ISSN 2500-1175 (PRINT)
ISSN 2712-7958 (ONLINE)

АЛЛЕРГОЛОГИЯ И ИММУНОЛОГИЯ В ПЕДИАТРИИ

ALLERGOLOGY AND IMMUNOLOGY IN PEDIATRICS

https://adair.elpub.ru/

TOPICS IN THE ISSUE:

ТОМ 23, ВЫПУСК 1
ISSUE: ISSUE 1

МАРТ 2025
MARCH 2025

Ассоциация детских аллергологов и иммунологов России
Наш подписной индекс: 47432

March 2025

ISSN 2712-7958 online | **Allergologiya i immunologiya v pediatrii** | **ISSN 2500-1175** print

ALLERGOLOGY AND IMMUNOLOGY IN PEDIATRICS

Volume 23, Issue 1, *March 2025*

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OFFICIAL JOURNAL OF THE ASSOCIATION OF PEDIATRIC ALLERGISTS AND IMMUNOLOGISTS OF RUSSIA (APAIR)

Founder and publisher of the journal: Association of Pediatric Allergists and Immunologists of Russia, 6 Ostrovityanova Str., Moscow, 117513, Russian Federation, phone: +7 495 225 71 04, www.adair.ru • adair@adair.ru

With support of
Kazan State Medical University
Samara State Medical University
Academy of postgraduate education under FSBU FSCC of FMBA of Russia

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The journal «Allergology and Immunology in Pediatrics» is registered with the Ministry of Press, Broadcasting and Mass Communications Russian Federation. Registration number: PI No. 77-17742 dated March 9, 2004. The journal was printed in the printing house of JSC «PFOP», Russia, 142100, Podolsk, Revolutionary avenue, 80/42. Edition: 1000 copies. The issue is signed for publication: March 20, 2025. The journal materials are distributed under a Creative Commons license.
The journal is published 4 times a year. A subscription to the journal «Allergology and Immunology in Pediatrics» can be issued at any post office in Russia.
The subscription index of the publication is 47432. The price is free.

ISSN 2712-7958 online | **Allergologiya i immunologiya v pediatrii** | **ISSN 2500-1175** print

АЛЛЕРГОЛОГИЯ И ИММУНОЛОГИЯ В ПЕДИАТРИИ

Том 23, выпуск 1, *март 2025*

Журнал «Аллергология и иммунология в педиатрии» — рецензируемое научно-практическое периодическое издание, предназначенное для педиатров, аллергологов-иммунологов, а также специалистов разного профиля, работа которых связана с областью педиатрической аллергологии и иммунологии. Журнал является официальным печатным органом Ассоциации детских аллергологов и иммунологов России (АДАИР); издается при участии ведущих специалистов страны — педиатров, аллергологов, клинических иммунологов. На страницах издания — оригинальные статьи, образовательные программы для врачей, клинические наблюдения, дискуссии, информация о последних достижениях отечественной, зарубежной науки и практики. Все публикации журнала связаны с вопросами диагностики, лечения, профилактики аллергических и других иммуноопосредованных заболеваний у детей с акцентом на детскую аллергологию. Журнал основан в 2003 году. С 2003–2004 гг. носил название «Научно-практический журнал Аллергология и иммунология в педиатрии». В 2004 году переименован и носит название «Аллергология и иммунология в педиатрии».

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Учредитель и издатель: Общероссийская общественная организация «Ассоциация детских аллергологов и иммунологов России», Россия, 117513, г. Москва, ул. Островитянова, д. 6, тел.: +7 495 225 71 04, www.adair.ru • adair@adair.ru

При поддержке ФГБОУ ВО «Казанский государственный медицинский университет» Минздрава России
ФГБОУ ВО «Самарский государственный медицинский университет» Минздрава России
Академия постдипломного образования ФГБУ ФНКЦ ФМБА России

Редакция журнала «Аллергология и Иммунология в Педиатрии» 117513, г. Москва, ул. Островитянова, д. 6, офис 9, Тел.: 8(495) 225-71-04
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Решением Высшей аттестационной комиссии (ВАК) Министерства образования и науки РФ журнал «Аллергология и иммунология в педиатрии» включен в Перечень ведущих рецензируемых научных журналов и изданий, выпускаемых в Российской Федерации, в которых рекомендована публикация основных результатов диссертационных исследований на соискание ученых степеней доктора и кандидата наук по специальностям: 3.1.21. Педиатрия (медицинские науки), 3.1.23. Дерматовенерология (медицинские науки), 3.2.7. Аллергология и иммунология (биологические и медицинские науки). С 1.01.2024 присвоен К2 сроком на 3 года.

Журнал «Аллергология и иммунология в педиатрии» зарегистрирован в Министерстве по делам печати, телерадиовещания и средств массовых коммуникаций РФ. Регистрационный номер: ПИ №77-17742 от 9.03.2004 г. Журнал отпечатан в типографии ОАО «ПФОП», Россия, 142100, г. Подольск, Революционный проспект, д. 80/42. Тираж: 1000 экз. Номер подписан в печать: 20.03.2025 г. Материалы журнала распространяются под лицензией Creative Commons.
Журнал выходит 4 раза в год. Подписку на журнал «Аллергология и иммунология в педиатрии» можно оформить в любом отделении связи на территории России. Подписной индекс издания 47432. Цена свободная.

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КЛИНИЧЕСКИЕ СЛУЧАИ

Оригинальная статья / Original article

Adherence of doctors to clinical recommendations in the management of children and adolescents with allergic rhinitis

RAR — научная статья

https://doi.org/10.53529/2500-1175-2025-1-5-20

Date of receipt:19.08.2024
Date of acceptance: 23.10.2024
Date of publication: 21.03.2025

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Introduction. The Russian Federation has adopted international and national conciliatory documents and clinical guidelines covering the diagnosis and treatment of allergic rhinitis (AR). The extent to which doctors adhere to the guidelines remains unclear.
Methods: online survey of allergists (32.7%), pediatricians (54.4%) and others (total n = 364) in 2023–2024.
Results: Most specialists (81.6%) adhere to Russian official clinical recommendation, while about 4% of respondents adhere to international guidelines. A significant part of doctors actively uses the term "seasonal/perennial" AR (75.3%), less often the indication of the severity and course of the disease is used. Pediatricians don't use the classification more often than allergists. To determine the severity of the visual analog scale is used only in 23.0% of cases.
Among laboratory diagnostic methods, allergists are more likely to prescribe a specific examination than pediatricians (87.8% vs. 56.8%). Only 53.8% of respondents consider it mandatory to conduct an allergological examination for patients with AR.
57.4% of respondents believe that the amount of initial therapy depends on the severity of the disease. The most popular drugs for starting therapy are intranasal steroids (40.2%), antihistamines (23.5%), montelukast 4.0%, and intranasal antihistamines 4,8%.
If it is necessary to use concomitant therapy 56.4% of doctors choose a fixed combination of intranasal steroid + antihistamines as a first-line therapy, and an additional 20.9% consider this option in rare cases.
In severe cases, 16.9% of doctors prescribe oral steroids, 20.4% choose the parenteral route of corticosteroid administration, and 33.6% of respondents do not prescribe systemic corticosteroids. The majority of doctors surveyed are aware of the immunobiological therapy of AR — 73.0%, and 26.7% actively support the appointment of biological therapy for AR. Allergen-specific therapy is recommended to be considered by 61.9% of the surveyed doctors.
Conclusion: The study shows the need to train physicians facing AR problems in accordance with current clinical guidelines and international practice.

Keywords: allergic rhinitis, children, adolescents, doctors

Conflict of interest:
The article is supported by the Glenmark Company.

For citation: Smolkin Y.S., Masalskiy S.S., Shakhova N.V., Molochkova A.N. Adherence of doctors to clinical recommendations in the management of children and adolescents with allergic rhinitis. *Allergology and Immunology in Pediatrics*. 2025; 23 (1): 5-21. https://doi.org/10.53529/2500-1175-2025-1-5-20

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Оригинальная статья / Original article

Исследование приверженности врачей клиническим рекомендациям при ведении детей и подростков с аллергическим ринитом

https://doi.org/10.53529/2500-1175-2025-1-5-20

УДК 616-056.3
Дата поступления: 19.08.2024
Дата принятия: 23.10.2024
Дата публикации: 21.03.2025

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Введение. В РФ приняты международные и национальные согласительные документы и клинические рекомендации, в которых освещаются вопросы диагностики и лечения аллергического ринита (АР). Степень приверженности врачей гайдлайнам остается неясной.

Методы: онлайн-опрос врачей аллергологов (32,7%), педиатров (54,4%) и других специальностей (всего n = 364) в 2023–2024 годах.

Результаты. Большая часть специалистов (81,6%) придерживаются российских официальных документов, а международных гайдлайнов — около 4% опрошенных. Значительная часть врачей активно используют терминологию «сезонный/круглогодичный» АР (75,3%), реже используется указание степени тяжести и течения заболевания. Педиатры не пользуются классификацией чаще. Для определения степени тяжести визуальная аналоговая шкала используется только в 23,0% случаев.

Среди лабораторных методов диагностики аллергологи чаще назначают специфическое обследование, чем педиатры (87,8% vs 56,8%). Только 53,8% респондентов считают обязательным проведение аллергологического обследования пациентов.

57,4% опрошенных считают, что объем стартовой терапии зависит от степени тяжести заболевания. Наиболее популярными препаратами для стартовой терапии являются интраназальные стероиды (иГКС) (40,2%), антигистаминные препараты (АГ) (23,5%), монтелукаст 4,0%, интраназальные АГ 4,8%.

При необходимости использования сочетанной терапии 56,4% врачей выбирают фиксированную комбинацию иГКС + инАГ в качестве терапии первой линии, дополнительно 20,9% рассматривают этот вариант в редких случаях.

В тяжелых случаях 16,9% врачей назначают пероральные глюкокортикостероиды, 20,4% — выбирают парентеральный путь введения ГКС, 33,6% респондентов не назначают системные ГКС. Об иммунобиологической терапии АР осведомлее на большая часть опрошенных врачей — 73,0%, причем 26,7% активно поддерживают назначение биологической терапии при АР. Аллерген-специфическую терапию рекомендуют рассмотреть 61,9% опрошенных врачей.

Заключение: исследование показывает необходимость обучения врачей, сталкивающихся с проблемами АР, в соответствии с действующими клиническими рекомендациями и международной практикой.

Ключевые слова: аллергический ринит, дети, подростки, врачи

Конфликт интересов:
Статья создана при поддержке компании «Гленмарк».

Для цитирования: Смолкин Ю. С., Масальский С. С., Шахова Н. В., Молочкова А. Н. Исследование приверженности врачей клиническим рекомендациям при ведении детей и подростков с аллергическим ринитом. *Аллергология и иммунология в педиатрии*. 2025; 23 (1): 5-21. https://doi.org/10.53529/2500-1175-2025-1-5-20

Allergic rhinitis (AR) is a common problem in childhood and adolescence and negatively affects physical, social and psychological well-being [1]. AR affects about 40% of the world population, 23-30% of the European population and 12-30% of the US population [2]. According to the results of the large-scale "International Study of Asthma and Allergies in Childhood" (ISAAC), the prevalence of AR in different countries of the world varies from 0.8 to 14.9% among children 6-7 years old, from 1.4 to 39.7% among chil-

dren 13-14 years old [3]. Based on the data of research centers in Russia that participated in the study of AR prevalence under the international ISAAC program, the prevalence of AR in the Tomsk region among children aged 7-8 years old — 21,9%, among children 13-14 years old — 34.2% [4], in Stavropol Krai — 24.0% among children 7-8 years old and 41.1% among children 13-14 years old [5], in Krasnodar Krai — 25.4% among children 7-8 years old and 40.3% among children 13-14 years old [6], in Agin Buryat Autonomous Okrug — 10.2% among children 12-14 years old [7]. High prevalence of AR is also demonstrated by studies conducted among preschool children. Thus, according to Kong et al. data, the prevalence of AR among urban children 3-6 years old was 10.8% [8]. The results of Chinese colleagues are similar to the data of domestic researchers — the prevalence of AR among 3-6 years old children in Altai Krai was 10.6% [9], in Volgograd — 14.1% [10], the prevalence of AR symptoms among 3- year old children in Moscow — 5.2%, among 4 -year old children — 7.4% [11].

Currently, international and national consensus documents and clinical guidelines have been adopted, which cover the issues of AR diagnosis and treatment. In 2001, the WHO working group experts adopted the Allergic Rhinitis and its Impact on Asthma (ARIA) program, and in 2020 the fourth updated edition — Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence was published [12]. In 2013, the European Academy of Allergology and Clinical Immunology adopted the position paper Paediatric rhinitis [13]. In Russia, the third version of the scientific and practical program "RADAR. Allergic rhinitis in children" was published [14], and the Ministry of Health approved the clinical guidelines (CG) "Allergic rhinitis" developed by the Russian Association of Allergists and Clinical Immunologists, the National Medical Association of Otorhinolaryngologists, and the Union of Pediatricians of Russia.

According to the current legislation of the Russian Federation, medical care should be provided on the basis of CGs, as well as consider the standards drawn up on the basis of the CG provisions, including the prescription of drugs registered in Russia in accordance with the official instructions for their use. This is rational, as it is the CGs that reflect the currently known methods of diagnosis, treatment, prevention and rehabilitation of patients with certain nosologies, as well as the significance of these methods using evidence-based medicine data. To date, it has been confirmed that physicians' adherence to CGs reduces the likelihood of medical errors, improves the quality of prescribed treatment, and positively affects patients' adherence to therapy and their satisfaction with treatment [15]. However, in real clinical practice, physicians do not always follow the current CGs and have their own preferences when choosing methods of diagnosis and treatment of patients [16].

STUDY OBJECTIVE: to study diagnostic and therapeutic approaches of physicians from different regions of the country in managing children and adolescents with AR.

MATERIALS AND METHODS

We conducted a prospective cross-sectional study with questionnaires to physicians in different regions of the country about the tactics of managing children and adolescents with AR. The survey was conducted using a questionnaire developed by the Association of Pediatric Allergists and Immunologists of Russia (ADAIR), which was posted on the open Internet resources of the Association (ADAIR website: https://adair.ru/). All interested physicians could take part in the survey; no certificate was required. The survey was conducted between June 2023 and July 2024. Physicians from various specialties participated in the survey, but the majority of polled physicians were pediatricians and allergists.

The questionnaire included 43 questions, which were organized into 5 sections.

Section 1 contained general questions (region, length of service, type of treatment and prevention institution, specialty).

Section 2 — questions about CGs and consensus documents used in actual practice for managing children and adolescents with AR.

Section 3 — diagnosis formulation questions.

Section 4 — questions devoted to the diagnosis of AR in children and adolescents (terms of diagnosis, preferred laboratory and instrumental diagnostic methods, allergological examination, consultations with specialists).

Section 5 — questions on AR therapy in children and adolescents.

The full version of the questionnaire is presented in Appendix 1.

Table 1. **Characteristics of physician respondents included in the survey (author's table)**
Таблица 1. **Характеристика врачей-респондентов, принявших участие в опросе (таблица автора)**

Features		*abs (%)*
Specialty	Allergist-immunologist	119 (32,7)
	Primary care pediatrician	198 (54,4)
	Otolaryngologist	20 (5,5)
	Other	23 (6,4)
	Total	364 (100,0)
Type of treatment facility	Outpatient	305 (83,8)
	Stationary	59 (16,2)
	Total	364 (100,0)
Form of ownership of the institution	State	267 (73,4)
	Private	97 (26,6)
	Total	364 (100,0)
Population of the settlement	Over 500,000 population	198 (54,4)
	150–500 k.	62 (17,0)
	Less 150 thousand	104 (28,6)
	Total	*364 (100,0)*

LEC: the study is non-interventional; ethics committee approval is not required. Respondents gave their consent to the processing of personal data.

STATISTICAL ANALYSIS

Statistical analysis procedures were performed using JASP 0.19.2 statistical packages. Pearson's chi-square test was used to compare the frequencies of qualitative features. The data are given in the form of relative frequencies.

RESULTS AND DISCUSSION

Characteristics of study participants

A total of 364 physicians of various specialties from different regions of the country took part in the survey. Among the respondents, pediatricians — primary care pediatricians — 54.4% and allergologists-immunologists — 32.7% prevailed, while otorhinolaryngologists accounted for only 5.5% of respondents. More than half of the respondents — 54.4% live in large megacities with a population of more than 500 thousand people, 17.0% — in cities with a population of 150,000 to 500,000, 28.6% — in small towns with a population of less than 150,000. Primary care physicians prevailed among the respondents (83.8%), with more than half of all respondents working in public institutions (73.4%). 26.6% of respondents work in hospitals. Thus, the cohort of physicians is represented mainly by allergologists-immunologists and pediatricians working mainly in outpatient and polyclinic medical institutions of large cities with a population of more than 500 thousand. The average work experience of the respondents amounted to 19 years. The characteristics of the study participants are presented in Table 1.

Physicians' awareness of clinical guidelines and consensus documents related to AR

Of particular interest is the result of a survey of physicians on awareness and use in real clinical prac-

Table 2. **Frequency of respondents' use of clinical guidelines on allergic rhinitis (author's table)**
Таблица 2. **Частота применения респондентами клинических рекомендаций по АР (таблица автора)**

Document title	%	Note
Clinical guidelines «Allergic rhinitis»	59,6	Approved by the Scientific and Practical Council of the Ministry of Health of the Russian Federation in 2020; developers: Russian Association of Allergists and Clinical Immunologists, National Medical Association of Otorhinolaryngologists, Union of Pediatricians of Russia (expired in 2024)
Federal Clinical Recommendations for the provision of medical care to children with allergic rhinitis	22,0	Approved by the Scientific and Practical Council of the Ministry of Health of the Russian Federation Year 2015; developers: Russian Association of Allergists and Clinical Immunologists, Union of Pediatricians of Russia (lost in 2020)
Scientific and practical program «Radar. Allergic rhinitis in children. Recommendations and algorithm in pediatric allergic rhinitis»	17,6	Edition Fourth, revised and supplemented, 2023, edited by V. A. Revyakina, N. A. Daiches, N. A. Geppe
Clinical guidelines «Allergic rhinitis»	13,5	Developers: Russian Society of Rhinologists, edited by A.S. Lopatin and V.V. Shilenkova. Shilenkova. approval year 2022
«Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence»	6,0	Year of approval 2020
ICAR-Allergic Rhinitis 2023	2,5	Year of approval 2023

tice of CGs, scientific and practical programs and consensus documents when working with patients suffering from AR.

The survey showed that the majority of surveyed physicians are familiar with several documents regulating the work with patients suffering from AR. A significant part of respondents noted the CG "Allergic rhinitis" approved in 2020 and 2015 by the Ministry of Health of the Russian Federation — 75,5% and 55,2% respectively. The scientific and practical program "Radar. Allergic rhinitis in children. Recommendations and algorithm for pediatric allergic rhinitis" was known to 37.4% of respondents. Only 15% of respondents were familiarized with international recommendations and consensus documents on AR.

