boys and 95 (54.9%) girls. The main group comprised 94 children with a birth weight below 2500 g. Based on birth weight, the main group (n=94) was stratified into three subgroups. Subgroup 1 consisted of children with extremely low birth weight (ELBW) (n=15), Subgroup 2 — chil-

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dren with very low birth weight (VLBW) (n=25), and Subgroup 3 — children with low birth weight (LBW) (n=54). The control group consisted of children with a birth weight exceeding 2500 g (n=79).

Inclusion criteria for the main group were: preterm infants with a birth weight below 2500 g, physical development parameters appropriate for gestational age, and natural conception. *Inclusion criteria for the control group were:* full-term birth with a birth weight exceeding 2500 g, and natural conception. *Exclusion criteria were:* the presence of congenital or genetic pathology, and physical development parameters inappropriate for gestational age. Written informed voluntary consent for the examination and publication of the results obtained was provided by the children's parents (legal representatives).

Electrocardiography was performed using a Fukuda CardiMax FX 8222 device (Japan). Standard 12-lead ECG was recorded at a paper speed of 50 mm/s, with a 1 mV calibration signal applied to each tracing. ECGs were obtained at rest with the patient lying in the supine position. Alongside visual assessment, the following ECG parameters were analyzed: heart rate (HR), QRS duration, Q–T and Q–Tc intervals, P- and T-wave amplitudes, and ST-segment pattern.

Statistical analysis was performed using conventional methods of descriptive and variational statistics implemented in Microsoft Excel 2010, STATISTICA 12, and MedCalc software. Normality of distribution was verified prior to analysis. Between-group comparisons were performed accounting for sample size and distribution type using nonparametric tests (Pearson's χ^2 test, Mann–Whitney U test, Kruskal–Wallis test). Data are presented as median and interquartile range: Me [Q25; Q75], where Me is the median, and Q25 and Q75 are the lower and upper quartiles. The significance level for hypothesis testing in the study was set at 0.05.

RESULTS

ECG findings in the main group revealed abnormalities in the form of cardiac rhythm and conduction disturbances, as well as altered myocardial repolarization. A normal ECG was recorded in 5 (33.3%) children born with ELBW, 8 (32%) children born with VLBW, and 27 (50%) children born with LBW. In the control group, 38 (48.1%) children had a normal ECG. No statistically significant differences in the frequency of various cardiac rhythm and conduction abnormalities were observed across the study groups. Among cardiac arrhythmias in children born with ELBW, VLBW, and LBW, the most frequently recorded were sinus bradycardia, atrial rhythm, and wandering pacemaker (Fig. 1), which, according to some reports, are considered functional in nature.

Repolarization abnormalities were detected in 27.6% of children with ELBW, 4% of children with VLBW, and 17.0% of children with LBW at birth, as well as in 8.9% of children in the control group (p_{1-2}=0.06, p_{1-3}=0.2, p_{1-4}=0.06, p_{2-3}=0.2, p_{2-4}=0.4, p_{3-4}=0.4).

Q–T interval prolongation exceeding 460 ms was recorded in children with ELBW, VLBW, and LBW at birth and in the control group in 6.7, 8.0, 3.7, and 2.5% of cases, respectively (Table 1).

ECG analysis revealed a vertical cardiac electrical axis in 7 (46.7%) children with ELBW, 10 (40.0%) children with VLBW, 16 (29.6%) children with LBW at birth, and 42 (52.3%) children in the control group. A horizontal axis was identified in 3 (20.0%) children with ELBW, 1 (4.0%) child with VLBW, 2 (3.7%) children with LBW at birth, and 4 (5.1%) children in the control group. Right axis deviation was observed in 3 (5.6%) children with LBW at birth and 7 (8.9%) children in the control group, whereas left axis deviation was observed

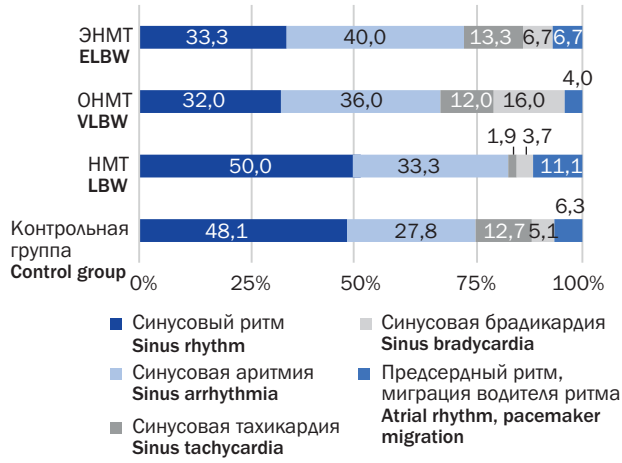

Fig. 1. Distribution of heart rate types in the studied groups: LBW — low body weight; VLBW — very low body weight; ELBW — extremely low body weight (the figure is prepared by the authors using their own data)

Рис. 1. Распределение видов сердечного ритма в исследуемых группах: НМТ — низкая масса тела; ОНМТ — очень низкая масса тела; ЭНМТ — экстремально низкая масса тела (рисунок подготовлен авторами по собственным данным)

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Table 1. Results of electrocardiographic examination in observed children

Таблица 1. Результаты электрокардиографического исследования у наблюдаемых детей

ЭКГ-признак ECG sign	ЭНМТ ELB (n=15)	ОНМТ VLBW (n=25)	НМТ LBW (n=54)	Контрольная группа Control group (n=79)	p
	1	2	3	4	
Нарушение процессов реполяризации Violation of repolarization processes	4 (26,7%)	1 (4%)	7 (13%)	7 (8,9%)	p_{1-2}=0,06 p_{1-3}=0,2 p_{1-4}=0,06 p_{2-3}=0,2 p_{2-4}=0,4 p_{3-4}=0,4
Нарушения сердечной проводимости: НБПНПГ, ПБПНПГ Cardiac conduction disorders: IRBBB, CRBBB	1 (6,7%)	2 (8%)	1 (1,9%)	3 (5,6%)	p_{1-2}=0,9 p_{1-3}=0,3 p_{1-4}=0,6 p_{2-3}=0,2 p_{2-4}=0,4 p_{3-4}=0,5
Блокада передней ветви ЛНПГ Anterior branch block LBB	1 (6,7%)	0	1 (1,9%)	1 (1,3%)	p_{1-2}=0,1 p_{1-3}=0,3 p_{1-4}=0,2 p_{2-3}=0,8 p_{2-4}=0,9 p_{3-4}=0,8
Укорочение интервала P–Q (P–Q <0,1 с) Shortening of the P–Q interval (P–Q <0.1 s)	0	1 (4%)	1 (1,9%)	1 (1,3%)	p_{1-2}=0,6 p_{1-3}=0,9 p_{1-4}=0,6 p_{2-3}=0,6 p_{2-4}=0,4 p_{3-4}=0,8
Удлинение интервала Q–T (Q–Tc >0,46 с) Prolongation of the Q–T interval (Q–Tc >0.46 s)	1 (6,7%)	2 (8%)	2 (3,7%)	2 (2,5%)	p_{1-2}=0,9 p_{1-3}=0,6 p_{1-4}=0,4 p_{2-3}=0,4 p_{2-4}=0,2 p_{3-4}=0,7

The table is prepared by the authors using their own data

Таблица составлена авторами по собственным данным

Note: LBB — left bundle branch; IRBBB — incomplete right bundle branch block; LBW — low body weight; VLBW — very low body weight; CRBBB — complete right bundle branch block; ECG — electrocardiography; ELBW — extremely low body weight.

Примечание: ЛНПГ — левая ножка пучка Гиса; НБПНПГ — неполная блокада правой ножки пучка Гиса; НМТ — низкая масса тела; ОНМТ — очень низкая масса тела; ПБПНПГ — полная блокада правой ножки пучка Гиса; ЭКГ — электрокардиография; ЭНМТ — экстремально низкая масса тела.

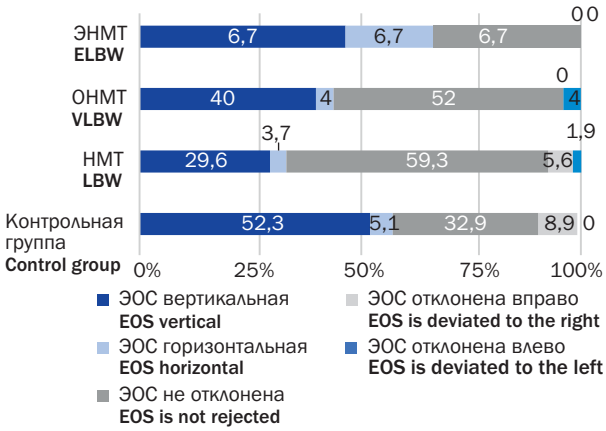

Fig. 2. Distribution of the direction of the electrical axis of the heart in the studied groups: LBW — low body weight; VLBW — very low body weight; ELBW — extremely low body weight; EOS — electrical axis of the heart (the figure is prepared by the authors using their own data)

Рис. 2. Распределение направления электрической оси сердца в исследуемых группах: НМТ — низкая масса тела; ОНМТ — очень низкая масса тела; ЭНМТ — экстремально низкая масса тела; ЭОС — электрическая ось сердца (рисунок подготовлен авторами по собственным данным)

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in 1 (4.0%) child with VLBW at birth and 1 (1.9%) child with LBW at birth. In the majority of children in both the main and control groups, the cardiac electrical axis was within normal limits (Fig. 2). The above findings are consistent with a normal variant for children of this age.

Comparative analysis of the main ECG parameters revealed no significant differences between the study groups. Median heart rate values across all groups fell within age-appropriate normal ranges, with no appreciable between-group differences observed (p=0.8). QRS duration, reflecting the velocity of electrical impulse conduction through the ventricles, was also comparable across groups (p=0.1). Q–T interval values, which characterize the duration of the ventricular repolarization phase, showed no statistically significant variation between the groups (p=0.3). The most clinically relevant parameter was the corrected Q–T interval (Q–Tc), which adjusts for the heart rate dependence of the interval. The statistical significance of the differences was at the trend level (p=0.06) and did not reach the conventional threshold of p<0.05.

In all examined children in both groups, the main ECG intervals remained within age-appropriate normal limits. The obtained values of the main ECG intervals in the groups of children born with ELBW, VLBW, and LBW did not differ significantly from those in the control group (Table 2).

DISCUSSION

The findings of the present study are of interest in the context of the fetal programming hypothesis (DOHaD). According to this concept, adverse intrauterine conditions can lead to structural and functional cardiovascular alterations that become apparent in the long term. Our results demonstrate, however, that by six years of age children born with low birth weight do not develop persistent electrophysiological abnormalities detectable on a standard resting ECG. The absence of significant differences in the main intervals (HR, QRS, Q–T, Q–Tc) and in the frequency of rhythm disturbances may be explained by several factors. First, by preschool age the principal processes of morphofunctional maturation of the myocardium are completed. Second, perinatal hemodynamic disturbances undergo effective compensation. Third, subclinical changes detectable on stress testing or by highly sensitive imaging modalities (speckle-tracking echocardiography, magnetic resonance imaging) may not be apparent on a resting ECG. Our results are consistent with the study by T. Salaets et al., who likewise found no QTc prolongation in adolescents born extremely preterm [11]. Conversely, P.E. Khodkevich et al. demonstrated that certain electrophysiological features may persist in preterm children during early childhood [10], which underscores the importance of longitudinal follow-up and suggests possible normalization of parameters by the preschool period. From a clinical standpoint, the absence of significant ECG abnormalities in the majority of the children examined supports the recommendation of standard follow-up without the need for advanced instrumental investigations in the absence of cardiac complaints and auscultatory abnormalities.

Table 2. Electrocardiographic indicators of the examined children, Me [Q25; Q75]

Таблица 2. Электрокардиографические показатели обследуемых детей, Me [Q25; Q75]

Показатели **Indicators**	**ЭНМТ** **ELB** **(n=15)**	**ОНМТ** **VLBW** **(n=25)**	**НМТ** **LBW** **(n=54)**	**Контрольная группа** **Control group** **(n=79)**	**p**
	1	**2**	**3**	**4**	
ЧСС, уд./мин HR, beats per minute	84 [75;102]	87 [81;102]	87,5 [81;97]	89 [81;100]	p=0,8
QRS, с	86 [85;91]	87 [83;96]	85 [80;91]	90 [85;92]	p=0,1
Q–T, с	331 [297;376]	345 [301;356]	350 [336;365]	355 [339;368]	p=0,3
Q–Tc, с	415 [397;425]	424 [405;439]	428 [412;435]	431 [423;444]	p=0,06

The table is prepared by the authors using their own data

Таблица составлена авторами по собственным данным

Note: LBW — low body weight; VLBW — very low body weight; HR — heart rate; ELBW — extremely low body weight.

Примечание: НМТ — низкая масса тела; ОНМТ — очень низкая масса тела; ЧСС — частота сердечных сокращений; ЭНМТ — экстремально низкая масса тела.

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Children found to have abnormalities (repolarization disturbances, QTc prolongation, clinically significant arrhythmias) should be referred for echocardiography, Holter monitoring, and consultation with a pediatric cardiologist.

