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АЛЛЕРГОЛОГИЯ И ИММУНОЛОГИЯ В ПЕДИАТРИИ

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Summary

Relevance. Food allergy (FA) is an important public health concern, particularly among children, with an increasing prevalence. It is associated with a significant decrease in the quality of life for patients and their families due to the need to avoid allergens and the risk of severe allergic reactions, such as anaphylaxis. Despite active research, the primary treatment remains elimination diets, which limit patients' options and highlight the need for new therapeutic solutions.

Aim of the review. This review aims to summarize the current treatment methods for food allergy, discuss the challenges in evaluating the effectiveness of interventions, and highlight the importance of standardizing outcomes in clinical trials to improve comparability and practical relevance.

Content. The review discusses modern therapeutic approaches for food allergy, such as oral, epicutaneous, and sublingual immunotherapies, which have shown positive results in achieving tolerance to allergens. Special attention is given to safety concerns, particularly for children, emphasizing the need for further research. The potential use of biological agents, such as omalizumab, in food allergy treatment is also explored. The review addresses challenges in choosing and standardizing endpoints in clinical trials, where most focus on desensitization and immunological markers, while patient-centered outcomes, such as quality of life, remain under-researched. The implementation of "core outcome sets" is highlighted as an important step toward improving data comparability and forming a more objective basis for clinical recommendations.

Conclusions. The review emphasizes significant progress in food allergy treatment but notes the need for further research to ensure the safety of new therapies, particularly for children. Standardizing outcomes in clinical trials plays a key role in improving the quality and comparability of research, which will, in turn, help develop more effective clinical guidelines and improve patients' quality of life.

Keywords: harmonization, food allergy, clinical trials, treatment, core outcome sets

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Пищевая аллергия у детей: вызовы терапии и стандартизация исходов

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Резюме

Актуальность. Пищевая аллергия (ПА) является серьезной проблемой здравоохранения, особенно среди детей, с возрастающей распространенностью. Она оказывает значительное влияние на качество жизни пациентов и их семей из-за необходимости избегать аллергенов и рисков тяжелых аллергических реакций, таких как анафилаксия. Несмотря на активные исследования, основное лечение по-прежнему заключается в элиминационной диете, что ограничивает возможности пациентов и требует поиска новых терапевтических решений.

Цель обзора. Настоящий обзор направлен на обобщение современных методов лечения пищевой аллергии, рассмотрение актуальных проблем при оценке эффективности интервенций и обсуждение важности стандартизации исходов клинических исследований для улучшения их сопоставимости и практической значимости.

Содержание. Обзор включает обсуждение современных терапевтических подходов к лечению пищевой аллергии, таких как оральная, эпикутанная и сублингвальная иммунотерапии, которые демонстрируют положительные результаты в достижении толерантности к аллергенам. Особое внимание уделяется проблемам безопасности этих методов, особенно у детей, что подчеркивает необходимость дальнейших исследований. Кроме того, рассматриваются перспективы использования биологических препаратов, таких как омализумаб, в терапии пищевой аллергии. Также обсуждаются сложности в выборе и стандартизации конечных точек в клинических исследованиях, где большинство фокусируется на десенсибилизации и иммунологических показателях, тогда как такие пациент-ориентированные исходы, как качество жизни, остаются недостаточно изученными. Внедрение «наборов основных исходов» представляет важный шаг для улучшения сопоставимости данных и формирования более объективной базы для клинических рекомендаций.

Выводы. Обзор подчеркивает значительный прогресс в лечении пищевой аллергии, однако отмечает необходимость дальнейших исследований для обеспечения безопасности новых терапий, особенно для детей. Стандартизация исходов в клинических испытаниях играет ключевую роль для улучшения качества и сопоставимости исследований, что, в свою очередь, будет способствовать разработке более эффективных клинических рекомендаций и улучшению качества жизни пациентов.

Ключевые слова: гармонизация, пищевая аллергия, клинические исследования, лечение, набор ключевых исходов

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INTRODUCTION

Food allergy (FA) is a significant and growing public health problem worldwide. FA is an immunologically mediated body reaction to certain foods that can range from mild skin reactions to severe and life-threatening conditions such as anaphylaxis.

The prevalence of FA, especially among children, has increased significantly over the past decades, making it a subject of intense scrutiny by researchers and clinicians [1].

Despite the development of diagnostic and treatment methods, allergen elimination remains the main

List of abbreviations/ Список сокращений:

CI:	confidence interval
OIT:	oral immunotherapy
FA:	food allergy
RCT:	randomized clinical trial
EoE:	eosinophilic esophagitis
CDLQI:	children's dermatology life quality index
COMFA:	core outcome measures for food allergy
COS:	core outcome set
DLQI:	dermatology life quality index
EASI:	eczema area and severity index
EPIT:	epicutaneous immunotherapy
EREFS:	endoscopic reference evaluation scale of EoE
FLG:	filaggrin
FAQLQ:	quality of life questionnaire in patients with food allergy
HLA:	human leukocyte antigen
HOME:	harmonization of "outcome measures for eczema" initiative
IDQoL:	infant dermatology quality of life index
IL:	interleukin
POEM:	patient-oriented eczema measure
PROMs:	patient-reported outcome measures
RR:	relative risk
sIgE:	specific immunoglobulin E
SCIT:	subcutaneous immunotherapy
SLIT:	sublingual immunotherapy
SPINK5:	serine protease inhibitor type 5
SPIRIT:	standard protocol items: recommendations for interventional trials
SPT:	prick test
Th:	T-helpers
Tregs:	T regulatory cells

method of managing FA at the moment, which significantly limits the quality of patients' life and their families [2]. This is especially true for children whose social activity and psychological state are directly associated with dietary restrictions and the risk of accidental contact with allergens [3]. Modern interventional techniques, such as immunotherapy, aim at improving allergen tolerance and potentially achieving remission, but challenges remain regarding the safety and efficacy of these approaches.

Besides, the question arises what outcomes and results are most relevant for evaluating the effectiveness of FA treatment [4]. Traditionally, many trials focus on outcomes such as desensitization and immunological changes, while patient-oriented outcomes such as quality of life and subjective perceptions of treatment are often overlooked. This highlights the need for standardization and harmonization of data in FA clinical trials [5].

The purpose of this article is to provide an overview of potential treatment approaches for food allergy, discuss key issues in assessing the effectiveness of interventions, and provide perspectives on standardizing outcomes in research and practice, given their importance to patients and clinical decisions.

FOOD ALLERGY EPIDEMIOLOGY

The increasing incidence of pediatric PA is a complex public health problem and is most likely caused by a combination of genetic, environmental, and dietary factors. FA has become a major threat in recent decades, especially in economically developed countries, where lifetime prevalence ranges from 4% to 7% [6]. In the United States, the incidence of pediatric FA increased by 50% between 1997 and 2011 [7]. This increase emphasizes the multifactorial nature of PA, which is affected by both hereditary factors, environmental exposures, and dietary changes.

A recently published systematic review summarizing data on the prevalence of FA in Europe [8], has demonstrated that the cumulative lifetime prevalence

of "self-reported" FA was 19.9% (95%; confidence interval (CI) 16.6- 23.3) and the point prevalence was 13.1% (95%; CI 11.3-14.8). The point prevalence of sensitization by specific immunoglobulin E (sIgE) was 16.6% (95%; CI 12.3-20.8), 5.7% (95%; CI 3.9-7.4) by prick tests (SPT), and 0.8% (95%; CI 0.5-0.9) by provocation tests. Although the lifetime prevalence of FA, as both "self-reported" and measured by positive provocation tests has changed insignificantly, the point prevalence of "self-reported" FA, sIgE, and SPT has increased compared to previous estimates. This may reflect both a real rise in FA cases and increased awareness, an expansion of the list of products evaluated, or an increase in the number of studies in countries with insufficient data in previous reviews.

The most common allergens causing reactions in children include cow's milk, chicken eggs, peanuts, peanuts, nuts, fish and seafood. According to a systematic review by Panesar et al. [9], cow's milk protein was responsible for 29% of pediatric PA cases, and chicken egg protein — for 25%. The proteins in these products often cause reactions in infants and young children. However, the prevalence of FA varies according to geographical and ethnic factors. For example, studies show that Asian children in Australia have a higher prevalence of atopic dermatitis and peanut allergy compared to children of other ethnic groups [10].

FA is often accompanied by other atopic diseases such as asthma and atopic dermatitis. For example, up to two thirds of children with atopic dermatitis may exhibit symptoms of FA despite the absence of sensitization to common environmental allergens [11]. The fact that FA is combined with other allergic diseases indicates the presence of common pathophysiologic mechanisms, which emphasizes the importance of searching for integrative treatment strategies aimed at alleviating the manifestations of several allergic diseases at once.

Genetic factors also play a key role in the development of FA. Suaini et al. identified specific genetic polymorphisms associated with FA in a systematic review that included data from 32 studies [12]. Associations have been identified for the FLG, HLA, IL10, and IL13 genes, and other variants including SPINK5, SERPINB, and C11orf30 have been identified. Nevertheless, genetic factors cannot fully explain the rapid increase in FA incidence. Environmental factors, especially those associated with diet and early allergen exposure, appear to play an important role in shaping the immune response. Studies show that early introduction of allergenic foods such as peanuts may reduce the risk of developing FA [13], which in recent years has influenced the revision of infant nutrition guidelines in many countries [14].

FA has a significant impact on the mental well-being of children and their families. Children with food allergies are more likely to experience anxiety disorders, depression and social isolation compared to their peers [15]. The constant need to avoid allergens and the fear of possible severe reactions create significant emotional stress for children and their parents. This emotional burden emphasizes the importance of incorporating psychological support into FA treatment plans, ensuring that both mental and physical health are given equal consideration.

APPROACHES TO TREATMENT OF FOOD ALLERGY

Despite active research into interventional therapies for FA, elimination of the causative allergen remains the mainstay of treatment [1]. Elimination is most commonly used in routine clinical practice and in the Russian Federation, in the absence of other alternatives. Although this approach reduces the risk of acute allergic conditions, long-term avoidance of "allergens" significantly affects the quality of life by restricting the child's diet and creating psychological difficulties for their families. In recent years, various

treatments have sought to overcome these limitations with the aim of active desensitization and the search for effective interventional strategies.

One of the most promising methods is oral immunotherapy (OIT), which involves the gradual introduction of allergenic foods under medical supervision to raise the "allergic response threshold." OIT has demonstrated its efficacy in improving the quality of life of children with food allergy. A study by Epstein-Rigbi et al. [16] showed that OIT has a positive effect on both children and their parents, reducing anxiety and improving daily life. However, the safety of OIT remains a matter of concern, as adverse reactions, including anaphylaxis, have been reported during therapy, which requires strict medical supervision.

Some experts believe that OIT can lead to "sustained insensitivity" in a significant proportion of children [17], which raises the hope that long-term remission can be developed in patients with FA. The mechanism of OIT effect is to switch from a Th2 response, which promotes IgE production and allergic reactions, to a more balanced Th1/Th2 response, which promotes tolerance formation [18]. This is supported by changes in cytokine profile and immune cell composition after OIT, including decreased levels of Th2-related cytokines and increased numbers of regulatory T cells [19]. However, the combination of OIT with adjuvants such as omalizumab (anti-IgE monoclonal antibody), has demonstrated efficacy in improving treatment outcomes, especially in children with multiple food allergies [20, 21], and this approach has yielded encouraging results in patients with more complex allergy profiles.

Epicutaneous immunotherapy (EPIT) offers a less invasive alternative by delivering "allergens" through the skin using special patches. This method has attracted attention due to the potentially lower risk of systemic reactions compared to OIT. Clinical trials have demonstrated the efficacy of EPIT for peanuts, resulting in an increase in the amount of peanut protein tolerated.

In a recent study, a positive outcome was reported in 67% of children in the intervention group compared with 33.5% in the placebo group (risk difference was 33.4 percentage points; 95% confidence interval 22.4-44.5; $p < 0.001$) [22]. The mechanism of action of EPIT involves activation of regulatory T cells (Tregs), including modulation of local immune responses in the skin, potentially causing the development of systemic tolerance [23]. The lower risk of severe side effects makes EPIT an attractive option for young children, who are at higher risk of serious allergic reactions [18].

Sublingual immunotherapy (SLIT) involves placing allergen extracts under the tongue for absorption through the oral mucosa. This technique is used extensively in the treatment of allergic rhinitis, but a number of studies have evaluated its efficacy in the treatment of FA. In two clinical trials comparing the efficacy of oral immunotherapy (OIT) and sublingual immunotherapy (SLIT) for peanut and cow's milk allergy, OIT was found to be more effective in inducing desensitization compared with SLIT [24, 25]. However, SLIT was also associated with a higher incidence of symptoms and moderate-to-severe reactions requiring epinephrine, as well as a higher number of discontinuations. Thus, the data suggest that SLIT may offer a higher safety profile, with fewer systemic reactions than OIT [26]. The immunologic mechanisms of SLIT are similar to OIT and include Tregs induction and switching of the immune response toward tolerance [18].

Subcutaneous immunotherapy (SCIT), traditionally used for pollen and house dust mite allergies, is also being studied as an alternative for the treatment of FA. SCIT involves administering allergen extracts by injection, which may cause desensitization over time. Although SCIT is effective for the treatment of allergies to "classical environmental allergens," its use in PA is limited due to the high risk of severe anaphylactic reactions [17].

In 2024, the U.S. Food and Drug Administration (FDA) in the USA approved omalizumab for the

treatment of children and adults with one or more food allergies. The decision was based primarily on the results of a randomized clinical trial (RCT) published in the New England Journal of Medicine [27]. Of the 118 participants receiving omalizumab, 67% met the primary endpoint (participants' ability to tolerate 600 mg or more of peanut protein), compared to 7% receiving placebo. In terms of safety, there were no significant differences between groups, with the exception of more frequent injection site reactions in the omalizumab group.

The study of interventional approaches for the treatment of pediatric PA continues to evolve rapidly, and techniques such as OIT, EPIT, SLIT and SCIT offer various benefits and challenges. Continued research is needed to optimize these techniques, improve safety, and increase understanding of the immunologic mechanisms underlying them. The consideration of psychosocial factors remains an important aspect, which will allow a more comprehensive and patient- oriented treatment approach to be developed.

EFFICACY EVALUATION IN CLINICAL TRIALS

RCTs aim to determine the efficacy of a particular treatment, but we most often do not think about the nuances of defining efficacy. The assessment of efficacy is closely linked to the selection of appropriate outcomes/endpoints that serve as key indicators of treatment success and patient benefit. Clearly defined and clinically relevant outcomes are essential for the proper interpretation of research results, allowing useful conclusions to be drawn for clinical practice. The importance of careful and thorough selection of primary endpoints is discussed in many areas of medicine, such as in studies related to neurocognitive outcomes in infant formula testing [28], where the clarity and relevance of endpoints are crucial for informative results. Experts point to the need for a clearer definition of indicators based on "evaluation of patient-reported outcomes" (PROMs), in oncology trials to accurately reflect the impact of treatment on patients' quality of life [29].

The measurement of PROMs, of which quality of life assessment is a classic example, is extremely important as it provides an opportunity to capture patients' own experience and perception of treatment, which helps to better understand its efficacy with no regard to the field of medicine in which the study is being conducted. D'Souza et al. demonstrated the value of PROMs in amyloidosis studies, where patient-centered outcomes provide important insights into the impact of treatment on daily life [30], and Taylor et al. recommend that aspects such as participation in activities of daily living be included as an additional indicator in chronic pain studies, which helps to further and better assess the impact of therapy on patients [31].