When asked "Which CGs do you use in your practice?", the majority of respondents (59.6%) pointed to the CG "Allergic rhinitis" approved in 2020. Another

22% use an older version of the 2015 CGs, which together account for 81.6% of physicians adhering to official documents. International recommendations and concordance documents are used in real practice on average by about 4% of respondents. It is noteworthy that 5.5% of the respondents do not take into account the existing CGs and rely on their personal clinical experience when managing AR patients.

Diagnostic formulation in real clinical practice

AR is a disease characterized by IgE-mediated inflammation of the nasal mucosa and the presence of at least two of the following symptoms that occur daily for an hour or more: nasal congestion (obstruction), nasal discharge (rhinorrhea), sneezing, itching in the nasal cavity. Allergic rhinitis is classified into "seasonal" and "year-round", intermittent (symptoms occur less than 4 days a week or less than 4 weeks a year) and persistent (symptoms occur more than 4 days a week or more than 4 weeks a year), and mild, moderate, and severe, according to MH CG 261 "Allergic Rhinitis".

According to the survey, 75.3% of respondents find it useful to distinguish seasonal and year-round AR when formulating a diagnosis, while the course (intermittent/persistent) and severity of AR are indicated by only 37.9% and 43% of physicians, respectively.

There is no disagreement among allergists and pediatricians on the issue of "seasonal/year-round" AR. Allergists specify the severity of allergic AR in 77.8% of cases, while pediatricians do so in 28.5% (among pediatricians, 41.4% do not use and 30.1% do not know the criteria of AR severity). The situation is similar with the indication of the course of the disease: 74.1% of respondents-allergologists use the classification "persistent/intermittent", pediatricians use it only in 18.6% of cases (50.1% of pediatricians know the difference but do not use it and 24.1% do not know the criteria).

AR DIAGNOSIS IN ACTUAL CLINICAL PRACTICE

Laboratory methods of examination

The diagnosis of AR is determined on the basis of allergologic anamnesis, characteristic clinical symptoms and the results of specific allergologic examination of the patient. According to the CG MH 261, all patients with symptoms of AR in the period of exacerbation should undergo a general clinical blood test (analysis) to detect increased eosinophil levels and cytologic examination of upper respiratory tract flushes to detect nasal secretion eosinophilia. According to the results of our study, only 40.9% of surveyed physicians consider it necessary to perform a "general blood test" to detect eosinophilia and 50.3% — to perform cytologic examination of upper respiratory tract flushes to detect nasal secretion eosinophilia.

Clinical general therapeutic examination and auscultation to exclude bronchial asthma and other diseases are performed by 85.5% of respondents, the "breathing with closed mouth" test is used by 61.4% of physicians. Visual analog scale is used to diagnose the severity of rhinitis only in 23.0% of cases, and 43.4% of respondents know about the method but do not use it. All mentioned tests are mandatory according to CG 261 "Allergic rhinitis".

To confirm the diagnosis of AR and identify causative allergens, all patients are recommended to undergo allergologic examination, which can be performed by skin testing (skin tests with allergens) or by determining the level of specific IgE in serum. The choice of allergy testing method is determined by the availability and equipment of the allergy room and the presence/absence of contraindications to skin testing. According to our survey, 53.8% of respondents consider allergologic examination mandatory, while the rest of the respondents consider it possible to establish the diagnosis of AR on the basis of the clinical picture of the disease without allergologic examination. Allergologists consider allergological examination to be mandatory only in 74.8% of cases, pediatricians — in 41.7%.

According to the CG, it is not recommended that all patients with AR should undergo a study of the total level of immunoglobulin E in the blood due to the low specificity of this parameter, while 47.3% of respondents prescribe this test in the initial diagnosis of AR. Table 4 presents the frequency of laboratory tests prescribed by physicians of different specialties in diagnosing AR in children and adolescents.

According to the data presented in the table, from the point of view of existing CGs, the most correct approach to diagnosing AR is by allergologists-immunologists, but even allergologists-immunologists prescribe allergologic diagnostics (determination of specific IgE or skin tests) only in 88% of cases, and determination of eosinophils in nasal secretion — in 61% of cases. Only 57% of pediatricians recommend allergological diagnostics necessary to confirm AR.

Table 3. **Frequency of prescription of laboratory methods of research in primary diagnosis of AR by doctors of different specialties (author's table)**
Таблица 3. **Частота назначения лабораторных методов исследования при первичной диагностике АР врачами разных специальностей (таблица автора)**

Specialty	Total IgE		Blood eosinophils		Nasal secretion eosinophils		Specific IgE to allergens or skin tests		Number of respondents
	n	%	n	%	n	%	n	%	
Allergist	28	23,7%	46	37,4%	73	61,8%	105	87,8%	131
Pediatrician	116	58,8%	86	43,7%	99	50,3%	112	56,8%	199
Total (including other specialties)	**157**	**46,6%**	**142**	**40,8%**	**183**	**54,0%**	**226**	**66,7%**	**378**

Instrumental methods of examination

According to CG 261, all patients with suspected AR should undergo anterior rhinoscopy to identify characteristic signs of AR, anatomical features and differential diagnosis with other pathologies. Only 28.0% of pediatricians and allergists-immunologists perform rhinoscopy in patients with AR, the rest either do not consider it necessary, or do not perform it due to lack of skills and tools, or refer to ENT doctors for examination. In case of ineffectiveness of standard therapy, severe and prolonged nasal obstruction, it is recommended to perform endoscopic endonasal revision of the nasal cavity, nasopharynx and paranasal sinuses, computerized tomography of the sinuses for differential diagnosis and identification of other causes of nasal obstruction. According to our survey, 33.2% of respondents recommended endoscopic endonasal revision of the nasal cavity when indicated, and 83.8% of respondents recommended CT scanning.

AR TREATMENT IN REAL CLINICAL PRACTICE

The goal of AR therapy is to achieve complete control of the disease symptoms. The main directions of treating patients with AR are elimination measures, drug therapy and allergen-specific immunotherapy (ASIT).

Elimination measures

All patients with AR are recommended to carry out elimination measures in relation to causative allergens in order to reduce the severity of the disease symptoms (use of special filters, daily wet cleaning, avoiding contact with pets, moving to another climatic zone for the time of flowering of causative allergens, etc.). As elimination measures it is also recommended to use preparations for moisturizing, cleansing and protection of the nasal mucosa — isotonic saline solutions in order to prevent contact of aeroallergens with the nasal mucosa. The vast majority of physicians (86.5%) recommend elimination measures after

Table 4. **First-line drugs for monotherapy according to pediatricians and allergists-immunologists (author's table)**
Таблица 4. **Стартовые препараты для монотерапии по мнению врачей педиатров и аллергологов-иммунологов (таблица автора)**

Drug group	Pediatricians, %	Allergists, %	All respondents*, %
Oral antihistamines	14,5	38,2	23,5
Intranasal antihistamines	7,0	0,8	4,8
Antileukotrienes	7,0	0,8	4,0
Intranasal steroides	39,2	38,9	40,2
Any option other than Intranasal steroides	6,5	0,76	4,6
Any option, including Intranasal steroides	17,9	14,2	15,6

* Including physicians of other specialties.

identification of the causative allergen. Opinions were divided regarding the use of nasal mucosal cleansing preparations and nasal shower prescription: 41.2% of physicians prescribe isotonic solutions during exacerbation, 39.3% of respondents prescribe nasal shower for AR patients even outside exacerbation as an element of daily nasal hygiene.

Drug therapy

Drug therapy of AR is based on a stepwise approach, when the amount of therapy depends on the severity of the disease, and as the severity of the disease changes, it is possible to adjust the amount of therapy.

When asked about the starting therapy of AR, 57.4% of respondents answered that the amount of therapy depends on the severity of the disease, which is in line with existing clinical guidelines, with 19.3% of respondents usually prescribing 2 drugs and 11.7% prescribing one drug. Allergologists are guided by the degree of severity in 71.6%, and pediatricians in 46.2% of cases. Pediatricians are characterized by a more formal approach — about half of these doctors use established treatment regimens.

16.1% of pediatricians and only 4.6% of allergist-immunologists are committed to starting monotherapy, while 24.6% and 15.3% prescribe 2 drugs simultaneously. Despite the fact that mild allergic rhinitis predominates in the disease structure, patients with uncontrollable complaints usually present at the doctor's office, and generally doctors tend to prescribe several drugs according to the severity of the disease.

In case of monotherapy, 40.1% of the respondents choose intranasal corticosteroids as the first-choice drug, 23.6% choose systemic antihistamines, 4.9% choose intranasal antihistamines, and 4.1% choose antileukotriene receptor inhibitors (Table 4).

When analyzing the table, it is noticeable that the most preferable option for doctors is the prescription of intranasal GCS, which have a good efficacy and safety profile. Perhaps the experience of specialists was influenced by the fact that patients who had previously used over-the-counter drugs came to the doctor. However, the unusually low frequency of use of oral antihistamines in the group of pediatricians compared to allergists (14.5% vs 38.2%) attracts attention. In contrast, allergists hardly use intranasal AG and montelukast in starting monotherapy.

Despite active educational efforts and existing CGs, 42.7% of respondents consider sedating antihistamines for use, "as the fastest and strongest drugs", with 5.4% doing so frequently and the remaining 39.7% rarely but using outdated first-generation AHs. Among allergists, 22.9% sometimes use sedating AHs, with 8.0% of pediatricians doing so frequently and 48.7% sometimes. Both generations of antihis-

tamines have similar effects; the claim that the first generation is faster and more active does not stand up to criticism [17].

As a means of emergency therapy on demand and in short courses, CG 261 support the use of decongestants. The questionnaire asked about the frequency of using this group of drugs. Respondents mostly used decongestants occasionally (65.9%), but 17.2% of physicians prescribe the drug to almost all patients. The prescriptions of allergists and pediatricians regarding decongestants differ significantly: 27.1% of pediatricians prescribe vasoconstrictors to almost everyone and 55.3% sometimes; among allergists, 3.1% prescribe often and 81.6% sometimes.

The combination of decongestant and intranasal AH may be more effective than each drug alone. Such medications are used frequently by 20.9% of all physicians, 57.4 use them occasionally.

Cromoglycic acid drugs are prescribed by 59.7% of respondents, of which 13.4% prescribe drugs of this group frequently, and 55.2% — in rare cases.

According to CG 261, oral glucocorticoids are recommended for patients with AR in case of severe exacerbation and (or) ineffectiveness of drugs used in the 3rd stage of therapy. According to the results of our study, 16.9% of surveyed physicians prescribe oral glucocorticosteroids when indicated, 20.4% choose parenteral route of administration of systemic glucocorticosteroids, 33.6% of respondents do not basically prescribe systemic glucocorticosteroids, and 20.3% of physicians do not know about the possibility to use systemic corticosteroids in AR.

Deposited corticosteroids were previously popular for use, now their role is declining. Deposited corticosteroids were previously popular for use, now their role is declining. CG 261 does not recommend the use of depot GCS by injection. Intranasal use of short-acting GCS is also unacceptable. Nevertheless, 13.8% of physicians indicate that they have patients who receive intranasal GCS injections in rare cases (9.9% of allergists and 16.5% of pediatricians), 40.0% are not aware of this possibility, and 38.1% do not generally prescribe intranasal GCS injections.

Similar results were obtained with regard to deposited drugs: 13.8% rarely prescribe deposited GCS, 1.6% do so frequently and 73.8% are against prescribing. Among allergists, 84.7% are strong opponents of depot GCSs and 9.1% prescribe them occasionally. Among pediatricians, 68.8% never prescribe, 15.1% use occasionally and 2% prescribe frequently.

The use of combined drugs for AR therapy is a promising direction. When comparing the efficacy of different variants of AR therapy, it should be noted that, according to ARIA recommendations, combinations of nasal GCS with oral AGPs have no advantages over nasal GCS monotherapy, which is confirmed by the data of meta-analysis of 13 studies [18]. However, fixed combinations of nasal GCS with nasal AGPs are superior in efficacy to the isolated use of topical GCSs.

This conclusion is supported by the current clinical practice guideline CG 261, according to which combination therapy may be considered when combined use of anti-allergic drugs in AR is necessary. Intranasal corticosteroid + intranasal antihistamine and tablet non-sedating systemic antihistamine in combination with a leukotriene receptor antagonist are presented.

To the general question “Do you support starting combination therapy for AR?” 91.6% of allergists and 65.8% of pediatricians responded positively.

According to the results of our study, 56.4% of physicians support the use of combined iGCS + INAH in moderate to severe AR as first-line therapy, with an additional 20.9% considering this combination in rare cases. Among allergists, 66.4% approve

of the use of the combination of IGCS + INAH, and another 24.2% recognize the usefulness of the combination but use it infrequently. Among pediatricians, there is a slightly lower frequency of specialists who strongly endorse starting with the combination agent (53.8%), and another 23.6% rarely use it. Thus, most specialists are aware of the availability of a new group of drugs and actively use it in practice.

At the same time, more than half of physicians (56.4%) prescribe a non-sedative systemic antihistamine in combination with a leukotriene receptor antagonist, 11.4% consider this combination unnecessary, and 24.1% do not know about this possibility. 74.8% of allergists approve of the use, 13% have a negative view of "montelukast + AH" drugs, and 6.1% are unaware of the possibility. Among pediatricians, one-third of physicians are unfamiliar with this type of combination (35.2%) and 45.7% support the existence of the combination drug, while 10.1% are against this type of medication.

In patients with severe persistent AR with ineffectiveness of drugs used in the 3rd step of therapy, according to step therapy, it is recommended to consider prescribing immunobiologic therapy with monoclonal antibody to immunoglobulin E — omalizumab. Most of the surveyed physicians are aware of immunobiologic therapy of AR — 73.0%, and 26.7% actively support the prescription of biological therapy in AR. It should be noted that 12.2% of allergists and 22.1% of pediatricians do not know about the existence of biological therapy for AR treatment.

The questionnaire contained questions about the use in practice of drugs not recommended for use due to insufficient evidence base or side effects, such as sedative systemic antihistamines, depot corticosteroids. About half of the respondents — 43.0% periodically prescribe sedative antihistamines, 15.6% of respondents do not exclude the possibility of prescribing depot corticosteroids parenterally during AR exacerbation.

Allergen-specific immunotherapy (ASIT) is the main method of pathogenetic treatment of IgE-mediated allergic diseases, consisting in the introduction of increasing doses of the allergen responsible for the clinical manifestations of the disease in a given patient [14]. This method of therapy is recommended to be considered for all patients with AR in order to reduce the severity of AR symptoms and reduce the need for drug therapy. According to our survey, 61.9% of physicians surveyed are aware of this method of therapy and recommend considering its prescription, while 12.4% of respondents, despite being aware of ASIT, do not recommend it to patients, and 1.6% of respondents are not familiar with ASIT. Some physicians, 14.8%, recommend ASIT only for seasonal rhinitis, and 1.6% recommend it only for year-round rhinitis. Allergologists naturally recommend ASIT for any AR, while 20.0% of pediatricians do not recommend or are not aware of the treatment methodology.

CONCLUSION AND DISCUSSION

Our study showed a rather high adherence of physicians, especially allergists-immunologists, to the provisions of clinical guidelines in the management of children and adolescents with AR. However, the study demonstrated a number of inconsistencies between the diagnostic and therapeutic approaches of physicians and the provisions of clinical recommendations on AR. These include a high frequency of prescribing for diagnostic purposes general immunoglobulin E, which has low specificity (47.3% of respondents), while ignoring allergologic examination and determination of eosinophils in nasal secretion to confirm AR. Allergological examination by skin testing or determination of specific IgE levels in blood serum is prescribed on average by 67% of physicians, and determination of nasal secretion eosinophils by 54% of physicians. Inconsistencies of therapeutic tactics with existing clinical recommendations include the use of sedative antihistamines (43%), depot corticosteroids (15%) in some groups (pediatricians), low frequency of recommendations for the prescription of ASIT, including due to insufficient awareness of this method of therapy (61%).

It is noteworthy that the choice of AR therapy step is recommended to be made according to the ARIA 2020 algorithm, as interpreted in the clinical guidelines CG 261, using VAS results. Our respondents use VAS only in 23.0% of cases, despite the fact that the method is a recommended tool for assessing the severity of AR symptoms and is described in the appendix to the Federal Clinical Recommendations on Allergic Rhinitis Therapy.

Note that according to the results of the Russian online survey of patients with AR (n = 328) performed in 2021, the respondents were significantly overrepresented among those with moderate-to-severe/severe AR (VAS symptom score ⩾ 5) — 83 vs. 17% with mild AR (VAS score < 5). In the same study by Nenasheva N. M. 2021, 52% of patients reported the severity of the disease as moderate, 26% of respondents reported intense symptoms and impaired daytime activity and sleep, and 5% of respondents had extremely severe disease, i.e. symptoms significantly impaired quality of life [19].

According to the algorithm of therapy prescription for patients with symptom severity on VAS ⩾ 5, combination therapy of intranasal GCS and intranasal AH is recommended [20]. According to a number of studies, fixed combinations (such as mometasone + olopatadine) for nasal administration have demonstrated not only better efficacy compared to monotherapy with topical GCS, but also a rapid onset of action (from 10 min.) [21, 22].

Combinations of intranasal steroids with antihistamines are now available: olopatadine 600 mcg and mometasone furoate 25 mcg (from 6 years of age for seasonal and from 12 for year-round AR); azelastine 137 mcg + fluticasone 50 mcg/dose (from 12 years of age), azelastine 140 mcg + mometasone 50 mcg (from 18 years of age). Combination therapy of fluticasone with azelastine and mometasone furoate with olopatadine demonstrated comparable efficacy [23].

In a comparative study of intranasal AHs, olopatadine has a better tolerability profile than azelastine for adverse events such as bitter taste, nasal burning, and sneezing [24]. As such, patients may have a higher adherence to the olopatadine-containing formulation, which in turn may contribute to better control of disease symptoms through good compliance. The fixed combination of mometasone + olopatadine is the only one authorized in the Russian Federation for use in children from 6 years of age and can be used in pediatric practice for severe pollen allergy symptoms.

New combinations of oral drugs are also emerging. For patients who cannot use nasal forms of drugs, it is reasonable to recommend the combination of the antileukotriene drug montelukast and oral AH. Along with a mono-drug, a fixed combination of montelukast with AH levocetirizine is available in Russia from 15 years of age.

The Association of Pediatric Allergists and Immunologists of Russia supports the prescription of combination therapies based on current clinical guidelines and data from meta-analyses. A meta-analysis of 167 studies, published in 2025, evaluating the efficacy of intranasal medications in AR, including combination therapies, confirmed the high efficacy of combination therapy compared to monotherapy [25]. The use of a spray with a reduced concentration of mometasone (Rialtris spray, Glenmark Pharmaceuticals Ltd, India) is preferable in pediatrics due to the high safety profile of the drug. According to published studies, the combination of mometasone furoate with olopatadine is safe and well tolerated, and the incidence of adverse events is similar to that of placebo or monotherapy, even in the long term [26].

The results of the survey of specialists show the direction of training activities: more attention should be paid to the ways of assessing patients' condition and choosing effective combinations of drugs. It is obvious that monotherapy will be in demand in special

groups of patients: in case of a mild course or when there is a need for increased safety — pregnancy, early age. In other situations, adequate symptom control is achievable with combination therapy. The choice based on symptom severity is the preferred therapeutic option.