CONCLUSION

The present study found no significant differences in ECG parameters between six-year-old children born with low birth weight and their peers with a birth weight exceeding 2500 g. Nonetheless, children born with low, very low, and extremely low birth weight constitute a population at risk for the development of cardiovascular disease. This underscores the need for the application of more extensive and refined diagnostic modalities in these children to enable timely detection of potential abnormalities. Further studies are warranted to achieve a more comprehensive understanding of the cardiovascular status of preschool-aged children born with low birth weight and of the influence of various factors upon it.

ADDITIONAL INFORMATION

Authors' contribution. The concept of the article was developed and the text was written by A.I. Mulyukova, L.V. Yakovleva, Z.K. Galysheva, G.N. Shangareeva; the article was edited by A.I. Mulyukova, L.V. Yakovleva, G.N. Shangareeva; and the final version of the article was approved by L.V. Yakovleva.

All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Consent for publication. Legal representatives gave informed voluntary consent for the examination and publication of the results obtained.

The study was approved by the decision of the Ethics Committee FSBEI HE BSMU of the Russian Ministry of Health of the dated 13.02.2025.

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REFERENCES

1. Baryshnikova I.Yu., Gasanova R.M. Prematurity is a risk factor for early heart failure. *The Bulletin of Bakoulev Center. Cardiovascular Diseases*. 2024;25(2):107–113. (In Russ.). https://doi.org/10.24022/1810-0694-2024-25-2-107-113. EDN: VCKMJC.
2. Khodkevich P.E., Kulikova K.V., Gorev V.V., Deev I.A. The echographic characteristics of structural and functional development of organs and systems in children born with low birth weight, very low birth weight and extremely low birth weight. *Russian Pediatric Journal*. 2020;1(3):11–17. (In Russ.). https://doi.org/10.15690/rpj.v1i3.2170. EDN KZEGCG.
3. Schuermans A., Lewandowski A.J. Understanding the preterm human heart: What do we know so far? *Anat Rec*. 2022;305(9):2099–2112. https://doi.org/10.1002/ar.248752112.
4. El-Khuffash A., Jain A., Lewandowski A.J., Levy P. Preventing disease in the 21st century: Early breast milk exposure and later cardiovascular health in premature infants. *Pediatr Res*. 2020;87(2):385–390. https://doi.org/10.1038/s41390-019-0648-5.
5. Kovtun O.P., Tsyvian P.B., Markova T.V., Chumarnaya T.V. Remodeling of the Heart of the Premature Child. *Annals of the Russian academy of medical sciences*. 2020;75(6):631–637. (In Russ.). https://doi.org/10.15690/vramn1268. EDN: HXVKLQ.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

6. Pavlyukova E.N., Kolosova M.V., Neklyudova G.V. et al. Pediatric heart physiology and pathogenetic mechanisms affecting the process of growth and development of the cardiovascular system premature infants: a modern view at the problem. *Siberian Journal of Clinical and Experimental Medicine*. 2024;39(4):26–37. (In Russ.). https://doi.org/10.29001/2073-8552-2024-39-4-26-37. EDN: TKUHNM.
7. Pavlyukova E.N., Kolosova M.V., Neklyudova G.V., Karpov R.S. Left ventricle longitudinal strain of the endocardial and epicardial layers and left ventricle remodelling in children born with low and extremely low body weight aged from one to five years old. *Translational Medicine*. 2021;8(2):23–36. (In Russ.). https://doi.org/10.18705/2311-4495-2021-8-2-23-36. EDN: ICKKRZ.
8. Igisheva L.N., Zvyagina Zh.A., Tsoy E.G. et al. Open ductus arteriosus in premature infants with extremely low and very low body weight. *Mother and Baby in Kuzbass*. 2025;1(100):59–65. (In Russ.). https://doi.org/10.24412/2686-7338-2025-1-59-65. EDN: JAADRW.
9. Tumaeva T.S., Balykova L.A. Newborns of high risk groups and electrophysiological cardiac activity during the period of early adaptation. *Current Pediatrics*. 2014;13(1):141–147. (In Russ.). EDN: RXPVTT.
10. Khodkevich P.E., Kulikova K.V., Fedorova O.S. et al. Early childhood cardiological profile of premature infants with a birth weight below 2500 gram. *Pediatria n.a. G.N. Speransky*. 2024;10(1):30–38. (In Russ.). https://doi.org/10.24110/0031-403X-2024-103-1-30-38. EDN: WDZGPO.
11. Salaets T., Raaijmakers A., Zhang Z.Y., Yu Y.L., Wei D.M., Staessen J.A., Allegaert K. QTc intervals are not prolonged in former ELBW infants at pre-adolescent age. *Pediatr Res*. 2022;92(3):848–852. https://doi.org/10.1038/s41390-021-01877-w.
12. Gervais A.S., Flahault A., Chan T. et al. Electrocardiographic features at rest and during exercise in young adults born preterm below 30 weeks of gestation. *Pediatr Res*. 2020;88(2):305–311. https://doi.org/10.1038/s41390-020-0814-9.

ЛИТЕРАТУРА

1. Барышникова И.Ю., Гасанова Р.М. Недоношенность – фактор риска развития ранней сердечной недостаточности. *Бюллетень НЦССХ им. А.Н. Бакулева РАМН. Сердечно-сосудистые заболевания*. 2024;25(2):107–113. https://doi.org/10.24022/1810-0694-2024-25-2-107-113. EDN: VCKMJC.
2. Ходкевич П.Е., Куликова К.В., Горев В.В., Деев И.А. Эхоструктурные и функциональные особенности органов и систем у детей с низкой, очень низкой и экстремально низкой массой тела при рождении (обзор литературы). *Российский педиатрический журнал*. 2020;1(3):11–17. https://doi.org/10.15690/rpj.v1i3.2170. EDN: KZEGCG.
3. Schuermans A., Lewandowski A.J. Understanding the preterm human heart: What do we know so far? *Anat Rec*. 2022;305(9):2099–2112. https://doi.org/10.1002/ar.248752112.
4. El-Khuffash A., Jain A., Lewandowski A.J., Levy P. Preventing disease in the 21st century: Early breast milk exposure and later cardiovascular health in premature infants. *Pediatr Res*. 2020;87(2):385–390. https://doi.org/10.1038/s41390-019-0648-5.
5. Ковтун О.П., Цывьян П.Б., Маркова Т.В., Чумарная Т.В. Ремоделирование сердца недоношенных детей. *Вестник РАМН*. 2020;75(6):631–637. https://doi.org/10.15690/vramn1268. EDN: HXVKLQ.
6. Павлюкова Е.Н., Колосова М.В., Неклюдова Г.В. и др. Физиология детского сердца и патогенетические механизмы, оказывающие влияние на процесс роста и развития сердечно-сосудистой системы у рожденных преждевременно: современный взгляд на проблему. *Сибирский журнал клинической и экспериментальной медицины*. 2024;39(4):26–37. https://doi.org/10.29001/2073-8552-2024-39-4-26-37. EDN: TKUHNM.
7. Павлюкова Е.Н., Колосова М.В., Неклюдова Г.В., Карпов Р.С. Деформация эндокардиального, эпикардиального слоев левого желудочка в продольном направлении и ремоделирование левого желудочка у детей в возрасте от одного года до пяти лет, рожденных с очень низкой и экстремально низкой массой тела. *Трансляционная медицина*. 2021;8(2):23–36. https://doi.org/10.18705/2311-4495-2020-8-2-23-36. EDN: ICKKRZ.
8. Игишева Л.Н., Звягина Ж.А., Цой Е.Г. и др. Открытый артериальный проток у недоношенных детей с экстремально низкой и очень низкой массой тела. *Мать и дитя в Кузбассе*. 2025;1(100):59–65. https://doi.org/10.24412/2686-7338-2025-1-59-65. EDN: JAADRW.
9. Тумаева Т.С., Балыкова Л.А. Новорожденные группы высокого риска и электрофизиологическая активность сердца в период ранней адаптации. *Вопросы современной педиатрии*. 2014;13(1):141–147. EDN: RXPVTT.
10. Ходкевич П.Е., Куликова К.В., Федорова О.С. и др. Кардиологический профиль недоношенных новорожденных с массой тела при рождении менее 2500 граммов в раннем детском возрасте. *Педиатрия. Журнал им. Г.Н. Сперанского*. 2024:103(1):30–38. https://doi.org/10.24110/0031-403X-2024-103-1-30-38. EDN: WDZGPO.
11. Salaets T., Raaijmakers A., Zhang Z.Y., Yu Y.L., Wei D.M., Staessen J.A., Allegaert K. QTc intervals are not prolonged in former ELBW infants at pre-adolescent age. *Pediatr Res*. 2022;92(3):848–852. https://doi.org/10.1038/s41390-021-01877-w.
12. Gervais A.S., Flahault A., Chan T. et al. Electrocardiographic features at rest and during exercise in young adults born preterm below 30 weeks of gestation. *Pediatr Res*. 2020;88(2):305–311. https://doi.org/10.1038/s41390-020-0814-9.

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The use of removable dentures in different age periods

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ABSTRACT. ***Introduction.*** Removable dentures are aesthetic and hygienic; they can be used in patients who have lost from one to all natural teeth in each jaw. Despite extensive research on the use of removable dentures, the frequency of their use among people in different age groups remains unknown. ***The aim of the study*** was to investigate the frequency of removable denture use among patients in different age groups. ***Materials and methods.*** A clinical study examined 2,831 individuals (1,282 men (45.28%) and 1,549 women (54.72%)) aged 15 to 96 years who sought dental care at municipal or departmental dental healthcare facilities. Age grouping followed the World Health Organization's age periodization recommended for use in 2025. During the medical history collection and dental examination, patients were asked whether they used removable dentures — partial or complete. The materials used to manufacture the dentures were not specified. ***Results.*** The study found that removable dentures are widely used across various age groups. In late adolescence, removable dentures are used due to impossibility of fabricating fixed dentures or implant-supported prostheses because of ongoing jaw growth. Among young, middle-aged, and elderly individuals, removable dentures were used by 23.89, 70.36 and 89.25% of patients, respectively. Among centenarians, the usage rate reached 93.33%. The main reasons for the widespread use of removable dentures include their relatively low cost and the possibility for privileged categories of citizens to receive them free of charge in public healthcare facilities through budgetary funding. ***Conclusion.*** The widespread use of removable dentures in modern healthcare practice across different age groups necessitates the search for new inert materials for denture bases, as well as adhesive agents that reduce the likelihood of inflammatory complications in the denture-bearing area when using partial or complete removable dentures.

KEYWORDS: *people in different age groups, removable denture, frequency of removable denture use, young adults, middle-aged adults, older adults, centenarians, reasons for removable denture use*

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Использование съемных зубных протезов в разные возрастные периоды

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РЕЗЮМЕ. ***Введение.*** Съемные зубные протезы эстетичны, гигиеничны и их можно применять у пациентов, которые имеют потерю естественных зубов от одного до всех на каждой из челюстей. Несмотря на многостороннее изучение проблемы пользования съемными зубными протезами, до сих пор неизвестна частота их применения у людей разных возрастных групп. ***Цель исследования*** – изучить частоту применения пациентами разных возрастных групп съемных зубных протезов. ***Материалы и методы.*** В ходе клинического исследования были осмотрены 2831 (1282 (45,28%) мужчин и 1549 (54,72%) женщин) человек в возрасте от 15 до 96 лет, которые обращались в муниципальные или ведомственные стоматологические медицинские организации для оказания всех видов стоматологической медицинской помощи. Для распределения пациентов на группы исследования использована возрастная периодизация Всемирной организации здравоохранения, рекомендованная к применению в 2025 г. При сборе анамнеза и стоматологическом осмотре пациентов выясняли, пользуются ли пациенты съемными зубными протезами (частичными или полными съемными). При этом не уточняли материал, из которого они были изготовлены. ***Результаты.*** Установлено, что съемные зубные протезы широко применяются у пациентов различных возрастных групп. В позднем юношеском возрасте съемные зубные протезы применяют в связи с невозможностью изготовления несъемных зубных протезов или имплантационных протезов из-за продолжающегося роста челюстей. Среди людей молодого, зрелого и старческого возраста съемными зубными протезами пользовались 23,89, 70,36 и 89,25% пациентов соответственно. Долгожители использовали съемные зубные протезы в 93,33% случаев. Основной причиной широкого применения съемных зубных протезов являются их сравнительно низкая стоимость, а также возможность льготной категории граждан получить их в государственных медицинских организациях за счет средств бюджета. ***Заключение.*** Широкое применение съемных зубных протезов в современном практическом здравоохранении у людей разных возрастных групп диктует поиск новых инертных материалов для базисов протезов, а также адгезивных средств, снижающих вероятность возникновения воспалительных осложнений протезного ложа при пользовании частичными или полными съемными зубными протезами.

КЛЮЧЕВЫЕ СЛОВА: *люди разных возрастных групп, съемный зубной протез, частота применения съемных зубных протезов, люди молодого возраста, зрелые люди, люди старших возрастных групп, долгожители, причины применения съемных зубных протезов*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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INTRODUCTION

The disadvantages of removable dentures are well recognised today, the principal ones being poor restoration of masticatory function and the occurrence of inflammatory changes in the oral mucosa beneath the denture base [1, 2]. At the same time, removable dentures have advantages that allow them to remain in use in broad dental practice, both in the Russian Federation and internationally [3, 4]. Removable dentures are aesthetic, hygienic, and can be applied in patients with the loss of natural teeth ranging from a single tooth to all teeth in each jaw [5]. In addition, for eligible groups of citizens of the Russian Federation, including pensioners, removable dentures are provided in state (municipal, departmental) healthcare organizations at the expense of the budget [6]. Despite the extensive study of the problem of removable denture use, the frequency of their application in people of different age groups remains unknown to date.