The high heterogeneity of definitions and methods for measuring outcomes across clinical trials presents a significant obstacle to meta-synthesizing data and conducting systematic reviews. As noted by Gianola et al. [32], inconsistencies in outcome reporting make it difficult to compare data between studies, making it difficult to build an evidence base for use in developing clinical guidelines and then making decisions in routine clinical practice. This issue is compounded by a lack of consensus on which outcomes are most appropriate for evaluating the efficacy of therapy for different diseases, which may lead to misunderstanding and misrepresentation of results [33].

Along with the choice of outcomes, the methodology of clinical trials plays a key role in ensuring the reliability and applicability of the results. The use of rigorous statistical methods and sufficient sample sizes are necessary for studies to be powerful enough to determine clinically meaningful differences. However, as has been repeatedly pointed out by experts, many studies do not meet these requirements, making their results less general or clinically meaningful [32]. It should also be remembered that statistical significance does not always correlate with clinical rele-

vance, which emphasizes the importance of cautious interpretation of RCT results.

In addition to the problems described above, the results of RCTs can be adversely affected by systematic errors in outcome reporting that occur when there are discrepancies between study protocols and published results. Kirkham et al. emphasize that such discrepancies reduce the accuracy of systematic reviews, making it necessary to document changes in outcomes more transparently [34]. Ioannidis et al. also express concern that covert modifications of outcomes may distort the true effectiveness of an intervention [35]. These errors can mislead clinicians and patients alike, ultimately leading to inappropriate decisions and negatively impacting medical care [36].

It is also important to remember that regulatory standards play a significant role in shaping the design of clinical trials. In the United States, regulatory approval of new medicines is based on a demonstration of clinical benefit supported by evidence from well-controlled trials [37]. This requires a thorough understanding of disease progression, the impact of treatment, and the use of various outcomes that reflect patients' multifaceted experience.

An important step towards improving the quality of RCTs is the development and implementation of Core Outcome Sets (COS), which standardize the measurement of outcomes across studies and are described in later sections of this article. The use of COS improves comparability of data and facilitates their synthesis in systematic reviews. Many experts advocate the implementation of COS in clinical trials, as recommended in the guidelines of the Standard Protocol Elements Recommendations for Interventional Trials (SPIRIT), to ensure that the endpoints assessed in trials are relevant to patients and to increase harmonization of their evaluation [38]. This is important and relevant also in allergology, where RCTs of FA treatment have mainly focused on outcomes, that are meaningful to researchers and commercial investors, such as "reactivity threshold" and "immunologic changes" [39].

ENDPOINTS IN RCT OF FOOD ALLERGY THERAPY

When discussing the problems of measuring outcomes in clinical trials of food allergy treatment, it is evident that the lack of standardization and focus on patient-centered outcomes significantly limits the ability to apply the results of studies in clinical practice [4]. First of all, most studies focus on objective indicators such as desensitization and remission, which, although useful from the point of view of the scientific community, does not always reflect the real needs and priorities of patients.

The most frequent outcome assessed in RCTs of FA therapy is desensitization (Table 1) [40]. Desensitization is usually understood as an increase in the patient's tolerance to the food allergen, but this tolerance is maintained only with continuous exposure to the allergen [41]. This outcome is usually demonstrated in a study by increasing the threshold of response to the allergen. In contrast, "remission" implies the absence of clinical response after discontinuation of therapy for a certain period of time [42]. Patients who have achieved desensitization are protected against allergic reactions in case of accidental exposure to the allergen, but they must continue daily treatment, e.g. immunotherapy, and strictly avoid contact with the causative allergen. In case of remission, however, patients can discontinue therapy and freely include the allergen in their diet without restrictions [4].

In RCTs, the increase in allergen tolerance is usually assessed using provocation tests, which are still not very widespread in the Russian Federation. However, attempts to introduce provocative tests into clinical practice are actively being made in various institutions. For example, the feasibility of using provocation testing as a method of diagnosing FA in children is currently being evaluated as part of the

Table 1. **Examples of clinical trials for the treatment of food allergy in children and the outcomes used to assess the effectiveness of therapy (author's table)**
Таблица 1. **Примеры клинических исследований по лечению пищевой аллергии у детей и исходов, используемых для оценки эффективности терапии (таблица автора)**

Author, year	Country	Sample size and age	Allergen	Intervention	Treatment duration	Main outcome	Outcome determination
Cohen et al, 2022 [53]	Canada	69 children, median age is 12 years (9–15)	Cow's milk	OIT Dose escalation from 4 ml to 200 ml (equivalent to 8000 mg of cow's milk protein)	Median 24 (17,7–33,4) weeks	Desensitization	Probability of achieving the maintenance dose of 200 mL of cow's milk, given factors such as sIgE levels to milk, accumulated dose at initiation, and adverse events
Maeda et al, 2021 [54]	Japan	28 children, 3–12 years	Cow's milk	OIT 3300 mg of cow's milk protein (100 ml a day)	1 year	Desensitization	Efficacy of OIT in achieving tolerance to 100 ml of milk, specific IgE levels, adverse events
Palosuo et al, 2021 [55]	Finland	50 children, 6–17 years	Chicken egg	OIT, dose up to 1 g of egg white	8 and 18 months	Desensitization	Tolerance of 1000 mg in 8/18 months, change in levels of specific antibodies (IgE, IgG4, IgA) to egg protein components (Gal d 1-4), adverse events
Fleischer et al, 2019 [56]	USA, Canada, Australia, Germany, Ireland	356 children, 4–11 years	Peanut	EPIT, 250 µg of peanut protein	12 months	Desensitization	Percentage of participants who were able to increase the peanut dose to ⩾300 mg or ⩾1000 mg or more, side effects such as skin reactions and anaphylactic reactions
Takaoka et al, 2019 [57]	Japan	33 children, median age is 6 years	Chicken egg	OIT with low-allergen cookies (79–110 mg of egg white)	4 months	Desensitization	Percentage of "well-responsive" patients (those who passed the food test without allergy to 2 g of cooked egg white), incidence of adverse events

ОИТ, оральная иммунотерапия; EPIT, эпикутанная иммунотерапия; sIgE, специфический иммуноглобулин Е.

study "Provocation tests for polyvalent allergy in the intensive care unit. It is implemented by a team of specialists on the basis of GBHI CSCH № 9 named after G. N. Speransky.

There is some evidence to suggest that OIT induces desensitization in many patients undergoing treatment, and some may experience remission of their allergies.

However, the long-term sustainability of remission remains uncertain and varies from patient to patient. Despite the effectiveness of OIT in increasing allergen tolerance, the impact on patient- oriented outcomes such as quality of life remains poorly understood. It is still not fully understood whether OIT improves the life quality of patients receiving therapy.

In a meta-analysis of 12 RCTs published in The Lancet, it was noted that although OIT given to patients with peanut allergy effectively increases the threshold of allergen response in a controlled clinical setting, it does not reduce the incidence of allergic reactions and anaphylaxis in real life [43]. On the contrary, the study demonstrated that OIT increases the relative risk of anaphylaxis (RR 3.12) and the use of adrenaline (RR 2.21) compared to allergen elimination or placebo. This highlights the contradiction between the desensitization achieved and the actual clinical results, such as the incidence of allergic reactions. In addition, the results of the study have shown that OIT does not improve the quality of patients' lives. This conclusion is based on the analysis of two RCTs that used the parent-child quality of life questionnaire (FAQLQ). The findings showed that there was no significant difference in the improvement of quality of life between patients receiving OIT and the control group who were on an elimination regimen.

Although there are a number of validated qualities of life assessment tools specifically designed for patients with FA, their use in RCTs remains inconsistent, and when they are used, it is not with the same rigor as for assessing clinical and intervention safety outcomes. In particular, several large studies only reported changes in quality of life in the active treatment group, without comparing these changes with the placebo group [44]. This aspect is important, as participation in RCTs may itself have significant benefits due to the so-called placebo effect.

To date, only a very small number of randomized placebo-controlled trials have provided data comparing post-treatment quality of life measures between active and placebo groups [45]. At the same time, there is increasing evidence that clinical conditions (directly native FA, desensitization without remission and remission) as well as the ability to freely consume the allergen without restrictions are closely associated with quality of life in food allergy [46].

It has also been found that the amount and frequency of allergen consumption may affect quality of life measures. In the PPOIT-003 peanut OIT clinical trial, children who were in remission and able to freely consume peanuts showed a significant improvement in quality of life 12 months after completion of treatment compared to those who were desensitized but had to continue daily intake of a fixed allergen dose [46].

HARMONIZING OUTCOMES IN FOOD ALLERGY STUDIES

COS are standardized sets of outcomes that should be measured and reported in all clinical trials for a particular disease or condition [5]. These sets include the most important and relevant outcomes that are meaningful to both researchers and patients. COSs play a key role in ensuring comparability and consistency of data between different studies, which ultimately improves the quality of medical decisions and clinical practice.

The need to develop and implement COSs is driven by several important factors. First of all, they allow researchers to compare and pool data from different studies, since all studies use the same key outcomes. This is particularly important for meta-analyses and systematic reviews that form the basis for clinical guidelines. Without a standardized set of outcomes, results from individual studies can be hard to compare, making it difficult to build a robust evidence base.

In addition, COSs help prevent publication bias, where researchers may choose to publish only those outcomes that are statistically significant or interesting, ignoring other important data [34]. COS also helps to ensure that all key outcomes are measured

and reported, which improves the quality of reporting and reduces the risk of distorted information.

Another important reason to implement COS is patient- orientedness

Another important reason to implement COS is patient-centeredness and the inclusion of the patient in the decision-making process. COSs are usually designed involving not only researchers, but also patients, clinicians and other parties concerned. This ensures that studies include outcomes that matter most to patients, such as quality of life, functional ability, and other aspects that directly affect people's well-being. The inclusion of patient-centered indicators helps to better understand how treatment affects patients' daily life [47].

The development of COS for RCTs of allergic diseases is actively pursued. Atopic dermatitis is probably the most developed nosology. The development of COS for eczema, or atopic dermatitis, was undertaken as part of the international Harmonization of Outcome Measures for Eczema (HOME) initiative launched in 2010. The goal of this initiative was to create a standardized set of outcomes that could be used in all clinical trials for atopic dermatitis. The COS for atopic dermatitis includes key outcomes that should be measured and recommends specific tools to assess these outcomes [48].

In the first stages, the COS developers focused on determining which aspects of the disease should be measured in the RCT. The primary outcomes chosen were: clinical symptoms (e.g. itching and sleep loss), clinical signs (skin inflammation), quality of life, and long-term disease control. An important feature of the process was patient participation, which made COS more patient-oriented, taking into account not only medical but also psychological and social aspects of the disease [48].

For each of the main outcomes, appropriate measurement tools were selected. For example, the Patient-Oriented Eczema Evaluation Measure (POEM) scale, which has proven valid and reliable in various studies, was chosen to assess symptoms. The Eczema Area and Severity Index (EASI) was recommended to assess clinical features, and the Dermatology Quality of Life Index (DLQI) and its pediatric and infant versions were recommended to measure quality of life (CDLQI и IDQoL).

These tools allow to standardize the results of clinical trials, improving the possibility of data comparison and subsequent analysis [49, 50].

COS development processes for FA research have been initiated relatively recently. For example, the results of the eosinophilic esophagitis (EoE) project were published in 2022. The creation of COS was a necessary step due to the significant heterogeneity in the assessment of study outcomes and the lack of harmonized measures that could be used to compare the efficacy of different therapy approaches. COS for EoE, called COREOS, was developed in collaboration with international experts including gastro-enterologists, allergists, pathomorphologists, nutritionists and patients.

During the development of COS for EoE, four key outcome domains were identified that should be considered in every study: histopathology, endoscopy, patient-reported symptoms, and EoE-specific quality of life. These outcomes were selected as the most important for assessing treatment efficacy. For example, histologic changes, such as the number of eosinophils in esophageal tissue, and endoscopic parameters, such as the Endoscopic EoE Reference Evaluation Scale (EREFS) score, play an important role in determining disease activity. Simultaneously, subjective data such as improvement in dysphagia symptoms and improved quality of life have also been found to be critical for patients, highlighting the need to consider not only biomarkers but also patient- oriented outcomes in clinical trials [51].

Table 2. **Outcomes and their definitions used in the Core Outcomes for Food Allergy (COMFA) consensus process [52]**
Таблица 2. **Исходы и их определения, использовавшиеся в рамках консенсусного процесса основные меры оценки исходов для пищевой аллергии (COMFA) [52]**

Outcome	Outcome determination
Adherence	The degree to which the individual is following agreed upon treatment for food allergies (e.g., taking medication, following a diet and/or adhering to/changing lifestyle).
Concomitant allergic diseases	Occurrence of new concomitant allergic diseases or change in the degree of control of current concomitant allergic diseases such as eosinophilic esophagitis, eczema, asthma, allergic rhinitis, etc., with or without exposure to food containing the causative allergen.
Allergic symptoms	Onset and incidence of allergic symptoms (tingling and itching; raised itchy blisters (urticaria); swelling of the face, lips (angioedema), throat and other parts of the body; difficulty swallowing; wheezing or shortness of breath; hoarse voice; sensation of dizziness, confusion, nausea or vomiting, dysphagia; abdominal pain or diarrhea; anaphylaxis; manifestations of allergic rhinitis such as runny nose (rhinitis), itchy eyes (allergic conjunctivitis) associated with intentional or unintentional consumption of food containing the causative allergen.
Desensitization	The ability to consume (as a result of the intervention) a predetermined amount of food containing a trigger allergen without allergic symptoms that bother a person with food allergies. *(This outcome can be assessed either at a specific point in time or at multiple points in time, continuously.)*
Economic impact	Financial consequences associated with medication, food and non-health related expenses due to food allergies. Frequency of visits to health care professionals (e.g., physician, psychotherapist, psychologist), emergency medications, hospital visits or emergency medical calls, including alternative medicine (e.g., acupuncturists, naturopaths); indirect costs (lost time, lost productivity and additional costs due to food allergies); health care system costs.
Behavior as part of food allergy treatment	Degree of confidence, motivation and current knowledge of being able to help manage food allergies (ability to talk about allergies in restaurants, carry emergency medications (such as epinephrine, antihistamines, inhaled steroids)).
Psychological distress associated with food allergies	Anxiety (including phobias), fear associated with food allergies.
Personal and family aspects	Including, but not limited to food intake, preparing meals together, including impact on people who live with the person with food allergies; effect on friends, maintaining and being able to make new acquaintances, build romantic and personal relationships, participate in community life. The impact of food allergies on people who live with the person with food allergies; relationships within the family and with friends.
Remission/sustained non-response	The ability to safely consume (without restriction) foods containing the causative allergen.
Work, study and leisure	The impact of food allergies on work, school, attendance, participation and engagement in various activities.
Satisfaction with the intervention (treatment)	The extent to which the intervention (meaning any type of treatment) has met the expectations of the person with food allergies and their caregivers, family members.
Stigma	Fears or experience of discrimination, bullying, exclusion from any activity, being ignored by employer/school/kindergarten/university, healthcare professional, social group, family/friends/neighbors and others.
Achieving the initial expectations of the intervention (treatment)	The extent to which expectations (beliefs) of the health system intervention (treatment) or interventions will be achieved.
Quality of life	A person's perception of their position in life in the cultural context and in relation to the value system in which they live and in relation to their goals, expectations, standards and concerns. It is a generalized term covering at least physical, mental and social health.

The development of COS for FA research was initiated within the framework of the international study "Core Outcome Measures for Food Allergy" (COMFA). The main objective of this project was to standardize outcomes for clinical trials and observational studies aimed at evaluating interventional tactics for IgE-mediated FA. The study was a Delphi consensus study, involving a variety of participants: patients with FA and their family members, members of the medical community, and researchers.

This has led to the development of a uniform set of key outcomes that should be measured and reported in every FA study [52].

The development process began with a systematic literature review that produced an initial version of the list of outcomes, which was then reduced to 14 outcomes submitted for voting in a consensus process (Table 2). Allergic symptoms and quality of life were considered key for inclusion as endpoints in all FA studies because they reflect the direct impact of allergy on the patient and their daily life.