The Association supports and provides resources to educate a wide range of physicians facing the problems of allergic rhinitis, using distance technology, lecture and teaching materials to bring the knowledge of specialists in line with current clinical guidelines and international practice.

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THE AUTHORS` CONTRIBUTION TO THE WORK

Sergey S. Masalskiy — development of research design, participation in research, analysis of results, statistical data processing, writing and editing the text of the article.

Natal'ya V. Shakhova — review of publications on the topic of article, writing and editing the text of the manuscript.

Yuri S. Smolkin — development of research design, verification of the critical content of the article.

Aleksandra N. Molochkova — analysis of results, preparation of a draft manuscript, preparation of the article for publication.

ВКЛАД АВТОРОВ В РАБОТУ

Масальский С. С. — разработка дизайна исследования, участие в проведении исследования, анализ результатов, статистическая обработка данных, написание и редактирование текста статьи.

Шахова Н. В. — обзор публикаций по теме статьи, написание и редактирование текста рукописи.

Смолкин Ю. С. — разработка дизайна исследования, проверка критически важного содержания статьи.

Молочкова А. Н. — анализ данных, подготовка черновика рукописи, подготовка статьи к публикации.

APPENDIX 1. THE QUESTIONNAIRE USED IN THE STUDY

ПРИЛОЖЕНИЕ 1. ОПРОСНИК, ИСПОЛЬЗУЕМЫЙ В ИССЛЕДОВАНИИ

Section 1. Respondents' characteristics	
Full name, city, work experience, medical and preventive institution, type of institution	
Section 2. Awareness of clinical guidelines	
What clinical guidelines do you know:	Clinical Recommendations of the Ministry of Health of the Russian Federation CG 261 "Allergic Rhinitis" (Russian Association of Allergists and Clinical Immunologists, National Medical Association of Otorinolaryngologists, Union of Pediatricians of Russia) Federal clinical guidelines for medical care of children with allergic rhinitis. Baranov A. A. 2015 (Union of Pediatricians of the Russian Federation) Radar. Allergic rhinitis in children recommendations and algorithm in pediatric allergic rhinitis. Edited by V. A. Revyakina, N. A. Daiches, N. A. Geppe. 2020 Allergic rhinitis: clinical recommendations; ed. by A. S. Lopatin and V. V. Shilenko. V. Shilenko-voy. 2022 Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence. Bousquet J., et al. 2020 ICAR. International consensus statement on allergy and rhinology: Allergic rhinitis. 2018
What clinical guidelines do you actually adhere to in your work?	
Section 3. Diagnosis formulation	
Do you find it necessary to use the terms "seasonal" and "year-round" rhinitis, are they useful in your work?	
Do you use the definition of rhinitis severity in your work, do you specify it in the diagnosis?	
Do you use the terms "persistent" and "intermittent" rhinitis in your work, are they useful and necessary?	
Section 4. Screening	
Do you think it is necessary to use specific allergy screening in all patients to confirm the diagnosis of allergic rhinitis?	
Who should perform the allergy screening?	
What tests are you sure to perform for initial confirmation of the diagnosis of allergic rhinitis?	
Do you use anterior rhinoscopy (examining the nasal cavity from the front with light from the front through the nostrils) when examining children with a suspected or established diagnosis of AR? (question for non-otolaryngologist physicians)	
Do you perform general physical examination, particularly auscultation, in patients with AR?	
Do you use a visual analog scale of allergic rhinitis symptoms in the majority of your patients?	
Do you assess the patient's condition using the normal "breathing with mouth closed" test?	
Do you think it is necessary to use radiation diagnostic methods (radiography, CT, MRI of the sinuses) for most patients?	
What methods of instrumental diagnostics do you consider necessary in patients with suspected AR?	
Do you prescribe and detail elimination measures for the patient?	
Section 5. Treatment	
Do you recommend elimination therapy in the form of Weber's douches with isotonic or hypertonic saline solutions?	
What starting therapy do you prescribe for allergic rhinitis?	

Starting drug for the treatment of rhinitis in case of monotherapy
Do you prescribe sedative antihistamines?
Do you use parenteral depot corticosteroids?
Do you prescribe systemic corticosteroids exceptionally for severe exacerbations of AR?
Do you prescribe corticosteroids in injections intranasally for AR exacerbations?
How often do you prescribe decongestants?
How often do you prescribe cromoglycic acid drugs?
How often do you prescribe decongestant + antihistamine combination therapy intranasally?
What is your opinion on the starting prescription of combination drugs: antihistamines intranasally + corticosteroids intranasally in one spray?
How do you feel about the starting prescription of combination drugs: antihistamines + leukotriene receptor blockers in one pill?
Do you support the starting prescription of combination therapy for allergic rhinitis, such as moderate allergic rhinitis?
Do you support immunobiologic therapy (monoclonal antibodies) for AR?
Do you consider it necessary to prescribe and recommend allergen-specific immunotherapy in AR?

Оригинальная статья / Original article

Prognostic value of peripheral blood lymphocytes in community-acquired pneumonia in children

RAR — научная статья

https://doi.org/10.53529/2500-1175-2025-1-21-31

Date of receipt: 19.09.2024
Date of acceptance: 30.10.2024
Date of publication: 21.03.2025

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Absract

Introduction. Despite a significant decrease in mortality from pneumonia, pneumonia remains the main cause of death in children outside the neonatal period. As a key component of the immune system, $CD4^+$ T cells significantly affect lung tissue damage. Prior to the initiation of an adaptive immune response, NK cells not only produce cytokines associated with antiviral immunity, but are also directly involved in the rapid elimination of infected cells.

Objective. To determine changes in lymphocyte subpopulations in peripheral blood in children in different age groups with community-acquired pneumonia and and to assess their prognostic significance depending on the severity of community-acquired pneumonia.

Materials and methods. 117 children aged 1 to 18 years with radiologically confirmed diagnosis of community-acquired pneumonia were examined, severe (29 children) and mild (88 children). All children were divided into 4 age groups (1–3 years old, 4–7 years old, 8–12 years old, 13–18 years old). Blood levels of lymphocytes and their subpopulations were determined in all children using flow cytometry.

Results. According to the results of the study, a decrease in the number of NK-lymphocytes in the peripheral blood of children with severe community-acquired pneumonia was revealed compared with children with mild community-acquired pneumonia in all age groups, and an association of NK-lymphocytes and TNK-lymphocytes with the severity of community-acquired pneumonia in children was found.

Conclusions. A decrease in the number of NK-lymphocytes in peripheral blood in children with severe community-acquired pneumonia in all age groups compared with children with mild community-acquired pneumonia, as well as the association between a decrease in the number of NK-lymphocytes and TNK-lymphocytes and the severity of community-acquired pneumonia in children can be considered an independent marker of the severity of this disease.

Keywords: community-acquired pneumonia, children, prognosis, severe pneumonia, lymphocyte subpopulations

Conflict of interest:
The authors declare no conflict of interest related to the publication of this article.

For citation: Izyurova N.V., Savochkina A.Y. Prognostic value of peripheral blood lymphocytes in community-acquired pneumonia in children. *Allergology and Immunology in Pediatrics*. 2025; 23 (1): 21–31. https://doi.org/10.53529/2500-1175-2025-1-21-31

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Оригинальная статья / Original article

Прогностическое значение лимфоцитов периферической крови при внебольничной пневмонии у детей

https://doi.org/10.53529/2500-1175-2025-1-21-31

УДК 616.24-002-053.3-06:616.15-07
Дата поступления: 19.09.2024
Дата принятия: 30.10.2024
Дата публикации: 21.03.2025

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Аннотация

Актуальность. Несмотря на существенное снижение заболеваемости пневмонией, внебольничная пневмония остается одной из основных причин смерти детей вне неонатального периода. Являясь ключевым компонентом иммунной системы, $CD4^+$ Т-клетки значительно влияют на повреждение легочной ткани. До инициации адаптивного иммунного ответа NK-клетки не только продуцируют цитокины, связанные с противовирусным иммунитетом, но также непосредственно участвуют в быстром выведении инфицированных клеток.

Цель. Определить изменения субпопуляций лимфоцитов в периферической крови у детей в разных возрастных группах с внебольничной пневмонией и оценить их прогностическую значимость в зависимости от тяжести внебольничной пневмонии.

Материалы и методы. Было обследовано 117 детей в возрасте от 1 года до 18 лет с рентгенологически подтвержденным диагнозом внебольничной пневмонии тяжелой (29 детей) и нетяжелой (88 детей). Все дети были разделены на 4 возрастные группы (1–3 года, 4–7 лет, 8–12 лет, 13–18 лет). Фенотипирование и дифференцировка субпопуляций лимфоцитов проводились методом проточной цитометрии.

Результаты. По результатам исследования было выявлено снижение количества NK-лимфоцитов в периферической крови у детей с тяжелой внебольничной пневмонией по сравнению с детьми с нетяжелой внебольничной пневмонией во всех возрастных группах, а также обнаружена ассоциация NK-лимфоцитов и TNK-лимфоцитов с тяжестью внебольничной пневмонии у детей.

Заключение. Снижение количества NK-лимфоцитов в периферической крови у детей с тяжелой внебольничной пневмонией во всех возрастных группах по сравнению с детьми с нетяжелой внебольничной пневмонией, а также связь между снижением количества NK-лимфоцитов и TNK-лимфоцитов и тяжестью внебольничной пневмонии у детей может рассматриваться независимым маркером тяжести данного заболевания.

Ключевые слова: внебольничная пневмония, дети, прогноз, тяжелая пневмония, субпопуляции лимфоцитов

Конфликт интересов:
Авторы заявляют об отсутствии конфликта интересов, связанных с публикацией настоящей статьи.

Для цитирования: Изюрова Н.В., Савочкина А.Ю. Прогностическое значение лимфоцитов периферической крови при внебольничной пневмонии у детей. *Аллергология и иммунология в педиатрии*. 2025; 23 (1): 21–31. https://doi.org/10.53529/2500-1175-2025-1-21-31

INTRODUCTION

Despite a significant reduction in overall child mortality, community-acquired pneumonia (CAP) remains one of the causes of death in children beyond the neonatal period. It can also cause exacerbation of chronic diseases and worsen long-term lung health by reducing lung function [1].

The etiologic structure of pneumonia in children is very diverse and depends on the child's age. Data on the etiology of community-acquired pneumonia in children vary greatly, which can be explained by the different epidemic conditions in which the studies were conducted. Various bacteria and viruses are the most common causative agents of CAP in children, but in most cases the etiology of CAP remains unidentified [2]. According to a large population-based study in the United States, viruses were detected in 66.2% of children under 18 years of age who were hospitalized with CAP, had radiologic confirmation of CAP, and from whom samples for etiologic

testing were obtained (n = 2222) [3]. The severity of clinical manifestations of community-acquired pneumonia varies considerably. Consequently, both differentiation of viral and bacterial infection and accurate assessment and prediction of disease severity are critical for effective management of patients with community-acquired pneumonia, including the decision to prescribe antibiotics and hospitalization. Both of these goals are much easier to achieve in adults than in children, especially in the early years of life. The limited ability to obtain lower respiratory tract secretions or sputum from young children, given their poor expectorative capacity and inability to expectorate sputum, is the most important obstacle to obtaining sufficient respiratory specimens for etiologic identification by microbiologic methods in young patients [4].

One of the easiest ways to monitor pneumonia patients is through a general blood count, which usually measures the white blood cell count, neutrophil count, monocyte count, and lymphocyte count. Among these, neutrophils, lymphocytes and monocytes are common indicators of human inflammation and immune status [5]. Total leukocyte counts fluctuate in the pediatric population, especially in early life. Consequently, reference values differ between age groups. In general, a value greater than 11×10^9/L is considered leukocytosis [2, 6]. Some studies have emphasized that leukocytes had the lowest positive predictive value compared with serum levels of procalcitonin and C-reactive protein [7]. In a study by Zhu F. et al. it was noted that the percentage of neutrophils compared to the total leukocyte count reflected the presence of bacterial infection better [8].

Given the viral-bacterial etiology of pneumonia, especially in children under 5 years of age, cellular and humoral immunity plays a key role in the body's defense against viral infections, and activation and impairment of immune function have a significant impact on disease progression and prognosis. In recent years, it has been found that respiratory viral infections often cause a decrease in the number of lymphocytes in peripheral blood [9]. Previous studies have suggested that this may be due to virus-induced destruction of T cells. For example, Liu B. et al. demonstrated that, influenza A (H1N1) infection can induce thymus cell apoptosis and atrophy [10].

As a key component of the immune system, $CD4^+$ T-cells significantly influence lung damage caused by viral infection. $CD4^+$T-cells stimulate the activation and differentiation of B-cells. $CD4^+$ T cells also promote the differentiation of $CD8^+$ T-cells into cytotoxic effectors and memory cells, as well as the localization of $CD8^+$ memory T-cells in infected airways. In addition, cytotoxicity, which has the potential to directly destroy infected cells, is an increasingly proven function of $CD4^+$ T-cells. $CD8^+$ cytotoxic T cells recognize virus-infected cells, induce apoptosis, and produce pro-inflammatory cytokines to inhibit viral replication, such as IFNγ. In a study by Liu B. et al. 2023 there was a significant decrease in NK cells in children with severe influenza B virus-induced pneumonia [9].

To date, there is little information on the status of lymphocytes and their subpopulations in viral-bacterial pneumonias in children in different age groups, which was the purpose of this study.

STUDY OBJECTIVE — Determine changes in lymphocyte subpopulations in peripheral blood in children in different age groups with community-acquired pneumonia and assess their prognostic significance depending on the severity of community-acquired pneumonia.

MATERIALS AND METHODS

The work was carried out at the Department of Microbiology, Virology and Immunology, the Department of Propaedeutics of Children's Diseases and Pediatrics and at the Research Institute of Immunology of the South Ural State Medical University of the Ministry of Health of the Russian Federation.

The study involved 117 children aged 1 to 18 years with radiologically confirmed diagnosis of severe (29 children) and non-severe (88 children) community-acquired pneumonia hospitalized in respiratory infections departments of MBHI CCCH No. 7 and CHCH No. 8 in Chelyabinsk. All children were divided into 4 age groups (1-3 years, 4-7 years, 8-12 years, 13–18 years) and comparable by sex and age. Inclusion criteria of patients in the study: age from 1 year to 17 years 11 months and 30 days, diagnosis of community-acquired pneumonia made according to the criteria specified in the 2015 Clinical Guidelines for

Community-acquired Pneumonia in Children, edited according to the 2022 guidelines adopted in the Russian Federation [2].

Exclusion criteria: parental refusal to participate in the proposed study, history of chronic diseases, including bronchial asthma, allergic rhinitis, juvenile rheumatoid arthritis, diffuse connective tissue diseases, diabetes mellitus, HIV infection, cancer, central nervous system pathology.

Phenotyping and differentiation of lymphocyte subpopulations were performed by flow cytometry using Navios 6/2 (Beckman Coulter, USA). Blood was collected in tubes with anticoagulant K2 EDTA on the 1st day after hospitalization in the morning on an empty stomach. Markers of subpopulations were determined: T-lymphocytes ($CD3^+$), T-helper ($CD3^+CD4^+$), T-cytotoxic ($CD3^+CD8^+$), TNK-lymphocytes ($CD3^+CD16^+CD56^+$), NK-lymphocytes ($CD3^-CD16^+CD56^+$), B-lymphocytes ($CD3^-CD19^+$).

The results were processed using statistical programs in IBM SPSS package (v. 23). The Kraskell-Wallis and Mann-Whitney criteria were used to judge the reliability of differences in quantitative features in independent groups. In case of 3 or more repeated observations, the Friedman criterion was used, followed by pairwise comparison in two related or dependent groups using the Wilcoxon test. To assess the differences between the main group and the comparison group, the data were summarized in contiguity tables, which were analyzed using the likelihood ratio criterion (chi-square of maximum likelihood). In case of low saturation of conjugacy table cells (minimum expected less than 4), statistical significance was assessed using the exact permutation method in Cytel Studio StatXact (version 7.0; Cytel Software Corporation). Correlation analysis was performed using the Spearman rank correlation method.

In all cases, the detected effects were considered statistically significant at $p \leqslant 0{,}05$.

STUDY RESULTS AND THEIR DISCUSSION

The results of the study showed a decrease in the absolute number of TNK-lymphocytes ($CD3^+CD16^+CD56^+$) in children with severe CAP in all age groups, with the exception of children from 13 to 18 years of age, compared to children with mild community-acquired pneumonia. When comparing the level of NK-lymphocytes ($CD3^-CD16^+CD56^+$) in the peripheral blood of children with CAP, a decrease in both relative and absolute values of these indicators was found in children with severe CAP in all age groups. The relative number of B-lymphocytes ($CD3^-CD19^+$) was higher in the group of children with severe CAP in the age group from 4 to 7 years and from 8 to 12 years in relation to children with mild community-acquired pneumonia. In addition, a decrease in the number of T-helper cells ($CD3^+CD4^+$) was observed in children from 1 to 3 years of age with severe CAP compared with children with mild CAP (Table 1).

The correlation analysis between the severity of pneumonia and immunologic indices revealed negative correlations with the number of TNK-lymphocytes and NK-lymphocytes (Table 2).