Fig. 1. Distribution of patients by age and gender, persons (the figure is prepared by the authors using their own data)

Рис. 1. Распределение пациентов по возрасту и полу, человек (рисунок подготовлен авторами по собственным данным)

AIM

The aim of this study was to investigate the frequency of removable denture use in patients of different age groups.

MATERIALS AND METHODS

To achieve the stated aim, a single-center, prospective, clinical dental study was carried out. A total of 2831 patients (1282 (45.28%) men and 1549 (54.72%) women) aged 15 to 96 years were examined. All patients attended municipal or departmental dental healthcare organizations to receive various types of dental care, including surgical, therapeutic, orthopedic, and orthodontic treatment. The World Health Organization (WHO) age periodization, recommended for adoption on 15 March 2025, was used to allocate the patients into the study groups (Fig. 1). In accordance with this age periodization, the following groups were identified: late adolescence (15–24 years), young age (25–59 years), mature age (60–74 years), old age (75–90 years), and long-livers (over 90 years).

The late adolescence group comprised 337 individuals (11.90%; 220 men and 117 women). At the time of the examination, there were 1130 individuals (39.92%; 474 men and 656 women) in the young age group. In the mature age group, 884 individuals (31.23%; 396 men and 488 women) were examined. The old age group consisted of 465 individuals (16.43%; 189 men and 276 women). Among the 15 long-livers (0.52%), there were 3 men and 12 women.

During history-taking and the dental examination of the patients, it was determined whether the patients used partial or complete removable dentures. The material from which they were fabricated was not specified.

The study fully complied with the ethical standards set forth in the Declaration of Helsinki of 1975 and its revision of 2000.

For all statistical analysis procedures, the attained significance level (p) was evaluated, with the critical significance level set at 0.05.

RESULTS

The study established that, among patients in the late adolescence period, removable dentures were used by 6 (1.78%) individuals, of whom 2 (0.91%) were men and 4 (3.42%) were women. It is noteworthy that in all cases these were removable maxillary dentures that replaced a defect of the dental arch involving the

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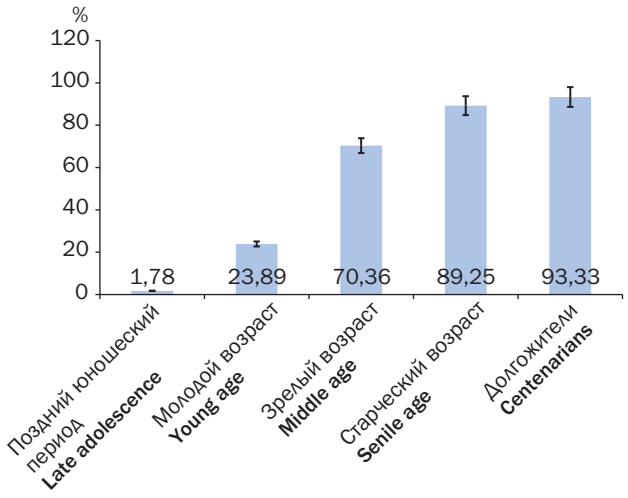

Fig. 2. The frequency of using removable dentures among people of different age groups, % (the figure is prepared by the authors using their own data)

Рис. 2. Частота пользования съемными зубными протезами у людей разных возрастных групп, % (рисунок подготовлен авторами по собственным данным)

premolars and anterior teeth. Thus, they served to correct an aesthetic defect and not merely to restore the continuity of the maxillary dental arch.

In people of young age (25–59 years), the prevalence of removable denture use rose to 23.89% (270 individuals). Within this age group, removable dentures were used by 43 (9.07%) men and 227 (34.6%) women. Removable dentures were used most often by people of mature age, old age, and long-livers (Fig. 2).

Among patients of mature age (60–74 years), removable dentures were used by 70.36% (622 individuals), of whom 205 (51.77%) were men and 417 (85.45%) were women. A similar trend was noted among people of old age, of whom 89.25% (415 individuals) used removable dentures, including 162 (85.71%) men and 253 (91.67%) women. Among long-livers (over 90 years), removable dentures were used by 14 (93.33%) individuals, of whom 2 (66.67%) were men and 12 (100.0%) were women. Thus, of all 2831 individuals examined, 46.87% used removable dentures, that is, 1327 people.

DISCUSSION

The clinical study established that women use partial and complete removable dentures more often, which aligns with earlier reports [7, 8]. With advancing age, the frequency of denture use rose, reaching 93.3% in long-livers. It is worth noting that, in the late adolescence period, the use of removable dentures was driven by the impossibility of placing fixed dentures on dental implants because of incomplete jaw formation (growth). In young, mature, and old age, the principal reason for using removable dentures was economic: these dentures are relatively inexpensive. For eligible groups of citizens, they were provided at the expense of the budget, that is, free of charge to the patient. It is also important to highlight the following difference. In people of young and mature age, removable dentures largely required no adjustment or restoration and were in a satisfactory hygienic state. By contrast, in people of old age and long-livers, the majority of dentures needed replacement, as many of them had been in use for longer than 5 years. In older age groups, the denture bases frequently failed to fit the tissues of the denture-bearing area, causing food to become trapped under the dentures and leading to chronic inflammation of the oral mucosa (denture stomatitis).

CONCLUSION

In summary, it can be concluded that removable dentures are widely used in patients across various age groups. In the late adolescence period, the primary reason for using removable dentures is medical indications stemming from the inability to fabricate fixed structures or implant-supported prostheses because of ongoing jaw growth. By contrast, in people of young, mature, and old age, as well as long-livers, the main reason for their widespread application (ranging from 23.89% to 93.33% of cases) lies in the financial capacity to restore the integrity of the dental arches with comparatively inexpensive removable dentures. An additional factor is the opportunity for eligible categories of citizens to obtain them in state healthcare organizations at the expense of the budget. Considering the extensive use of removable dentures in modern practical healthcare, the search for new inert materials for denture bases is of great importance. Equally important is the development of adhesive agents that reduce the risk of inflammatory complications of the denture-bearing area associated with the use of partial or complete removable dentures.

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ADDITIONAL INFORMATION

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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REFERENCES

1. Kerimkhanov K.A., Iordanishvili A.K. Complications in the use of full removable dentures. *Medicine and Education*. 2025;1(21):13–18. (In Russ.). EDN: NFULHJ.
2. Le Bars P., Kouadio A.A., Bandiaky O.N., Le Guéhennec L., de La Cochetière M.F. Host's immunity and *Candida* species associated with denture stomatitis: a narrative review. *Microorganisms*. 2022;10(7):1437. https://doi.org/10.3390/microorganisms10071437.
3. Iordanishvili A.K., Leontiev V.K. Removable dentures: peculiarities of use and hygienic care. *Medicine and Education*. 2025;1(21):36–40. (In Russ.). EDN: ZCBJHD.
4. Komarov F.I., Shevchenko Yu.L., Iordanishvili A.K. Longevity: remarks on dental and periodontal pathology. *Periodontology*. 2017;1(82):13–15. (In Russ.). EDN: YPRZPN.
5. Griffin S.O, Jones J.A, Brunson D., Griffin P.M, Bailey W.D. Burden of oral diseas eamong older adultsan dimplications for public health priorities. *Am J Public Health.* 2012;102(3):411–418. https://doi.org/10.2105/AJPH.2011.300362.
6. Kerimkhanov K.A., Bobintsev I.I., Iordanishvili A.K. The influence of adhesive cream on the stability of removable acrylic prosthesis in case of complete tooth loss. *Medicine and Education*. 2025;2(22):66–73. (In Russ.). EDN: LCRCMR.
7. Iordanishvili A.K., Kerimkhanov K.A. Fundamentals of dental rehabilitation in complete tooth loss. Saint Petersburg: Chelovek; 2024. 84 p. (In Russ.). EDN: WKKDJU.
8. Iordanishvili A.K., Kerimkhanov K.A., Barinov E.Kh., Bedelov N.N. Optimizing the use of removable dentofacial prostheses. *Tver Medical Journal*. 2024;(2):60–62. (In Russ.). EDN: WOHVWU.

ЛИТЕРАТУРА

1. Керимханов К.А., Иорданишвили А.К. Осложнения при пользовании полных съемных зубных протезов. *Медицина и образование*. 2025;1(21):13–18. EDN: NFULHJ.
2. Le Bars P., Kouadio A.A., Bandiaky O.N., Le Guéhennec L., de La Cochetière M.F. Host's immunity and *Candida* species associated with denture stomatitis: a narrative review. *Microorganisms*. 2022;10(7):1437. https://doi.org/10.3390/microorganisms10071437.
3. Иорданишвили А.К., Леонтьев В.К. Съемные зубные протезы: особенности пользования и гигиенического ухода. *Медицина и образование*. 2025;1(21):36–40. EDN: EDN: ZCBJHD.
4. Комаров Ф.И., Шевченко Ю.Л., Иорданишвили А.К. Долгожительство: ремарки к патологии зубов и пародонта. *Пародонтология*. 2017;1(82):13–15. EDN: YPRZPN.
5. Griffin S.O, Jones J.A, Brunson D., Griffin P.M, Bailey W.D. Burden of oral diseas eamong older adultsan dimplications for public health priorities. *Am J Public Health.* 2012;102(3):411–418. https://doi.org/10.2105/AJPH.2011.300362.
6. Керимханов К.А., Бобынцев И.И., Иорданишвили А.К. Влияние адгезивного крема на устойчивость съемного акрилового протеза при полной потере зубов. *Медицина и образование*. 2025;2(22):66–73. EDN: LCRCMR.
7. Иорданишвили А.К., Керимханов К.А. Основы стоматологической реабилитации при полной потере зубов. СПб.: Человек, 2024. 84 с. EDN: WKKDJU.
8. Иорданишвили А.К., Керимханов К.А., Баринов Е.Х., Беделов Н.Н. Оптимизация пользования съемными зубочелюстно-лицевыми протезами. *Тверской медицинский журнал*. 2024;(2):60–62. EDN: WOHVWU.

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Intensive care of acute respiratory syndrome in a child with community-acquired pneumonia (clinical case)

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ABSTRACT. Severe pneumonia is an urgent problem in pediatrics, since it is the leading cause of morbidity and mortality in children under 5 years old, mortality can reach 14%. The article discusses a clinical case of severe community-acquired pneumonia in a child, complicated by grade III respiratory failure. The child was hospitalized in an infectious diseases hospital on the 8th day of the disease. However, despite the therapy, due to the deterioration of the condition and progression of the respiratory failure clinic on the third day after hospitalization, the child was transferred to the intensive care unit. Acute respiratory distress syndrome developed, requiring invasive ventilation and therapy adjustment. The key aspects of intensive care aimed at stabilizing the patient's condition are described, including respiratory support, antibacterial, antiviral, antifungal, infusion therapy, immunomodulatory drugs and pulse therapy with glucocorticosteroids. Exogenous surfactant was also used, which contributed to the improvement of gas exchange and reduction of artificial ventilation parameters. Complex therapy was carried out in accordance with modern international recommendations for the treatment of severe pneumonia complicated by acute respiratory distress syndrome in children. The presented clinical case demonstrates the critical importance of timely and adequate therapy, as well as a multidisciplinary approach to the treatment of severe pneumonia in children.

KEYWORDS: *pneumonia, respiratory failure, intensive care, respiratory support, antibiotic therapy, clinical case, pediatrics, children*

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Оригинальная статья

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Интенсивная терапия острого респираторного синдрома у ребенка на фоне внебольничной пневмонии (клинический случай)

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РЕЗЮМЕ. Тяжелая пневмония — актуальная проблема педиатрии, поскольку она является ведущей причиной заболеваемости и смертности у детей до 5 лет, летальность может достигать 14%. В статье рассматривается клинический случай тяжелой внебольничной пневмонии у ребенка, осложненной дыхательной недостаточностью III степени. Ребенок был госпитализирован в инфекционный стационар на восьмые сутки заболевания. Однако, несмотря на проводимую терапию, в связи с ухудшением состояния и прогрессированием клинической картины дыхательной недостаточности на третьи сутки после госпитализации ребенок был переведен в отделение реанимации и интенсивной терапии. Развился острый респираторный дистресс-синдром, что потребовало применения инвазивной вентиляции легких и коррекции терапии. Описаны ключевые аспекты интенсивной терапии, направленной на стабилизацию состояния пациента, включая респираторную поддержку, антибактериальную, противовирусную, противогрибковую, инфузионную терапию, препараты-иммуномодуляторы и пульс-терапию глюкокортикостероидами. Использовался также экзогенный сурфактант, что способствовало улучшению газообмена и снижению параметров искусственной вентиляции легких. Проводилась комплексная терапия согласно современным международным рекомендациям по лечению тяжелой пневмонии, осложненной острым респираторным дистресс-синдромом у детей. Представленный клинический случай демонстрирует критическую важность своевременной и адекватной терапии, а также мультидисциплинарного подхода к лечению тяжелой пневмонии у детей.

КЛЮЧЕВЫЕ СЛОВА: *пневмония, дыхательная недостаточность, интенсивная терапия, респираторная поддержка, антибиотикотерапия, клинический случай, педиатрия, дети*

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INTRODUCTION

Despite significant advances in the diagnosis and treatment of infectious diseases, pneumonia remains one of the leading causes of hospitalization and pediatric mortality in many countries worldwide [1, 2]. Severe disease carries an exceedingly high risk of rapidly progressive respiratory failure, hypoxemia, and the development of acute respiratory distress syndrome (ARDS) and sepsis. These conditions represent major causes of death in pediatric intensive care units (PICUs) [3–6].