Other important outcomes, such as desensitization and remission, did not meet the threshold of agreement for inclusion in the core set, but were considered significant and recommended for consideration in separate trials. It is important to note that the results of the COMFA study also emphasize the need for mandatory consideration of adverse events, such as side effects and anaphylaxis, in clinical trials.

CONCLUSION

FA remains a major public health problem, especially in the pediatric population. The mainstay of treatment to date is allergen elimination, but this approach has a significant impact on the quality of patients' and their families' lives. Therefore, current treatment strategies such as oral, epicutaneous and sublingual immunotherapies offer promising alternatives, although they require further development to improve safety and efficacy. The introduction of new techniques, such as the use of monoclonal antibodies (e.g., omalizumab), also opens new horizons in FA therapy.

Standardization of outcomes is an essential step to improve the quality of ongoing clinical trials on the treatment of FA. The use of COS not only improves the quality of studies, but also makes their results more comparable and applicable in practice. COSs facilitate the inclusion of critical outcomes, including allergy symptoms, patient quality of life, and side effects of therapy, which is particularly important in the context of diverse treatments and heterogeneous clinical data.

Further progress in the treatment of FA requires additional research to improve existing therapies as well as to develop new approaches that address both the clinical and psychosocial aspects of the disease. Particular attention should be paid to those outcomes that have been identified as critical by the COS processes that have been implemented.

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Anatoly A. Korsunsky — text evaluation and editing.
Daniil B. Munblit — concept development, idea formation; formulation and development of key goals and objectives, preparation and creation, text evaluation and editing, taking responsibility for all aspects of the work, ensuring the integrity of all parts of the article and its final version, approval of the final version of the article.

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Review / Обзор

Reintroduction of excluded food triggers as a crucial step in managing patients with food allergies

REV — обзорная статья

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Abstract

Introduction. Despite active research into the mechanisms of food allergies (FA), the main approach to managing patients with this condition remains the complete exclusion of causative allergens from the diet for a certain period. At the same time, the question of timely reintroduction of excluded food triggers into the diet is frequently raised, which is important both for maintaining oral tolerance and reducing the negative effects of long-term elimination diets, such as nutritional and eating behavior disorders, as well as financial burdens on families. However, clear recommendations on the reintroduction of previously excluded foods have not existed until recently. Regarding cow's milk protein allergy (CMPA), such recommendations were provided in 2023 in the consensus document of the World Allergy Organization (WAO) — DRACMA.

Aim. The aim of this review is to present current approaches to the reintroduction of food allergens into the diets of patients with food allergies and to evaluate various reintroduction protocols, including those used for cow's milk protein allergy (CMPA).

Material and methods. This review provides a concise summary of current approaches to reintroducing food allergens into the diet, covering both IgE-mediated and non-IgE-mediated forms of food allergy. The advantages of different patient management protocols are discussed, with special attention given to CMPA as one of the most common manifestations of FA in children.

Results. An analysis of modern approaches has demonstrated that modern recommendations regarding the reintroduction of allergens, including those presented in the document of the World Allergological Organization — DRACMA for allergy to cow's milk proteins, allow for a more personalized and safe approach to the reintroduction of allergens, which helps reduce risks and maintain food tolerance.

Conclusions. The introduction of new guidelines for the reintroduction of food allergens is an important step in managing patients with food allergies. These recommendations provide a more personalized approach to treating food-allergic patients, including those with cow's milk protein allergy, reducing the risks associated with reintroducing allergens into the diet. They also help to mitigate the negative effects of elimination diets and maintain oral tolerance in patients, which is particularly important for children with FA.

Keywords: food allergy, cow's milk allergy, children, reintroduction, tolerance

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

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Реинтродукция исключенных пищевых триггеров как важный этап ведения пациентов с пищевой аллергией

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Аннотация

Актуальность. Несмотря на активное изучение механизмов пищевой аллергии (ПА), основным подходом к ведению пациентов с этой патологией остается полное исключение причинно-значимых аллергенов из рациона на определенный период. В то же время постоянно поднимается вопрос о необходимости своевременного повторного введения в рацион исключенных из питания значимых пищевых триггеров, что важно как с точки зрения поддержания оральной толерантности, так и в отношении снижения таких негативных эффектов длительной элиминационной диеты, как нарушение пищевого статуса и пищевого поведения, а также финансового бремени на семью. В то же время четких рекомендаций по реинтродукции (обратному введению в рацион) ранее исключенных пищевых продуктов до недавнего времени не существовало. В отношении аллергии к белкам коровьего молока (АБКМ) такие рекомендации даны 2023 году — в согласительном документе Всемирной аллергологической организации (WAO) — DRACMA.

Цель. Целью данного обзора является изложение современных подходов к реинтродукции пищевых аллергенов в рацион пациентов с пищевой аллергией, а также оценка различных протоколов реинтродукции, включая те, которые применяются при аллергии к белкам коровьего молока (АБКМ).

Материалы и методы. Настоящий обзор представляет собой краткое изложение современных подходов к реинтродукции пищевых аллергенов в рацион, в том числе при различных формах пищевой аллергии — как IgE-опосредованных, так и не-IgE-опосредованных, рассмотрены преимущества различных протоколов ведения пациентов. Особое внимание уделено АБКМ как одной из наиболее распространенных проявлений ПА у детей.

Результаты. Анализ современных подходов продемонстрировал, что современные рекомендации, касающиеся реинтродукции аллергенов, включая те, которые представлены в документе Всемирной аллергологической организации — DRACMA для аллергии на белки коровьего молока, позволяют обеспечить более персонализированный и безопасный подход к реинтродукции аллергенов, что способствует снижению рисков и поддержанию пищевой толерантности.

Заключение. Введение новых рекомендаций по реинтродукции пищевых аллергенов является важным шагом в ведении пациентов с пищевой аллергией. Данные рекомендации позволяют обеспечить более персонализированный подход к лечению пациентов с пищевой аллергией, в том числе к белкам коровьего молока, что снижает риски, связанные с повторным введением аллергенов в рацион, а также способствует уменьшению негативных эффектов элиминационных диет и поддержанию пищевой толерантности у пациентов, что особенно важно для детей с ПА.

Ключевые слова: пищевая аллергия, аллергия к белкам коровьего молока, дети, реинтродукция, толерантность

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INTRODUCTION. Food allergy (FA) is a serious and widespread public health problem worldwide. The prevalence of FA diagnosed on the basis of history and allergy examination varies depending on the diagnostic criteria used, methodological approaches and can range from 0.3% to 6% [1, 2]. Cow's milk protein allergy (CMPA) is the most common and difficult to manage in infants and young children.

Despite a growing body of research into the diagnosis, treatment and finding ways to desensitize to certain food allergens, the mainstay of FA treatment remains the complete elimination of the causative allergen from the diet for a period of time [2, 3, 4]. After

a negative food provocative test, patients are advised to reintroduce the product into their daily diet [2, 4]. Periodic food provocative testing is important because it helps to reduce unnecessary dietary restrictions and helps to maintain oral tolerance. However, once the elimination diet is completed, questions remain about the safe and effective management of patients during the dietary expansion phase. It is noteworthy that despite a negative food provocative test result, up to 44% of children cannot successfully reintroduce a previously eliminated product into the diet in the full age range [5- 7]. The reasons for the failure of reintroduction in children may be atypical symptoms during reintroduction, fear of a repeated allergic reaction, uncertainty about the result of the food provocative test, and formed features of food behavior [5, 7-9].

MANAGEMENT TACTICS FOR CHILDREN WITH CMPA

According to the latest World Allergy Organization (WAO) guidelines, a stepwise approach is recommended for the diagnosis and treatment of suspected mild or moderate CMPA, including an elimination diet and reintroduction of the causative protein (the term reintroduction is used in the English-language literature) both at the diagnostic stage and during the dietary expansion stage [10].

Reintroduction is the process of reintroducing a food previously excluded due to FA into the patient's diet after a negative oral food provocative test. This process is aimed at confirming tolerance to the previously allergenic product and expanding the dietary intake [10, 11].

CMPA is a difficult diagnostic challenge, as both hypo- and hyperdiagnosis are common, both of which can cause adverse health consequences and a heavy financial burden [12]. In the first stage, when CMPA is suspected, a short-term diagnostic elimination diet lasting 2-4 weeks is prescribed. During this period, cow's milk proteins (CMPs) are eliminated from the child's diet and the CoMiss (Cow's Milk-related Symptom Score) tool can be used to quickly assess symptoms associated with milk intake.

CoMiSS — is a rating scale that takes into account skin, gastrointestinal and respiratory symptoms. If the symptoms are completely or significantly resolved, the reintroduction phase of CMP is performed. If symptoms are not resolved, this may indicate that CMPA can be ruled out and other causes of symptoms should be sought. In IgE-mediated FA, food provocative tests should be performed under medical supervision, whereas in non-IgE-mediated FA, reintroduction can be done at home. At the same time, it is not recommended to perform a food provocative test at the diagnostic stage in patients with a history of anaphylaxis or Food Protein Induced Enterocolitis Syndrome (FPIES) if there is no doubt that milk or a specific product is the cause of the allergic reaction [10].

If symptoms return after reintroduction, the diagnosis of CMPA is confirmed and the child is advised to continue on a therapeutic dairy-free diet for 6-12 months. At the end of the therapeutic elimination diet, reintroduction is repeated; if negative, the diagnosis of CMPA is removed and dairy products are reintroduced. If CMPA is confirmed, the patient is reintroduced to a long-term therapeutic dairy-free diet and continues to be monitored, with the possibility of reassessment after 6-12 months. [10].

The DRACMA consensus document, 2023 [10], for the first time provides detailed practical recommendations for the reintroduction of CMP-containing foods into the diet. Prior to reintroduction, a thorough assessment of the patient's medical history, including analysis of provocative test results and the presence of allergic comorbidities, should be performed [10]. The timing for milk reintroduction after a therapeutic elimination diet remains controversial, as no randomized controlled trial has been conducted

to determine this point [10]. With a controlled and safe return of previously excluded foods to the diet, the body can gradually develop tolerance to dietary proteins.

It is believed that the development of food tolerance is modulated by a combination of dendritic, regulatory T and B cells (Treg and Breg), as well as by the participation of the microbiome and the intestinal barrier, which causes a decrease in inflammation [13, 14]. Breg and Treg cells contribute to the production of anti-inflammatory cytokines such as IL-10 and TGF-β, which play an important role in maintaining immune homeostasis, preventing allergic sensitization and promoting tolerance [15]. Whereas prolonged exclusion of a product from the diet can break tolerance and increase the risk of allergic reactions [16].

It is believed that reintroduction should be staged and carefully monitored. Initial doses should be minimized to reduce the risk of allergic reactions [10]. When reintroduction of a causative protein is performed at home, patients and family members should be informed about the reintroduction process, possible allergy symptoms, and first aid measures if reactions occur. Education has been shown to reduce anxiety and increase patient adherence to the process [17]. After successful reintroduction of the product, it is recommended to continue its regular consumption to maintain tolerance [10]. Regular patient follow-up allows timely detection of possible allergic reactions and adjustment of dietary therapy if necessary. The process of reintroducing a food trigger into the diet should be adapted to the individual characteristics of the patient, including age, type and severity of allergic reaction, and the presence of other allergic diseases. An individualized approach helps minimize risk and improve outcomes [10].

As already mentioned, the duration of the therapeutic elimination diet is at least 6 months or until the age of 9-12 months. [10, 18]. The timing of elimination is based primarily on the observation that many infants with CMPA develop tolerance around this age, especially in non-IgE-mediated FA. However, there is little scientific evidence on this topic. In a small study, 80% with food protein-induced allergic proctocolitis (FPIAP), "outgrew" CMPA by 6.3 months, suggesting that dairy products can be reintroduced after 6 months. [18]. However, this requires further investigation as one large study demonstrated an association of FPIAP with an increased risk of developing IgE-mediated CMPA later in life [20]. Prolonged elimination diets, even when they are justifiably prescribed, cause many patients to have difficulty reintroducing excluded foods into their diet [21].

The timing of tolerance development in IgE-mediated FA may be slower than in non-IgE-mediated FA. A food provocative test to establish tolerance is needed in most patients with IgE-mediated FA and FPIES who have been on a strict elimination diet [10].

In the expansion phase, if the causative allergen is reintroduced after an elimination diet, if symptoms return, it is recommended to continue the diet for another 3-6 months. However, there is also no evidence to support this recommendation for the duration of the elimination diet. If increased levels of specific IgE to causative allergens persist, reintroduction is done under medical supervision, especially for severe symptoms. For mild to moderate non-IgE-mediated FA, it is recommended to start with small amounts of allergen, e.g., following the ladder principles [21, 23].

Reintroduction of foods using the "milk ladder" principle, used to gradually introduce food allergens into the diet, is becoming increasingly common.

Table 1. **Reintroduction of cow's milk proteins after a period of therapeutic elimination diet in IgE-mediated food allergy (adapted from Meyer R. et al. [10])**
Таблица 1. **Повторное введение белков коровьего молока после периода лечебной элиминационной диеты при IgE-опосредованной ПА (адаптировано из Meyer R. et al. [10])**

IgE-mediated CMPA		
	Milk ladder	**Whole milk**
Conditions	• Usually under the supervision of a physician in a medical facility • Individual cases may be considered for reintroduction at home • Under 3 years of age • No anaphylaxis or wheezing from any cause • Blister diameter less than 8 mm on milk skin test	• Usually under the supervision of a physician in a medical setting • At the discretion of the physician, the introduction of milk at home may be considered for children who have tolerated baked milk well in the past and have had only mild symptoms when consuming large amounts of whole milk
Pros	• Up to 70% of children who react to whole milk tolerate it in baked goods • High chance of success • Minimizes unnecessary exclusion of milk from the diet when access to nutritional testing is limited	• Simple approach • Short period • Easy to find products
Cons	• Longer process requiring more effort • Some baked products may not be suitable for young children • Children who react to milk in baked products are prone to more severe symptoms and have a higher risk of anaphylaxis	• A more allergenic form of milk may cause more severe symptoms • Children with feeding difficulties may refuse to try new foods in a health care setting and time constraints

Initially, the milk ladder protocol was created for the management of patients with non-IgE-mediated CMPA. However, the DRACMA consensus document provides an analysis of studies conducted in a number of countries, which allowed to develop recommendations for the use of this protocol in other forms of ABKM [10]. The "ladder" protocol can be used for the purpose of reintroduction in non-IgE-mediated PA, such as FPIAP and FPE, as well as in some cases in FPIES (enterocolitis induced by food proteins). In addition, this protocol may also be considered in IgE-mediated forms of FA to assess tolerance and gradually introduce milk protein into the diet after a period of therapeutic elimination diets [10]. The basic principle is to introduce the allergenic product into the diet in a heat-treated form: initially in baked

Table 2. **Reintroduction of cow's milk proteins after a period of therapeutic elimination diet in non-IgE-mediated food allergy, FPIAP, FPE (adapted from Meyer R, et al. [10])**
Таблица 2. **Повторное введение белков коровьего молока после периода лечебной элиминационной диеты при не-IgE-опосредованной ПА (адаптировано из Meyer R, et al. [10])**

Non-IgE-mediated CMPA: FPIAP, FPE		
	Milk ladder	**Whole milk**
Conditions	• Usually conducted in the home • Needs an actively involved family member or caregiver	• Can be carried out at home, as symptoms are usually delayed, e.g. after a few days • Lower GI tract is usually involved: bloody stools, diarrhea, discomfort
Pros	• Start with less allergenic forms of the product, using smaller doses • Milder symptoms	• Simpler approach • Short period • Easy to find the product
Cons	• Longer process • More labor intensive • Some baked goods may not be suitable for babies and young children	• The more allergenic form of milk can cause pronounced symptoms

Table 3. **Reintroduction of cow's milk proteins after a period of therapeutic elimination diet in non-IgE-mediated food allergy, *FPIES* (adapted from Meyer R, et al. [10])**
Таблица 3. **Повторное введение белков коровьего молока после периода лечебной элиминационной диеты при не-IgE-опосредованной ПА, *FPIES* (адаптировано из Meyer R, et al. [10])**

FPIES		
	Milk ladder	**Whole milk**
Conditions	• Usually under the supervision of a physician in a medical setting • Patients with mild symptoms with a history of high milk consumption may be considered for gradual reintroduction at home	• Usually under the supervision of a physician in health care facilities
Pros	• Some children with FPIES on CMP can tolerate milk in baked goods • More gradual introduction, starting at the bottom of the ladder • The home environment is usually more comfortable for infants and parents. • Children are more likely to try a new food in a familiar environment and when there are no time constraints • May cause milder lower gastrointestinal symptoms compared to indomitable vomiting in acute FPIES	• No special preparation of the product with CMP is required
Cons	• It is unclear what percentage of patients with FPIES tolerate milk in baked goods • If the patient tolerates milk in baked goods, another whole/raw milk sample will be needed • Risk of FPIES symptoms at home • Unclear whether symptoms will be milder on baked milk than on whole milk • Long process requiring a lot of effort on the part of the caregiver/parent • Some baked goods may not be suitable for or tolerated by infants and young children. • If introduction is discontinued due to mild non-specific gastrointestinal symptoms, it may cause unnecessary prolonged exclusion of milk from the diet	• Large dose may cause more severe vomiting • Intravenous access may be required and safety may be difficult to ensure • Child may refuse to try new foods in unfamiliar surroundings and time constraints

goods in small quantities, followed by higher doses of the allergen with less heat treatment.