The study revealed changes in T-lymphocytes, in particular, a decrease in T-helper cells ($CD3^+CD4^+$) in children aged 1-3 years with severe CAP compared to children with mild CAP. Effector $CD4^+$ cells are able to provide the assistance needed by both $CD8^+$ T-cells and B cells to reach their full functional potential, as well as to exert direct effector functions through cytolysis of virus-infected cells. After virus infection, $CD4^+$ T-cells persist long term with an increased ability to protect against secondary infec-

Table 1. **Indicators of lymphocyte subpopulations in children with community-acquired pneumonia, severe and mild, at different age periods, Me ($Q_{0,25}$–$Q_{0,75}$) (author's table)**
Таблица 1. **Показатели субпопуляций лимфоцитов у детей с внебольничной пневмонией тяжелой и нетяжелой в различные возрастные периоды, Me ($Q_{0,25}$–$Q_{0,75}$) (таблица автора)**

Age group, years	Mild pneumonia (n = 29, 21, 20, 18)	Severe pneumonia (n = 12, 9, 4, 4)	Significance of differences *p*
T-lymphocytes ($CD3^+$), %			
1–3	70,0 (47,8–80,3)	68,7 (44,4–80,2)	p_{1-2}=0,4 p_{1-3}=0,5 p_{2-3}=0,9
4–7	68,4 (51,7–83,8)	67,2 (49,1–81,5)	p_{1-2}=0,1 **p_{1-3}=0,02** p_{2-3}=0,9

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T-lymphocytes ($CD3^+$), %			
8–12	70,4 (61,9–88,1)	68,7 (76,5–68,7)	p_{1-2}=0,1 p_{1-3}=0,1 p_{2-3}=0,4
13–18	73,9 (63,8–80,5)	68,4 (68,2–79,4)	p_{1-2}=0,3 p_{1-3}=0,5 p_{2-3}=0,2
T-lymphocytes ($CD3^+$), abs			
1–3	1950,0 (757,0–3996,0)	1267,0 (374,0–3993,0)	p_{1-2}=0,1 p_{1-3}=0,8 p_{2-3}=0,05
4–7	1667,0 (755,0–3424,0)	1267,0 (968,0–4050,0)	**p_{1-2}=0,02** **p_{1-3}=0,008** p_{2-3}=0,9
8–12	1659,0 (768,0–3974,0)	1267,0 (1267,0–2234,0)	p_{1-2}=0,9 p_{1-3}=0,2 p_{2-3}=0,5
13–18	1207,5 (680,0–2401,0)	1222,0 (977,0–1374,0)	p_{1-2}=0,07 p_{1-3}=0,06 p_{2-3}=0,4
T-helpers ($CD3^+CD4^+$), %			
1–3	35,7 (21,8–50,6)	33,0 (17,7–40,3)	**p_{1-2}=0,009** **p_{1-3}=0,001** p_{2-3}=0,3
4–7	34,3 (24,2–54,4)	33,0 (22,7–49,2)	p_{1-2}=0,3 p_{1-3}=0,06 p_{2-3}=0,6
8–12	36,5 (19,1–62,4)	33,0 (33,0–50,9)	p_{1-2}=0,05 p_{1-3}=0,1 p_{2-3}=0,4
13–18	44,0 (29,4–51,6)	45,7 (33,0–48,7)	**p_{1-2}=0,01** p_{1-3}=0,1 p_{2-3}=0,6
T-helpers ($CD3^+CD4^+$), abs			
1–3	1022,0 (393,0–3083,0)	610,0 (149,0–1788,0)	p_{1-2}=0,4 p_{1-3}=0,3 **p_{2-3}=0,021**
4–7	805,0 (401,0–2257,0)	655,0 (610,0–2428,0)	**p_{1-2}=0,03** **p_{1-3}=0,005** p_{2-3}=0,8
8–12	880,5 (322,0–1997,0)	610,0 (610,0–1675,0)	p_{1-2}=0,3 p_{1-3}=0,2 p_{2-3}=0,3
13–18	758,0 (11,0–1544,0)	654,0 (610,0–844,0)	p_{1-2}=0,3 p_{1-3}=0,1 p_{2-3}=0,4
T-cytotoxic ($CD3^+CD8^+$), %			
1–3	26,3 (10,9–44,3)	25,3 (20,1–36,8)	**p_{1-2}=0,008** **p_{1-3}=0,001** p_{2-3}=0,7
4–7	26,0 (18,7–42,8)	25,3 (20,9–29,4)	p_{1-2}=0,3 p_{1-3}=0,3 p_{2-3}=0,8
8–12	25,5 (15,3–43,1)	25,3 (12,1–25,3)	p_{1-2}=0,9 p_{1-3}=0,5 p_{2-3}=0,3

Table 1. **Indicators of lymphocyte subpopulations in children with community-acquired pneumonia, severe and mild, at different age periods, Me ($Q_{0,25}$–$Q_{0,75}$) (author's table)**
Таблица 1. **Показатели субпопуляций лимфоцитов у детей с внебольничной пневмонией тяжелой и нетяжелой в различные возрастные периоды, Me ($Q_{0,25}$–$Q_{0,75}$) (таблица автора)**

T-cytotoxic ($CD3^+CD8^+$), %			
13–18	25,7 (16,6–47,6)	22,6 (19,9–26,7)	**p_{1-2}=0,02** p_{1-3}=0,7 p_{2-3}=0,4
T-cytotoxic ($CD3^+CD8^+$), abs			
1–3	827,0 (252,0–1797,0)	466,0 (195,0–1865,0)	**p_{1-2}=0,01** p_{1-3}=0,2 p_{2-3}=0,1
4–7	636,0 (328,0–1395,0)	466,0 (286,0–1429,0)	p_{1-2}=0,2 p_{1-3}=0,3 p_{2-3}=0,9
8–12	625,5 (229,0–1530,0)	466,0 (399,0–466,0)	p_{1-2}=0,9 p_{1-3}=0,1 p_{2-3}=0,2
13–18	448,5 (240,0–861,0)	374,0 (284,0–466,0)	p_{1-2}=0,9 p_{1-3}=0,7 p_{2-3}=0,3
Immunoregulatory index Tx/Tz			
1–3	1,3 (0,6–4,1)	1,3 (0,7–1,6)	**p_{1-2}=0,001** **p_{1-3}=0,001** p_{2-3}=0,1
4–7	1,3 (0,7–2,7)	1,3 (0,9–2,1)	p_{1-2}=0,1 p_{1-3}=0,08 p_{2-3}=0,6
8–12	1,3 (0,4–3,2)	1,3 (1,3–4,2)	p_{1-2}=0,6 p_{1-3}=0,7 p_{2-3}=0,5
13–18	1,6 (0,6–2,9)	2,0 (1,3–2,3)	**p_{1-2}=0,01** p_{1-3}=0,8 p_{2-3}=0,4
TNK-lymphocytes ($CD3^+CD56^+$), %			
1–3	1,1 (0,1–50,4)	0,2 (0,2–1,4)	p_{1-2}=0,7 p_{1-3}=0,1 **p_{2-3}=0,014**
4–7	2,8 (0,9–7,2)	1,0 (0,2–23,0)	p_{1-2}=0,6 p_{1-3}=0,1 **p_{2-3}=0,006**
8–12	2,8 (0,2–6,8)	0,2 (0,0–0,2)	p_{1-2}=0,7 **p_{1-3}=0,01** **p_{2-3}=0,004**
13–18	2,9 (0,5–9,6)	1,3 (0,2–5,3)	**p_{1-2}=0,01** p_{1-3}=0,06 p_{2-3}=0,2
TNK-lymphocytes ($CD3^+CD56^+$), abs			
1–3	40,0 (6,0–17,82)	7,5 (4,0–46,0)	p_{1-2}=0,06 p_{1-3}=0,08 **p_{2-3}=0,003**
4–7	73,0 (9,0–306,0)	19,0 (4,0–752,0)	p_{1-2}=0,7 p_{1-3}=0,1 **p_{2-3}=0,037**
8–12	61,5 (3,0–205,0)	4,0 (1,0–4,0)	p_{1-2}=0,7 **p_{1-3}=0,04** **p_{2-3}=0,004**
13–18	52,0 (17,0–148,0)	19,0 (4,0–93,0)	p_{1-2}=0,3 **p_{1-3}=0,01** p_{2-3}=0,1

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NK-lymphocytes ($CD3^+CD56^+$), %			
1–3	10,0 (4,2–20,6)	5,8 (3,4–28,4)	p_{1-2}=0,06 p_{1-3}=0,3 **p_{2-3}=0,001**
4–7	14,5 (5,1–26,9)	5,8 (3,4–8,3)	p_{1-2}=0,06 p_{1-3}=0,1 **p_{2-3}<0,001**
8–12	12,2 (3,3–24,5)	5,8 (3,6–5,8)	p_{1-2}=0,6 p_{1-3}=0,5 **p_{2-3}=0,002**
13–18	9,1 (3,0–23,0)	5,8 (4,8–5,8)	p_{1-2}=0,1 **p_{1-3}=0,005** **p_{2-3}=0,009**
NK-lymphocytes ($CD3^+CD56^+$), abs			
1–3	313,0 (113,0–650,0)	107,0 (89,0–318,0)	p_{1-2}=0,5 p_{1-3}=0,6 **p_{2-3}<0,001**
4–7	392,0 (46,0–938,0)	107,0 (84,0–272,0)	p_{1-2}=0,6 p_{1-3}=0,1 **p_{2-3}=0,003**
8–12	284,0 (50,0–1234,0)	107,0 (107,0–119,0)	p_{1-2}=0,6 p_{1-3}=0,3 **p_{2-3}=0,013**
13–18	201,0 (67,0–501,0)	84,0 (84,0–107,0)	**p_{1-2}=0,02** **p_{1-3}=0,005** **p_{2-3}=0,013**
B-lymphocytes ($CD3^-CD19^+$), %			
1–3	17,5 (10,7–34,3)	22,5 (13,3–33,0)	p_{1-2}=0,5 p_{1-3}=0,08 p_{2-3}=0,1
4–7	14,5 (7,0–32,4)	22,5 (10,7–43,8)	p_{1-2}=0,9 **p_{1-3}=0,005** **p_{2-3}=0,01**
8–12	13,8 (6,5–29,1)	22,5 (19,3–22,5)	p_{1-2}=0,3 **p_{1-3}=0,004** **p_{2-3}=0,007**
13–18	13,8 (7,5–26,9)	23,8 (13,4–25,1)	p_{1-2}=0,7 p_{1-3}=0,7 p_{2-3}=0,05
B-lymphocytes ($CD3^-CD19^+$), abs			
1–3	601,0 (190,0–1171,0)	415,0 (222,0–1351,0)	p_{1-2}=0,1 p_{1-3}=0,2 p_{2-3}=0,1
4–7	336,0 (85,0–765,0)	415,0 (360,0–1453,0)	p_{1-2}=0,2 p_{1-3}=0,1 p_{2-3}=0,08
8–12	278,0 (106,0–766,0)	415,0 (415,0–639,0)	p_{1-2}=0,5 **p_{1-3}=0,01** p_{2-3}=0,1
13–18	251,0 (81,0–920,0)	362,0 (234,0–416,0)	p_{1-2}=0,1 p_{1-3}=0,9 p_{2-3}=0,1

Note: p_{2-3} — statistically significant differences between children with severe and mild community-acquired pneumonia and in the comparison group ($p < 0.05$).

Table 2. **The relationship between the severity of community-acquired pneumonia and the number of TNK-lymphocytes, NK-lymphocytes in children with community-acquired pneumonia (author's table)**
Таблица 2. **Взаимосвязи между степенью тяжести внебольничной пневмонии и количеством TNK-лимфоцитов, NK-лимфоцитов у детей с внебольничной пневмонией (таблица автора)**

Children with severe and mild community-acquired pneumonia (n = 117)		
Indicator	Correlation coefficient (ϱ)	p
Severity of community-acquired pneumonia — TNK-lymphocytes ($CD3^+CD16^+CD56^+$), abs	−0,468	**<0,001**
Severity of community-acquired pneumonia — NK-lymphocytes ($CD3^-CD16^+CD56^+$), abs	−0,511	**<0,001**

tion due to their ability to respond more rapidly and robustly upon antigen exposure. In addition, unlike naive cells, which remain in the lymphoid tissue, memory cells are localized in peripheral sites, ready to respond to a secondary challenge in the focus of infection [11, 12].

The decrease in NK-lymphocytes in all age groups in children with severe community-acquired pneumonia obtained in our study is consistent with similar studies in adult patients. Numerous studies on influenza A virus have shown that a decrease in peripheral blood leukocytes, lymphocytes and lymphocyte subsets is an immune process of the body in the early stages of the disease [13, 14].

Previous studies have also shown that total CD3+, $CD4^+$ and $CD8^+$ T-cell counts were significantly reduced in the acute phase in adults with influenza B virus-induced pneumonia [15].

In recent years, respiratory viral infections have also been found to frequently cause a decrease in the number of lymphocytes in the peripheral blood. A large number of studies have shown that the number of CD4+, CD8+ T-cell and NK-cell counts were significantly reduced in patients with COVID-19 and were associated with COVID-19 severity and prognosis, and both CD8+ and CD4+ T-cell counts were diagnostic markers of COVID-19 and predictors of disease severity, which is consistent with the findings of our study [16, 17].

Natural killer cells (NK-cells) are an early line of defense against infection. Before the initiation of the adaptive immune response, NK-cells not only produce cytokines associated with antiviral activity, but also directly participate in the rapid removal of virus-infected cells and interact with dendritic cells to directly regulate the adaptive immune response [9].

A study by Ma L. et al. showed that in the early stage of pneumonia caused by influenza B virus, the level and percentage of NK-cells were significantly lower in the group of patients with severe infection. Clinical symptoms were more pronounced in the severe patient group, causing organ dysfunction in addition to pneumonia, providing further evidence that NK-cells play an important role in the progression of infection [9].

One important function of humoral immunity in viral infection is antibody-mediated neutral-

ization of the virus. In a study by Xu et al. 2013, it was shown that B-lymphocyte counts, although decreased in adult patients after influenza B virus infection, were similar between the mild and severe groups. In the total lymphocyte count, the percentage of B-lymphocytes was higher in severe patients than in the mild group, a consequence of a greater decrease in T-lymphocytes and NK-cells in the severe group. In our study, the percentage content of B-lymphocytes was higher in the group of children 4-7 and 8-12 years old in severe community-acquired pneumonia, which may be due to the peculiarities of immune system activation in different age groups [18].

Patients with severe influenza A (H1N1) infection are thought to have high levels of functional humoral immune response and low levels of antibody affinity, and it has been hypothesized that antibody levels increase with disease severity and that high viral load may enhance the humoral immune response [19].

CONCLUSION. Thus, the analysis revealed a decrease in the number of NK-lymphocytes in peripheral blood in children with severe community-acquired pneumonia in all age groups compared to children with mild community-acquired pneumonia. The association between the decrease in the number of NK-cells and TNK-cells with the severity of community-acquired pneumonia may be related to the direction of disease progression and may be considered an independent risk factor for the development of severe pneumonia in children.

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FUNDING SOURCES

The authors declare that they received no funding for this study.

ИСТОЧНИКИ ФИНАНСИРОВАНИЯ

Авторы заявляют об отсутствии финансирования при проведении исследования.

THE AUTHORS' CONTRIBUTION TO THE WORK

Natalia V. Iziurova — review of publications on the topic of the article, design development, data analysis and interpretation, responsibility for the integrity of all parts of the article, writing and formatting of the article.

Albina Yu. Savochkina — discussion and editing of the article, final approval for the submission of the manuscript.

ВКЛАД АВТОРОВ В РАБОТУ

Изюрова Н. В. — обзор публикаций по теме статьи, разработка дизайна, анализ и интерпретация данных, ответственность за целостность всех частей статьи, написание и оформление статьи.

Савочкина А. Ю. — обсуждение и редактирование статьи, окончательное утверждение на представление рукописи.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Prior to carrying out the prescribed procedures, the child's legal representative has signed an informed consent. The study was approved by the local ethics committee of the Federal State Budgetary Educational Institution of Higher Education "South-Ural State Medical University" of the Ministry of Healthcare of the Russian Federation (protocol No. 1 dated 15.01.2015).

ЭТИЧЕСКОЕ ОДОБРЕНИЕ И СОГЛАСИЕ НА УЧАСТИЕ

До проведения предусмотренных процедур законным представителем ребенка подписано информированное согласие. Исследование одобрено локальным этическим комитетом ФГБОУ ВО ЮУГМУ Минздрава России (протокол от 15.01.2015 г. № 1).

Оригинальная статья / Original article

Epidemiological trends of bronchial asthma symptoms in adolescent children in the Udmurt Republic. The results of long-term research

RAR — научная статья

https://doi.org/10.53529/2500-1175-2025-1-32-39

Date of receipt:19.08.2024
Date of acceptance:23.10.2024
Date of publication: 21.03.2025

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Annotation. Taking into account the spread of asthma symptoms in dynamics in different regions using proven techniques allows you to get the most complete picture of this process and identify regional features.
Materials and methods. Monitoring of the spread of asthma symptoms was carried out within the confines of the ISAAC program from 2002 to 2019–2020. The results obtained were compared with the results of 1999. Udmurt teenagers aged 13–14, studying in schools of the republic, participated in the survey, a total of 12 856 people.
Results. By 2019–2020, the prevalence of asthma symptoms increased compared to 1999 and was 10.2%. The problem of underdiagnosis of the disease persists. There is a decrease in severe forms of asthma and the frequency of recurrence of night and daytime symptoms. The number of children who responded to physical activity with difficulty breathing, as well as respondents with frequent attacks of non-infectious cough, increased significantly. In general, a negative trend is observed in the statistics of bronchial asthma symptoms.
Conclusions. Long-term observation allowed us to obtain data that are an important contribution to understanding not only the trends of BA in the Udmurt Republic, but also in their further study.

Keywords: asthma symptoms, bronchial asthma, adolescents, prevalence

Conflict of interests:
The authors declare no conflict of interest.

For citation: Matveeva L.P., Ermakova M.K., Kapustina N.R. Epidemiological trends of bronchial asthma symptoms in adolescent children in the Udmurt Republic. The results of long-term research. *Allergology and Immunology in Pediatrics*. 2024; 23 (1): 32–39. https://doi.org/10.53529/2500-1175-2025-1-32-39

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Оригинальная статья / Original article

Эпидемиологические тенденции симптомов бронхиальной астмы у детей подросткового возраста в Удмуртской Республике. Результаты многолетнего наблюдения

https://doi.org/10.53529/2500-1175-2025-1-32-39

УДК 616.248-036.22-053.2(470.51)
Дата поступления: 19.08.2024
Дата принятия: 23.10.2024
Дата публикации: 21.03.2025

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Аннотация. Изучение распространенности бронхиальной астмы с использованием стандартизованных методик в динамике позволяет сформировать наиболее полное представление о трендах заболевания в своем регионе и контролировать его дальнейшее распространение.

Материалы и методы. Проведены когортные исследования частоты проявления симптомов бронхиальной астмы среди подростков по протоколам программы «Международное изучение астмы и аллергии у детей» с 2002 по 2019–2020 годы и сравнение полученных результатов с итогами 1999 года. Всего в исследовании приняло участие 12 856 удмуртских школьников 13–14 лет.

Результаты. К 2019–2020 годам распространенность симптомов астмы увеличилась по сравнению с 1999 годом и составила 10,2%. Сохранялась проблема гиподиагностики заболевания. На фоне уменьшения тяжелых форм астмы и частоты реци% дивирования ночных и дневных симптомов было выявлено достоверное увеличение числа детей, реагирующих одышкой на физическую нагрузку, и респондентов с частыми эпизодами неинфекционного кашля. Зарегистрирован общий негаи тивный статистический тренд симптомов и диагноза «бронхиальная астма», имеющий незначительный прогредиентный рост.

Выводы. Выявленные негативные и позитивные эпидемиологические тенденции свидетельствуют об актуальности представленной проблемы в Удмуртской Республике, о необходимости дальнейшего мониторирования статистики броне хиальной астмы у подростков и совершенствованию программ ее профилактики.

Ключевые слова: симптомы астмы, бронхиальная астма, подростки, распространенность

Конфликт интересов:
Авторы заявляют об отсутствии конфликта интересов.

Для цитирования: Матвеева Л.П., Ермакова М.К., Капустина Н.Р. Эпидемиологические тенденции симптомов бронхиальной астмы у детей подросткового возраста в Удмуртской Республике. Результаты многолетнего наблюдения. *Аллергология и иммунология в педиатрии*. 2024; 23 (1): 32–39. https://doi.org/10.53529/2500-1175-2025-1-32-39

INTRODUCTION

Regular monitoring of the prevalence of bronchial asthma (BA) in different regions allows to create the most accurate picture of this process in the pediatric population. This approach helps to identify children at risk of the disease, to take timely preventive measures and to control its further spread [1, 2]. For more than 30 years, validated methods have been used to determine global trends in the prevalence of BA, which make it possible to obtain comparable data [3, 4]. A particularly accurate picture of BA prevalence trends is becoming clearer through a unique study of more than two million participants from around the world, the ISAAC (International Study of Asthma and Allergy in Children) program [5]. The results of this large-scale study are a valuable tool for assessing the dynamics of BA prevalence at the global level. Local observations conducted in different regional medical centers of the country revealed a positive dynamic pattern of asthma symptom prevalence in children of different age groups [6, 7, 8, 9, 10, 11, 12, 13, 14, 15].