According to the World Health Organization (WHO), pneumonia accounted for the deaths of an estimated 740,000 children under the age of five in 2019, representing approximately 14% of all deaths within this age group. Although this figure declined to 672,000 in 2021, the disease continues to rank among the leading causes of death in pediatrics. Mortality is particularly high in countries with limited healthcare resources, such as Nigeria, India, and Pakistan. Together, these three countries account for over half of all child deaths from pneumonia. Yet, even in countries with well-developed healthcare systems, pneumonia remains a pressing challenge in pediatrics. Although the incidence of ARDS is relatively lower in children than in adults, the associated mortality in the pediatric population is extremely high, ranging from 18% to 27%. In some countries, this figure reaches adult levels of 35% [7–10].

In recent years, a persistent trend has been observed toward an increase in severe forms of pneumonia in children. This trend has been driven by the spread of atypical pathogens (*Mycoplasma pneumoniae, Chlamydia pneumoniae*), viral infections, and COVID-19 [11, 17].

High levels of antimicrobial resistance further aggravate the course of severe pneumonia. Current treatment strategies for severe pediatric pneumonia encompass timely diagnosis, empirical antibiotic therapy, respiratory support, vital function monitoring, and complication prevention [12–14].

Clinical guidelines underscore the importance of prompt inpatient management. The presence of complications, severe or protracted disease, and progressing respiratory failure constitute indications for emergency hospitalization and transfer to a PICU. In the PICU, etiotropic, pathogenetic (fluid resuscitation, volume expansion, and hemodynamic support), and symptomatic therapy is delivered under monitoring of blood gas parameters and acid-base balance [15, 16].

Effective management of severe pneumonia in children therefore requires a comprehensive, multidisciplinary approach that integrates timely diagnosis, individualized treatment, continuous patient monitoring, and complication prevention.

AIM

The aim of this study was to present a clinical case illustrating the successful management of severe acute respiratory distress syndrome in a preschool-aged child with community-acquired pneumonia.

CASE PRESENTATION

A 2-year-8-month-old girl was admitted to the emergency department of an infectious diseases hospital with complaints of dry cough, fever reaching 38 °C, and general weakness. These complaints were reported by her mother.

At the time of admission, the child had already been unwell for seven days. The illness began with a temperature rise to 38 °C and cough, for which ibuprofen was prescribed. Despite treatment, her condition progressively worsened: the cough became more intense, dyspnea developed, and the fever persisted. On the eighth day of illness, the child was hospitalized. Her past medical history was notable for frequent acute respiratory infections and absence of vaccination due to the family's religious beliefs.

On admission, her condition was severe. She was tachypneic with a respiratory rate of 37 breaths per minute and tachycardic with a heart rate of 126 beats per minute. Oxygen saturation (SpO_2) was 99%, and body temperature was 37 °C. Auscultation of the lungs revealed harsh breath sounds conducted throughout all lung fields, with no rales. The admission diagnosis was acute respiratory viral infection complicated by acute bronchitis.

Laboratory findings are presented in Tables 1–3.

For two days, the child received antibacterial therapy in the specialized department in accordance with international guidelines and the local protocol. However, her condition deteriorated over time, with progressive respiratory failure, necessitating transfer to the PICU.

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Table 1. Results of clinical and biochemical blood tests

Таблица 1. Результаты клинического и биохимического анализов крови

День болезни Day of illness	Гемоглобин, г/л Hemoglobin, g/l	Лейкоциты, $\times 10^9$/л White blood cells, $\times 10^9$/L	Палочкоядерные Band neutrophils, %	Сегментоядерные Segmented, %	Лимфоциты Lymphocytes, %	Тромбоциты, $\times 10^9$/л Platelets, $\times 10^9$/l	СОЭ, мм/час Erythrocyte sedimentation rate, mm/hour	СРБ, мг/л CRP, mg/L
При поступлении Upon admission	114	5,1		65	32,7	357	5	40,6
Перевод в ОАРИТ Transfer to the ICU	98	4,5	6	60	30	549	15	40,6
На момент перевода на ИВЛ At the time of transfer to AVL	85	8.9	6	73	30	455	44	
7-й день госпитализации 7th day of hospitalization	121	13	15	55	26	641	65	139,7
12-й день госпитализации 12th day of hospitalization	92	13	7	57	30	746	58	178,6
25-й день госпитализации 25th day of hospitalization	113	10	3	65	28	620	24	7,7
Выписка из стационара Discharge from hospital	115	9,8	3	63	30	580	20	3,3

The table is prepared by the authors using their own data

Таблица составлена авторами по собственным данным

Note: ALV — artificial ventilation of the lungs; ICU — intensive care unit; ESR — erythrocyte sedimentation rate; CRP — C-reactive protein.

Примечание: ИВЛ — искусственная вентиляция легких; ОАРИТ — отделение анестезиологии, реанимации и интенсивной терапии; СОЭ — скорость оседания эритроцитов; СРБ — С-реактивный белок.

Table 2. Gas composition and acid-base balance of venous blood

Таблица 2. Газовый состав и кислотно-основное состояние венозной крови

День болезни Day of illness	pH	pCO_2, мм рт.ст. mm Hg	pO_2, мм рт.ст. mm Hg	HCO_3, ммоль/л mmol/L	Лактат, ммоль/л Lactate, mmol/L	OSI
Перевод в ОАРИТ Transfer to the ICU	7,32	48	34	25,9	1,9	11
На момент перевода на ИВЛ At the time of transfer to AVL	7,422	38,6	31,6	24,6	1,43	14
7-й день госпитализации 7th day of hospitalization	7,432	34,6	26,6	22,6	1,21	10
12-й день госпитализации 12th day of hospitalization	7,4	42,7	50,5	29,4	1,88	–
25-й день госпитализации 25th day of hospitalization	7,49	38,5	32,0	28,7	1,89	–
Выписка из стационара Discharge from hospital	7,492	35,0	34,4	26,2	1,88	–

The table is prepared by the authors using their own data

Таблица составлена авторами по собственным данным

Note: ALV — artificial ventilation of the lungs; ICU — intensive care unit; OSI — oxygen saturation index.

Примечание: ИВЛ — искусственная вентиляция легких; ОАРИТ — отделение анестезиологии, реанимации и интенсивной терапии; OSI — оксигенационно-сатурационный индекс (oxygen saturation index).

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Table 3. Coagulogram

Таблица 3. Коагулограмма

День болезни Day of illness	ПТИ, % PTI, %	Фибриноген, г/л Fibrinigene, g/l	АЧТВ, с APTT, s	D-димер, нг/мл D-dimer, ng/ml	ПВ, с Pt, s
Перевод в ОАРИТ Transfer to the ICU	89	2,5	33	–	–
На момент перевода на ИВЛ At the time of transfer to AVL	90,7	3	32,8	1237	11,1
7-й день госпитализации 7th day of hospitalization	106,0	2,70	39,00	1786,2	10,20
12-й день госпитализации 12th day of hospitalization	98,8	2,73	31,50	1589,1	10,60
25-й день госпитализации 25th day of hospitalization	110,0	3,10	50,50	3136,7	10,0
Выписка из стационара Discharge from hospital	108,0	2,60	34,50	1646,3	10,10

The table is prepared by the authors using their own data

Таблица составлена авторами по собственным данным

Note: APTT — activated partial thromboplastin time; ALV — artificial ventilation of the lungs; ICU — intensive care unit; Pt — prothrombin time; PTI — Prothrombin index.

Примечание: АЧТВ — активированное частичное тромбопластиновое время; ИВЛ — искусственная вентиляция легких; ОАРИТ — отделение анестезиологии, реанимации и интенсивной терапии; ПВ — протромбиновое время; ПТИ — протромбиновый индекс.

On arrival in the PICU, her body temperature was 38 °C. She was tachypneic, with a respiratory rate of 40–45 breaths per minute, an SpO_2 of 85%, a productive cough, and chest wall retractions. Noninvasive ventilation via a nasal mask was initiated. With respiratory support, SpO_2 rose to 90%. Venous blood gas analysis revealed respiratory acidosis: pH 7.32; pCO_2 48 mm Hg; pO_2 34 mm Hg; BE −2 mmol/L; lactate 1.9 mmol/L.

Based on the presumed susceptibility, antibacterial agents were prescribed (ceftazidime 80 mg/kg/day and amikacin 15 mg/kg/day), and mucolytic, bronchodilator, and symptomatic therapy was initiated.

Two days later, the patient's condition deteriorated sharply, with the clinical manifestation of ARDS. Her SpO_2 was 83%, the respiratory rate was 50 breaths per minute, and auscultation of the lungs revealed diminished breath sounds bilaterally. A follow-up chest radiograph showed negative dynamics with an increase in the zones of infiltration (Fig. 1).

On emergency indications, tracheal intubation was performed, and invasive mechanical ventilation was initiated using pressure-controlled ventilation with an FiO_2 of 0.9. SpO_2 ranged between 50% and 70%. Venous blood gas analysis performed immediately before intubation revealed decompensated respiratory acidosis: pH 7.20; pCO_2 82 mm Hg; pO_2 33 mm Hg; BE −2 mmol/L; lactate 1.8 mmol/L. A chest radiograph showed further progression of infiltrative changes (see Fig. 1).

Given the constellation of clinical and laboratory findings and the progressively severe course of the disease, a decision was made to modify the therapeutic regimen. Pentaglobin was prescribed for passive immunization at a dose of 5 mL/kg intravenously for three days. To suppress the pronounced inflammatory response and cytokine cascade, pulse methylprednisolone therapy was administered at a dose of 30 mg/kg for three days.

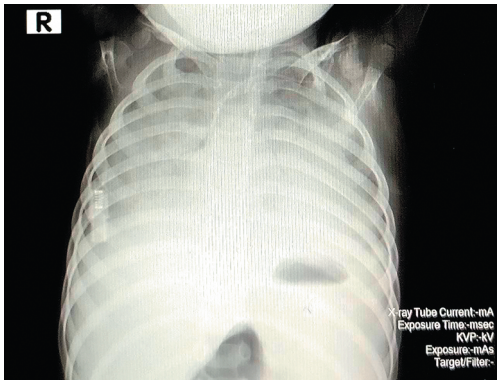

Fig. 1. Chest radiography (4th day of hospitalization). Bilateral pneumonia. Pulmonary edema? (photo from the authors' personal archive)

Рис. 1. Рентгенография органов грудной клетки. Двусторонняя пневмония. Отек легких? (фото из личного архива авторов)

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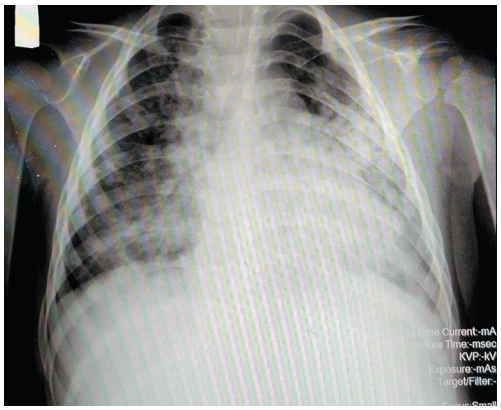

Fig. 2. Chest radiography (7th day of hospitalization) (photo from the authors' personal archive)

Рис. 2. Рентгенограмма органов грудной клетки на 7-й день госпитализации (фото из личного архива авторов)

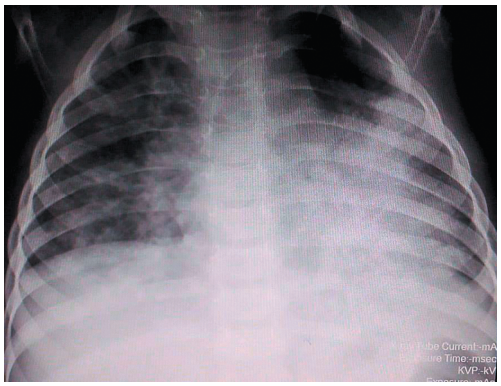

Fig. 3. Chest radiography (12th day of hospitalization) (photo from the authors' personal archive)

Рис. 3. Рентгенограмма органов грудной клетки на 12-й день лечения в стационаре (фото из личного архива авторов)

As part of the respiratory support strategy and to promote alveolar recruitment, poractant alfa was administered endotracheally on two occasions at a dose of 120 mg.

The ongoing therapy was associated with positive clinical dynamics: gas exchange improved, ventilatory parameters decreased, and SpO_2 rose to 92% at a fraction of inspired oxygen of 50%. The SpO_2/FiO_2 ratio was 184.

A follow-up chest radiograph demonstrated a reduction in infiltrative changes, decreased density of inflammatory foci, and partial clearing of the lung fields compared with the previous examination (Fig. 2).

By day 5 of intensive combined therapy in the hospital (day 12 of illness), the child showed unequivocal positive dynamics across clinical, laboratory, and instrumental parameters. Blood gas values stabilized, infiltrative changes on the chest radiograph diminished, and systemic hemodynamic parameters normalized.

Given the sustained clinical improvement, a decision was made to extubate the patient and transition her to noninvasive ventilation. The patient was conscious, oriented, and responsive. She was able to drink and eat independently, although her appetite remained reduced. Mild mixed dyspnea persisted but did not necessitate an increase in the level of respiratory support.