The process of increasing the dose of an allergenic product is slow and gradual. There is no set minimum or maximum time to complete the milk ladder protocol or the duration of each step, as these are adjusted based on individual patient factors, such as the specific clinical manifestations of FA, age, type of allergic reaction and other clinical factors. Children may tolerate clarified milk, milk in baked goods, or yogurt, but continue to react to whole raw milk [24].

In the WAO consensus document, experts for the first time provided a comparative analysis of the features of milk protein reintroduction using the "milk ladder" protocol and open provocative test using whole milk [10]. The document also discusses the pros and cons of these two methods at the stage of reintroduction in different forms of CMPA.

In Ig-E-mediated FA, criteria such as skin results and levels of specific IgE to thermostable proteins can be used to predict a positive food provocative test and tolerated dose. In CMPA, the level of specific IgE to casein is an important predictor, with threshold values ranging from 0.72 to 1.47 kU/L depending on the study. For skin samples, the threshold value is greater than 4.5 mm [25]. In the case of reaction to baked eggs, an important predictor is the level of specific IgE to ovomucoid, which is 1.09 kU/L, and the threshold value of skin tests for egg white is 10 mm [26, 27].

Similar "ladders" are considered for other food allergens. The introduction of wheat, as with the "milk ladder" is often started under medical supervision, especially if there is a history of severe allergic reactions [10]. In some cases where the risk is low, reintroduction can be started at home. The initial phase of introduction involves the use of minimal amounts of the product (e.g., ¼ slice of bread or 10 grams of boiled pasta). Each subsequent phase consists of a gradual increase in the amount of allergen consumed, up to the age-appropriate intake rate [11].

Egg reintroduction is often initiated in a health care facility. Home introduction is possible if the child has previously tolerated heat-treated forms of eggs and has had only mild reactions to them. They start with baked foods such as muffins or bread, where the egg has been subjected to prolonged high-temperature processing, causing a number of proteins to denature and reducing their allergenicity. The next stage involves the introduction of boiled eggs or omelettes, where the eggs are subjected to less processing. The final stage involves the introduction of raw (in a glaze or sauce) or minimally heat-treated eggs [12].

Research continues on the potential use of oral immunotherapy (OIT) for FA, including CMPA. OIT is administered exclusively to patients with IgE-mediated FA and is the preferred method to prevent anaphylaxis and severe reactions from accidental allergen exposure. This method involves daily consumption of gradually increasing doses of allergen in a dose escalation phase, followed by maintenance of a constant dose in a maintenance phase to modulate the specific immune response to milk proteins, according to specifically designed protocols [13, 15].

Despite the differences between published protocols, they share some common key features [15]. Typically, the OIT protocol includes a ramp-up phase in which increasing amounts of milk are administered under the supervision of a physician in a specialized clinical facility properly equipped in case of anaphylaxis develops [16].

The maximum tolerated dose is then taken daily at home. Doses are usually increased either weekly or every two weeks until a certain threshold dose is reached. At this point, the maintenance phase of therapy begins, during which patients usually consume a constant dose of cow's milk and dairy products daily (often the maximum tolerated amount at the end of the build-up phase) [17]. The schedules differ in the number of doses, the product administered (fresh or melted milk mixed with different types of fillers), the amount of milk proteins per dose, the interval between doses and the maintenance dose [13].

CONCLUSION.

Prolonged avoidance of food allergens can cause impaired oral tolerance and an increased risk of allergic reactions. The other side of the problem is the risk of impaired nutritional status and eating behavior of the child. Thus, it is important to investigate strategies to safely reintroduce foods in tolerable amounts to maintain tolerance and improve patients' quality of life. Effective reintroduction should include a stepwise increase in allergen dose under medical supervision to help minimize the risks of developing allergic reactions. An individualized approach based on a thorough assessment of the patient's medical history and characteristics, taking into account age, severity of clinical symptoms, and form of FA, is a key element in successful restoration of food tolerance and gradual expansion of food tolerance and gradual expansion of the diet with previously excluded foods.

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THE AUTHORS' CONTRIBUTION TO THE WORK

Albina A. Galimova — collection and processing of medical documentation; development of the overall concept of the article, preparation of the initial draft.

Svetlana G. Makarova — development of the overall concept of the article, editing and revision of the text.

ВКЛАД АВТОРОВ В РАБОТУ

Галимова А. А. — сбор и обработка медицинской документации; разработка общей концепции статьи, подготовка первоначального текста.

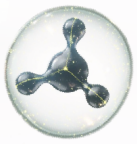
Макарова С. Г. — разработка общей концепции статьи, редактирование и доработка текста.

ИДЕАЛЬНОЙ ПИЩЕЙ ДЛЯ ГРУДНОГО РЕБЕНКА ЯВЛЯЕТСЯ МОЛОКО МАТЕРИ

NAN® ГИПОАЛЛЕРГЕННЫЙ 1

Эффективность, подтвержденная исследованием GINI на протяжении 20 лет[1]

Уникальный частично гидролизованный белок OPTIPRO® HA



- Доказанное снижение риска развития аллергических заболеваний[1]
- Легкое усвоение и переваривание[2]
- Здоровый рост и развитие[3,4]

Пробиотик B. lactis

- Формирование здоровой кишечной микробиоты[5]
- Укрепление иммунитета[6,7]

НА 41% снижение риска развития атопического дерматита к 20 годам[1]

НА 55% снижение риска развития бронхиальной астмы в возрасте 16-20 лет[1]

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ВАЖНОЕ ЗАМЕЧАНИЕ: Мы считаем, что грудное вскармливание является идеальным началом питания для младенцев и полностью поддерживаем рекомендацию Всемирной организации здравоохранения об исключительно грудном вскармливании в течение первых шести месяцев жизни с последующим введением адекватного питательного прикорма вместе с продолжением грудного вскармливания до двухлетнего возраста. Мы также понимаем, что грудное вскармливание не всегда возможно для родителей. Мы рекомендуем медицинским работникам информировать родителей о преимуществах грудного вскармливания. Если родители решают отказаться от грудного вскармливания, медицинские работники должны проинформировать родителей о том, что такое решение может быть трудно отменить и что введение частичного кормления из бутылочки уменьшит количество грудного молока. Родители должны учитывать социальные и финансовые последствия использования детской смеси. Поскольку младенцы растут по-разному, медицинские работники должны посоветовать родителям подходящее время для введения прикорма. Детские смеси и продукты прикорма всегда следует готовить, использовать и хранить в соответствии с инструкциями на этикетке, чтобы избежать риска для здоровья ребенка.

ИНФОРМАЦИЯ ТОЛЬКО ДЛЯ МЕДИЦИНСКИХ РАБОТНИКОВ

Fecal zonulin as a prognostic marker of atopic march in children with food allergy

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Abstract

Introduction. The onset of allergic diseases most often occurs in early childhood with the onset of food allergies, which can subsequently lead to the implementation of the atopic march. Increased intestinal permeability with high production of zonulin, the main moderator of intestinal tight junctions, can be an important link in the development of comorbid allergic diseases.

Material and methods. In order to study the significance of fecal zonulin as a marker for predicting the atopic march in children with food allergy, a cross-sectional retrospective study was conducted on 73 children aged 5 years who were diagnosed with food allergy (FA) to cow's milk proteins in the first year of life. In all children, when the diagnosis was made in the first year of life, the content of zonulin in feces was determined using the ELISA method.

Results. As a result of dynamic observation, all children with food allergy were divided into 2 groups: the first group consisted of children with food allergy who developed allergic rhinitis and/or bronchial asthma within 5 years (group I, n = 39), group 2 consisted of 34 children with food allergy who did not implement the atopic march within 5 years of observation (group II, n = 34). Our study showed statistically significant differences in the fecal zonulin level in the first year of life: group I Me = 2.39 ng/ml (Q1-Q3: 1.78–2.65 ng/ml), group II Me = 1.85 ng/ml (Q1-Q3: 0.49–0.91 ng/ml), p = 0.034. Strong direct correlations were found (Spearman correlation coefficient S = 0.681 ($p < 0.05$)) between the zonulin level in feces at the onset of the disease and the development of allergic rhinitis and/or bronchial asthma up to 5 years of age, the data were confirmed by comparing the areas under the curves during ROC analysis, AUC in the study of fecal zonulin as a prognostic marker of the risk of atopic march in children is 0.887, the optimal threshold (cutoff point) is 1.94 ng/ml.

Conclusions. Fecal zonulin level in children with food allergy can be an effective prognostic marker of atopic march development, its values in feces above 1.94 ng/ml allow us to predict with a high degree of probability the risk of atopic march development in children with food allergy to cow's milk proteins within 5 years.

Keywords: fecal zonulin level, atopic march, food allergy, children, intestinal barrier permeability

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

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Фекальный уровень зонулина как прогностический маркер атопического марша у детей с пищевой аллергией

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Аннотация

Актуальность. Дебют аллергических заболеваний чаще всего происходит в раннем детском возрасте с появления пищевой аллергии, что в последующем может привести к реализации атопического марша. Повышенная проницаемость кишечника при высокой продукции зонулина, основного модератора плотных контактов кишечника, может являться важным звеном развития коморбидных аллергических заболеваний.

Материалы и методы. С целью изучения значимости фекального зонулина как маркера прогнозирования атопического марша у детей с пищевой аллергией было проведено кросс-секционное ретроспективное исследование 73 детей в возрасте 5 лет, у которых на первом году жизни был выставлен диагноз пищевой аллергии (ПА) к белкам коровьего молока. У всех детей при постановке диагноза на первом году жизни в кале определяли содержание зонулина методом ELISA.

Результаты. В результате динамического наблюдения все дети с пищевой аллергией были разделены на 2 группы: первую группу составили дети с пищевой аллергией, у которых в течение 5 лет развился аллергический ринит и (или) бронхиальная астма (I группа, n = 39), вторую группу составили 34 ребенка с пищевой аллергией, которые не реализовали атопический марш в течение 5 лет наблюдения (II группа, n = 34). Наше исследование показало статистически значимые различия в фекальном уровне зонулина на первом году жизни: I группа Me = 2,39 нг/мл (Q1-Q3: 1,78–2,65 нг/мл), II группа Me = 1,85 нг/мл (Q1-Q3: 0,49–0,91 нг/мл), p = 0,034. Выявлены сильные прямые корреляционные связи (коэффициент корреляции Спирмена S = 0,681 (p < 0,05)) между уровнем зонулина в кале в дебюте заболевания и развитием аллергического ринита и (или) бронхиальной астмы до 5 лет, данные подтверждены при сравнении площадей под кривыми при проведении ROC-анализа, AUC при изучении фекального зонулина как прогностического маркера риска реализации атопического марша у детей составляет 0,887, оптимальный порог (точка отсечения) 1,94 нг/мл.

Выводы. Фекальный уровень зонулина у детей с пищевой аллергией может являться эффективным прогностическим маркером развития атопического марша, его значение в кале выше 1,94 нг/мл свидетельствовало о высоком риске развития у детей с пищевой аллергией к белкам коровьего молока аллергического ринита и (или) бронхиальной астмы в течение 5 лет.

Ключевые слова: фекальный уровень зонулина, атопический марш, пищевая аллергия, дети, проницаемость кишечного барьера

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A global burden on health care and the quality of life of patients in general is the widespread increase in the incidence, duration and severity of allergic diseases over the last few decades. Allergic diseases most commonly begin to manifest in young children, with food allergy (PA) being the starter disease, which is becoming more common each year. According to various authors, up to 10% of children in the first year of life are currently suffer from food allergies [1, 2]. It has also been observed that children with FA early in life have an increased risk of developing other allergic diseases later in life, including after the acquisition of immune tolerance to primary food allergens, which contributes to the realization of the atopic march (AM) [3, 4]. AM is characterized by significant costs to the health care

system and to families, and is practically the most expensive allergic condition [5, 6].

A number of authors have found that the development of clinical manifestations of FA in children is preceded by an increase in the permeability of the intestinal mucosa to macromolecules [7, 8]. Thus, the authors pointed out the relationship between increased permeability of the intestinal barrier and the development of allergic diseases of the respiratory system (allergic rhinitis and bronchial asthma); a direct correlation between the severity of diseases and intestinal permeability has been established [7]. This can be explained by the fact that the simultaneous presence of mucosal defects can be observed in many organs, and, in turn, antigenic load and the influence of environmental factors can cause the onset of clinical manifestations of this defect initially in one organ with subsequent accession of symptoms of damage to other organs and systems [9, 10]. For example, the same histologic changes were observed in the mucous membrane of duodenum and bronchi [11, 12].

Currently, only one physiologic mediator responsible for the regulation of intestinal permeability has been determined, and it is human zonulin [13, 14]. Zonulin has been shown to reversibly open tight junctions in protease-activated receptor 2 (PAR2) and epidermal growth factor receptor (EGFR), causing ZO-1 to be displaced from tight junctions. Under physiologic conditions, there is a tight control of mucosal antigen transport (antigen selection) that, in combination with specific immune cells and mediators of chemokines and cytokines, causes anergy and therefore mucosal tolerance [14]. Inadequate production of increased amounts of zonulin and subsequent loss of intestinal barrier function causes antigen transport from the lumen into the intestinal lamina, triggering innate and immunoregulatory reactions, forming a pro-inflammatory microenvironment. If this process continues, an adaptive immune response is determined, causing the production of proinflammatory cytokines, including interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α), which cause further opening of the paracellular pathway and antigen passage, creating a vicious cycle [15]. Moreover, antigen presentation in human macrophages has been shown to be regulated by zonulin.

This changes the cytokine profile and causes the transition from immune tolerance to pathological reactions with the subsequent onset of allergic or chronic inflammatory disease, the nature of which depends on the genetic status of the individual, which determines which organ or tissue will be the target of the inflammatory process [16]. Increased intestinal permeability due to increased levels of zonulin is a key factor in hypersensitivity to exogenous allergens and the realization of atopic march [15–16].

OBJECTIVE of the present study was to investigate the significance of fecal zonulin levels as a marker for predicting atopic march in children with food allergy.

STUDY MATERIAL AND METHODS.