The first steps to study the prevalence of allergopathology using ISAAC protocols in the Udmurt Republic were taken in 1999. At that time, the prevalence of asthma symptoms was 7,5% in first-graders and 9.3% in eighth-graders. Although the figures obtained correlated with the results of other Russian researchers, they nevertheless became an alarming signal for the

Table 1. **Quantitative characteristics of the compared groups of eighth graders (authors' table)**
Таблица 1. **Количественная характеристика сравниваемых групп восьмиклассников (табл. авторов)**

Indicator	2002	2009	2014	2019–2020
Number of schools	38	35	36	51
Number of eight-graders	3943	2788	2845	3280

republican public health service. Asthma schools were organized in the capital and cities of the republic, and in remote rural areas they were held online. A screening table developed for pediatricians made it possible to identify children at risk of BA and to organize dynamic monitoring of them, taking into account the individual characteristics of each patient [16]. The effectiveness of the conducted measures was assessed by the results of repeated monitoring of the prevalence of asthma symptoms. Thus, according to the data of the 2019-2020 survey, the prevalence of BA symptoms in first-graders was 7.7%, which indicated the stabilization of the situation among junior schoolchildren [17].

STUDY OBJECTIVE

To identify key epidemiologic trends of BA by analyzing the prevalence of the disease in dynamics over 20 years among Udmurt adolescents.

MATERIALS AND METHODS

A large-scale study of the prevalence of BA symptoms was conducted within the framework of the ISAAC program [18]. Four cohort studies were conducted: in 2002, stage III according to the methodological recommendations of the standardized program, the next three in 10, 15 and 20 years from the beginning of the first observation in 1999 (Table 1). A total of 12,856 Udmurt adolescents aged 13-14 from urban and rural schools of the republic took part in the study. The survey of schoolchildren was conducted in the fall and winter as part of the "class hour" lesson with the informed consent of parents and children themselves. The study was conducted with the approval of the local ethical committee of the Medical Academy according to the legislation, which guaranteed compliance with all ethical norms and principles of medical research.

The result of long-term observation was the creation of a database. The database was analyzed using Microsoft Excel and SPSS programs via parametric criteria. The significance of differences and reliability of the results were assessed using Student's t-test. Differences in all types of analysis were considered reliable at $p < 0.05$.

RESULTS AND DISCUSSION

The study found that in 2002, there was a 6.5% increase in the number of students with the symptom of "wheezing ever" by 6.5%, 1.3 times higher than in the first phase of the study. An important observation was that the prevalence of the symptom remained stable for 5 years, with a subsequent decrease in this rate. More detailed information on the dynamics of changes in the prevalence of asthma symptoms is presented in Table 2. The second question of the questionnaire, concerning the presence of "wheezing and rale in the chest during the last 12 months", turned out to be the key to determine the prevalence of BA symptoms among the adolescent population of the republic. Comparison of the results of this question for 2019-2020 with the 1999 premiere survey showed an increasing trend from 9.3±0.5% to 10.2±0.5% ($p > 0.05$). The observed changes were not random, they reflected a real trend of increasing prevalence of BA symptoms. It should be emphasized that the results obtained were nationwide and not limited to a particular region [19].

Overall, over the past two decades, by 2020, there has been a positive downward trend in the number of severe cases. Analysis of the database, including the results of the questionnaire, revealed a marked decline in the number of participants experiencing "severe breathing difficulties", a 1.6-fold decrease compared to 1999. This decrease is statistically significant ($p < 0.01$). Throughout the study, the majority of children surveyed favored mild manifestations of the disease, with the frequency of symptoms less than

Table 2. **Dynamics of symptoms and diagnosis of asthma in adolescents over 20 years (authors' table)**
Таблица 2. **Динамика симптомов и диагноза БА у подростков за 20 лет (табл. авторов)**

Symptoms	Monitoring period / symptom prevalence (%)				
	1999	2002	2009	2014.	2019–2020
Wheezing and rale in his chest has ever	19,9±0,7	26,4±0,7	26,1 ±0,8¤¤¤	22,9±0,8	23,5 ±0,7***
Wheezing and rale in his chest during the last 12 months (actual)	9,3 ±0,5	10,7 ±0,5	10,3 ±0,6	9,5 ±0,5	10,2 ±0,5
Nocturnal wheezing episodes less frequently than once a week during the last 12 months	2,1 ±0,3	3,6 ±0,3	3,3 ±0,3¤	2,1 ±0,3	2,5 ±0,3
Nocturnal wheezing episodes more than once a week during the last 12 months	1,7 ±0,2	1,4 ±0,2	1,7 ±0,2	1,5 ±0,2	1,1 ±0,8
Severe shortness of breath or episodes of heavy breathing during the last 12 months	3,3 ±0,3	3,8 ±0,3	2,3 ±0,3¤¤	2,9 ±0,3	2,1 ±0,3**
Diagnosed BA	2,4 ±0,3	2,1 ±0,2	3,0 ±0,3	3,2 ±0,3	3,5 ±0,3*
Shortness of breath after physical activity during the last 12 months	7,5 ±0,5	10,7 ±0,5	9,1 ±0,5¤	9,7 ±0,6	10,1 ±0,5***
Dry cough not associated with a respiratory infection during the last 12 months	7,2±0,5	10,9±0,5	10,3 ±0,6¤¤¤	12,8±0,8	13,1 ±0,6***

Note: ¤ <0,05, ¤¤ <0,01, ¤¤¤ <0,001 — significance of differences compared to 1999; * <0,05, ** <0,01, *** <0,001 — significance of differences compared to 1999.

four times a year (Fig. 1). However, the 2014 survey showed a sharp increase in moderately severe asthma compared to 2009, 3.1 times, which persisted for the second decade ($p < 0.001$). Meanwhile, the number of learners with severe asthma symptoms decreased consistently throughout the follow-up, with a 1.3-fold decrease by 2019-2020.

Another favorable downward trend was observed when comparing the frequency of nocturnal symptoms of "coughing or difficulty breathing" in interviewed children in the second research decade.

With the introduction of baseline therapy and the use of a stepwise approach depending on the severity of the disease, Udmurt adolescents achieved progress

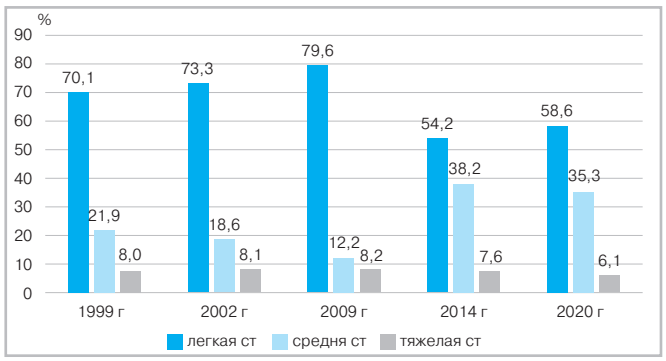

Fig. 1. **The structure of BA by severity in eighth graders, (%) (authors' ill.)**
Рис. 1. **Структура БА по степени тяжести у восьмиклассников, (%) (рис. авторов)**

in the course of AD in the form of a decrease in the frequency of exacerbation and the severity of daytime and nighttime symptoms. In addition, in our opinion, these favorable trends were a consequence of the organization of preventive measures implemented at the republican level: specially designed thematic lessons in educational institutions, adapted to the understanding of adolescents, school-wide parent-teacher meetings, contributing to raising awareness of the problem of bronchial asthma; organization of online consultations and asthma-schools, providing specialized information to patients with newly diagnosed asthmatic symptoms and build adherence to treatment. This was confirmed by the data obtained in the course of monitoring.

The ISAAC program's dynamic follow-up revealed some negative trends. As the number of respondents with severe asthma manifestations decreased, such a symptom as difficulty breathing during physical activity became a more urgent problem. Thus, in the period 2019-2020, adolescents complained about this symptom 1.6 times

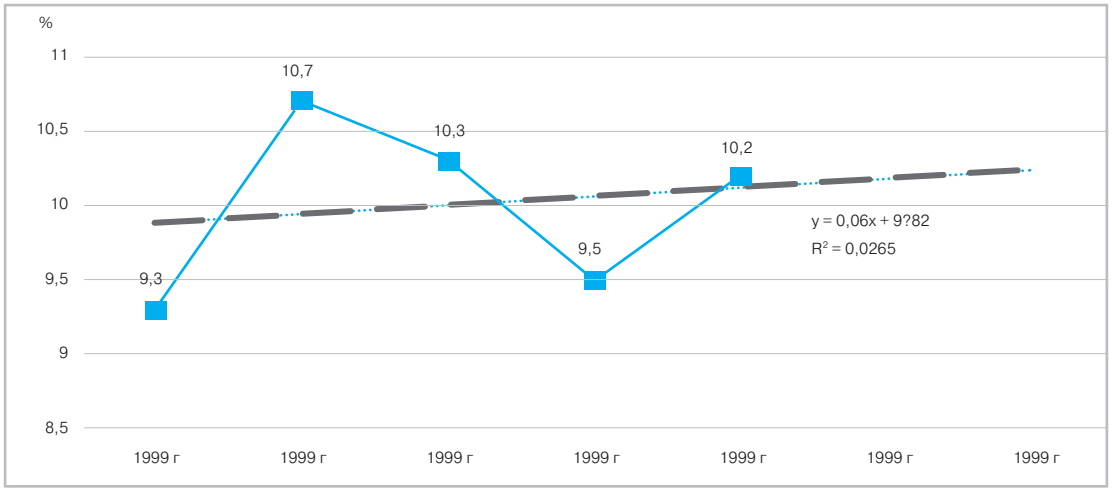

Fig. 2. **Prevalence of current asthma symptoms in eighth graders, trend line, (%) (authors' ill.)**
Рис. 2. **Распространенность текущих симптомов БА у восьмиклассников, линия тренда, (%) (рис. авторов)**

more often than in 1999 ($p < 0.001$). Another alarming signal was the increase in the rate of "dry cough unrelated to cold", compared to 1999, it increased 1.8 times by 2019-2020 ($p < 0.001$) Such cough can be one of the signs of developing asthma, and it is important to differentiate it in time. In our opinion, the increase in these symptoms is due to schoolchildren smoking.

Nowadays, adolescents more often use more modern means of nicotine delivery. Studies conducted in the Udmurt Republic show a 1.3-fold increase in the number of adolescent smokers over the last 10 years. Such indicators can be explained by the wide choice and availability of modern nicotine delivery devices and smoking mixtures, which, in turn, lead to the formation of hyperreactivity of the respiratory tract mucosa and become triggers for the development of symptoms such as asthma [20].

According to the 2019-2020 survey, 3.5% of schoolchildren surveyed confirmed their diagnosis of BA, 1.5 times higher than in 1999. This positive trend in improving the quality of asthma diagnosis is the result of targeted work on training of primary care physicians. More than 90% of pediatricians in the republic have attended seminars, aimed at improving theoretical knowledge in the field of modern therapeutic and diagnostic approaches to BA. But, as the observation showed, the difference between the actual symptoms of the disease and the established diagnosis remained fundamental. These data confirm the official statistics of morbidity, based on cases of applications mainly with moderate and severe manifestations of BA [21].

Long-term scientific experience allowed us to identify a trend in the prevalence of BA symptoms among adolescents of the republic until 2029, which had a progredient orientation.

CONCLUSION

Dynamic follow-up conducted in the Udmurt Republic using standardized ISAAC methodology over a 20-year period revealed negative and positive trends in the prevalence of BA. Data were obtained on the increasing prevalence of actual asthma symptoms, the persistent difference between diagnosed and detected cases of the disease, despite the improvement of BA diagnostics in the child and adolescent population. Symptoms corresponding to mild disease predominated in each follow-up period, but in the second decade of the study there was a trend towards an increased prevalence of symptoms with more frequent recurrences. There was a decrease in the detection of severe manifestations of the disease and in the frequency of recurrence of nocturnal and diurnal symptoms. There was a significant increase in the number of adolescents responding with breathing difficulties to physical activity and respondents with frequent episodes of non-infectious cough. The results were based on questionnaire data. It is possible that some participants may have underestimated and others

may have overestimated the frequency and severity of their symptoms, which could have affected the results. However, examination of long-term data from 1999 to 2019-2020 allowed us to recognize a general negative trend in adolescents in the republic. The comprehensive preventive measures carried out at the level of republican health care did not allow the prevalence trend to have a significant progressive growth. Thus, long-term follow-up allowed us to obtain data that are an important contribution to the understanding of BA trends in the Udmurt Republic. The identified epidemiological trends indicate the relevance of further monitoring of BA statistics in adolescents and improvement of medical prevention programs.

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FINANCING SOURCE

The authors declare the lack of sponsorship during the research and publication of the article.

ИСТОЧНИК ФИНАНСИРОВАНИЯ

Авторы заявляют об отсутствии спонсорской поддержки при проведении исследования и публикации статьи.

THE AUTHORS' CONTRIBUTION TO THE WORK

Larisa P. Matveeva — conducting research, developing the design of the publication, working with the text of the manuscript.

Margarita K. Ermakova — review of publications on the topic of the article, working with data, editing the text of the article.

Natalia R. Kapustina — conducting research, working with data.

ВКЛАД АВТОРОВ В РАБОТУ

Матвеева Л. П. — проведение исследования, разработка дизайна публикации, работа с текстом рукописи.

Ермакова М. К. — обзор публикаций по теме статьи, работа с данными, редактирование текста статьи.

Капустина Н. Р. — проведение исследования, работа с данными.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the local ethics committee of Izhevsk State Medical Academy of the Ministry of Health of Russia.

ЭТИЧЕСКОЕ ОДОБРЕНИЕ И СОГЛАСИЕ НА УЧАСТИЕ

Данное исследование одобрено локальным этическим комитетом ФГБОУ ВО ИГМА Минздрава России.

Оригинальная статья / Original article

Comparison of vaccination coverage of children of the first year of life in the pre-pandemic period and during the COVID-19 pandemic

RAR — научная статья

https://doi.org/10.53529/2500-1175-2025-1-40-49

Date of receipt: 09.12.2024
Date of acceptance: 03.03.2025
Date of publication: 21.03.2025

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Abstract

Introduction. Vaccination remains the most effective measure to combat infectious diseases. The COVID-19 pandemic has made adjustments to the work of pediatric health services around the world, which has affected all aspects of life, including routine immunization of children.

Objective. To analyze the indicators of coverage and timeliness of vaccination of children of the first year of life in the pre-pandemic period and during the COVID-19 pandemic, to assess the frequency and severity of post-vaccination reactions in children of the first year of life.

Materials and methods. A retrospective single-center study of medical documentation (form 112/y) of 414 children was conducted on the basis of GBU RO "City Children's Polyclinic No. 3" in Ryazan, who were divided into 2 groups: group 1 — children born in 2018 (n = 256), among whom 47.5% (n = 122) were girls, 51.5% (n = 134) are boys, group 2 are children born in 2020 (n = 158), of which 49% (n = 77) are girls, 51% (n = 81) are boys. The assessment of intergroup differences was carried out using the Pearson criterion (χ^2), adjusted for small samples. The difference in values was considered statistically significant at $p < 0.05$.

Results. Vaccination coverage in 2018 and 2020 was 95% and 98%, respectively ($p < 0.05$). The post-vaccination period in the majority of vaccinated children in group 1 (85%, n = 208) and in group 2 (81%, n = 128) proceeded smoothly ($p = 0.04$).

Conclusion. The COVID-19 pandemic did not have a negative impact on routine vaccination in the population of children in the first year of life.

Keywords: vaccination, children, pandemic, COVID-19

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

For citation: Belykh N.A., Kotova P.O., Pisnyur I.V., Stezhkina E.V. Comparison of vaccination coverage of children of the first year of life in the pre-pandemic period and during the COVID-19 pandemic. *Allergology and Immunology in Pediatrics*. 2025; 23 (1): 40–49. https://doi.org/10.53529/2500-1175-2025-1-40-49

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Оригинальная статья / Original article

Сравнение охвата вакцинацией детей первого года жизни в допандемийный период и во время пандемии COVID-19

https://doi.org/10.53529/2500-1175-2025-1-40-49

УДК 614.47-053.36
Дата поступления: 09.12.2024
Дата принятия: 03.03.2025
Дата публикации: 21.03.2025

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Аннотация

Актуальность. Вакцинопрофилактика остается наиболее эффективной мерой борьбы с инфекционными заболеваниями. Пандемия COVID-19 внесла коррективы в работу педиатрической службы здравоохранения во всем мире, что отразилось на всех аспектах жизнедеятельности, в том числе на проведении плановой иммунизации детей.

Цель. Проанализировать показатели охвата и своевременности вакцинации детей первого года жизни в допандемийный период и во время пандемии COVID-19, оценить частоту и тяжесть поствакцинальных реакций у детей первого года жизни.

Материалы и методы. На базе ГБУ РО «Городская детская поликлиника № 3» г. Рязань проведено ретроспективное одноцентровое исследование медицинской документации (форма 112/у) 414 детей, которые были разделены на 2 группы: 1-я группа — дети 2018 года рождения (n = 256), среди которых 47,5% (n = 122) девочки, 51,5% (n = 134) мальчики, 2-я группа — дети 2020 года рождения (n = 158), из них 49% (n = 77) девочки, 51% (n = 81) мальчики. Оценка межгрупповых различий осуществлялась с использованием критерия Пирсона (χ^2) с поправкой для малых выборок. Разницу значений считали статистически значимой при $p < 0,05$.

Результаты. Охват вакцинацией в 2018 году и 2020 году составил 95% и 98% соответственно ($p < 0,05$). Поствакцинальный период у большинства вакцинированных детей в 1-й группе (85%, n = 208) и во 2-й группе (81%, n = 128) протекал гладко ($p = 0,04$).

Заключение. Пандемия COVID-19 не оказала негативного влияния на проведение плановой вакцинации в популяции детей первого года жизни.

Ключевые слова: вакцинация, дети, пандемия, COVID-19

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

Для цитирования: Белых Н.А., Котова П.О., Пизнюр И.В., Стежкина Е.В. Сравнение охвата вакцинацией детей первого года жизни в допандемийный период и во время пандемии COVID-19. *Аллергология и иммунология в педиатрии*. 2025; 23 (1): 40–49. https://doi.org/10.53529/2500-1175-2025-1-40-49

INTRODUCTION. Routine immunization is one of the most effective and cost-effective public health measures to control infectious diseases in children [1, 2]. Experts estimate that immunization of the pediatric population saves 2 to 3 million lives annually worldwide, which contributes significantly to the reduction of the global infant mortality rate. As a result of collaborative international initiatives, vaccination coverage rates for children in low-income countries have increased from 50% to 80% over the past two decades [3]. As vaccination coverage has improved and protection of both vaccinated and unvaccinated populations has increased due to the phenomenon of collective immunity, there has been a significant decline in the registration of infections on the vaccination calendar [4].