By day 7 of inpatient treatment (day 14 of illness; hospital day 12), the girl was successfully transitioned to spontaneous breathing with humidified oxygen delivered via binasal cannulae at a flow rate of 2 L/min. Follow-up chest radiographs demonstrated unequivocal positive dynamics (Fig. 3).

Throughout the PICU stay, the patient received comprehensive therapy aimed at suppressing the severe infectious and inflammatory process, stabilizing respiratory function, and preventing systemic complications.

Given that sputum culture on day 5 of inpatient treatment yielded *Pseudomonas aeruginosa* susceptible to meropenem and colistimethate sodium, antibacterial therapy was adjusted accordingly. The regimen included meropenem (60 mg/kg/day), colistin (1,500,000 IU/kg/day), and linezolid (30 mg/kg/day).

As IgM and IgG antibodies against herpes simplex virus and Epstein–Barr virus were positive, antiviral therapy (acyclovir at 80 mg/kg/day) was initiated to reduce the risk of viral coinfection.

For prophylaxis of fungal complications, fluconazole was prescribed at the initial stage of treatment at a dose of 6 mg/kg every 48 hours. Subsequently, when *Candida lipolytica* was isolated from urine on day 11 of hospitalization, caspofungin was added to the therapeutic regimen at a dose of 50 mg/m^2/day for 7 days.

To manage broncho-obstructive syndrome, aminophylline (1 mg/kg/hour for three days) and nebulized ipratropium bromide 150 μg every 6 hours were administered.

The comprehensive therapy resulted in sustained positive dynamics. The patient's condition stabilized: gas exchange parameters and laboratory values normalized, and the foci of pulmonary infiltration diminished significantly (Fig. 4).

Thirty-five days after admission, the patient was discharged from the hospital in satisfactory condi-

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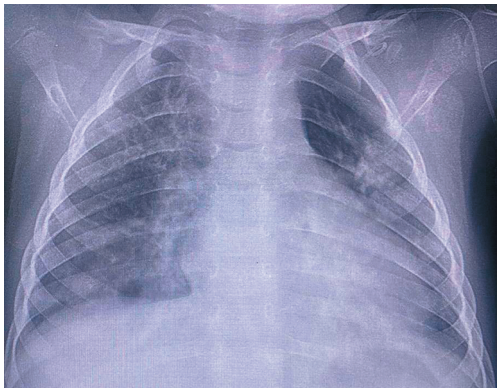

Fig. 4. Chest radiography (25th day of hospitalization) (photo from the authors' personal archive)

Рис. 4. Рентгенография органов грудной клетки (25-й день госпитализации) (фото из личного архива авторов)

tion with recommendations for further outpatient follow-up. A consultation with a pediatric pulmonologist was scheduled. The recommendations also included dynamic monitoring via follow-up laboratory and instrumental investigations and continuation of rehabilitative therapy in the outpatient setting.

DISCUSSION

This clinical case describes severe acute respiratory distress syndrome in a preschool-aged child with community-acquired bilateral polysegmental pneumonia. It underscores the critical importance of a comprehensive and timely approach to the management of severe community-acquired pneumonia in pediatric practice.

Despite the availability of modern diagnostic and therapeutic modalities, pneumonia remains the leading cause of child mortality worldwide. According to current WHO and UNICEF data, pneumonia-related mortality among children under five years of age has declined only marginally: from approximately 740,000 deaths in 2019 to approximately 725,000 in 2023–2024.

In the present case, despite treatment initiation in the infectious diseases hospital, the patient developed progressive respiratory failure necessitating transfer to the PICU. The subsequent development of ARDS provided the rationale for invasive mechanical ventilation and treatment modification in accordance with the PALICC-2 recommendations [4, 18].

A comprehensive therapeutic strategy encompassing broad-spectrum antibacterial agents, immunomodulators, and antiviral and antifungal medications was implemented. Together with pulse glucocorticoid therapy, this strategy allowed stabilization of the patient's condition [19–23].

The administration of surfactant contributed to improved gas exchange and a reduction in ventilatory parameters. This outcome aligns with current recommendations for the management of severe pneumonia and ARDS in children [4, 5, 24, 25]. In our opinion, such an approach substantially enhances the effectiveness of treatment for severe forms of community-acquired pneumonia in children. The successful outcome was achieved through effective multidisciplinary collaboration among pediatricians, intensivists, infectious disease specialists, and other healthcare professionals working in close coordination within the intensive care unit.

CONCLUSION

This clinical case illustrates the severe course of ARDS secondary to community-acquired pneumonia in a child, marked by rapidly progressive severe hypoxemic respiratory failure that necessitated intensive care with invasive respiratory support. The application of current clinical guidelines substantially increases the likelihood of a favorable outcome even in the most critical situations, and this principle formed the basis of the child's recovery in the present case.

ADDITIONAL INFORMATION

Authors' contribution. G.N. Alimkhanova – development of the research concept; A.B. Ibraimova, N. Bokenuly — collection, data analysis and preparation of illustrations; A.B. Ibraimova, N. Bokenuly — writing the first text; G.N. Alimkhanova, A.K. Tulebayeva — scientific advice and guidance; G.N. Alimkhanova, A.K. Tulebayeva — editing the final text; G.N. Alimkhanova, A.K Tulebayeva, A.B. Ibraimova, N. Bokenuly — approval of the final text.

All authors read and approved the final version before publication.

Competing interests. The authors declare that they have no competing interests.

Consent for publication. Written consent was obtained from legal representatives of the patient for publication of relevant medical information within the manuscript.

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REFERENCES

1. Killien E.Y., Keller M.R., Watson R.S., Hartman M.E. Epidemiology of intensive care admissions for children in the US From 2001 to 2019. *JAMA Pediatr*. 2023;177(5):506–515. https://doi.org/10.1001/jamapediatrics.2023.0184
2. Friedman M.L., Nitu M.E. Acute Respiratory Failure in Children. *Pediatr Ann*. 2018;47(7):e268–e273. https://doi.org/10.3928/19382359-20180625-01.
3. Panetti B., Bucci I., Di Ludovico A. et al. Acute respiratory failure in children: a clinical update on diagnosis. *Children (Basel)*. 2024;11(10):1232. https://doi.org/10.3390/children11101232.
4. Aleksandrovich Yu.S., Pshenisnov K.V., Kolodyazhnaya V.I. Acute respiratory distress syndrome in pediatric practice, diagnosis, and intensive care: A review. *Russian Journal of Pediatric Surgery, Anesthesia and Intensive Care*. 2024;14(1):83–95. (In Russ.). https://doi.org/10.17816/psaic1569.
5. Pshenisnov K.V., Aleksandrovich Yu.S., Felker E.Yu., Dmitrieva E.M., Meshkov A.V., Razgon M.V. et al. Features of mechanical ventilation in acute respiratory distress syndrome complicated by bronchopulmonary fistula (case report). *Messenger of Anesthesiology and Resuscitation*. 2025;22(1):120–128. (In Russ.). https://doi.org/10.24884/2078-5658-2025-22-1-120-128.
6. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. 2015;16(5):428–439. https://doi.org/10.1097/PCC.0000000000000350.
7. López-Fernández Y., Azagra A.M., de la Oliva P. et al. Pediatric acute lung injury epidemiology and natural history study: Incidence and outcome of the acute respiratory distress syndrome in children. *Crit Care Med*. 2012;40(12):3238–3245. https://doi.org/10.1097/CCM.0b013e318260caa3.
8. López-Fernández Y.M., Smith L.S., Kohne J.G. et al. Prognostic relevance and inter-observer reliability of chest-imaging in pediatric ARDS: A pediatric acute respiratory distress incidence and epidemiology (PARDIE) study. *Intensive Care Med*. 2020;46(7):1382–1393. https://doi.org/10.1007/s00134-020-06074-7.
9. Schneider N., Johnson M. Management of paediatric acute respiratory distress syndrome. *BJA Educ*. 2022;22(9):364–370. https://doi.org/10.1016/j.bjae.2022.04.004.
10. Pujari C.G., Lalitha A.V., Raj J.M., Kavilapurapu A. Epidemiology of acute respiratory distress syndrome in pediatric intensive care unit: Single-center experience. *Indian J Crit Care Med*. 2022;26(8):949–955. https://doi.org/10.5005/jp-journals-10071-24285.
11. Yu Huang, Yi Chen, Min Liu, Lan-Fang Tang, Lan-Fang Tang. Comparative analysis of Chlamydia pneumoniae pneumonia (CPP) and Mycoplasma pneumoniae pneumonia in children and risk factors of severe CPP. *BMC Infect Dis.* 2025;25(1):993. https://doi.org/10.1186/s12879-025-11405-4.
12. Pain C.E., Felsenstein S., Cleary G., Mayell S., Conrad K., Harave S. et al. Novel paediatric presentation of COVID-19 with ARDS and cytokine storm syndrome without respiratory symptoms. *Lancet Rheumatol*. 2020;2(7):e376–e379. https://doi.org/10.1016/S2665-9913(20)30137-5.
13. Woodruff R.C., Campbell A.P., Taylor C.A., Chai S.J., Kawasaki B., Meek J. et al. Risk factors for severe COVID-19 in children. *Pediatrics*. 2022;149(1):e2021053418. https://doi.org/10.1542/peds.2021-053418.
14. Di Filippo P., Attanasi M., Dodi G., Porreca A., Raso M., Di Pillo S., Chiarelli F. Evaluation of sleep quality and anxiety in Italian pediatric healthcare workers during the first wave of COVID-19 Pandemic. *BMC Res. Notes*. 2021;14(1):219. https://doi.org/10.1186/s13104-021- 05621-9.
15. Qing Qing, Ping Zha, Li-Ying Dai, Yang Wang. Effect of different ventilation methods combined with pulmonary surfactant on neonatal acute respiratory distress syndrome. *World J Clini Cases*. 2023;11(25):5878–5886. https://doi.org/10.12998/wjcc.v11.i25.5878.
16. Duffett M., Choong K., Ng V., Randolph A., Cook D.J. Surfactant therapy for acute respiratory failure in children: a systematic review and meta-analysis. *Crit Care*. 2007;11(3):R66. https://doi.org/10.1186/cc5944.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

17. Gorelov A.V., Avdeev S.N., Esaulenko E.V. et al.; National Association of Infectious Disease Specialists named after Academician V.I. Pokrovsky et al. Viral pneumonia. Epidemiology, diagnostics, therapy, prevention. Moscow: Media Sphere; 2024. P. 118–143. (In Russ.).
18. Wong J.J.M., Lee S.W., Tan H.L., Ma Y.J., Sultana R., Mok Y.H., Lee J.H. Lung-Protective Mechanical Ventilation Strategies in Pediatric Acute Respiratory Distress Syndrome. *Pediatr Crit Care Med*. 2020;21(8):720–728. https://doi.org/10.1097/PCC.0000000000002324.
19. Schneider N., Johnson M. Management of paediatric acute respiratory distress syndrome. *BJA Educ.* 2022;22(9):364–370. https://doi.org/10.1016/j.bjae.2022.04.004.
20. Ren X., Jiang Q., Wang L., Yuan X., Chen D., Xu G. Safety and efficacy of pulmonary surfactant therapy for acute respiratory distress syndrome in children: a systematic review and meta-analysis. *BMC Pulm Med.* 2025;25(1):1–10. https://doi.org/10.1186/s12890-025-03728-4.
21. Geropeppa M., Tsagkli P., Papadatou I., Efthymiou V., Tagarro A., Galanakis E., Spoulou V. Systemic Corticosteroids in Children With Pneumonia: A Systematic Review and Meta-analysis. *Pediatr Infect Dis J*. 2025. https://doi.org/10.1097/INF.0000000000005106.
22. Muravyev A.A., Bekezin V.V., Kozlova L.V. Pneumococcal infection in children: ways to solve the global problem. *Vestnik of the Smolensk State Medical Academy*. 2023;22(3):133–140. (In Russ). https://doi.org/10.37903/vsgma.2023.3.18.
23. Chen L., Qi X., Li R., Wang X., Shi B., Meng Q. Injection of immunoglobulin in the treatment process of children with severe pneumonia. *Pak J Med Sci*. 2019;35(4):940–944. https://doi.org/10.12669/pjms.
24. De Luca D., Cogo P., Kneyber M.C., Biban P., Semple M.G., Perez-Gil J., Conti G., Tissieres P., Rimensberger P.C. Surfactant therapies for pediatric and neonatal ARDS: ESPNIC expert consensus opinion for future research steps. *Crit Care*. 2021;25(1):75. https://doi.org/10.1186/s13054-021-03489-6.
25. Cattel F., Giordano S., Bertiond C., Lupia T., Corcione S., Scaldaferri M., Angelone L., De Rosa F.G. Use of exogenous pulmonary surfactant in acute respiratory distress syndrome (ARDS): Role in SARS-CoV-2-related lung injury. *Respir Physiol Neurobiol*. 2021;288:103645. https://doi.org/10.1016/j.resp.2021.103645.