This work is a continuation and addition to the research work carried out by FGBOU VSMU of the Ministry of Health of Russia. Some results of this study were published earlier [17-18]. A cross-sectional retrospective study of 73 children aged 5 years who were diagnosed with food allergy (FA) to cow's milk proteins in the first year of life was conducted. The diagnosis was made in accordance with federal clinical guidelines, recommendations of the European Society of Pediatric Gastroenterologists, Hepatologists and Nutritionists, the European Academy of Allergology and Clinical Immunology, and the European Academy of Allergology and Clinical Immunology. To confirm the diagnosis, sIgE to cow's milk was tested using a PHADIA 250 analyzer (Immuno CAP technology, the range of sIgE measurement to molecular components is from 0.10 to 100 kUA/l). The comparison group consisted of 20 healthy children of the

Table 1. **Mean values, median, interquartile range of fecal zonulin levels in children with food allergy and healthy children (author's table)**
Таблица 1. **Средние значения, медиана, интерквартильный размах фекального уровня зонулина у детей с пищевой аллергией и здоровых детей (таблица автора)**

Zonulin, ng/mL	FA (n = 73)	Control group (n = 20)
Mean	2,18	0,76
Minimum	0,84	0,26
Maximum	4,64	1,51
Mean deviation	0,35	0,19
Median	2,28	0,705
Quartile 1	1,75	0,49
Quartile 3	2,65	0,91

control group, with an unremarkable allergic history. All patients gave written consent to participate in the study.

In all children at diagnosis in the first year of life, the content of zonulin was determined in feces using reagents from Immundiagnostik (Germany) by enzyme-linked immunosorbent assay (ELISA). All children with food allergy were prescribed a strict elimination diet with the exclusion of cow's milk protein. Dynamic follow-up of the patients was carried out for 5 years

The study results were processed on a personal computer using the application program package STATISTICA 13.3 by StatSoft Inc. (USA). Methods of nonparametric statistics were used. Data are presented as median and quartiles (Me (Q1; Q3)). The nonparametric Mann-Whitney test was calculated for comparing quantitative indices, correction for multiple comparisons was performed using the Hill method. Correlation analysis with determination of Spearman correlation coefficient was used to identify the relationship, its degree and significance of differences between the signs. Sensitivity (Se), as well as specificity (Spe) of the identified predictors were assessed using ROC-curves, cutoff thresholds were determined.

RESLUTS. The mean age of the children at the time of diagnosis was 7.0 [4.0-10.0] months, 48 (65.7%) boys and 25 (34.3%) girls. The first symptoms of food allergy occurred in the first six months of life in 50 children (68.5%), with 27.4% (n = 20) in the first three months of life.

The most frequent manifestation of food allergy at the time of diagnosis in our study was gastrointestinal symptoms (regurgitation and vomiting, changes in the nature and consistency of stools, poor weight gain, malabsorption syndrome), which were observed in 78% of children (n = 57). Stools were unstable in 50 children (68.5%), intestinal colic and increased gas formation in 27 children (36.9%), diarrheal syndrome was characteristic of 18 patients (24.7%), constipation in 12 children (16.4%), regurgitation was noted in 49 patients (67.1%), and vomiting in 9 children (12.3%).

Skin symptoms were observed in 49 patients (67.1 %). In the majority of children (n = 42, 57.5 %) skin manifestations were mild, quickly regressed on the background of dietary therapeutic measures and external therapy. In 4 children (5.5 %), the skin syndrome manifested as urethral rashes after consumption of products containing cow's milk; the rashes disappeared independently or with the use of antihistamines.

There was a combination of symptoms of skin lesions and gastrointestinal tract in 45.2% (n = 33) of children, skin symptoms in these children were characterized by more pronounced rashes, torpid to the applied therapy.

Fecal zonulin levels were determined in all children with food allergy during acute clinical manifestations at diagnosis (Table 1). Our study showed a statistically significant (p = 0.014) increase in fecal zonulin in patients with FA (Me = 2.28 ng/mL, Q1-Q3: 1.75-2.65 ng/mL) compared with that of the control group (Me = 0.76 ng/mL, Q1-Q3: 0.49-0.91 ng/mL).

As a result of dynamic observation it was found that tolerance to cow's milk protein was formed by 15.1% of children (n = 11) aged, 41.1% of children (n = 30) aged 3 years, 36.9% of children (n = 27) aged 5 years. In 6.9% of children (n = 5), signs of FA to cow's milk protein persisted 5 years after diagnosis.

Allergic rhinitis developed in 17 children (23.3%), bronchial asthma in 12 (16.4%), and allergic rhinitis and bronchial asthma in 10 (13.7%) during the observation period. 34 children (46.6%) had no comorbid allergic conditions.

We analyzed the initial level of zonulin at the onset of the disease in all observed children depending on the realization of the atopic march. The first group consisted of children with food allergy who developed allergic rhinitis and/or bronchial asthma within 5 years (group I, n=39), the second group included 34 children with food allergy who did not realize the atopic march within 5 years of observation (group II, n=34).

Mean fecal zonulin concentrations in group I children were Me = 2.39 ng/mL (Q1-Q3: 1.78-2.65 ng/mL), in group II children — Me = 1.85 ng/mL (Q1-Q3: 0.49-0.91 ng/mL), in comparison group children were (Me = 0.76 ng/mL, Q1-Q3: 1.38-2.19 ng/mL), p = 0.034. Strong direct correlations (Spearman correlation coefficient S = 0.681 ($p < 0.05$)) were found between the level of zonulin in feces at the onset of the disease and the development of allergic rhinitis and/or bronchial asthma (realization of atopic march).

The following tests were used to evaluate the diagnostic values of the obtained results: diagnostic sensitivity (Se), diagnostic specificity (Sp), predictive value of positive result (PPV), predictive value of negative result (NPV), test accuracy (diagnostic efficiency of the test) (De). The distribution of groups was based on discriminant analysis.

The test result analysis of the analyzed groups revealed the sensitivity of the prediction model at the level of 90.9 %, and specificity — 76.4 %. At the same time, the predictive value of a positive result was 85.7 %, and that of a negative result — 74.6 %.

This suggests that the level of zonulin in feces at disease onset is non-invasive criterion of the risk of atopic march realization in children with food allergy and can be used as an objective prognostic marker indicating the risk of allergic rhinitis and/or bronchial asthma development.

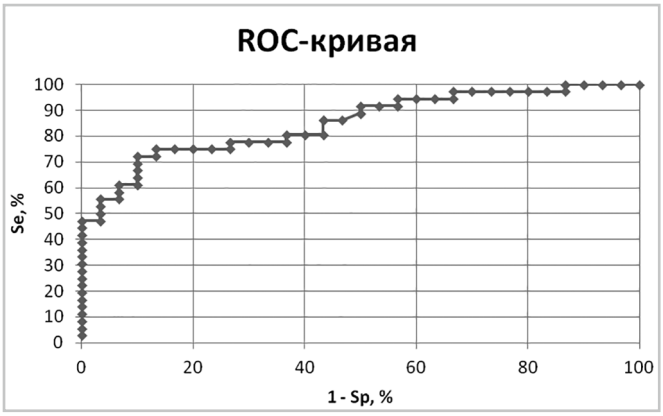

Fig. 1. **ROC analysis when comparing areas under the curves (illustration by the author)**
Рис. 1. **ROC-анализ при сравнении площадей под кривыми (иллюстрация автора)**

These observations were confirmed using ROC analysis when comparing the Area Under Curve (AUC) (Figure 1).

The AUC value in the study of fecal zonulin as a prognostic marker of the risk of atopic march in children is 0.887, the optimal threshold (cut-off point) is 1.94 ng/ml. According to the existing approaches to the evaluation of ROC-analysis results, the AUC value at the level of 0.8-0.9 corresponds to good quality of the model and can be used in clinical practice.

DISCUSSION OF FINDINGS.

The formation of the syndrome of increased epithelial permeability occupies a special place in the pathogenesis of allergic diseases. Disruption of barrier function, caused by defects in dense epithelial contacts, has a systemic effect and allows environmental triggers to penetrate more easily into the respiratory

tract and then interact with immune and inflammatory cells, in fact, being a factor in the realization of systemic allergic inflammation and the formation of atopy march [19, 20]. In continuation of our previous studies [18], we found that in patients with realized atopic march had significantly higher fecal zonulin levels at the debut of food allergy than children who had developed tolerance to cow's milk and had not realized other allergic diseases during 5 years. Zonulin is one of the few physiological mediators of paracellular intestinal permeability and is associated with the development of persistent inflammation. Inadequate activation of zonulin production causes functional loss of the epithelial barrier and causes a tolerance disorder with subsequent development of allergic intestinal diseases [21]. A number of studies have demonstrated that patients with bronchial asthma and allergic rhinitis have higher serum zonulin levels and concomitant increased intestinal permeability [22, 23], prolonged antigenic stimulation of the immune system subsequently causes inflammation of the airways [24].

These data are consistent with the results of a systematic review conducted by Alduray-wish S. A. et al [25], who showed that children with FA had a 2.1-5.3-fold and 1.6-5.1-fold higher risk of allergic rhinitis and bronchial asthma than children without FA, respectively. Moreover, sensitization to food allergens before 2 years of age increased the risk of asthma (pooled odds ratio OR 2.9, 95% confidence interval (CI) 2.0-4.0), atopic dermatitis (pooled OR 2.7, 95% CI 1.7-4.4) and allergic rhinitis (pooled OR 3.1, 95% CI 1.9-4.9) [25]. The authors have convincingly demonstrated that young children with food allergy have a high risk of additional allergic diseases with progression of atopic march. Therefore, preventing the development of atopic march and/or its progression at an early stage is important.

Our study showed that the threshold value of fecal zonulin level of 1.94 ng/mL is effective in predicting the risk of atopic march. This method allows to predict with high probability the risk of atopic march within 5 years in children with food allergy to cow's milk proteins with high sensitivity and specificity and provides an opportunity to carry out preventive measures for patients from the risk group.

The predictive value of the negative test is also high, which allows to predict reliably enough not only high but also low risk of atopic march realization.

Currently, various strategies have been proposed to moderate environmental factors, the microbiome, and to modify nutritional approaches in children at risk for allergy and atopy [25-30]. Given the multifactorial nature of allergic pathology, there are currently no evidence-based recommendations on the efficacy of any specific preventive approaches, but some measures currently proposed and used may indeed reduce the risk of atopic march. The nutrition of children in the first year of life is considered one of the most significant modifiable factors in early life and an important target for personalized interventions to prevent atopic marshes.

In most studies known to date, the protective effect of long-term (more than 6 months of life) breastfeeding has been proven, as it reduces not only the incidence of atopic dermatitis, but also other allergic diseases [25].

Analysis of data from the German Infant Nutritional Intervention (GINI) cohort at 20-year follow-up showed that, if breastfeeding is not possible, interventional use of a formula based on partially hydrolyzed whey proteins (NAN® Hypoallergenic 1, Nestle, Germany) in the first 4 months of life has a significant preventive effect on the risk of atopic dermatitis throughout the 20 years of follow-up, and reduces the prevalence of bronchial asthma and allergic rhinitis [26].

The data obtained in clinical studies by different authors on the possible preventive efficacy of different mixtures based on partially hydrolyzed proteins (pHF-W) served as a basis for rethinking the results of numerous studies on the effectiveness of pHF-W in preventing the development of allergic diseases.

The hydrolysis process of proteins is a key factor determining their biological function involving the formation of specific peptides. Peptide size alone is too simplistic to assess allergenic and tolerogenic potential. The amino acid sequence in peptides, which is directly affected by the method of hydrolysis, plays an important role in their ability to induce an allergic response and/or immune tolerance. The data presented in numerous sources show that not all pHF-Ws are equal with respect to their tolerogenic potential, as different pHF-Ws differ in their peptide composition, which depends on the production technology used for each particular mixture. In this context, the meta-analysis by H. Szajewska and A. Horvath [27], which included randomized trials evaluating the efficacy of a single formula based on partially hydrolyzed whey proteins (NAN® Hypoallergenic 1, Nestle, Germany) for allergy prevention in children, is of particular interest. The data presented in these studies provided further evidence that this pHF-W is tolerogenic and able to reduce the risk of atopic dermatitis in children at risk. Li X. et al. (2024) also found sufficient evidence that pHF-W reduces the risk of eczema in children younger or older than 2 years of age (OR: 0.71; 95% CI: 0.52, 0.96 and OR: 0.79; 95% CI: 0.67, 0.94, respectively). The authors also found moderate systematic evidence indicating that pHF-W reduces the risk of wheezing at age 0-2 years (OR: 0.50; 95% CI: 0.29, 0.85) [28].

A recent experiment evaluated the effect of NAN® Hypoallergenic infant formula (Nestle, Germany) on transepidermal water loss (TEWL) and allergic antibody production in mice dermally exposed to Aspergillus fumigatus [29]. Addition of the mixture to the diet of newborn mice caused a significant reduction in TEWL and total IgE, and aquaporin-3 gene expression, which is associated with skin hydration, was found to be modulated in mouse skin and human primary keratinocytes after exposure to pHF-W. Improvement of the skin barrier may be an additional mechanism by which pHF-W in NAN® Hypoallergenic formula may potentially reduce the risk of atopic march.

One of the key questions in developing preventive strategies for atopic march is to promote effective immunologic tolerance when introducing potentially allergenic foods into the infant's diet. As a result of several intervention studies, a scientific consensus is developing that earlier (but not earlier than 4 months of age) introduction of these foods may be recommended to improve prognosis and prevent the development of atopic marsch [31].

Thus, the global increase in allergic diseases significantly reduces the quality of life and necessitates the search for new approaches to their treatment and prevention. The atopic march theory facilitates our understanding of the pathophysiology of allergic disease comorbidity and further contributes to the early detection, prevention and treatment of children at risk of atopic march progression. Our study demonstrated the feasibility of investigating fecal zonulin levels to predict the risk of atopic marsch realization. Further studies are needed to validate and standardize the threshold value of zonulin as a biomarker of allergic inflammation. Currently, therapeutic and preventive strategies for food allergy are shifting from a "passive" elimination diet to an "active dietary therapy" that can shorten the duration of the disease and protect against the onset of an atopic march.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted taking into account the requirements of the Helsinki Declaration of the World Association "Ethical Principles of Conducting Scientific Medical Research with human Participation" as amended in 2000 and the "Rules of Clinical Practice in the Russian Federation" approved by Order of the Ministry of the Russian Federation dated 06/19/2003, No. 266. This study was approved by the Interdisciplinary Local Ethics Committee of the Pacific State Medical University of the Ministry of Health of the Russian Federation.

ЭТИЧЕСКОЕ ОДОБРЕНИЕ И СОГЛАСИЕ НА УЧАСТИЕ

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THE AUTHORS' CONTRIBUTION TO THE WORK

Nelly G. Prikhodchenko — conceptualization, formal analysis, investigation, visualization, writing — original draft.

Tatyana A. Shumatova — conceptualization, formal analysis, investigation, visualization, writing — review & editing.

Darya V. Kovalenko — investigation, conducting a research and investigation process, specifically performing the experiments, and data/evidence collection. Specifically writing the initial draft (including substantive translation). Provision of study materials, and patients.

ВКЛАД АВТОРОВ В РАБОТУ

Приходченко Н. Г. — разработка концепции, формирование идеи; формулировка и развитие ключевых целей и задач, анализ и интерпретация полученных данных, применение статистических и математических методов для анализа и синтеза данных исследования, подготовка и создание, оценка и редактирование текста, принятие ответственности за все аспекты работы, целостность всех частей статьи и ее окончательный вариант.

Шуматова Т. А. — развитие ключевых целей и задач, проведение исследований, в частности сбор данных, ресурсное обеспечение исследования, утверждение окончательного варианта статьи, контроль и ответственность руководства за планирование и проведение научной деятельности.