On March 11, 2020, the World Health Organization declared COVID-19 a pandemic and a threat to public health and health systems worldwide. One of the pressing issues raised by the pandemic conditions was the continued implementation of routine vaccination as part of the National Vaccination Calendar [1]. The need for self-isolation, social distancing and other quarantine measures significantly reduced the demand for vaccination, and the population became fearful of becoming infected when visiting health facilities [5, 6]. As Henrietta Fore, Executive Director of the United Nations International Children's Emergency Fund (UNICEF), aptly describes this phenomenon: "COVID-19 has turned routine vaccination into a daunting challenge..." [7]. Disruption of immunization schedules, even for short periods, causes an increase in the number of susceptible individuals and increases the likelihood of infectious disease outbreaks. Such outbreaks can cause increased morbidity and mortality, mainly among young children as well as other vulnerable groups [8, 9].

Most studies worldwide have reported decreased rates or delayed routine vaccination during the COVID-19 pandemic. Brazilian researchers Santos V. et al (2023) conducted a retrospective analysis of all administered vaccine doses to children under 6 years of age from January 2019 to December 2020, in which the authors concluded that vaccination coverage decreased during the COVID-19 pandemic [10]. A team of clinicians from the University Clinical Research Center of Bamako, Mali, compared vaccination coverage during the pre-pandemic period in 2019 and during the COV- ID-19 pandemic in 2020. Coverage in 2019 was higher than in 2020 (88.7% vs. 71.6%), with the lowest proportion of vaccinated children (51.1%) observed in May 2020, two months after the first COVID-19 case in Mali [11]. A similar study was conducted in the United States (2023), where the authors analyzed data from 48,576 children under 24 months of age from 2018 to 2021 using a special questionnaire of the National Immunization Survey-Child (NIS-Child). It is reported that there was no overall decrease in vaccination coverage associated with the COVID-19 pandemic among all children, but vaccination coverage for children living below the poverty line or living in rural areas was reduced [3].

Russian vaccination studies confirm low vaccine coverage during the pre-pandemic period and its decline during the COVID-19 pandemic. For example, the Research Institute of Pediatrics and Child Health Protection (Moscow) conducted a single-stage multicenter study (2020) that included data from 2687 children from different regions of Russia. The authors concluded that immunization coverage and vaccination rates vary widely by age and region, vaccination timelines are not respected, and influenza vaccination coverage is catastrophically low [12].

The role of pediatricians in the development of vaccination adherence is undeniable [13]. It is worth noting that the low level of adherence and the majority of vaccination refusals are due to parents' lack of knowledge on this issue, which is confirmed by numerous studies in this area [13, 14]. However, for many parents, the doctor's opinion is a priority, and that is why it is so important for health workers to be able to build a friendly dialogue and provide up-to-date information about the importance and safety of vaccination [13, 14].

The first case of COVID-19 in the Ryazan region was detected in an adult patient on March 19, 2020. Thereafter, there has been a steady increase in the number of cases, including 530 children as of July 21, 2020. Forced self-isolation and physical distancing measures could undoubtedly have affected routine vaccination of children, especially those in the first year of life.

STUDY OBJECTIVE. Analyze the rates of coverage and timeliness of vaccination of children of the first year of life in the pre-pandemic period and during the COVID-19 pandemic, assess the frequency and severity of post-vaccine reactions in children of the first year of life.

MATERIALS AND METHODS. A retrospective single-center study of medical records (form 112/u) of 414 children living in the city of Ryazan was conducted. Children were divided into 2 groups:

Group 1 included children born in 2018 (n = 256), among whom 47.5% (n = 122) were girls and 51.5% (n = 134) boys. Group 2 included children born in 2020 (n = 158), among whom 49.0% (n = 77) were girls and 51.0% (n = 81) were boys ($p > 0.05$).

The base for the study was SBI RO "City Children's Polyclinic № 3" (chief physician A. O. Burdukova), Ryazan.

Statistical processing of the results was performed using Microsoft Office Excel 2016. Intergroup differences were assessed using Pearson's criterion (χ^2) with correction for small samples. The difference in values was considered statistically significant at $p < 0.05$.

RESULTS. The analysis of vaccination coverage of children in the first year of life showed the following data: in Group 1, 95.7% of children (n = 245) were vaccinated in accordance with the National Vaccination Calendar, of whom 53.0% (n = 130) were fully vaccinated, 47.0% (n = 115) were partially vaccinated, and the parents of 4.3% of children (n = 11) completely refused preventive vaccinations for personal reasons. In Group 2, vaccination coverage was 100% (n = 158 children), of whom 56.0% (n = 88) were fully vaccinated by one year, 44.0% (n = 70) — partially ($p = 0.02$) [15].

When assessing vaccination coverage against viral hepatitis B (HBV), an increase in the proportion of vaccinated children in Group 2 was noted. Thus, in Group 1, hepatitis B vaccination coverage by the age of 6 months was 47.0% (n = 121), and 86.0% of children (n = 222) had been vaccinated by the end of the first year of life. In Group 2, 60.0% of children (n = 95) were fully immunized against HBV in a timely manner, and 83.0% of children (n = 132) were immunized by the end of the 1st year of life ($p = 0.02$) (Table 1).

According to our data, in Group 1, 4.5% of children (n = 11) were not vaccinated against tuberculosis before 1.5 years of age, 7.0% (n = 18) were vaccinated before 1.5 years of age due to temporary contraindications, but the majority 88.5% (n = 227) were vaccinated on time. In Group 2, all children received BCG-M vaccine, with 94.0% (n = 149) of children vaccinated on time and 6.0% (n = 9) vaccinated in the 1st year of life ($p > 0.05$) (Table 1).

It is worth noting that children receive their first HBV and BCG-M vaccine in the newborn period, and most received them on time, both pre-pandemic and during the COVID-19 pandemic period.

Vaccination coverage against pneumococcal infection (PCI) was significantly higher in Group 2: 63.0% of children (n = 100) were vaccinated on time, compared to only 29.0% (n = 74) in Group 1 ($p = 0.001$), and against Haemophilus influenzae (Hib): 28.5% of children (n = 73) in Group 1 and 89.0% of children (n = 40) in Group 2 ($p = 0.000$) (Table 1). This was facilitated by the active use of combined pentavalent vaccine, which entered the national calendar of preventive vaccinations in 2017, and has received the most active use in the last five years.

When analyzing influenza vaccination coverage among children, disappointing results were obtained. In Group 1, only 1.6% of children (n = 4) were vaccinated before the age of 1.5 years, and in Group 2, no one received an influenza vaccine ($p > 0.05$) (Table 1). At the same time, according to the National Preventive Vaccination Calendar, annual influenza vaccination is recommended for all children starting from 6 months of life.

IIWhen assessing the vaccination coverage of children against diphtheria, tetanus, and pertussis, the following data were obtained: in Group 1, only 38.0% of children (n = 97) were immunized three times by 6 months of age, and 48.0% of children (n = 122) by one year of age; in Group 2, 68.0% of children (n = 107) were immunized on time, and 86.0% (n = 136) by one year of age ($p > 0.05$) (Table 1). A similar situation was observed when assessing poliomyelitis vaccination coverage.

When assessing measles, mumps and rubella (MMR) vaccination coverage, it was found that the proportion of children who did not receive the vaccine before 1.5 years of age increased in Group 2. In group 1 this indicator amounted to 5.0% (n = 15), in group 2 — 14.0% (n = 23) ($p = 0.005$). At the same time, in Group 2, the number of children who received the MMR vaccine in time increased almost 1.5-fold (Table 1).

Table 1. **Comparison of vaccination coverage in children of the 1st year of life (author's table)**
Таблица 1. **Сравнение охвата вакцинацией детей 1-го года жизни (таблица автора)**

Vaccine	Done on time				Done from infancy up to 1 year				Done from infancy up to 1,5 years				Not done until 1.5 years			
	Group 1 (n=256)	Group 2 (n=158)	p	OR (CI)	Group 1 (n=256)	Group 2 (n=158)	p	OR (CI)	Group 1 (n=256)	Group 2 (n=158)	p	OR (CI)	Group 1 (n=256)	Group 2 (n=158)	p	OR (CI)
V1 HBV	204 (80,0%)	146 (92,0%)	0,001	3,530 (1530–8,141	36 (13,8%)	7 (4,0%)	0,003	3,530 (1,530–8,141)	3 (1,2%)	2 (1,0%)	0,807	0,925 (0,153–5,597)	13 (5,0%)	3 (2,0%)	0,171	2,764 (0,775–9,857)
V2 HBV	143 (56,0%)	111 (70,0%)	0,005	0,536 (0,352–0,816)	97 (38,0%)	37 (23,0%)	0,003	1,995 (1,277–3,118)	2 (1,0%)	7 (5,0%)	0,026	0,170 (0,035–0,828)	14 (5,0%)	3 (2,0%)	0,128	2,989 (0,845–10,571)
V3 HVB	121 (47,0%)	95 (60,0%)	0,015	0,594 (0,89–0,398)	101 (39,0%)	37 (23,0%)	0,001	2,131 (1,365–3,327)	20 (8,5%)	17 (12,0%)	0,311	0,703 (0,356–1,387)	14 (5,5%)	9 (5,0%)	0,902	0,958 (0,405–2,268)
V BCG	227 (88,5%)	149 (94,0%)	0,080	0,473 (0,218–1,027)	—	—	—	—	18 (7,0%)	9 (6,0%)	0,740	1,252 (0,548–2,860)	11 (4,5%)	0	0,020	—
V1 PCI	80 (37,0%)	108 (68,0%)	0,000	0,210 (0,137–0,322)	67 (31,0%)	17 (11,0%)	0,000	2,940 (1,654–5,226)	14 (7,0%)	12 (8,0%)	0,230	0,704 (0,317–1,563)	55 (25,0%)	21 (13,0%)	0,050	1,785 (1,032–3,087)
V2 PCI	61 (29,0%)	100 (63,0%)	0,000	0,178 (0,115–0,274)	65 (31,0%)	12 (8,0%)	0,000	4,140 (2,156–7,951)	26 (12,0%)	6 (4,0%)	0,030	2,675 (1,075–6,660)	57 (28,0%)	40 (25,0%)	0,553	0,845 (1,088–1,344)
V1 CDTV	141 (55,0%)	121 (77,0%)	0,000	0,375 (0,241–0,584)	93 (36,5%)	34 (21,5%)	0,002	2,081 (1,318–3,286)	9 (3,5%)	2 (1,0%)	0,235	2,842 (0,606–13,327)	13 (5,0%)	1 (0,5%)	0,031	8,399 (1,088–64,840)
V2 CDTV	104 (41,0%)	113 (71,0%)	0,000	0,272 (0,178–0,417)	123 (48,0%)	29 (18,0%)	0,000	4,114 (2,567–6,592)	15 (6,0%)	12 (8,0%)	0,755	0,757 (0,345–1,663)	14 (5,0%)	4 (3,0%)	0,240	2,277 (0,720–6,891)
V3 CDTV	94 (37,0%)	107 (68,0%)	0,000	0,277 (0,182–0,421)	115 (45,0%)	21 (13,0%)	0,000	5,321 (3,160–8,960)	34 (13,0%)	20 (13,0%)	0,981	1,057 (0,585–1,910)	13 (5,0%)	10 (6,0%)	0,750	0,742 (0,339–1,851)
V1 IPV	141 (55,0%)	121 (77,0%)	0,000	0,226 (0,241–0,584)	93 (36,5%)	34 (21,5%)	0,002	2,081 (1,318–3,286)	9 (3,5%)	2 (1,0%)	0,235	2,842 (0,606–13,327)	13 (5,0%)	1 (0,5%)	0,031	8,399 (1,088–64,840)
V2 IPV	104 (41,0%)	113 (71,0%)	0,000	0,272 (0,178–0,417)	123 (48,0%)	29 (18,0%)	0,000	4,114 (2,567–6,592)	15 (6,0%)	12 (8,0%)	0,624	0,757 (0,345–1,663)	14 (5,0%)	4 (3,0%)	0,240	2,277 (0,720–6,891)
V3 OPV	94 (37,0%)	107 (68,0%)	0,000	0,277 (0,178–0,417)	115 (45,0%)	21 (13,0%)	0,000	5,246 (3,117–8,832)	34 (13,0%)	20 (13,0%)	0,857	1,057 (0,585–1,910)	13 (5,0%)	10 (6,0%)	0,750	0,742 (0,339–1,851)
V MMR	128 (50,0%)	106 (67,0%)	0,001	0,491 (0,325–0,711)	—	—	—	—	113 (45,0%)	30 (12,0%)	0,000	3,372 (2,112–5,383)	15 (5,0%)	23 (14,0%)	0,005	0,365 (0,184–0,724)
V HIB	73 (28,5%)	140 (89,0%)	0,000	0,051 (0,029–0,090)	—	—	—	—	—	—	—	—	183 (71,5%)	18 (11,0%)	0,000	19,498 (11,123–34,161)
V flu	4 (1,6%)	0	0,289	—	—	—	—	—	—	—	—	—	252 (98,4%)	158 (100%)	0,299	—

In the pre-pandemic period and during the COVID-19 pandemic, there was non-compliance with the vaccine administration dates regulated by the National Vaccination Calendar. Thus, 88.5% of children in Group 1 (n = 227) were timely immunized against tuberculosis, and 94.0% of children in Group 2 (n = 149) ($p > 0.05$). In Group 1, 60.0% of children (n = 126) and 71.0% of children (n = 112) in Group 2 received timely PCI ($p = 0.000$). Against diphtheria, pertussis and tetanus, 48.0% of children (n = 122) in Group 1 and 86.0% of children (n = 136) in Group 2 were immunized three times before the age of 1 year ($p = 0.001$). In Group 1, 50.0% of children (n = 128) received the MMR vaccine on time, and 67.0% of children (n = 106) in Group 2 ($p = 0.001$). At the same time, the proportion of children who received all vaccines on time increased in Group 2 (Figure 1).

The postvaccinal period in 85.0% of children (n = 208) in Group 1 and in 81.0% of children (n = 128) in Group 2 proceeded smoothly ($p > 0.05$). In the structure of postvaccinal reactions in Group 1 children, the leading conditions were temperature reaction (87.0%, n = 32) and local reaction in the form of local hyperemia (13.0%, n = 5). In Group 2 children, the following structure of postvaccinal reactions was observed: in 93.0% of children (n = 28) — temperature reaction, in 7.0% (n = 2) — local hyperemia ($p > 0.05$).

DISCUSSION

In our study, there was no negative impact of the new coronavirus pandemic on routine immunization of children in the first year of life. Vaccination coverage remained high despite the ongoing pandemic, moreover, the proportion of children immunized against pneumococcal and Haemophilus influenzae infections increased significantly, but the percentage of influenza vaccine coverage among children remained low.

CONCLUSION. Vaccination coverage of children of the 1st year of life in GBI RO “City Children's Polyclinic № 3” in Ryazan in 2018 and 2020 remained high and amounted to 95.0% and 98.0%, respectively. Pandemic COVID-19 did not have a negative impact on the implementation of routine vaccination, moreover, parents have become more responsible for immunization. Thanks to effective measures carried out in GBI RO “City Children's Polyclinic № 3” in Ryazan, it was possible to implement the plan for immunization of children in 2020, despite the ongoing pandemic of a new coronavirus infection.

The role of immunization in improving the quality of life of the population is undeniable. Insufficient immunization coverage may be related to lack of knowledge and awareness of parents about the importance of vaccination, safety and efficacy of modern vaccines, accessibility issues [16, 17, 18].

Despite the challenges to preventive health care services during the COVID-19 pandemic, continuity of immunization services for children, especially

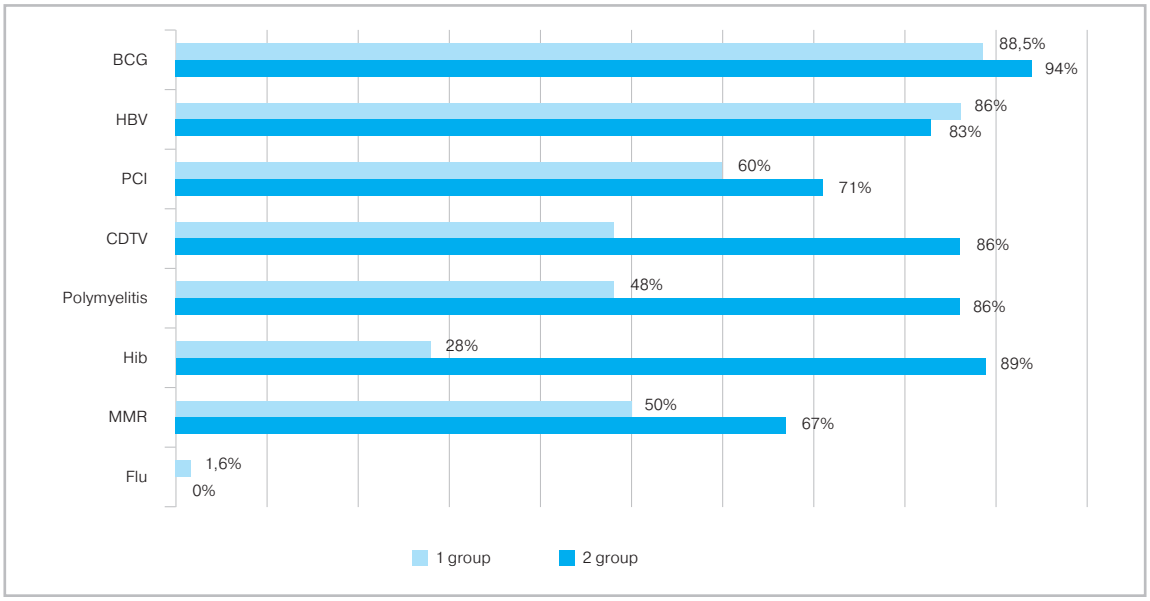

Fig. 1. **Comparison of the timeliness of vaccination coverage for children 1 year of age (illustration by the author)**
Рис. 1. **Сравнение своевременности охвата вакцинацией детей 1 года жизни (иллюстрация автора)**

those in the first year of life, is essential to make progress in vaccination as well as to prevent outbreaks of infectious diseases [1, 5]. Against the backdrop of the COVID-19 pandemic and non-compliance with the National Calendar's vaccination schedule or refusal to vaccinate, pediatricians and other health care providers have a particular influence on increasing population adherence to immunization [19, 20]. If it is not possible to ensure routine vaccination within the National Calendar dates, district pediatricians should use the opportunity of an individual approach to conduct "catch-up" vaccination using highly effective and safe combination vaccines [21]. Special attention should be paid to influenza vaccination in designated age groups [22].

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FUNDING SOURCES

This study was not supported by any external sources of funding.