ЛИТЕРАТУРА

1. Killien E.Y., Keller M.R., Watson R.S., Hartman M.E. Epidemiology of intensive care admissions for children in the US From 2001 to 2019. *JAMA Pediatr*. 2023;177(5):506–515. https://doi.org/10.1001/jamapediatrics.2023.0184.
2. Friedman M.L., Nitu M.E. Acute Respiratory Failure in Children. *Pediatr Ann*. 2018;47(7):e268–e273. https://doi.org/10.3928/19382359-20180625-01.
3. Panetti B., Bucci I., Di Ludovico A. et al. Acute respiratory failure in children: a clinical update on diagnosis. *Children (Basel)*. 2024;11(10):1232. https://doi.org/10.3390/children11101232.
4. Александрович Ю.С., Пшениснов К.В., Колодяжная В.И. Острый респираторный дистресс-синдром в педиатрической практике: диагностика и интенсивная терапия. Обзор литературы. *Российский вестник детской хирургии, анестезиологии и реаниматологии*. 2024;14(1):83–95. https://doi.org/10.17816/psaic1569.
5. Пшениснов К.В., Александрович Ю.С., Фелькер Е.Ю., Дмитриева Е.М., Мешков А.В., Разгон М.В. и др. Особенности искусственной вентиляции легких при остром респираторном дистресс-синдроме, осложнившемся бронхопульмональным свищом (клиническое наблюдение). *Вестник анестезиологии и реаниматологии*. 2025;22(1):120–128. https://doi.org/10.24884/2078-5658-2025-22-1-120-128.
6. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. 2015;16(5):428–439. https://doi.org/10.1097/PCC.0000000000000350.
7. López-Fernández Y., Azagra A.M., de la Oliva P. et al. Pediatric acute lung injury epidemiology and natural history study: Incidence and outcome of the acute respiratory distress syndrome in children. *Crit Care Med*. 2012;40(12):3238–3245. https://doi.org/10.1097/CCM.0b013e318260caa3.
8. López-Fernández Y.M., Smith L.S., Kohne J.G. et al. Prognostic relevance and inter-observer reliability of chest-imaging in pediatric ARDS: A pediatric acute respiratory distress incidence and epidemiology (PARDIE) study. *Intensive Care Med*. 2020;46(7):1382–1393. https://doi.org/10.1007/s00134-020-06074-7.
9. Schneider N., Johnson M. Management of paediatric acute respiratory distress syndrome. *BJA Educ*. 2022;22(9):364–370. https://doi.org/10.1016/j.bjae.2022.04.004.
10. Pujari C.G., Lalitha A.V., Raj J.M., Kavilapurapu A. Epidemiology of acute respiratory distress syndrome in pediatric intensive care unit: Single-center experience. *Indian J Crit Care Med*. 2022;26(8):949–955. https://doi.org/10.5005/jp-journals-10071-24285.
11. Yu Huang, Yi Chen, Min Liu, Lan-Fang Tang, Lan-Fang Tang. Comparative analysis of Chlamydia pneumoniae pneumonia (CPP) and Mycoplasma pneumoniae pneumonia in children and risk factors of severe CPP. *BMC Infect Dis*. 2025;25(1):993. https://doi.org/10.1186/s12879-025-11405-4.
12. Pain C.E., Felsenstein S., Cleary G., Mayell S., Conrad K., Harave S. et al. Novel paediatric presentation of COVID-19 with ARDS and cytokine storm syndrome without respiratory symptoms. *Lancet Rheumatol*. 2020;2(7):e376–e379. https://doi.org/10.1016/S2665-9913(20)30137-5.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

13. Woodruff R.C., Campbell A.P., Taylor C.A., Chai S.J., Kawasaki B., Meek J. et al. Risk factors for severe COVID-19 in children. *Pediatrics*. 2022;149(1):e2021053418. https://doi.org/10.1542/peds.2021-053418.
14. Di Filippo P., Attanasi M., Dodi G., Porreca A., Raso M., Di Pillo S., Chiarelli F. Evaluation of sleep quality and anxiety in Italian pediatric healthcare workers during the first wave of COVID-19 Pandemic. *BMC Res. Notes*. 2021;14(1):219. https://doi.org/10.1186/s13104-021- 05621-9.
15. Qing Qing, Ping Zha, Li-Ying Dai, Yang Wang. Effect of different ventilation methods combined with pulmonary surfactant on neonatal acute respiratory distress syndrome. *World J Clini Cases*. 2023;11(25):5878–5886. https://doi.org/10.12998/wjcc.v11.i25.5878.
16. Duffett M., Choong K., Ng V., Randolph A., Cook D.J. Surfactant therapy for acute respiratory failure in children: a systematic review and meta-analysis. *Crit Care.* 2007;11(3):R66. https://doi.org/10.1186/cc5944.
17. Горелов А.В., Авдеев С.Н., Эсауленко Е В. и др.; Национальная ассоциация специалистов по инфекционным болезням имени академика В.И. Покровского и др. Вирусные пневмонии: эпидемиология, диагностика, терапия, профилактика. М.: Медиа Сфера; 2024. С. 118–143.
18. Wong J.J.M., Lee S.W., Tan H.L., Ma Y.J., Sultana R., Mok Y.H., Lee J.H. Lung-Protective Mechanical Ventilation Strategies in Pediatric Acute Respiratory Distress Syndrome. *Pediatr Crit Care Med*. 2020;21(8):720–728. https://doi.org/10.1097/PCC.0000000000002324.
19. Schneider N., Johnson M. Management of paediatric acute respiratory distress syndrome. *BJA Educ.* 2022;22(9):364–370. https://doi.org/10.1016/j.bjae.2022.04.004.
20. Ren X., Jiang Q., Wang L., Yuan X., Chen D., Xu G. Safety and efficacy of pulmonary surfactant therapy for acute respiratory distress syndrome in children: a systematic review and meta-analysis. *BMC Pulm Med.* 2025;25(1):1–10. https://doi.org/10.1186/s12890-025-03728-4.
21. Geropeppa M., Tsagkli P., Papadatou I., Efthymiou V., Tagarro A., Galanakis E., Spoulou V. Systemic Corticosteroids in Children With Pneumonia: A Systematic Review and Meta-analysis. *Pediatr Infect Dis J*. 2025. https://doi.org/10.1097/INF.0000000000005106.
22. Муравьев А.А., Бекезин В.В., Козлова Л.В. Пневмококковая инфекция у детей: пути решения глобальной проблемы. *Вестник Смоленской государственной медицинской академии*. 2023;22(3):133–140. https://doi.org/10.37903/vsgma.2023.3.18.
23. Chen L., Qi X., Li R., Wang X., Shi B., Meng Q. Injection of immunoglobulin in the treatment process of children with severe pneumonia. *Pak J Med Sci*. 2019;35(4):940–944. https://doi.org/10.12669/pjms.
24. De Luca D., Cogo P., Kneyber M.C., Biban P., Semple M.G., Perez-Gil J., Conti G., Tissieres P., Rimensberger P.C. Surfactant therapies for pediatric and neonatal ARDS: ESPNIC expert consensus opinion for future research steps. *Crit Care*. 2021;25(1):75. https://doi.org/10.1186/s13054-021-03489-6.
25. Cattel F., Giordano S., Bertiond C., Lupia T., Corcione S., Scaldaferri M., Angelone L., De Rosa F.G. Use of exogenous pulmonary surfactant in acute respiratory distress syndrome (ARDS): Role in SARS-CoV-2-related lung injury. *Respir Physiol Neurobiol*. 2021;288:103645. https://doi.org/10.1016/j.resp.2021.103645.

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A multidisciplinary approach to the diagnosis and treatment of isolated 17,20-lyase deficiency: a case report

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ABSTRACT. Isolated 17,20-lyase deficiency is an extremely rare form of congenital adrenal hyperplasia caused by mutations in the *CYP17A1* gene, characterized by impaired androgen synthesis with preserved cortisol production. The clinical picture is often subtle, leading to delayed diagnosis. The description of clinical cases is crucial for understanding the features of this pathology. The article presents a detailed clinical description and analysis of the diagnostic pathway in a 13-year-old female patient with primary amenorrhea and delayed puberty. The examination included assessment of the hormonal profile, pelvic imaging, cytogenetic study, and molecular genetic Sanger sequencing of the *CYP17A1* gene with verification of findings in the parents. The patient with a 46,XX karyotype was found to have hypergonadotropic hypogonadism, cystic transformation of the ovaries, and an abnormally elevated level of 17-OH-progesterone. Genetic analysis revealed compound heterozygous pathogenic variants in the *CYP17A1* gene: c.1039C>T (inherited from the mother) and c.1319G>A (inherited from the father), confirming the diagnosis of isolated 17,20-lyase deficiency. Prescription of combined therapy with low doses of dexamethasone and estradiol valerate led to positive dynamics: the appearance and progression of secondary sexual characteristics, menarche, normalization of the hormonal profile, and regression of ovarian cysts. This case demonstrates the successful diagnosis of an extremely rare isolated form of 17,20-lyase deficiency, which requires a multidisciplinary approach and targeted genetic testing. The combination of pathogenic variants c.1039C>T and c.1319G>A in the *CYP17A1* gene leading to this form of congenital adrenal hyperplasia is described for the first time. Personalized therapy aimed at suppressing the ACTH-dependent pathway and replacing estrogen deficiency proved to be highly effective clinically and in laboratory findings, ensuring normal pubertal development.

KEYWORDS: *congenital adrenal hyperplasia, 17,20-lyase deficiency, CYP17A1, primary amenorrhea, delayed puberty, hypergonadotropic hypogonadism, compound heterozygous mutations, adolescents*

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Оригинальная статья

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Междисциплинарный подход к диагностике и лечению изолированного дефицита 17,20-лиазы: описание клинического случая

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РЕЗЮМЕ. Изолированный дефицит 17,20-лиазы — крайне редкая форма врожденной дисфункции коры надпочечников, обусловленная мутациями в гене *CYP17A1* и характеризующаяся нарушением синтеза андрогенов при сохранной продукции кортизола. Клиническая картина часто стерта, что приводит к поздней диагностике. Описание клинических случаев имеет ключевое значение для понимания особенностей течения этой патологии. В статье представлено подробное клиническое описание и анализ диагностического пути у пациентки 13 лет с первичной аменореей и задержкой полового развития. В рамках обследования выполнены оценка гормонального профиля, визуализация органов малого таза, цитогенетическое исследование и молекулярно-генетическое секвенирование гена *CYP17A1* с верификацией находок у родителей. У пациентки с кариотипом 46,XX выявлены гипергонадотропный гипогонадизм, кистозная трансформация яичников и аномально повышенный уровень 17-ОН-прогестерона. Генетический анализ выявил компаунд-гетерозиготные патогенные варианты в гене *CYP17A1*: c.1039C>T (унаследован от матери) и c.1319G>A (унаследован от отца), что подтвердило диагноз изолированного дефицита 17,20-лиазы. Назначение комбинированной терапии низкими дозами дексаметазона и эстрадиола валерата привело к положительной динамике: появлению и прогрессированию вторичных половых признаков, менархе, нормализации гормонального профиля и регрессу кист яичников. Представленное наблюдение демонстрирует успешную диагностику крайне редкой изолированной формы дефицита 17,20-лиазы, требующей междисциплинарного подхода и целенаправленного генетического тестирования. Впервые описана комбинация патогенных вариантов c.1039C>T и c.1319G>A в гене *CYP17A1*, приводящая к данной форме врожденной дисфункции коры надпочечников. Персонализированная терапия, направленная на подавление адренокортикотропного гормон-зависимого пути и замещение эстрогенового дефицита, доказала свою высокую клиническую и лабораторную эффективность, обеспечив нормальное пубертатное развитие.

КЛЮЧЕВЫЕ СЛОВА: *врожденная дисфункция коры надпочечников, дефицит 17,20-лиазы, CYP17A1, первичная аменорея, задержка полового развития, гипергонадотропный гипогонадизм, компаунд-гетерозиготные мутации, подростки*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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INTRODUCTION

17,20-lyase deficiency is the rarest form of congenital adrenal hyperplasia (CAH), characterized by impaired androgen and cortisol synthesis accompanied by excessive mineralocorticoid production [1]. This deficiency is caused by mutations in the *CYP17A1* gene, which encodes the enzyme 17α-hydroxylase that also possesses 17,20-lyase activity. 17α-hydroxylase converts pregnenolone and progesterone into 17-hydroxypregnenolone and 17-hydroxyprogesterone, while 17,20-lyase subsequently converts 17-hydroxypregnenolone into dehydroepiandrosterone (DHEA) (Fig. 1) [2]. The molecular mechanisms underlying this dual catalytic activity and the imbalance between the two functions in different mutations continue to be actively investigated [3]. The dual catalytic activity of the enzyme explains the existence of different forms of CAH: combined 17α-hydroxylase and 17,20-lyase deficiency, as well as isolated 17,20-lyase deficiency. Notably, most mutations in the CYP17A1 gene result in the loss of both enzymatic functions [4, 5].