Коваленко Д. В. — проведение исследований, в частности сбор данных, участие в научном дизайне, ресурсное обеспечение исследования, предоставление пациентов, лабораторных образцов для анализа, утверждение окончательного варианта статьи.

TREC and KREC values in patients with congenital heart defects — neonatal screening data

RAR — научная статья

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Abstract

Relevance. Children with congenital heart disease (CHD) are at high risk of infectious complications with unfavorable outcomes, which is associated with inadequate immune responses. TREC and KREC are recognized biomarkers of T- and B-cell lymphopoiesis.

Objective of the study: to evaluate the number of circular DNA segments — TREC and KREC in children with congenital heart defects.

Materials and methods. The study used data from neonatal screening for primary immunodeficiencies in the Stavropol region from January 1, 2023, to June 30, 2024. An analysis of TREC and KREC was conducted in 43 newborns with CHD compared to healthy infants.

Results. The levels of TREC and KREC in children with CHD were lower than in healthy children. A correlation was established between TREC levels and absolute lymphopenia, as well as the development of infectious complications. A decrease in KREC was identified in infants with CHD and genetic syndromes. It was shown that a TREC level of less than 650 copies per 10^5 cells may be a predictor of the development of infectious complications in newborns with CHD.

Conclusions. The reduction in the number of TREC and KREC copies in neonatal screening allows for the identification of children with CHD at high risk of infection, opening potential opportunities for preventive therapy.

Keywords: congenital heart defects, TREC, KREC

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

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Показатели TREC и KREC у пациентов с врожденными пороками сердца. Данные неонатального скрининга

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Аннотация

Актуальность. Дети с врожденными пороками сердца (ВПС) имеют высокий риск инфекционных осложнений с неблагоприятным исходом, что связано с неадекватным иммунным ответом. TREC и KREC являются признанными биомаркерами Т- и В-клеточного лимфопоэза у новорожденных.

Цель исследования: оценить количество кольцевых участков ДНК — TREC и KREC у детей с врожденными пороками сердца.

Материалы и методы. При проведении исследования использовались данные неонатального скрининга на первичные иммунодефициты в Ставропольском крае за период с 01.01.2023 по 30.06.2024. Осуществлен анализ TREC и KREC у 43 новорожденных с ВПС по сравнению со здоровыми младенцами.

Результаты исследования. Показатели TREC и KREC у детей с ВПС были ниже, чем у здоровых детей. Установлена связь уровней TREC с абсолютной лимфопенией, развитием инфекционных осложнений. Определено снижение KREC у младенцев с ВПС и генетическими синдромами. Установлено, что уровень TREC менее 650 копий на 10^5 клеток может быть предиктором развития инфекционных осложнений у новорожденных с ВПС.

Выводы: уменьшение числа копий TREC и KREC в неонатальном скрининге позволяет выявить детей с ВПС с высоким риском инфицирования, открывая потенциальные возможности для профилактической терапии.

Ключевые слова: врожденные пороки сердца, TREC, KREC

Конфликт интересов:
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Relevance. Excision rings of T-cell receptor rearrangement genes (TREC) and k-deletion excision circles (KREC) are formed during differentiation of immune cells in the territory of central organs of immunopoiesis at the stage of forming their antigen-recognizing repertoire and are markers of newly formed T- and B-lymphocytes [1, 2]. Multiplex real-time PCR assay of TREC and KREC is used in neonatal screening in many countries of the world to diagnose severe combined immune deficiency (SCID) and other congenital immune errors in newborns [1, 2]. In addition to TCIN, TREC detection can identify other forms of T-cell lymphopenia (TCL), including Di Giorgi, CHARGE, Jacobsen, Louis-Bar, Wiskott-Aldrich McKusick, Noonan, Down syndromes, as well as secondary TCL in infants with cardiac, gastroin-

testinal, neonatal leukemia, and profound prematurity syndromes [3, 4, 5, 6]. It has been shown that non-TREC TCL are 3-4 times more common than TREC [3, 7]. A high percentage of children with abnormal TREC indices have congenital heart disease (CHD) [3, 7].

It is known that infants with CHD suffer from frequent infections with a high risk of complications and fatal outcomes [8]. Clinical trials demonstrate low levels of T-lymphocytes and their subpopulations in children with CHD, which confirms the important role of TCL in the development of infectious complications [8, 9]. It has been previously shown that reduced TREC copy number in newborns may be associated with heart defects [3, 5, 7, 10]. However, the prevalence of T-cell lymphopenia in children with CHD has not been fully determined.

STUDY OBJECTIVE: evaluate the results of neonatal screening (TREC, KREC) in children with congenital heart disease.

MATERIALS AND METHODS. We conducted a single-center retrospective cohort study including infants with diagnosed structural CHD born in Stavropol Krai between 01.01.2023 and 30.06.2024. Patients were selected on the basis of Stavropol Clinical Perinatal Centers #1 and #2, as well as the Department of Pathology of Newborns and Prematurity of the Regional Children's Clinical Hospital of Stavropol city. The diagnosis of congenital heart disease was determined in accordance with clinical guidelines on the basis of clinical and instrumental data taking into account ICD-9. The archival case histories of patients were analyzed. Infants with CHD born at gestational age of more than 34 weeks were included in the study; infants with other causes of secondary lymphopenia, including profound prematurity, GI malformations, neonatal leukemia, and those born to HIV-infected mothers and mothers who received immunosuppressive therapy during pregnancy were excluded.

The results of TREC and KREC in 43 children with CHD and 100 healthy children were obtained

during neonatal screening and provided by the neonatal screening laboratory of the Stavropol Krai Clinical Perinatal Center (SKCCPC). Blood was collected at the age of 24-48 h from preterm neonates and 144-168 h from premature neonates (Order of the Ministry of Health of the Russian Federation from 21.04.2022 № 274N.) The study was approved by the Local Ethical Committee of StSMU. Parents of patients signed informed consent for participation in the study.

TREC and KREC were determined at the research center of the S. V. Ochapovsky Krai Clinical Hospital No. 1 (Krasnodar) by real-time quantitative polymerase chain reaction for analysis of dried blood spots. TK-SMA" test systems of Generium were used.

A threshold level of TREC and KREC of less than 100 per 100,000 cell copies was considered criteria for a positive result for SCID and other inborn errors of the immune system according to the screening procedure [11].

If low levels of TREC/KREC were obtained, the first stage of confirmatory diagnostics was performed on a test form in the Federal State Budgetary Scientific Institution "Medical and Genetic Research Center named after Acad. N. P. Bochkov". In newborns with abnormal TREC/KREC, according to the retest data, extended immunophenotyping (IPT) was performed in the immunologic laboratory of the Dm. Rogachev MDRC and molecular genetic study with determination of 22q11.2 and 10p14 deletion, as well as exome (NGS) and, if necessary, full exome (WGS) sequencing in the N. P. Bochkov Medical and Genetic Research Center. Patients with one or more IFT indices below the reference values (CD3 < 1500 kL/μL, CD3CD45RA < 60%, CD19 < 400 kL/μL) in the absence of pathogenic variants in the primary IDS genes were referred to the secondary lymphopenia group [11].

Statistical analysis of the data was performed using Statistica 10 software. Demographic data as well

as excision ring indices of rearrangement genes were presented using descriptive statistics in the form of median and interquartile range. The Mann-Whitney U-criterion was used to compare TREC and KREC values. ROC curve analysis was used to assess the significance of TREC/KREC as predictors of infectious complications. Values of $p < 0.05$ were considered statistically significant.

STUDY RESULTS. 43 infants (25 boys and 18 girls) with heart defects enrolled in a neonatal screening program for 1.5 years were included in the study. Cyanotic heart defects were verified in 5 (11.6%) infants, including tetrad of Fallot (2), single ventricle of the heart (1), and transposition of the main vessels (2). Among noncyanotic defects, aortic coarctation was diagnosed in 7.9 %, aortic valve stenosis in 10.5 %, atrial septal defects in 21.1 % and interventricular septal defects in 44.7 %, atrioventricular communication (7.9 %), and ductus arteriosus (7.9 %). In 9 (20.9 %) cases CHDs were found in the structure of genetically determined diseases: Edwards syndromes — 4.6 %, Aper syndromes — 2.3 %, Down syndromes — 13.9 %. Surgical treatment was performed in 15 (34.9%) patients.

40 children were born prematurely (gestational age ⩾37 weeks) and three were moderately premature (32-36 weeks). 9 (20.9%) children had low birth weight relative to gestational age. Hypoxic-ischemic encephalopathy (HIE) of moderate severity was diagnosed in 28 (65.1%) newborns, and severe HIE with development of IVH was diagnosed in 2 (4.7%). Serious infections developed in 28 (65.1%) infants, including pneumonia in 25 (58.1%), bronchiolitis/bronchitis in 1 (2.3%), necrotizing enterocolitis in 1 (2.3%), urinary tract infections in 5 (11.6%), and skin infections in 2.3%. (1).

Abnormal TRECs (less than 100 copies per 10^5 cells) were obtained in 2 children, representing 22.2% of 9 cases of secondary lymphopenia verified in SK within 1.5 years (01.01.23 to 01.07.24).

Patient 1. He was born at 39 weeks of gestation, with signs of asphyxia, grade 2 DN, hospitalized in the ORIT. A CHD was diagnosed in the newborn period: pulmonary artery stenosis, a functioning oval window. In the framework of neonatal screening low KREC number — 70 copies per 100 thousand leukocytes was detected and confirmed by retest. The hemogram at the age of 3 weeks of life revealed moderate lymphopenia — 2900 cells/μL. According to immunophenotyping data, normal content of CD3 — 2700 kl/μl, CD4 — 2300 kl/μl, CD8 — 490 kl/μl, significant decrease of CD19 — 50 kl/μl, and signs of transient infantile hypoimmunoglobulinemia (IgA — 0 g/L, IgG — 3.16 g/L, IgM — 0.51 g/L) were determined. Molecular genetic study revealed no clinically significant mutations by full-exome sequencing. The child underwent neonatal pneumonia, and there were no serious infectious diseases in the subsequent period. Lymphopenia resolved at the age of 3 months.

Patient 2. The boy was born prematurely at the 34th week of gestation with a weight of 1490 g and an Apgar score of 4. At the 22nd week of pregnancy, cordocentesis and karyotyping were performed, and Edwards syndrome was verified. At birth the condition was severe due to cardiovascular insufficiency, DN 2-3rd stage, hypoxic-ischemic encephalopathy 2nd stage. CHD of high complexity category was confirmed: common atrioventricular canal. The patient had a ASD (3.5 mm), VSD (5 mm), PDA (2.5 mm) with signs of pulmonary hypertension. The results of NS after the post-conceptional age of 37 weeks revealed low KREC — 96 copies per 100,000 cells. IFT results revealed normal CD3 counts of 3474 cells/μL, CD3CD4CD45RA counts of 1844 cells/μL, and low CD19 counts of 132 cells/μL. No clinically significant mutations were detected according to WGS data.

During 4 months of observation there were continuously recurrent bacterial infections (pneumonia, omphalitis, enterocolitis, otitis media, pyoderma), lack of weight gain, cytopenic syndrome (platelet count 50-90*10^9/l, anemia of 2-3rd degree), need for continuous antibacterial and antifungal therapy. During the monitoring of humoral immunity factors the decrease of serum immunoglobulins was determined (IgA — 0.1 g/l, IgG — 2.9 g/l, IgM — 0.35 g/l). He is in the intensive care unit of SKCPC, prognosis is doubtful.

When evaluating the screening results in the general CHD group, a statistically significant decrease in TREC — 1198 [698; 1717], ($p<0.05$) and KREC — 954 [587; 1253] copies per 10^5 cells, $p<0.01$ compared to healthy children was revealed (Fig. 1, 2). A decrease in TREC values in newborns with cyanotic CHD, genetic diseases in combination with CHD was determined, as well as in children with lethal out-

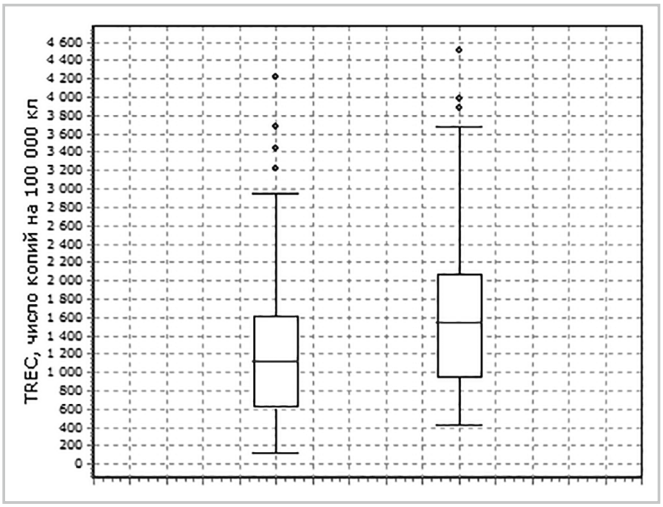

Fig. 1. **TREC indicators in children with congenital heart defects (illustration by the author)**
Рис. 1. **Показатели TREC у детей с врожденными пороками сердца (иллюстрация автора)**

Note: p — differences compared to healthy children (Mann — Whitney test)

Примечание: p — различия по сравнению со здоровыми детьми (критерий Манна — Уитни)

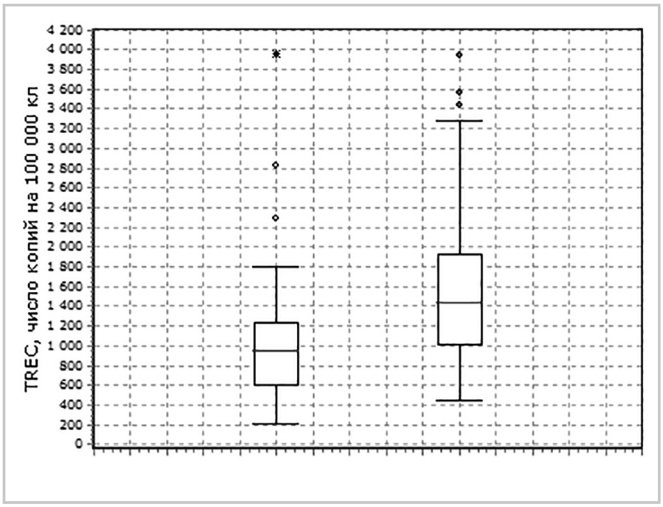

Fig. 2. **KREC indicators in children with congenital heart defects (illustration by the author)**
Рис. 2. **Показатели KREC у детей с врожденными пороками сердца (иллюстрация автора)**

Note: p — differences compared to healthy children (Mann — Whitney test)

Примечание: p — различия по сравнению со здоровыми детьми (критерий Манна — Уитни)

come (Table 1). However, due to the small number of groups, the differences were not statistically significant. As expected, TREC content was significantly lower in infants with lymphopenia (lymphocyte level less than 3000 cells/μL) — 729.0 [567.0; 1332.0] copies per 10^5 cells, p = 0.049.

KREC copy number was lower in newborns with CHD in the genetic disease pattern (1180.5 [573.5; 1579.5] copies per 10^5 cells, p = 0.04) compared to children with CHD without genetic syndromes. No statistically significant difference was obtained depending on the type of CHD, outcome of the disease.