ИСТОЧНИКИ ФИНАНСИРОВАНИЯ

Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

THE AUTHORS' CONTRIBUTION TO THE WORK

Natalia A. Belykh — conceptualization, formal analysis, visualization, writing: review & editing.
Polina O. Kotova — formal analysis, visualization, writing: original draft.
Inna V. Pisnyur — formal analysis, investigation, visualization.
Elena V. Stezhkina — investigation.

ВКЛАД АВТОРОВ В РАБОТУ

Белых Н. А. — разработка концепции, формальный анализ, подготовка текста: оценка и редактирование.

Котова П. О. — формальный анализ, работа с данными, подготовка текста.

Пизнюр И. В. — проведение исследования, формальный анализ, работа с данными.

Стежкина Е. В. — проведение исследования, работа с данными.

CONSENT FOR PUBLICATION

The legal representatives voluntarily signed an informed consent to the processing of personal data.

ИНФОРМИРОВАННОЕ СОГЛАСИЕ НА ПУБЛИКАЦИЮ

Законные представители добровольно подписали информированное согласие на обработку персональных данных.

Schimke immune-osseous dysplasia at the junction of specialties. A clinical case of disease diagnosis by allergologists and immunologists

RAR — научная статья

https://doi.org/10.53529/2500-1175-2025-1-50-57

Date of receipt: 28.10.2024
Date of acceptance: 19.12.2024
Date of publication: 21.03.2025

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Abstract

Introduction. Schimke immuno-osseous dysplasia (SIOD) is an autosomal recessive, ultrarare disorder characterized by multisystem involvement accompanied by spondyloepiphyseal dysplasia of the skeleton, steroid-resistant proteinuric nephropathy leading to progressive loss of renal function, impaired immunity, and vascular damage caused by atherosclerosis. SIOD is caused by biallelic pathogenic variations in the SMARCAL1 gene.

The clinical manifestations of SIOD are very diverse: from a rapidly progressive disease in which children die in the first years of life, to milder forms in which they survive to adulthood. The correlation between genotype and phenotype is extremely weak, so it is impossible to predict either the clinical course or the outcome of the disease. For this reason, patients with this pathology can be seen by various specialists.

Case report. The publication presents a clinical case of a 4-year-old boy with immunological deficiency, developmental disorders, and skeletal anomalies, indicating in favor of SIOD.

Whole exome sequencing in the SMARCAL1 gene revealed mutation variants c.2542G>T (p.Glu848Ter); c.1682G>T (p.Arg g561Leu) in a heterozygous state.

Based on the results of the genetic study, and also taking into account that the disease is multisystemic, the child was examined by a nephrologist, orthopedist, endocrinologist and geneticist.

Conclusions of the nephrologist: glomerulopathy in Schimke syndrome: isolated proteinuria. Left calicectasis. Chronic kidney disease (CKD), stage 2. Glomerular filtration rate (Schwartz test) — 69.01 ml/min/1.73 m^2.

Endocrinologist's conclusion: syndromic short stature. Protein-energy malnutrition grade 2.

A telemedicine consultation was conducted with the Federal State Budgetary Institution National Medical Research Center for Pediatric Hematology and Oncology named after D. Rogachev, based on the results of which replacement therapy with intravenous or subcutaneous immunoglobulins was recommended, as well as hospitalization in the immunology department of this federal center.

Conclusion. This description is the first case of diagnostics of an ultrarare disease (1:1–3,000,000 live births) in Krasnodar region by regional specialists. In this patient, the course of the disease is characterized by a non-severe, non-progressive renal dysfunction, which gives reason to assume a milder form of the disease. Conducting replacement therapy with immunoglobulins makes it possible to improve the prognosis in this patient.

Keywords: Schimke's immune-osseous dysplasia, immunodeficiency, nephropathy, skeletal dysplasia, SMARCAL1 gene

Conflict of interest:
The authors declare no conflict of interest.

For citation: Iljina E.S., Veyler D.A., Lashevich P.D. Schimke immune-osseous dysplasia at the junction of specialties. A clinical case of disease diagnosis by allergologists and immunologists. *Allergology and Immunology in Pediatrics*. 2025; 23 (1): 50–57. https://doi.org/10.53529/2500-1175-2025-1-50-57

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Иммунокостная дисплазия Шимке на стыке специальностей. Клинический случай диагностики заболевания врачами — аллергологами-иммунологами

https://doi.org/10.53529/2500-1175-2025-1-50-57

УДК 616.42-616.61
Дата поступления: 28.10.2024
Дата принятия: 19.12.2024
Дата публикации: 21.03.2025

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Резюме

Введение. Иммунокостная дисплазия Шимке (ИКДШ) представляет собой аутосомно-рецессивное, крайне редкое заболевание, характеризующееся мультисистемным поражением, сопровождающимся спондилоэпифизарной дисплазией скелета, стероидрезистентной протеинурической нефропатией, приводящей к прогрессирующей потере функции почек, нарушением иммунитета, а также поражением сосудов, вызванным атеросклерозом. ИКДШ вызывается биаллельными патогенными вариациями в гене SMARCAL1.

Клинические проявления ИКДШ очень разнообразны: от быстро прогрессирующего заболевания, при котором дети умирают в первые годы жизни, до более легких форм, при которых они доживают до зрелого возраста. Корреляция между генотипом и фенотипом крайне слабая, поэтому невозможно предсказать ни клиническое течение, ни исход заболевания. По этой причине пациенты с данной патологией могут попасть на прием к различным узким специалистам.

Описание клинического случая. В публикации представлен клинический случай 4-летнего мальчика с иммунологическим дефицитом, нарушением развития, а также скелетными аномалиями, свидетельствующими в пользу ИКДШ.

При полноэкзомном секвенировании в гене SMARCAL1 обнаружены варианты мутаций c.2542G>T (p.Glu848Ter); c.1682G>T (p.Arg561Leu) в гетерозиготном состоянии.

По результатам полученного генетического исследования, а также учитывая, что заболевание носит мультисистемный характер, ребенок был осмотрен нефрологом, ортопедом, эндокринологом и генетиком.

Заключение врача-нефролога: гломерулопатия при синдроме Шимке: изолированная протеинурия. Каликоэктазия слева. Хроническая болезнь почек (ХБП), стадия 2. Скорость клубочковой фильтрации (проба Шварца) — 69,01 мл/мин/1,73 м^2.

Заключение врача-эндокринолога: синдромальная низкорослость. Белково-энергетическая недостаточность 2-й степени.

Проведена телемедицинская консультация с ФГБУ НМИЦ ДГОИ им. Д. Рогачева, по результату которой было рекомендовано проведение заместительной терапии внутривенными или подкожными иммуноглобулинами, а также госпитализация в отделение иммунологии данного федерального центра.

Заключение. Данное описание является первым случаем диагностики краевыми специалистами крайне редкого заболевания (1:1–3000000 живорожденных) в Краснодарском крае. У данного пациента течение заболевания характеризуется не тяжелым, не прогрессирующим нарушением почечной функции, что дает повод предположить более легкую форму заболевания. Проведение заместительной терапии иммуноглобулинами дает возможность улучшить прогноз у данного пациента.

Ключевые слова: иммунокостная дисплазия Шимке, иммунодефицит, нефропатия, дисплазия скелета, ген SMARCAL1

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

Для цитирования: Ильина Э.С., Вейлер Д.А., Лашевич П.Д. Иммунокостная дисплазия Шимке на стыке специальностей. Клинический случай диагностики заболевания врачами — аллергологами-иммунологами. *Аллергология и иммунология в педиатрии*. 2025; 23 (1): 50–57. https://doi.org/10.53529/2500-1175-2025-1-50-57

INTRODUCTION

Schimke immune-osseous dysplasia (SIOD), first described by Schimke et al. in 1971, is an autosomal recessive extremely rare multisystem disease with a prevalence of 1:1-3000000 live births [1, 2]. It is characterized by multisystemic lesions accompanied

by spondyloepiphyseal skeletal dysplasia, steroidresistant proteinuric nephropathy causing progressive loss of renal function and immune dysfunction [1, 3, 4], as well as vascular damage caused by atherosclerosis [5]. SIOD is caused by biallelic pathogenic variations in the SMARCAL1 gene, which encodes a protein belonging to the SWI/SNF family of proteins involved in chromatin remodeling and regulation of transcription of certain genes [6].

SIOD diagnosis is usually first suspected in a child with nephrotic proteinuria and disproportionate growth retardation. Most children develop terminal renal disease before the age of 10 years. The most common histologic findings on renal biopsy are focal segmental glomerulosclerosis or minimal change disease (7). There is no effective therapy for this renal disease, so patients with terminal renal failure are treated with renal replacement therapy. Some authors suggest kidney transplantation with an abbreviated immunosuppression protocol because of the risk of infection in the post-transplantation period [8].

This disease belongs to congenital immunity errors, a group of combined immunodeficiencies with various syndromal manifestations. Along with cellular immunity disorders, a number of patients also have humoral immunity disorders with disturbances in the number of different classes of immunoglobulins and the level of memory B-cells. Infections associated with both T-cell deficiency (low number of CD4+ (cluster of differentiation) T cells and/or with altered function) and humoral deficiency are usually the most frequent complication of the disease and the main cause of mortality [9].

Skeletal dysplasia is manifested by fetal delay, short stature, femoral head anomalies, flat ovoid vertebrae, and hypoplastic pelvis [10]. Other frequent clinical manifestations include hyperpigmented spots mainly on the trunk, low nose bridge, convex nasal tip, short trunk and neck, lumbar lordosis, protruding abdomen, unusual hair, and malocclusion of teeth, Hypothyroidism, anemia, hypertension, recurrent infections, arteriopathy, episodic cerebral ischemia, bone marrow failure and corneal opacities [5].

Thus, the clinical manifestations of SIOD are very diverse: from rapidly progressive disease, in which children die in the first years of life, to milder forms in which they survive to adulthood. The correlation between genotype and phenotype is extremely weak, so neither the clinical course nor the outcome of the disease can be predicted [10]. For this reason, patients with this pathology may be seen by different subspecialists.

The objective of this study is to describe a clinical case of diagnosis of the extremely rare disease SIOD by specialists of the Children's Regional Clinical Hospital (CRCH) in Krasnodar, Russia.

CLINICAL CASE

The boy's parents have given consent for information about the child to be used for research and publications.

Patient K. (4 years 1 month old) was referred by his local pediatrician to see an allergologist-immunologist at the Children's Diagnostic Center in Krasnodar with complaints of low weight and height gain, leukopenia, lymphopenia in the general blood count (GBC), frequent acute respiratory infections (ARI) during the cold season.

Past medical history data. Child from an unrelated marriage, from the 2nd pregnancy (1st pregnancy in 2014 froze). Delivery of the 1st premature at 28 weeks 6 days of gestation. Birth weight 650 g, height 33 cm, Apgar score 6-7 points. He was discharged at 2 months of life with the diagnosis: “Congenital pneumonia on the background of respiratory distress syndrome (RDS), severe course. Bronchopulmonary dysplasia, new form, moderate severity. Cerebral ischemia of the 2nd degree, oppression syndrome. Prematurity 28 weeks 6 days. Small fetal size for gestational age (3rd degree intrauterine hypotrophy). Hydronephrotic transformation of the right kidney. Cholestasis syndrome”.

Table 1. **Immunoglobulin levels in the patient with SIOD (author's table)**
Таблица 1. **Показатели иммуноглобулинов у пациента с ИКДШ (таблица автора)**

Parameters	Boy K.	Normal value
Immunoglobulin A, g/L	1,18	0,48–3,45
Immunoglobulin M, g/L	1,08	0,4–1,8
Immunoglobulin G, g/L	14,26	5–13
Alpha fetoprotein, IU/mL	2,29	0–5,8

Up to 3 years old he was observed at the Children's Diagnostic Center of CRCH by a pediatrician, nephrologist, neurologist, ophthalmologist, endocrinologist, orthopedist. Since the age of 2 years, he had complaints about periodic onset of chalazion on his eyes, received symptomatic therapy and surgical treatment. At the age of 3 he was consulted by immunologist and hematologist of CRCH, immunologic examination was performed, moderate absolute lymphopenia, moderate decrease in absolute concentration of all subpopulations of T-lymphocytes was revealed, the following diagnosis was made: "Recurrent chalazion. Secondary dysfunction of the immune system. Leukopenia, secondary lymphopenia". At the age of 3, he had an acute community-acquired right-sided pneumonia, without complications.

At the age of 3 years and 6 months, the child's mother visited an endocrinologist with complaints of low growth rate and poor weight gain. A diagnosis was made: "Chronic nutritional deficiency of the 2nd degree. Growth retardation. Subclinical hypothyroidism. Cryptorchidism". L-thyroxine replacement therapy was prescribed.

At the age of 4, he was consulted by an immunologist again. Parents complained about frequent ARI in the cold season, antibiotic therapy twice a year with duration of 5-7 days, changes in blood tests (leukopenia, lymphopenia), poor weight gain and growth.

On examination, weight 10 kg, height 90 cm. Preventive vaccinations in full, according to the national calendar.

The following results were obtained in the CBC: leukopenia ($4{,}78\times10^9$/L), lymphopenia ($1{,}38\times10^9$/L), thrombocytopenia (88×10^9/L).

The results of the child's immunologic examination are presented in Table 1 and Table 2.

Hand radiography in direct projection was performed: bone age corresponds to 2 years (Sadofieva classification was used).

The patient was diagnosed with "unspecified primary immunodeficiency".

A telemedicine consultation (TMC) was held with the Dmitry Rogachev National Medical Research Center for Pediatric Hematology, Oncology and Immunology (FSBI NMRC CGOI named after D. Rogachev). Recommended: full-exome sequencing of deoxyribonucleic acid (DNA).

The child was consulted by a geneticist of the medical and genetic consultation, additional examination was carried out: karyotype 46 XY, normal, male; sex chromatin — 0%, normal, male; blood phenylalanine 1.35 mg/dL (normal); blood thyroid hormone

Table 2. **Main immunological parameters of the patient with SIOD (author's table)**
Таблица 2. **Основные иммунологические показатели пациента с ИКДШ (таблица автора)**

Parameters	Boy K.	Normal value
$CD3^+$, %	33,2	62–69
$CD3^+$, $\times10^9$/л	0,46	1,8–3
$CD4^+$, %	18,1	30–40
$CD8^+$, %	10,3	25–35
$CD3^+/CD4^+$,$\times10^9$/л	0,25	1–1,8
$CD3^+/CD8^+$,$\times10^9$/л	0,14	0,8–1,5
$CD19^+$, %	43,3	21–28
$CD19^+$, $\times10^9$/л	0,6	0,7–13
TREC, $\times10^5$/leukocytes TREC,	127	470–4100
KREC, $\times10^5$/leukocytes KREC,	3174	780–7700

CD — cluster of differentiation; **TREC** — T-receptor excision circle; **KREC** — kappadele recombination excision circle.

2.5 μME/mL (normal); thin layer chromatography of blood amino acids (normal).

Molecular genetic study result: full-exome sequencing: variants c.2542G>T (p.Glu848Ter); c.1682G>T (p.Arg561Leu) were detected in the SMARCAL1 gene in heterozygous state. Validation of the identified variants was performed by Sanger direct automated sequencing (trio). Both variants are of parental origin and are in transposition.

Thus, based on the presence of immune dysfunction, emerging nephropathy, delayed and impaired bone growth, as well as the data of molecular genetic methods of research, the child was diagnosed with "primary immune deficiency (immune-osseous dysplasia Schimke) D84.8".

Based on the results of the genetic study obtained, given that the disease is multisystemic in nature, the child was examined by a nephrologist, orthopedist, endocrinologist and geneticist.

Nephrologist's conclusion: glomerulopathy in Schimke's syndrome: isolated proteinuria. Calicoectasia on the left. Chronic kidney disease (CKD), stage 2.

Results of biochemical blood analysis: urea 7.7 mmol/l; creatinine 73 μmol/l.

Results of the general urinalysis: protein in urine — 0.68 g/L.

Results of estimation of glomerular filtration rate (GFR): Schwartz test 69.01 ml/min/1,73 m^2; Schwartz-Lyon test 46.08 ml/min/1,73 m^2.

Endocrinologist's conclusion: syndromal stunting. Protein-energy deficiency of the 2nd degree.

A repeated TMC with FSBI NMRC CGOI named after D. Rogachev was conducted, which resulted in the following recommendation: replacement therapy with intravenous (IVIG) or subcutaneous immunoglobulin (SCIG), as well as hospitalization in the Department of Immunology of this federal center.

DISCUSSION

We present a clinical case of a 4-year-old boy with immunologic deficits, developmental disorders, and skeletal anomalies suggestive of SIOD. The exact etiology of SIOD is unclear, but mutations in the SMARCAL1 gene have been found in about 50-60% of patients with SIOD [11], which explains the genetic heterogeneity of the disease. Nevertheless, differences in the SMARCAL1 structure have been described as an explanation for different disease severity in patients with the same mutation [12].

SIOD shows phenotypic heterogeneity [13], and disease severity ranges from mild to severe. Patients with SIOD with severe phenotype usually die before the age of five years and are characterized by bone dysplasia, specific facial dysmorphism and T-cell deficiency caused by repeated infection and chromosome fragility [14]. On the other hand, compared to patients with severe SIOD, patients with the mild form have a slower progression of symptoms. Some may present without infections or sometimes clinically asymptomatic, with proteinuria undetectable in early childhood. Patients with mild SIOD usually live to 15 years of age, while some patients may live to 36 years of age [15]. Boerkoel [6] reported heterozygous mutations corresponding to a mild course of the disease. The clinical phenotype found in our patient is exactly as described by Boerkoel [6]: a patient of short stature, with kidney disease and lymphocytopenia without recurrent infections.

In the boy in our study, according to the immunogram data, there are changes in the T-cell population, while no changes were found in humoral immunity (level of CD19+ B-cells, serum immunoglobulins, KREC concentration). Meanwhile, according to the authors' data, SIOD is accompanied by both isolated T-cell deficiency [16, 17] and combined B- and T-cell deficiency [18].

CONSTRAINTS

Constraints of our case report included limited access to the patient's medical history prior to the patient's admission to our facility, which prevented us from obtaining a detailed history of the patient's condition.

CONCLUSION

This description is the first case of diagnosis by regional specialists of an extremely rare disease (1:1-3000000 live births) in the Krasnodar region. In this patient, the course of the disease is characterized by not severe, not progressive impairment of renal function, which suggests a milder form of the disease. Immunoglobulin replacement therapy can improve the prognosis of this patient.

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FUNDING SOURCES

This study was not sponsored.

ИСТОЧНИКИ ФИНАНСИРОВАНИЯ

Исследование проводилось без участия спонсоров.

THE AUTHORS' CONTRIBUTION TO THE WORK

Eleonora S. Ilina — conceptualization, funding acquisition, verification, analysis and editing of literary data, research materials, investigation, resources, validation.

Daria A. Weiler — conceptualization, analysis and editing of literary data, research materials, investigation, resources.

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ВКЛАД АВТОРОВ В РАБОТУ

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CONSENT FOR PUBLICATION

Written consent for publication of relevant medical information within the manuscript was obtained from the patients and patient's parents.