Among all forms of congenital adrenal hyperplasia, 17α-hydroxylase/17,20-lyase deficiency accounts for less than 1% of cases. Based on a review

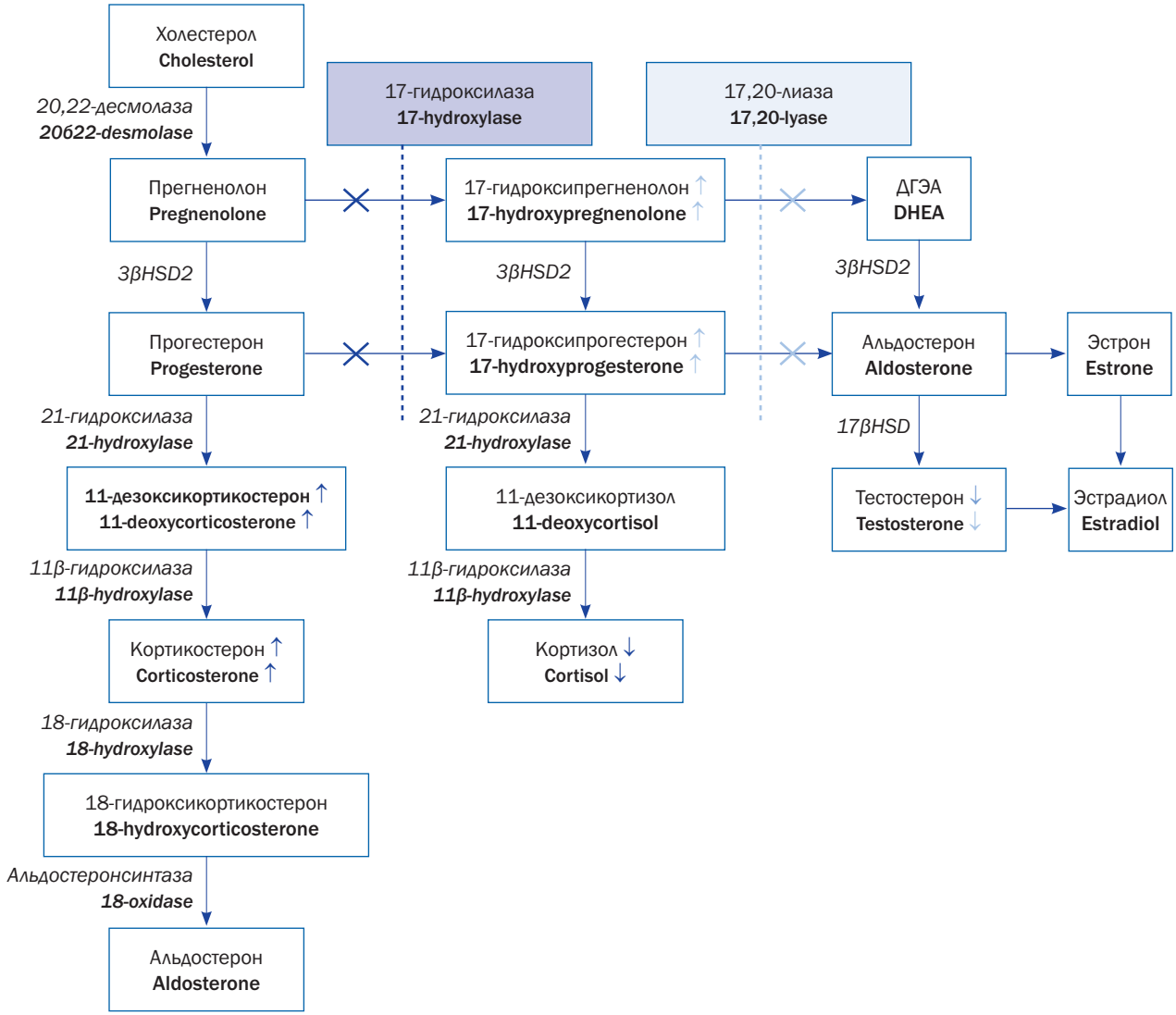

Fig. 1. Scheme of the main steroidogenesis pathways in the adrenal cortex and gonads: DHEA — dehydroepiandrosterone; 3βHSD2 — 3β-hydroxysteroiddehydrogenasetype 2; 17βHSD — 17β-hydroxysteroiddehydrogenase. Solid arrows indicate the direction of enzymatic reactions (adapted by [2])

Рис. 1. Схема основных путей стероидогенеза в коре надпочечников и гонадах: ДГЭА — дегидроэпиандростерон; 3βHSD2 — 3β-гидроксистероиддегидрогеназа типа 2; 17βHSD — 17β-гидроксистероиддегидрогеназа. Сплошные стрелки указывают направление ферментативных реакций (адаптировано по [2])

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of the literature, the prevalence of this deficiency remains uncertain due to the extreme rarity of the disorder and the limited number of clinical cases reported worldwide. To date, no more than 150 individuals with this condition have been described. These data refer primarily to the combined form of the enzyme deficiency, whereas the prevalence of isolated 17,20-lyase deficiency has not been established.

Herein, we present a clinical case of a patient with isolated 17,20-lyase deficiency confirmed by molecular genetic testing. The patient has a normal female karyotype (46,XX). We describe the diagnostic workup for delayed puberty and the observed response to hormone therapy.

CASE PRESENTATION

The patient was born from the second pregnancy and first term delivery. Her birth weight was 3500 g, length 51 cm, and Apgar scores were 8/9. At 7 months of age, she was diagnosed with hereditary spherocytosis (Minkowski–Chauffard syndrome). At 10 years of age, gallstones with clinical signs of cholestasis were detected. At 11 years of age, after prolonged conservative therapy had been ineffective, she underwent laparoscopic cholecystectomy and splenectomy. In the postoperative period, she developed recurrent adhesive disease, which led to a series of relaparotomies for adhesiolysis and abdominal drainage. At 12 years of age, she underwent appendectomy and ileostomy, followed by restoration of gastrointestinal patency and closure of the ileostomy. Only at the age of 13, when she presented with abdominal pain, ultrasound examination revealed uterine hypoplasia and cystic adnexal masses (up to 39 mm). Based on these findings, the girl was consulted by a gynecologist for the first time; there were no indications for surgical treatment, and endocrinological evaluation was recommended. Thus, at approximately 14 years of age, the child was first seen by a pediatric endocrinologist. In addition to abdominal pain, she reported the absence of menstruation and lack of hair growth in androgen-dependent areas. Family history revealed that the mother had menarche at 16 years of age and also had sparse axillary and pubic hair. Obtaining the paternal history was difficult because the parents lived separately.

At the time of examination by the pediatric endocrinologist, the patient had a proportional body habitus with evenly distributed subcutaneous fat. Notably, there was a complete absence of hair growth in androgen-dependent areas as well as on the shins and forearms. Tanner stage was B2, P1, with no menstruation (Me–); no axillary hair was observed, and the external genitalia were normally developed and of female type. Height was average at 163 cm (+0.41 SDS), and weight was appropriate for height at 57 kg (+0.71 SDS). Blood pressure was within the normal range for age.

Outpatient contrast-enhanced magnetic resonance imaging (MRI) of the pelvis was performed. It revealed a multicystic mass in the right ovary measuring 67×61×49 mm, with its medial border adjacent to the left ovary. The left ovary was normally positioned, measuring 28×22×16.8 mm, and contained follicles up to 18 mm within the stroma; no mass lesions were detected. The uterus was in *anteflexio* with no abnormalities; its dimensions were not specified.

Outpatient hormonal testing also demonstrated elevated levels of luteinizing hormone (LH) up to 26.0 mIU/mL and follicle-stimulating hormone (FSH) up to 13.9 mIU/mL. The estradiol level was normal (17 pg/mL). Given the finding of hypergonadotropic hypogonadism, further in-depth evaluation in a specialized endocrinology hospital was recommended.

Upon admission to the endocrinology department, serum electrolytes, liver enzymes, and glucose were within reference ranges. No evidence of thyroid pathology was found, and cortisol was normal. Androgen levels were as follows: 17-hydroxyprogesterone was elevated at 10.2 ng/mL, testosterone was elevated at 1.68 nmol/L. Dehydroepiandrosterone sulfate (DHEA-S) was normal at 0.8 μg/mL, and androstenedione was normal at 0.82 ng/mL. Pelvic ultrasound was performed. It revealed a uterine body length of 50 mm, width of 26.7 mm, and anteroposterior diameter of 12 mm. In place of the right ovary, a polycystic mass measuring 110×90×80 mm was observed. The left ovary measured 30×13×16.8 mm and contained small follicles. Due to the development of catarrhal symptoms, the evaluation was not completed.

One month later, the girl was readmitted, again presenting with abdominal pain. Repeat hormonal testing showed a decrease in androgen levels. Specifically, 17-hydroxyprogesterone was 6.87 ng/mL (previously 10.20 ng/mL), and androstenedione was 0.2 ng/mL (previously 0.82 ng/mL). DHEA-S was 0.03 μg/L (previously 0.8 μg/mL), and testo-

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sterone was 1.12 nmol/L (previously 1.68 nmol/L). LH and FSH levels remained elevated (23.06 and 13.5 mIU/mL, respectively), while estradiol was low at 21.5 pg/mL. Alpha-fetoprotein, beta human chorionic gonadotropin (β-hCG), and the tumor markers CA 19-9 and HE4 were within normal limits. CA 125 was 54 U/L, which decreased to 21 U/L one month later on follow up. Physical examination was unchanged, and sexual development remained the same. Follow up pelvic MRI, compared with previous imaging, showed marked progression of pathological findings. In the region of both ovaries, multilocular masses with heterogeneous (mucinous and hemorrhagic) contents and multiple septations were observed. The right mass measured 77×67×44 mm with a volume of 118 cm³, and the left mass measured 76×51×42 mm with a volume of 85 cm³. A significant amount of heterogeneous fluid was present around the masses. The uterus was hypoplastic, with dimensions including the cervix of 57×12×15 mm. Based on the MRI findings, bilateral ovarian biopsy and diagnostic vaginoscopy were performed. Histopathological examination of the biopsy specimens revealed a follicular cyst of the left ovary and a serous cyst of the right ovary.

The girl was consulted by a clinical geneticist. Given the delayed puberty, karyotyping was performed. Cytogenetic analysis revealed a normal female karyotype (46,XX). The genetic workup for the causes of delayed puberty then focused on monogenic etiologies. Polymerase chain reaction was used to screen for recurrent mutations in the *CYP21A2* gene to exclude the classic form of congenital adrenal hyperplasia (CAH). No variants in the *CYP21A2* gene were identified. A decision was made to rule out *CYP17A1* associated CAH. Sanger sequencing of the *CYP17A1* gene was performed, which identified two pathogenic variants in a heterozygous state: c.1039C>T and c.1319G>A. As a second step, the variants were confirmed by trio sequencing (the patient and her parents). The results confirmed biallelic involvement of the CYP17A1 gene in the patient. The c.1039C>T variant was inherited from the mother, and the c.1319G>C variant was inherited from the father.

Based on the comprehensive laboratory and instrumental findings, together with the clinical presentation, the girl was diagnosed with congenital adrenal hyperplasia due to isolated 17,20-lyase deficiency. The corresponding codes are OMIM #202110, ORPHA:90793, and ICD 10 E25.0.

Based on the above findings, the adolescent was started on replacement therapy with glucocorticoids (dexamethasone 0.25 mg/day) and estrogens (estradiol valerate 0.5 mg/day). On therapy, she developed hair growth on the labia and pubis, breast enlargement, and feminization of her body shape, with menarche occurring after 4 months.

Six months after starting therapy (at 14 years and 10 months of age), the girl was hospitalized in the endocrinology department for follow up assessment of treatment efficacy and safety. Positive changes were observed, including increased feminization of the body habitus with fat redistribution to the thighs and abdomen, breast enlargement, and the appearance of pubic hair (Fig. 2). Blood pressure and heart rate were within the normal range for age. Laboratory testing showed a decrease in LH to 5.63 mIU/mL (from 23.06 mIU/mL before therapy), while FSH remained elevated at 17.73 mIU/mL. Androgen levels also normalized. Specifically, 17-hydroxyprogesterone decreased to 2.24 ng/mL (from 6.87–10.2 ng/mL before therapy), and testosterone decreased to 0.1 ng/mL (from 1.12–1.68 ng/mL before therapy). DHEA S and androstenedione were unchanged, having previously been within reference ranges. Pelvic ultrasound demonstrated positive changes, including an increase in uterine size (length 50 mm, anteroposterior diameter 21.7 mm, width 28.7 mm, cervix 22×19 mm) and a reduction in ovarian volumes. The right ovary measured 49×23.4×23 mm with a volume of 13.8 cm³, and the left ovary measured 34×12.5×12.5 mm with a volume of 2.77 cm³. Given the positive clinical and laboratory response, the dexamethasone dose was maintained at 0.25 mg/day, while estradiol valerate was increased to 1.5 mg/day.

A subsequent laboratory follow up was performed another six months later (at 15 years and 4 months of age), i.e., one year after starting therapy. A height gain of 6 cm over the year was noted, while weight remained unchanged. Tanner stage was B4, P3 4, with menstruation present (Me+); no axillary hair growth was observed. FSH levels finally reached target values at 3.65 mIU/mL (previously 17.73 mIU/mL), and LH was 0.65 mIU/mL. Androgen levels remained low: DHEA S was 0.2 μmol/L, testosterone was 0.08 nmol/L, and 17 hydroxyprogesterone was 2.91 nmol/L. Pelvic ultrasound showed no adverse changes. No adjustment was made to hormone replacement therapy. The adolescent continued under regular follow up.

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Fig. 2. The patient's appearance during hormone replacement therapy (photos by the authors)

Рис. 2. Внешний вид пациентки на фоне заместительной гормональной терапии (фото авторов)

DISCUSSION

The most common clinical presentation of combined 17α-hydroxylase/17,20-lyase deficiency is a pubertal female patient with delayed puberty (primary amenorrhea and lack of secondary sexual characteristic development), hypertension, and hypokalemia [1, 6]. The classic triad of pronounced arterial hypertension has been repeatedly described in the literature [7]. Such children initially present to a pediatrician. However, the symptoms of arterial hypertension and hypokalemia are not consistently present [8–10] and occur mainly in cases of complete absence of 17α-hydroxylase activity [11]. Because of abdominal pain due to developing ovarian polycystosis, which may subsequently impair reproductive function [12], the next physician managing such a child is often a surgeon [13]. It is only after this that adolescent girls present to a pediatric gynecologist or endocrinologist, as illustrated by the present clinical case.