TREC values were found to be decreased in newborns with CHD and infectious complications, 923 [563; 1245] when compared to the group without infectious episodes — 1877 [1427; 2855] copies per 10^5 cells, p = 0.001. Similar patterns were found when analyzing KREC, 708.5

Table 1. **TREC and KREC indicators in newborns with heart defects, depending on demographic characteristics (author's table)**
Таблица 1. **Показатели TREC и KREC у новорожденных с пороками сердца в зависимости от демографической характеристики (таблица автора)**

Indicators	Genetic disease		Lymphocyte count		Nature of CHD		Outcome	
	with n = 8	without n = 35	>3000 kl/μl n = 14	<3000 kl/μl n = 29	with cyanosis n = 5	without cyanosis n = 38	alive n = 39	died n = 4
TREC, copies /10^5 cells	1180,5 [573,5; 1579,5]	1201,0 [702,0; 1800,0]	1233,0 [923,0;1 910,0]	729,0 [567,0; 1332,0]*	1201,0 [702,0; 1483,0]	1359,0 [694,0; 1800,0]	1198,0 [702,0; 1800,0]	959,5 [520; 1891,5]
KREC, copies /10^5 cells	533,5 [417,0; 792,5]**	1020,0 [632,0; 1451,0]	813,5 [585,0; 1514,0]	1020,0 [619,0; 1245,0]	954,0 [798,0; 1260,0]	944,0 [563,0; 1245,0]	943,0 [792,5; 2507,5]	954,0 [563,0; 1260,0]

Note: * — the reliability of differences in indicators depending on the number of lymphocytes, ** — the reliability of differences in indicators in children with and without genetic diseases, p < 0.05 (Mann — Whitney criterion)

Примечание: * — достоверность различий показателей в зависимости от числа лимфоцитов, ** — достоверность различий показателей у детей с генетическими заболеваниями и без них, p < 0,05 (критерий Манна — Уитни)

[430.3; 1047.8] and 1260 [954; 1747] copies per 10^5 cells, respectively, p = 0.01. By ROC analysis, a decrease in TREC of less than 650 copies per 10^5 cells was able to predict infectious complications in newborns with CHD (OR, 10.1; CI 2.35-43.3, p = 0.049) with sensitivity (87.4%), specificity (64.7%), positive (78.7%) and negative (73.3%) predictive value (AUC, 0.87).

A decrease in KREC less than 580 copies per 10^5 cells increased the risk of infectious complications in neonates with CHD (OR, 10.9; CI 2.34-51.2, p = 0.067), but the level of statistical significance was higher than 0.05.

DISCUSSION. Despite modern achievements in the therapy of congenital heart disease, children with CHD have a high risk of infectious morbidity and mortality during the newborn period [9, 12, 13]. It has been determined that structural CHD is accompanied by a decrease in the number and maturity of immune cells, decreased differentiation of T-lymphocytes in the thymus, IgG and IgA deficiency [14, 15]. Such features of immune status determine the increased incidence of RS-infection, increasing the risk of bronchopneumonia and bronchiolitis with lethal outcome at least 25 times [15].

It has been shown that CHD predispose to the development of sepsis and prolonged ALV, which is due not only to changes in the small circulation but also to immune compromise [16]. Routine thymectomy in the correction of CHD may exacerbate T-cell lymphopenia and sensitivity to infections subsequently [17, 18].

In the present study, newborns with CHD were found to have lower levels of TREC and KREC compared to healthy infants in our cohort, as well as when compared to reference values obtained previously using reported test systems [19].

Abnormal TREC indicators were detected in 2 (4.7 %) children who did not have molecular genetic features of primary IDS. Their share in the structure of secondary lymphopenia according to the results of NS in the region amounted to 22.2%.

A pattern of decreased TREC in patients with low absolute lymphocyte counts was obtained.

According to other research centers, the share of congenital heart defects in the structure of secondary lymphopenia ranges from 24 to 40% [1, 7, 20]. In the work by K. Kennedy et al. abnormal TREC levels (below the threshold values defined for PID) were determined in 0.99% of newborns with CHD [21].

In 9 children with CHD with a verified genetic defect (Down, Edwards, Aper syndromes), a reduced KREC copy number was found compared to infants with CHD without genetic syndromes. At least 13 diseases combining heart defects and genetically determined immunodeficiency are known, including Down syndromes [22, 23], Di Giorgi [24, 25, 26], Kabuki [27, 28], Turner [15], congenital asplenia [29]. TREC and KREC have been found to be decreased in these diseases [22, 24].

Some of the genes (CHD7, FOXN-1, GATA4, JAG1, NKX2, TBX1) associated with CHD play a key role not only in cardiac morphogenesis but also in thymus development [30]. Thus, haplonephrectomy of TBX1, a key gene in Di Giorgi disease, contributes to the development of heart defects, hypoplasia of the thymus and parathyroid glands, controlling the expression of almost 2000 genes [31, 32].

Most patients with Down syndrome have a small thymus with an abnormal structure [22]. Altered myelo- and lymphopoiesis causes a decrease in T- and B-cells in 90% of children [34]. Changes in microRNA expression in immune cells, increased signaling from TLR2 causing immune dysregulation are considered as potential mechanisms for the development of IDS [34]. Low TREC copy number in newborns with Down syndrome reflects a decrease in the differentiation of T-lymphocytes in the thy-

mus and their transport into the peripheral bloodstream [22].

Fundamental studies of recent years have been devoted to the study of the relationship between congenital heart defects and immune defects [9, 15, 35]. It has been shown that the embryonic development of thymus and heart are united by common precursor cells — neural crest cells involved in the development of the cardiovascular system, as well as the thymus capsule and pericytes [35]. Loss or dysregulation of neural crest cell signaling pathways contributes to both heart defects and thymic hypoplasia [35, 36].

In addition, perinatal risk factors such as medications, cigarette smoking, gestational diabetes mellitus, malnutrition or congenital infections are associated not only with the development of heart defects but also with intrauterine thymus atrophy [37, 38]. The defect in T-lymphocyte development in neonates with CHD is reflected in the peripheral compartment of immunocompetent cells [9]. Patients with heart defects and thymus atrophy have low numbers of T-lymphocytes, as well as naive T cells (RTE) that have recently completed intrathymic development and migrated into the peripheral bloodstream [9]. Low RTE counts correlate with reduced TREC levels [5, 39, 40].

In the study by B.T. Davey et al. study, the median TREC level in newborns with CHD was significantly lower than in the population [14]. Patients with CHD requiring hospitalization for an infectious disease had lower TREC values compared to children without infectious complications [14], which is consistent with our findings.

Low TREC values have been found in neonates with severe critical heart disease [35, 41, 42]. It has been determined that abnormal TREC and KREC can be used as predictors of potentially fatal infections in premature infants with CHD [14, 43].

Unlike other studies [41, 42, 44], we did not obtain statistically significant differences depending on the type of CHD and its severity, which may be due to the insufficient number of subjects in the groups with cyanotic heart defects and deceased children.

It should be considered that routine thymectomy early in the course of CHD correction may exacerbate T-cell lymphopenia and immune compromise in infants with low TREC at birth and worsen prognosis [17, 18].

CONCLUSION. Thus, TREC and KREC copy number reduction is observed in neonates with heart defects, which makes it possible to identify patients at high risk of infectious complications.

A reduction in TREC copy number below 650 copies per 10^5 cells in neonatal screening allows identification of children with CHD at high risk of infection, opening potential opportunities for preventive therapy.

Children with CHD and identified secondary lymphopenia may be recommended prophylactic courses of antimicrobial agents, immunoglobulin replacement therapy, use of palivizumab, and thymus preservation during correction of CHD [14].

Limitations of the present study include the retrospective design, small number of subjects, and short follow-up interval.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted taking into account the requirements of the Helsinki Declaration of the World Association "Ethical Principles of Conducting Scientific Medical Research with human Participation" as amended in 2000 and the "Rules of Clinical Practice in the Russian Federation" approved by Order of the Ministry of the Russian Federation dated 06/19/2003, No. 266. This study was approved by the Interdisciplinary Local Ethics Committee of the Stavropol State Medical University of the Ministry of Health of the Russian Federation.

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THE AUTHORS' CONTRIBUTION TO THE WORK

Lyudmila Y. Barycheva — research design and methodology, writing the text.
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The role of periostin as an inflammatory marker in bronchial asthma in children

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Abstract

Introduction. The extracellular matrix protein periostin, expressed in a number of body tissues, is considered as a marker of type 2 T cell inflammation and of asthma control.

Objective. To study the relationship the serum periostin concentration in blood serum depending on the severity of asthma and indicators of respiratory function in children.

Materials and methods. The cross-sectional (simultaneous) study included 80 children aged 6 to 17 years (average age 12±3.2), who were divided into 2 groups: 1st — children with asthma (n = 40); 2nd — comparison group (n = 40). The concentration of periostin in the blood serum was determined by the ELISA method. The spirographic study was performed on a computer spirometer Spirolab 1, MIR (Italy).

Results. The Me of periostin in group 1 was within the normal range (730.2 ng/ml), but statistically significantly exceeded the indicator of group 2 (539.7 ng/ml, $p < 0.05$) and did not depend on the age, duration and severity of asthma, anthropometric parameters of the examined. The level of periostin in the blood serum significantly correlated with the frequency of exacerbations of the disease during the year ($r = 0.74$, $p = 0.000$), with the status of asthma control ($r = 0.32$, $p = 0.04$). A moderate correlation was found between the level of periostin and FEV_1 ($r = -0.34$; $p = 0.03$).

Conclusions. In children with asthma, the median periostin in the blood serum increased in proportion to the severity of asthma, disease control and the frequency of exacerbation of the disease.

Keywords: periostin, bronchial asthma, children, spirometry

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

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Роль периостина как воспалительного маркера при бронхиальной астме у детей

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Аннотация

Актуальность. Белок внеклеточного матрикса периостин, экспрессируемый в ряде тканей организма, рассматривается в качестве маркера воспаления Т-клеток 2-го типа и контроля БА.

Цель. Изучить взаимосвязь концентрации периостина в сыворотке крови в зависимости от степени тяжести бронхиальной астмы и показателей функции внешнего дыхания у детей.

Материалы и методы. Проведено поперечное (одномоментное) исследование, куда были включены 80 детей в возрасте от 6 до 17 лет (средний возраст 12±3,2 года), которые были разделены на 2 группы: 1-я — дети с бронхиальной астмой (n = 40); 2-я — группа сравнения (n = 40). Концентрацию периостина в сыворотке крови определяли методом ИФА. Спирографическое исследование проводилось на компьютерном спирометре Spirolab 1, MIR (Италия).

Результаты. Медиана (Me) периостина в 1-й группе была в пределах нормы (730,2 нг/мл), но статистически значимо превышала показатель 2-й группы (539,7 нг/мл, $p < 0,05$) и не зависела от возраста, длительности и степени тяжести БА, антропометрических показателей обследованных. Уровень периостина в сыворотке крови значимо коррелировал с частотой обострений заболевания в течение года ($r = 0,74$, $p = 0,000$), со статусом контроля астмы ($r = 0,32$, $p = 0,04$). Выявлена умеренная корреляция между уровнем периостина и $ОФВ_1$ ($r = -0,34$; $p = 0,03$).

Заключение. У детей с БА медиана периостина в сыворотке крови возрастала пропорционально степени тяжести БА, контроля заболевания и частоты обострения заболевания.

Ключевые слова: периостин, бронхиальная астма, дети, спирометрия

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

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INTRODUCTION

BA continues to be the most common chronic respiratory disease in the world [1]. Currently, there is a need to search for new biomarkers that will help to distinguish and classify different phenotypes of asthma, predict the clinical course of the disease and response to drug treatment [2].

The discovery of biomarkers associated with underlying airway inflammation is an active area of research in adults and children. In recent years, studies have been published on the role of periostin in the pathogenesis of BA and it is considered as a marker of T2 inflammation (which is based on a type 2 immune response) of T2 inflammation (which is based on a type 2 immune response) [3-5].

Periostin was first discovered by Takeshita S. in 1993 from a mouse osteoblast cell line and was initially known as osteoblast-specific factor-2. It was subsequently renamed periostin (1999) due to its preferential expression in the periosteum and periodontal ligament in adult mice [6]. In 2006, the association of periostin with allergic diseases was first reported [7]. In 2009, Woodruff P. G. et al. showed that periostin expression is associated with type 2 inflammation in BA. The authors indicated that periostin was observed in the thickened basal membrane of bronchioles as well as in the serum of BA patients with eosinophilic airway inflammation [8].

To date, it is known that the periostin protein is encoded by the osteoblast-specific factor-2 gene,

which is the official name for periostin. In humans, this gene is also known as POSTN, PN, OSF-2 and PDLPOSTN (Gene ID: 10631). The human periostin gene is located on the long arm of chromosome 13 (13q13.3) with 24 exons [9]. Periostin is a protein with a molecular mass of 90 kDa. It belongs to the fasciclin family together with the protein induced by transforming growth factor β (TGF-β), which shows 48% homology with periostin [10]. Periostin can induce differentiation of fibroblasts into myofibroblasts and enhance fibrosis by binding to other extracellular matrix proteins such as collagen type I, fibronectin and tenascin C, by induction of collagen fibrillogenesis and cross-binding. Periostin can influence epithelial remodeling by promoting epithelial-mesenchymal transition, in which respiratory epithelial cells gradually transform into mesenchymal cells in the process of fibrosis development. Basal secretion of periostin by epithelial cells can alter the underlying matrix by modifying the deposition and cross-linking of collagen fibrils. Periostin can also induce activation of the TGF-β signaling pathway and increase collagen deposition, thereby promoting airway remodeling and potentially altering its biomechanical properties [11, 12].

Periostin levels are elevated in many pathologic conditions in blood, urine, sputum, exhaled air, and tears. This suggests that periostin is easily moved or secreted from inflamed areas into various body fluids, although the exact mechanism of movement or secretion still needs to be clarified [13]. Serum periostin levels are affected by many factors, including body mass index, age, active bone growth, etc. [2, 14].

In a study of age-related changes in serum periostin in allergic patients and healthy children Fujitani H. et al. (2019) found that serum periostin concentrations were highest in infants, decreasing by 7 years of age and then increasing again by 15 years of age due to age-related changes caused by bone metabolic activity.

Basal serum periostin levels in childhood and adolescence exceed 100 ng/mL; after cessation of bone growth, serum periostin concentrations decrease to ~50 ng/mL. The authors noted that healthy children showed higher serum periostin levels than children with allergic disease up to 5 years of age, with a subsequent decline. This finding supports the view that the contribution of allergic conditions to serum periostin levels cannot be assessed in children under 5 years of age, but in older children it can be investigated as a biomarker of allergic inflammation [15, 16].

STUDY OBJECTIVE. To study the concentration of periostin in serum depending on the severity of bronchial asthma and indicators of external respiratory function in children.

MATERIALS AND METHODS. A one-stage, single-center randomized study included 80 children aged 6 to 17 years (mean age — 12±3.2 years), permanently residing in Ryazan city. The children were divided into 2 groups: the 1st group included 40 children with BA. The average age of children was 12.0±2.8 years; 15 girls (37.5%), 25 boys (62.5%). 17 children (42,5%) had mild degree of BA, 23 children (57,5%) had moderate degree of BA severity.

The comparison group (group 2) consisted of 40 children: mean age — 11.9±3.3 years; 14 girls (35.0%), 26 boys (65.0%) ($p > 0.05$).

The study design was approved by the local ethical committee of the Federal State Budgetary Educational Institution of Higher Professional Education (FSBEI HE RYazHMU) of the Ministry of Health of Russia (Protocol of 09.03.2021). Parents of all children who participated in the study were familiarized with the study regulations and signed informed consent.

The bases for the study were GBI RO "City Children's Polyclinic No. 3" (chief physician — A. Burdukova). (chief physician — A. O. Burdukova), Central

Research Laboratory of FSBI HE RyazSMU of the Ministry of Health of Russia (head of the laboratory — Candidate of Medical Sciences, Associate Professor A. A. Nikiforov).

Inclusion criteria for the study: established diagnosis of bronchial asthma for at least 1 year, verified according to GINA 2022 [17] and Federal Clinical Guidelines [1]; age of patients from 6 to 17 years; obtaining informed consent of parents and patients for the study.