ИНФОРМИРОВАННОЕ СОГЛАСИЕ НА ПУБЛИКАЦИЮ

Пациенты и их законные представители добровольно подписали информированное согласие на публикацию персональной медицинской информации в обезличенной форме.

Experience of using the drug upadacitinib in a child with severe atopic dermatitis

RAR — научная статья

https://doi.org/10.53529/2500-1175-2025-1-58-64

Date of receipt: 30.10.2024
Date of acceptance: 03.03.2025
Date of publication: 21.03.2025

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Abstract

Introduction. Atopic dermatitis (AtD) is a genetically determined chronic dermatosis with heterogeneous manifestations that can significantly affect the quality of life of patients. The disease has a complex pathogenesis, which significantly complicates its treatment. The JAK-STAT signaling pathway plays a central role in the modulation of several immune axes involved in the immunopathogenesis of AtD. In particular, the action of Th2 cytokines, including IL-4, IL-5, IL-13, IL-31 and thymus stromal lymphopoietin, is mediated by transmission of the JAK-STAT signal, which makes this pathway a good target for targeted drugs.
Presentation of the clinical case. At the present stage, the problem of choosing tactics for the treatment of severe forms of ATD is important. In June 2021, the drug upadacitinib, a selective reversible type 1 janus kinase inhibitor, was registered in the Russian Federation for the treatment of moderate to severe AtD in adults and children 12 years and older. This publication presents our own successful experience of using upadacitinib in the form of a description of a clinical case in a 16-year-old child with uncontrolled severe AtD. Before the drug was prescribed, the patient's disease course was continuously recurrent, with severe exacerbations and short periods of remission, as well as resistance to standard therapy.
Conclusion. The use of upadacitinib at a dose of 15 mg for 11 months allowed the teenager to achieve rapid remission of the disease and successfully control such a complex symptom as itching.

Keywords: atopic dermatitis, upadacitinib, targeted therapy

Conflict of interests:
The authors declare no conflict of interest.

For citation: Alemanova G.D., Popova L. Yu., Zlodeeva E. A., Kirichenko O. V., Pogrebnova E. I. Experience of using the drug upadacitinib in a child with severe atopic dermatitis. *Allergology and Immunology in Pediatrics*. 2025; 23 (1): 58–64. https://doi.

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org/10.53529/2500-1175-2025-1-58-64

Опыт применения препарата упадацитиниб у подростка с тяжелым течением атопического дерматита

https://doi.org/10.53529/2500-1175-2025-1-58-64

УДК 615.036.8
Дата поступления: 30.10.2024
Дата принятия: 03.03.2025
Дата публикации: 21.03.2025

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Аннотация

Введение. Атопический дерматит (АтД) представляет собой генетически детерминированный хронический дерматоз с гетерогенными проявлениями, которые могут существенно влиять на качество жизни пациентов. Заболевание имеет сложный патогенез, что существенно затрудняет его лечение. Центральную роль в модуляции нескольких иммунных осей, участвующих в иммунопатогенезе АтД, играет сигнальный путь JAK-STAT. В частности, действие цитокинов Th2, включая IL-4, IL-5, IL-13, IL-31 и стромальный лимфопоэтин тимуса, опосредуется передачей сигнала JAK-STAT, что делает этот путь удачной мишенью для таргетных препаратов.

Изложение клинического случая. На современном этапе немаловажной является проблема выбора тактики лечения тяжелых форм АтД. В июне 2021 г. в РФ для лечения среднетяжелого и тяжелого АтД у взрослых и детей от 12 лет и старше был зарегистрирован препарат упадацитиниб — селективный обратимый ингибитор янус-киназы 1-го типа. В данной публикации представлен собственный успешный опыт применения упадацитиниба в виде описания клинического случая у ребенка 16 лет с неконтролируемым тяжелым течением АтД. До назначения препарата течение заболевания у пациента было непрерывно-рецидивирующим, с тяжелыми обострениями и короткими периодами ремиссии, а также резистентностью к стандартной терапии.

Заключение. Применение упадацитиниба в дозе 15 мг в течение 11 месяцев позволило добиться у подростка быстрой ремиссии заболевания и успешно контролировать такой сложный симптом, как зуд.

Ключевые слова: атопический дерматит, упадацитиниб, таргетная терапия

Конфликт интересов:
Авторы заявляют об отсутствии конфликта интересов.

Для цитирования: Алеманова Г. Д., Попова Л. Ю., Злодеева Е. А., Кириченко О. В., Погребнова Е. И. Опыт применения препарата упадацитиниб у подростка с тяжелым течением атопического дерматита. *Аллергология и иммунология в педиатрии*. 2025; 23 (1): 58–64. https://doi.org/10.53529/2500-1175-2025-1-58-64

Atopic dermatitis (AtD) is a multifactorial genetically determined dermatosis with a complex pathogenesis characterized by pruritus, chronic recurrent course, and age-related localization and morphology of lesions [1]. It is one of the most common skin diseases: according to the Federal Statistical Surveillance, in 2018, the incidence of AtD in the Russian Federation amounted to 188.2 cases, and the prevalence was 426.3 cases per 100,000 of the total population [2].

AtD usually develops in the first 2 years of life and in 20% of cases persists into adulthood [3]. Severe course significantly worsens the quality of children's life, causing frequent school absences, depression, se-

rious problems in the family, and social maladaptation in adulthood [4, 5].

Due to the fact that bronchial asthma (BA) and allergic rhinitis have a common pathophysiological connection with AtD, it can serve as a starting point for the development of the "atopic march" — a typical sequential progression of allergic diseases from AtD with concomitant food allergy in most cases to the formation of further BA and allergic rhinitis with the expansion of the sensitization spectrum [6].

The pathogenesis of AtD results from a combination of genetic and environmental factors that cause skin barrier dysfunction, cutaneous and systemic immune dysregulation, and disruption of the skin and gut microbiota [5].

Abnormal cytokine production plays a crucial role in pathogenesis [7]. The imbalance of pro- and anti-inflammatory signals stimulates a vicious circle, causing skin inflammation, pruritus and secondary epidermal barrier disruption [8]. AtD is a biphasic inflammatory process mediated by T cells. In the acute phase of the disease, the Th2 response with subsequent hyperproduction of specific IgE predominates; as the process becomes chronic, the immune response switches to Th1. Epidermal cells play an important role in the pathogenesis of AtD. The skin barrier defect induces the release of mediators by keratinocytes, such as TSLP, IL-25, IL-31, which causes increased production of cytokines: IL-4, IL-5, IL-13 and IL-31, contributing to local inflammation [3, 8]. Of note, most of the aforementioned inflammatory cytokines utilize the janukinase (JAK)/signal transducer and activation of transcription (STAT) pathway for subsequent signal transduction, making this pathway a successful target for targeting drugs [9].

ЛAtD treatment should have a complex and individual approach depending on age, prevalence of the skin process, severity of the disease and anamnestic data, including the elimination of provoking factors (irritants, allergens, stress), anti-inflammatory external treatment, control of the infectious process in the presence of complications, skin moisturizing with the restoration of the epidermal barrier [10].

The priority therapy for AtD is topical treatment with topical glucocorticosteroids (GCS), calcineurin inhibitors, and emollients. However, moderate to severe AtD may be associated with systemic immune activation, which explains the insufficiency of topical skin therapy and necessitates the use of systemic agents [4].

Until recently, the choice of systemic therapy for severe AtD was limited to the use of systemic GCS and cyclosporine. According to modern Russian and foreign clinical guidelines, recombinant monoclonal antibodies of the IgG4 isotype directed against the common subunit of the receptor for IL-4/13 and blocking the effects of IL-4 and IL-13 can be used in moderate to severe AtD in the absence of effect from standard methods of treatment. Dupilumab is the first biologic to inhibit IL-4 and IL-13 receptor activation in severe and moderate AtD [3].

Currently, the possibilities of systemic therapy for AtD patients have been expanded. In June 2021, the drug upadacitinib, which is a selective reversible inhibitor of type 1 janukinase, was registered in the Russian Federation for the treatment of moderate-to-severe AtD in adults and children aged 12 years and older. Upadacitinib (UPA) has undergone an extensive program of phase 2 and 3 clinical trials to evaluate its efficacy and safety in AtD before its introduction into clinical practice [11]. Registration studies involving adult patients and children over 12 years of age with moderate to severe AtD have been completed to date.

This article presents the experience of using the targeting drug upadacitinib in a 16-year-old patient with severe atopic dermatitis.

CLINICAL CASE

Patient M., 16 years old, was admitted to the Orenburg Regional Children's Clinical Hospital in May 2023 with complaints of widespread rashes accompanied by intense itching, pronounced dryness of the skin, scaling, scratching, chapped skin. According to the teenager's words, the skin is "red", flaky, rashes are constant ("there is no such thing as clean skin"), and he is concerned about itching at night, which disturbs his sleep. Due to his severe condition, the patient has to stay at home all the time, and he does not attend school.

Past medical history: child from the 1st pregnancy with toxicosis, 1st term delivery. Birth weight 4248 g, height 52 cm. He was breastfed until the age of 1 year. Vaccinated according to the calendar plan. Sick with ARI 2-3 times a year.

Allergologic history: heredity for allergic diseases is aggravated: the maternal grandmother has allergic rhinitis. The child has intolerance to food products (honey, chicken egg, citrus fruits, sweets), appearing with rashes, erythema, itching.

Disease history: skin rashes began to appear from the first months of life, atopic dermatitis was diagnosed, which was exacerbated 3-4 times a year (most often in the cold season), associated with errors in diet, acute respiratory tract infections.

During exacerbations he received sorbents, antihistamines, topical GCS, emollients. At the age of eight, nasal congestion and rhinorrhea began to appear in spring and summer, and seasonal allergic rhinitis was diagnosed. Several times the child suffered bronchitis with bronchial obstruction syndrome, the symptoms were treated with inhalations of berodual and pulmicort via nebulizer. Allergologic examination in 2018 revealed specific IgE to a mixture of house dust mites, a mixture of epidermal allergens of pets, tree pollen and meadow grasses. Allergy-specific therapy was not performed due to frequent severe exacerbations of AtD. In case of exacerbation of seasonal allergic rhinitis he received symptomatic therapy with a temporary effect. The child is observed by an allergist and immunologist at the place of residence, has been repeatedly hospitalized in Orenburg State Autonomous Institution of Health Care "OCCH". During hospitalizations he received treatment: systemic GCS intravenous drip, antihistamines, external therapy with topical GCS, emollients without any pronounced effect. Since 2021, the course of the disease worsened, which the patient himself attributes to the coronavirus infection, exacerbations of atopic dermatitis became monthly, the disease continuously recurred. Severe course of AtD and presence of concomitant allergic diseases was an indication for the patient to receive a disability group.

In 2023, the child was first diagnosed with a concomitant disease: according to EGD data, non-atrophic antral gastritis was diagnosed.

On admission, the condition is severe due to a pronounced skin syndrome, excoriating pruritus. The skin pathological process has a diffuse symmetrical character; it is localized on the skin of the face, neck, trunk, upper and lower extremities; is represented by multiple erythematous-squamous foci, serous-hemorrhagic crusts, excoriations, lichenoid desquamation with linear scaling over the entire skin surface, in the elbow folds, hamstring fossa and on the wrist joints — lichenification; on the face periorbital shadows. The area of the pink border of the lips is chapped and flaked as manifestations of cheilitis. Persistent white dermographism. Diffuse hyperemia of the skin, pronounced dryness. The skin is rough, rough to the touch, tissue turgor is preserved, skin elasticity is reduced. There are no signs of secondary infection. Scoring of Atopic Dermatitis (SCORAD) index — 84.7. Peripheral lymph nodes are not enlarged. Nasal breathing is difficult on both sides. There is a clear lung sound over the whole surface of the lungs. Vesicular breathing, no rales are heard. Respiratory rate 16 per minute. Heart tones clear, rhythmic. HR 72 per minute. BP 110/70 mm Hg. The abdomen is soft, painless on palpation. Liver, spleen are not enlarged. Stools are regular without pathologic impurities. Urination is painless. Thyroid gland is visually not enlarged, painless on palpation.

Laboratory tests on admission. No change in general clinical examinations.

Total IgE was found to be elevated — 1159.0 IU/mL (0.0-100.0 IU/mL). Specific IgE with a panel of food allergens: egg white — class 3; egg yolk, carrot, rye, mandarin, sunflower seed, potato — class 1.

Immunoglobulins A, M, G in serum: elevated IgA 2.54 g/l (N: 0.07-0.94 g/l). No evidence of helminthiasis and giardiasis was obtained during laboratory examination.

Thyroid hormones (TTG, T4): decreased free thyroxine — 9.1 pmol/l (N: 10.0-23.2 pmol/l) was detected.

Instrumental studies. ECG: sinus rhythm, HR 72 per minute. Spirometry: all indices are within normal limits. Ultrasound examination of abdominal cavity organs, thyroid gland and parathyroid glands: no pathology revealed.

On the basis of complaints, medical history, clinical picture and examination results the diagnosis was made: «Atopic dermatitis, adolescent form (diffuse neurodermatitis stage), widespread, severe, with eczematization, exacerbation. Seasonal allergic rhinitis, medium severity, persistent course, remission. Polyvalent sensitization. Chronic non-atrophic non-atrophic antral gastritis, remission. Subclinical hypothyroidism».

Inpatient treatment was provided: chloropyramine 2% 1 ml 2 times a day intramuscularly, prednisolone 60 mg intravenous drip in 500 ml of 0.9% NaCl solution, cetirizine 10 mg intravenously, skin UVI. Topical therapy: Acriderm GC 2 times a day on the affected areas of the skin of the trunk, upper and lower extremities, emollients of the Admera series of medical cosmetics. The effect of the treatment was insignificant: itching decreased slightly, fissures epithelialized, at discharge SCO- RAD — 50.1.

Due to the severe course of atopic dermatitis in the patient and the lack of effect from therapy, a discharge letter was sent to the Federal Center of "FRC Nutrition and Biotechnology", Moscow to consider the issue of target therapy, where the child was recommended to start therapy with the drug upadacitinib 15 mg/day orally for 12 months for vital indications.

In June 2023 the patient started taking UPA, also continued the use of topical GCS and emollients. Against the background of the therapy a significant improvement in the boy's well-being was noted: already in the first days of taking the drug he noted a decrease in the intensity of pruritus (from 10 to 5 points on NRS).

Accordingly, the significant primary effect of therapy was the normalization of sleep and daytime activity and, as a consequence, the restoration of normal psycho-emotional state and improvement of the patient's quality of life.

At examination after 1 month, significant positive dynamics was observed: the severity and area of skin rashes decreased, cracks in the elbow bends and hamstrings disappeared, the skin became more elastic, its dryness and desquamation decreased. Reduced itching and inflammatory changes also contributed to the cessation of scratching and healing of excoriations. SCORAD index at the time of examination 30.5. No adverse events were observed against the background of UPA administration. Dynamic evaluation of laboratory parameters (total blood count, urinalysis, biochemical blood count) did not reveal any deviations in the course of treatment. Given the rapid and significant effect, the patient had high adherence to the continuation of the prescribed therapy. At the moment the patient has been receiving the drug for 11 months. The adolescent has almost clear skin on the background of UPA intake.

In May 2024, against the background of acute respiratory viral infections and discontinuation of the drug, the boy's condition worsened, and he was hospitalized in the Orenburg Children's Clinical Hospital. Examination revealed erythematous-squamous foci on the skin of the face, trunk, upper and lower extremities. In the area of elbow bends, hamstring fossae, wrist joints — lichenification, hemorrhagic crusts, excoriations. SCORAD — 56.2. In the blood serum there was detected an increase in the total IgE level up to 2012 IU/mL.

Treatment was carried out: dexamethasone 8 mg diluted in 500 ml of 0.9% NaCL solution by IV drip #3, cetirizine 10 mg once a day, upadacitinib 15 mg once a day, externally Comfoderm once a day for rashes. On the background of the therapy the rashes regressed, SCO- RAD index at discharge — 27,6.

The statement was repeatedly sent to the Federal Center of "FRC Nutrition and Biotechnology" for extramural consultation to address the issue of prolongation of UPA target therapy, the answer has not been received yet.

Thus, the presented clinical case demonstrates the positive result of the use of UPA, a new drug for the treatment of AtD, which allowed the patient to achieve rapid remission of the disease and successfully control such a difficult symptom as pruritus. It is important to note that UPA not only showed high clinical activity, but, no less importantly, did not cause adverse events in the patient, which could cause the drug discontinuation.

AtD therapy should be comprehensive and individualized, taking into account the age of the patient and the severity of the disease. To prevent disease progression to more severe, disabling forms, it is necessary to create new treatment paradigms. Expansion of the spectrum of pathogenetic therapy of AtD with inclusion of the inhibitor of Janukinase type 1 UPA fully corresponds to modern trends. Upadacitinib has a good evidence base, its clinical efficacy and safety have been proven in many clinical trials, which allows its use for the therapy of moderate and severe AtD in both adults and adolescents 12-18 years old.

Our experience with UPA shows the high efficacy of daily administration of 15 mg of the drug for 11 months. Against the background of treatment, the adolescent showed significant positive dynamics: a rapid decrease in the activity of clinical symptoms, stability of the achieved results and absence of side effects. The skin remained practically clean, the reduction of itching contributed to a favorable emotional state and normalization of the patient's sleep. Due to the patient's good response to treatment and the occurrence of exacerbation upon withdrawal of UPA, there is a need to continue therapy with this drug.

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FUNDING SOURCES

The authors declare that no funding was received for this study.

ИСТОЧНИКИ ФИНАНСИРОВАНИЯ

Авторы заявляют об отсутствии спонсорской поддержки при проведении исследования.

THE AUTHORS' CONTRIBUTION TO THE WORK

Galina D. Alemanova — examination and treatment of patients, collection of clinical material, writing a manuscript.

Larisa Yu. Popova — examination and treatment of patients, collection of clinical material, approval of the manuscript.

Elena A. Zlodeeva — review of publications on the topic of the article.

Olga V. Kirichenko — review of publications on the topic of the article, writing a manuscript.

Elena I. Pogrebnova — examination and treatment of patients, collection of clinical material.

ВКЛАД АВТОРОВ В РАБОТУ

Алеманова Г. Д. — обследование и лечение пациентов, сбор клинического материала, написание рукописи.

Попова Л. Ю. — обследование и лечение пациентов, сбор клинического материала, утверждение рукописи.

Злодеева Е. А. — обзор публикаций по теме статьи.

Кириченко О. В. — обзор публикаций по теме статьи, написание рукописи.

Погребнова Е. И. — обследование и лечение пациентов, сбор клинического материала.

CONSENT FOR PUBLICATION

Written consent for publication of relevant medical information within the manuscript was obtained from the patients and patient's parents.

ИНФОРМИРОВАННОЕ СОГЛАСИЕ НА ПУБЛИКАЦИЮ

Пациенты и их законные представители добровольно подписали информированное согласие на публикацию персональной медицинской информации в обезличенной форме.

Ассоциация детских аллергологов
и иммунологов России

АЛЛЕРГОЛОГИЯ И ИММУНОЛОГИЯ
В ПЕДИАТРИИ
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IN PEDIATRICS