In our case, the patient presented with primary amenorrhea, lack of secondary sexual characteristic development, abdominal pain, and a history of multiple surgical interventions. At the same time, she had a complete absence of arterial hypertension and hypokalemia, which are characteristic of 17α-hydroxylase deficiency. This finding led us to suspect isolated 17,20-lyase deficiency.

Sanger sequencing of the *CYP17A1* gene revealed two pathogenic variants in a heterozygous state: c.1039C>T and c.1319G>A. The c.1039C>T variant in the *CYP17A1* gene is known to cause impaired interaction between cytochrome b5 and the 17α-hydroxylase/17,20-lyase enzyme, partially reducing its activity [14]. In this context, 17α hydroxylase activity is better preserved than 17,20-lyase activity [9,15]. Cases of compound heterozygous *CYP17A1* variants in 17α-hydroxylase/17,20-lyase deficiency have been reported in the literature, with the clinical presentation varying significantly depending on the mutation combination [10,16,17]. For example, Van Den et al. described two women with a 46,XY karyotype who carried compound heterozygous *CYP17A1* mutations [18]. S. Yamagata et al. reported a 67 year old patient with a homozygous c.1039C>T mutation in the *CYP17A1* gene and a normal female karyotype (46,XX) [9]. This patient had a muted clinical presentation of *CYP17A1* associated CAH, including developed secondary sexual characteristics, menstruation until menopause, hypertension, hypokalemia, and signs of hyperaldosteronism with suppressed renin activity. In our case, the c.1039C>T variant in the *CYP17A1* gene was inherited from the mother, who has sparse hair growth in hormone-dependent areas and relatively late menarche (at 16 years of age). The c.1319G>C variant was inherited from the father. Heterozygous carrier status of a *CYP17A1* mutation is hypothesized to lead to steroidogenesis insufficiency [15]. Our case is the first to report a combination of two heterozygous mutations, c.1039C>T and c.1319G>A, in the *CYP17A1* gene resulting in isolated 17,20-lyase deficiency in our patient.

CONCLUSION

This clinical case clearly demonstrates the effectiveness of a comprehensive approach to diagnosing rare forms of disorders of sex development. Targeted genetic testing played a key role by identifying two pathogenic variants in the *CYP17A1* gene in a compound heterozygous state in a patient with a 46,XX karyotype and primary amenorrhea. This is the first report of a combination of two heterozy-

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gous mutations, c.1039C>T and c.1319G>A, in the *CYP17A1* gene, which confirmed the diagnosis of isolated 17,20 lyase deficiency. Successful therapy combining suppression of ACTH dependent steroidogenesis with low dose dexamethasone and estrogen replacement therapy led to positive outcomes, including the onset of menstruation, development of female secondary sexual characteristics, and regression of cystic ovarian changes. These findings underscore the importance of personalized treatment and the need for lifelong multidisciplinary follow up of such patients.

ADDITIONAL INFORMATION

Authors' contribution. M.S. Ilchenko — collection and analysis of clinical data, writing the original draft (case description); S.A. Laptiev — performing and interpreting molecular genetic analysis, literature review; K.V. Skobeleva — conceptualization of the study, examination and treatment of the patient, manuscript editing; D.R. Tursumetova — literature review, writing the original draft, preparation of illustrations, bibliography design.

All authors read and approved the final version before publication.

Competing interests. The authors declare that they have no competing interests.

Consent for publication. Written consent was obtained from legal representatives of the patient for publication of relevant medical information within the manuscript.

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REFERENCES / ЛИТЕРАТУРА

1. Finkielstain G.P., Vieites A., Bergadá I., Rey R.A. Disorders of sex development of adrenal origin. *Front Endocrinol*. 2021;12:770782. https://doi.org/10.3389/fendo.2021.770782.
2. Singh H., Kumar R., Mazumder A., Salahuddin Mazumder R., Abdullah M.M. insights into interactions of human cytochrome P450 17A1: A review. *Curr Drug Metab*. 2022;23(3):172–187. https://doi.org/10.2174/1389200223666220401093833.
3. Lee S.G., Kim V., Lee G.H., Kim C., Jeong E., Guengerich F.P., Kim D. Hydroxylation and lyase reactions of steroids catalyzed by mouse cytochrome P450 17A1 (Cyp17a1). *J Inorg Biochem*. 2023;240:112085. https://doi.org/10.1016/j.jinorgbio.2022.112085.
4. Maheshwari M., Arya S., Lila A.R., Sarathi V., Barnabas R., Rai K. et al. 17α-hydroxylase/17,20-lyase deficiency in 46,XY: our experience and review of literature. J Endocr Soc. 2022;6(3):bvac011. https://doi.org/10.1210/jendso/bvac011.
5. Willemsen A.L., Torpy D.J., De Sousa S., Falhammar H., Rushworth R.L. 17α-hydroxylase/17,20-lyase deficiency (17-OHD): A meta-analysis of reported cases. *J Clin Endocrinol Metab*. 2025;110(4):e1261–e1271. https://doi.org/10.1210/clinem/dgae773.
6. Lee H.I., Kwon A., Suh J.H., Choi H.S., Song K.C., Chae H.W., Kim H.S. Two cases of 17α-hydroxylase/17,20-lyase deficiency caused by the CYP17A1 mutation. *Ann Pediatr Endocrinol Metab*. 2021;26(1):66–70. https://doi.org/10.6065/apem.2040184.092.
7. Zhao Y., Wang C., Guo Z., Yi C., Zhang W. Severe hypertension caused by 17α-hydroxylase deficiency: A case report. *Heliyon*. 2023;9(3):e14062. https://doi.org/10.1016/j.heliyon.2023.e14062.
8. Habib A., Shojazadeh A., Molayemat M., Jafari Khamirani H., Zoghi S., Dastgheib S.A., Habib A. A single-amino-acid in-frame deletion in CYP17A1 results in combined 17-hydroxylase and 17,20-lyase deficiency in an Iranian family despite the protein mutation site. *Hum Genome Var*. 2021;8(1):31. https://doi.org/10.1038/s41439-021-00160-y.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

9. Yamagata S., Kageyama K., Usui T., Saito K., Takayasu S., Usutani M., Terui K., Daimon M. Identification of a homozygous c.1039C>T (p.R347C) variant in CYP17A1 in a 67-year-old female patient with partial 17α-hydroxylase/17,20-lyase deficiency. *Endocr J*. 2022;69(2):115–120. https://doi.org/10.1507/endocrj.EJ21-0266.
10. Siklar Z., Camtosun E., Bolu S., Yildiz M., Akinci A., Bas F. et al. 17α-hydroxylase/17,20 lyase deficiency: clinical features and genetic insights from a large Turkey cohort. *Endocrine*. 2024;85(3):1407–1416. https://doi.org/10.1007/s12020-024-03962-6.
11. Li J., Zhang Q., Chen J., Fu X., Yang J., Liu L. Case report: 17α-hydroxylase deficiency due to a hotspot variant and a novel compound heterozygous variant in the CYP17A1 gene of five Chinese patients. *Front Pediatr*. 2022;10:935191. https://doi.org/10.3389/fped.2022.935191.
12. Gomes L.G., Bachega T.A.S.S., Mendonca B.B. Classic congenital adrenal hyperplasia and its impact on reproduction. *Fertil Steril*. 2019;111(1):7–12. https://doi.org/10.1016/j.fertnstert.2018.11.037.
13. Xia Y., Shi P., Xia J., Zhang H., Xu L., Kong X. Novel mutations of the CYP17A1 gene in four Chinese 46,XX cases with partial 17α-hydroxylase/17,20-lyase deficiency. *Steroids*. 2021;173:108873. https://doi.org/10.1016/j.steroids.2021.108873.
14. Tateishi Y., Webb S.N., Li B., Liu L., Lindsey Rose K., Leser M., Patel P., Guengerich F.P. Proteomics, modeling, and fluorescence assays delineate cytochrome b5 residues involved in binding and stimulation of cytochrome P450 17A1 17,20-lyase. *J Biol Chem*. 2024;300(3):105688. https://doi.org/10.1016/j.jbc.2024.105688.
15. Saltarelli M.A., Ferrante R., Marcello F.D., David D., Valentinuzzi S., Pilenzi L. et al. A novel heterozygous mutation of the CYP17A1 Gene in a child with a micropenis and isolated 17,20-lyase deficiency. *Int J Environ Res Public Health*. 2022;19(11):6880. https://doi.org/10.3390/ijerph19116880.
16. Kurnaz E., Kartal Baykan E., Türkyılmaz A., Yaralı O., Yavaş Abalı Z., Turan S. et al. Genotypic sex and severity of the disease determine the time of clinical presentation in steroid 17α-hydroxylase/17,20-lyase deficiency. *Horm Res Paediatr*. 2020;93(9-10):558–566. https://doi.org/10.1159/000515079.
17. Sun M., Mueller J.W., Gilligan L.C., Taylor A.E., Shaheen F., Noczyńska A. et al. The broad phenotypic spectrum of 17α-hydroxylase/17,20-lyase (CYP17A1) deficiency: a case series. *Eur J Endocrinol*. 2021;185(5):729–741. https://doi.org/10.1530/EJE-21-0152.
18. Van Den Akker E.L., Koper J.W., Boehmer A.L., Themmen A.P., Verhoef-Post M., Timmerman M.A., Otten B.J., Drop S.L., De Jong F.H. Differential inhibition of 17alpha-hydroxylase and 17,20-lyase activities by three novel missense CYP17 mutations identified in patients with P450c17 deficiency. *J Clin Endocrinol Metab*. 2002;87(12):5714–5721. https://doi.org/10.1210/jc.2001-011880.

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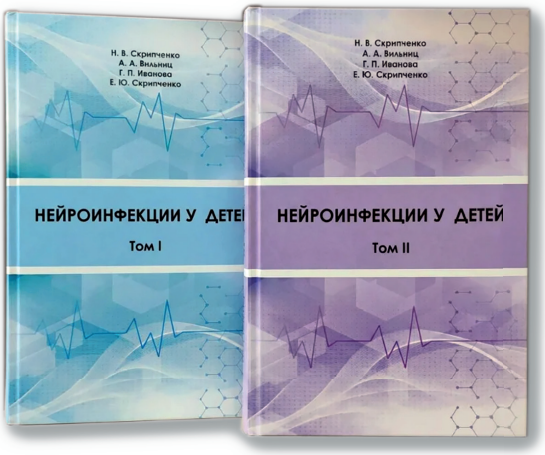

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В 2025 году вышло двухтомное руководство для врачей «Нейроинфекции у детей» — обновлённая и дополненная версия монографии 2015 года. Издание подготовлено ведущими отечественными специалистами в области нейроинфекций детского возраста, чей опыт в этой области общепризнан и бесценен. Это единственное в своём роде руководство не только в России, но и за рубежом, основной источник практической информации по инфекционным поражениям нервной системы у детей для врачей России и стран СНГ. Достоинства книги — доступность изложения, сводные таблицы, широкий охват нозологических форм, современность, достоверность данных и практическая направленность.

Первый том сочетает классические главы по менингококковой инфекции, гнойным и серозным менингитам, вирусным энцефалитам, миелитам, полиомиелиту, инфекционным невропатиям и полиневропатиям, острым вялым параличам, клещевым нейроинфекциям, энтеровирусным заболеваниям, ботулизму, бешенству и столбняку с новыми разделами. В них отражены уникальные сведения по неонатальным гнойным менингитам и вирусным энцефалитам, врождённым инфекциям, лимфоцитарному хориоменингиту, паразитарным болезням ЦНС, роли инфекции в развитии васкулитов и инсультов, а также нейродегенеративным и демиелинизирующим заболеваниям, миастении и миастеническим синдромам. Особое внимание уделено поражению нервной системы при ветряной оспе, опоясывающем лишае и ВИЧ-инфекции у детей разного возраста, с подробным описанием комплексной терапии и дозировок препаратов. Инновационным стал раздел по дифференциальной диагностике лихорадки при нейроинфекциях.

Второй том условно разделён на две части. В первой акцент сделан на неотложные состояния при нейроинфекциях — основную причину летальных исходов, с разбором их диагностики и терапии, включая экстракорпоральные методы гемокоррекции. Рассматриваются ятрогенные осложнения — полиневропатии, миопатии, энцефалопатии критических состояний. Важное место занимает раздел по интенсивной терапии нейроинфекций, изложенный по отечественным клиническим рекомендациям. Отдельно представлены методы диагностики: ликворологические, нейрофизиологические, лучевые и ультразвуковые. Особое внимание уделено поражению нервной системы при микозах, туберкулёзе, сифилисе, а также дифференциальной диагностике экзантем и судорожного синдрома у детей. Значительный интерес вызывает раздел о хронических нейроинфекциях с анализом причин хронизации и путей её минимизации. Неотъемлемой частью тома стали главы по вакцинопрофилактике и медицинской реабилитации детей-реконвалесцентов. Вторая часть тома посвящена сложным клиническим случаям из практики авторов, иллюстрирующим важность междисциплинарного подхода для современного врача.

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