Exclusion criteria: presence of malignant neoplasms, acute illness or exacerbation of other chronic diseases, endocrine or genetic pathology, surgical intervention within the last 4 weeks in the subjects.

Serum concentration of periostin was determined by ELISA method using ELISA Kit for Periostin, (Cloud-Clone Corp., USA) in the Central Research Laboratory of FSBEI HE RyazGMU of the Ministry of Health of Russia with further calculation of median and interquartile range (Me; 25-75%). Norms of periostin in human serum/plasma samples in 500-fold dilution: 132.4~859.6 ng/mL л [18].

Anthropometric measurements were performed during the medical examination. Body weight was measured in kilograms to the nearest 0.1 kg using portable electronic (digital) scales and corrected for clothing. Children's height was measured in centimeters using a medical height meter in the standing position to the nearest 0.1 cm. Body mass index (BMI) was calculated using the formula: m/h^2, where m — body weight (kg), h — height (m). Children's physical development was assessed using the WHO AnthroPlus program. (2009). Weight-for-Age Z-score (WAZ) and BMI-for-AgeZ-score (BAZ) were calculated. In accordance with WHO recommendations, the obtained Z-scores were interpreted according to the following criteria: malnutrition — at <-2SDS, undernutrition from -2 to -1SDS, normal — from -1 to +1SDS, overweight — at SDS from +1 to +2, obesity — at SDS > +2 [19]. According to anthropometry data, all children were divided into 2 subgroups. In group 1 of children with BA, 28 children (70.0%) had normal body weight (BM) and 12 children (30.0%) had excessive BM. In group 2, there were 33 children (82.5%) with normal BMI and 7 children with excessive BMI (17.5%). No obese children were found in the examined groups.

Questionnaires were administered to assess BA control: the c-ACT (Children Asthma Control Test) adapted for children aged 4-11 years (16 children) and the ACT (Asthma Control Test) for children aged 12 years and older (24 children). The degree of disease control was assessed according to the results of the tests: for ACT 25 points and more — complete control of BA, 20-24 points — insufficient control and less than 20 points — uncontrolled BA. For the c-AST test, 20 points or more corresponds to controlled asthma, while 19 points or less means that asthma is not controlled effectively [1]. The results of the questionnaire showed that 31 children (77.5%) had controlled asthma, 7 children (17.5%) had partially controlled asthma, and 2 patients (5.0%) had uncontrolled asthma.

There were no exacerbations of BA in 15 children (37.5%), 1 exacerbation of BA in 10 children (25.0%), 2 exacerbations in 6 children (15.0%), 3 or more exacerbations in 9 children (22.5%).

Spirographic examination was performed on a computerized spirometer Spirolab 1, MIR (Italy). The following parameters were assessed: vital lung capacity (VLC), forced expiratory vital capacity (FEV), forced expiratory volume in the first second (FEV_1), maximum expiratory volume velocity at 25% FEV (MOS_{25}), maximum expiratory volume velocity at 50% FGF (MOS_{50}), maximum expiratory volume velocity at 75% FGF (MOS_{75}), OPV_1/FGF ratio (Tiffno index), OPV_1/FGF ratio (Gensler index). The results were evaluated in accordance with the current spirometry guidelines [20].

Statistical processing of the data was performed using the standard software package MS Excel 2016 and Statistica 6.0. The Shapiro-Wilk criteria were used to analyze the normality of sign distribution. Continuous variables were presented as median (Me) with interquartile range (25-75 percentiles). Categorical variables were defined as percentages (%). Intergroup

Table 1. **Median concentration periostin in blood serum in children with asthma, depending on the duration of the disease and severity (ng/ml) (author's table)**
Таблица 1. **Медиана концентрации периостина в сыворотке крови у детей с БА в зависимости от длительности заболевания и степени тяжести (нг/мл) (таблица автора)**

Duration of BA disease	Mild BA Me [25%; 75%] n = 17	Moderate BA Me [25%; 75%] n = 23	p
1–3 years(n = 13)	267,0 [244,5; 292,5]	587,5 [357,2; 1122,2]	> 0,05
4–6 years (n = 15)	455,5 [277,5; 687,8]	617,0 [250,5; 1167,8]	
7–13 years (n = 12)	375,7 [307,75; 882,25]	505,0 [375,5; 622,7]	

differences were assessed using the nonparametric Mann-Whitney (U-test) and Pearson (χ^2) criteria with adjustments for small samples. The Spearman rank correlation method (r) was used to determine the strength and direction of the correlation between two traits. Differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

The median periostin concentration in the group of children with BA was statistically significantly higher than the control group, 730.0 ng/mL [390.8; 1109.7] versus 536.7 ng/mL [452.0; 666.2] in Group 2, respectively ($p = 0.044$).

In the 1st group of children the value did not depend on the duration of the disease, but it was twice as high at the average degree of BA severity, but statistically significant differences were not found (Table 1).

No gender differences were found among children with BA: in girls, the Me of periostin content was 954.0 [414.25; 1115.0] ng/mL vs. 760.0 [418.25; 1356.62] ng/mL ($p = 0.72$) in the girls of the comparison group, and in boys, 406.0 [261.0; 751.0] ng/mL vs. 614.0 [486.87; 923.12] ng/mL ($p = 0.017$), respectively.

There was no significant correlation between periostin levels and patient age in both the BA group and the comparison group.

Periostin levels were significantly higher in children with 3 or more exacerbations of BA per year: Me = 1283.0 [1140.0; 1490.0] ng/mL ($p = 0.0001$).

In the group of children without exacerbations during the year, periostin levels were 318.0 [262.5; 469.25], with 1 exacerbation of BA — 469.3 [253.5; 723.0] ng/mL, with 2 exacerbations of BA — 546.2 [333.25; 686.5] ng/mL, respectively ($p > 0.05$). There was a direct correlation of moderate intensity between serum periostin levels and the frequency of BA exacerbations during the year ($r = 0.74$; $p < 0.000$) (fig. 1).

Periostin levels were within normal limits in children with BA with complete disease control (n = 31), Me = 455.5 [265.5; 789.5] ng/mL, and with partial disease control (n = 7), Me = 740.5 [378.5; 1115.0] ng/mL, respectively ($p > 0.05$).

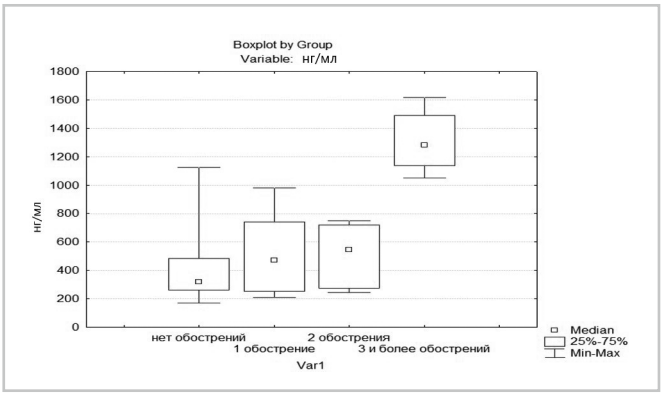

Fig. 1. **Median periostin in blood serum in children with asthma, depending on the frequency of exacerbations of the disease (ng/ml) (illustrations by the author)**
Рис. 1. **Медиана периостина в сыворотке крови у детей с БА в зависимости от частоты обострений заболевания (нг/мл) (иллюстрация автора)**

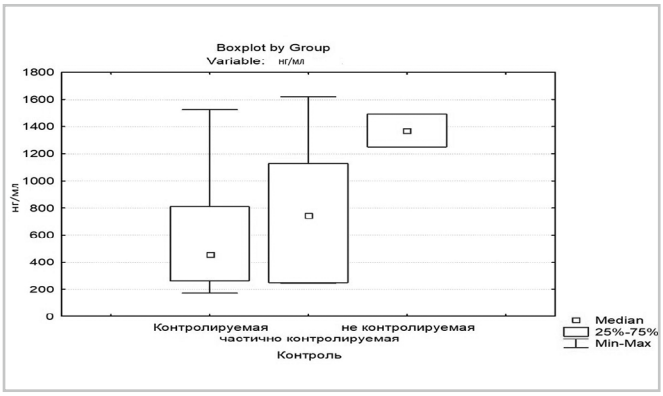

Fig. 2. **Median periostin in blood serum in children with asthma, depending on the degree of BA control (ng/ml) (illustrations by the author)**
Рис. 2. **Медиана периостина в сыворотке крови у детей с БА в зависимости от степени контроля БА (нг/мл) (иллюстрация автора)**

Table 2. **Spearman correlation coefficients between serum periostin levels and other clinical variables in children with asthma (author's table)**
Таблица 2. **Коэффициенты корреляции Спирмена между уровнем периостина в сыворотке крови и другими клиническими переменными у детей с БА (таблица автора)**

	Serum periostin (ng/mL)	
	r	p
Age	0,09	0,55
Duration of the disease	−0,03	0,82
Disease severity	−0,15	0,33
Degree of disease control	0,32	0,04
BMI	0,17	0,28
FEV_1, %	−0,34	0,03
AFR_{50}	−0,21	0,17
Frequency of disease exacerbations during the year	0,74	0,000

In the absence of disease control in patients with BA (n = 2), serum periostin levels exceeded normal values and corresponded to Me = 1369.5 [1309.25; 1429.75] ng/mL (p = 0.041) (Fig. 2).

Me periostin concentration was higher in children with uncontrolled BA 1369.5 [1309.25; 1429.75] ng/mL (p = 0.04). In the group of children with partially controlled course of the disease Me = 740.0 [378.5; 1115.0], with controlled Me = 455.5 [265.5; 789.5] (p = 0.39) (Fig. 2).

Serum periostin levels were found to be significantly correlated with the frequency of disease exacerbations during the year (r = 0.74, p = 0.000), with asthma control status (r = 0.32, p = 0.04), and with FEV_1 score (r = -0.34, p = 0.03), while no correlations were found with age, disease duration, and disease severity (Table 2).

Results of single-factor linear regression analysis showed an increase in periostin of 213.38 ng/mL per 1 exacerbation of BA (coefficient of determination 0.547, Fisher's criterion $F_{1,38} = 46.047$ ($p < 0,00002$).

The analysis also revealed a positive correlation of moderate intensity between BMI and BA severity (Table 3).

According to the data of spirographic study in children with BA during the examination period, the Me of lung vital capacity was 87.0 [81.0; 95.0] %, which corresponds to the norm. The values of forced lung vital capacity (FLVC) were also within the normal range, the median of FLVC in children with BA was 85.5 [82,8; 90,3] %.

Due to the fact that the severity of ventilatory disorders is usually assessed by changes in FEV1, we found a decrease in FEV_1 in our patients, which confirmed the diagnosis of BA. The FEV_1 median was 89.5 [79.8; 95.3] %. In 75.0 % (n = 30) of children, the values of FEV_1 corresponded to age criteria (> 80 % of the norm). Tiffno index and Genslar index values were normal (100.6 [92.5; 107.3] %, 102.4 [95.1; 109.9] %, respectively).

Spirography also showed a decrease in the maximum volumetric flow velocity in children with BA. Changes were noted at the point of 25, 50, 75 % (MOS_{25} — 79.0 [69.5; 87.8] %, MOS_{50} — 83.0 [71.8; 97.3] %, MOS_{75} — 85.5 [73.3; 103.3] %). Spirographic parameters in children with BA depending on severity are presented in Table 4.

When evaluating BA control by c-ACT and ACT tests, the median FEV_1 in patients with complete control of BA was 90.0 [85.0;95.5]%, with partial control 79.0 [78.5;90.5]%, and with no control 73.5 [72.75;74.25]% (p = 0,05).

Table 3. **Spearman's correlation coefficients of BMI with serum periostin levels in children with mild to moderate AD and control group (author's table)**
Таблица 3. **Коэффициенты корреляции Спирмена ИМТ с уровнем периостина в сыворотке крови у детей с легкой и средней степенью тяжести БА и контрольной группы (таблица автора)**

	Serum periostin (ng/mL)	
	r	p
BMI of children with mild BA	−0,38	0,12
BMI of children with moderate BA	0,65	0,0006
BMI of children in the control group	0,09	0,57

Table 4. **Spirometry indicators in children with asthma, depending on the severity, % (author's table)**
Таблица 4. **Показатели спирометрии у детей с БА в зависимости от степени тяжести, % (таблица автора)**

Spirographic values	Mild BA Me [25 %; 75 %] n = 17	Moderate BA Me [25 %; 75 %] n = 23	p
LVC	89,0 [81,0; 101,5]	87,0 [82,5; 91,0]	p > 0,05
FLVC	87,0 [84,0; 89,0]	84,0 [79,0; 91,5]	
FEV1	90,0 [84,8; 100,0]	87,5 [78,8; 94,0]	
MEF25	80,0 [68,0; 98,3]	83,0 [76,8; 93,3]	
Genslar Index	97,7 [94,6; 109,6]	103,7 [97,6; 109,9]	
Tiffno index	99,1 [92,3; 111,4]	100,6 [94,9; 105,2]	

The results obtained from the study are in accordance with the literature on the presence of a relationship between serum periostin levels and the activity of allergic inflammation in asthma. Inoue T. et al. (2016) in a cross-sectional study also found higher serum periostin levels in children with asthma compared to children without atopy and indicated a possible role of periostin assessment in the diagnosis of asthma in children. The authors stated that serum periostin levels in children are significantly higher than in healthy adults, which may be due to increased bone metabolism during childhood [21]. Song J. S. et al. (2015) showed that in children with BA, high serum periostin levels were associated with airway hyperresponsiveness [22]. Masalsky S. S. et al. (2018) found that serum periostin levels were significantly higher in children with BA compared to healthy children and directly correlated with the severity of BA [23]. In our study, serum periostin levels were higher in the group of children with BA, especially in moderate BA.

There are contradictory results about the relationship between serum periostin levels and asthma control status in children. El Basha N. R. et al. (2018) found significantly higher serum periostin levels in children during asthma exacerbation compared to children with stable BA and healthy children in control groups [24]. In contrast, Mena A. et al. (2017) found an inverse relationship — lower serum periostin levels occurred in children with uncontrolled asthma [25]. Licari A. et al. (2019) found no association between asthma control and serum periostin levels in 121 children with allergic asthma [26]. In our study, the serum periostin rate was higher in children with uncontrolled BA.

Asthma severity may be the best tool in the search for a biomarker reflecting the degree of inflammation in a chronic disease such as BA. There are controversial results of studies that have investigated the relationship between asthma severity and serum periostin levels. Licari A. et al. (2019) and Konradsen J. R. et al. (2015) found no association between asthma severity and serum periostin levels [5]. In our study, we also found no correlation between periostin levels and the severity of BA, the indicators were within the range of normal values, but the indicator was higher in moderate BA ($p < 0.05$).

According to Kimura H. et al. (2018) and Shirai T. et al. (2019), we found a negative correlation between serum periostin levels and body mass index in children with bronchial asthma, as well as in the control group [27-298]. We found a correlation between body mass index and periostin levels in children with BA of moderate severity, but no correlation in children in the control group ($p > 0,05$).

According to the literature, special attention has been paid to the study of the relationship

between periostin concentration and indicators of external respiratory function in patients with BA. Kanemitu Y. et al. (2013) in a study reported that high serum periostin levels correlated with decreased forced expiratory volume in one second with age in patients with asthma. Inoue T. et al. (2016) in a cross-sectional study found no correlation between periostin level and lung function [21]. Our study revealed a moderate correlation between periostin level and FEV_1 value, but no correlation between periostin and MOC_{50}. Obstructive changes in the spirogram are detected by the level of decrease in the FEV_1, VLC and their ratio (FEV_1/VLC — Tiffno index). In the absence of ventilatory disorders, the values of VLC, FEV_1, and FEV_1/VLC are within the normal range. According to the current clinical recommendations, the obstructive type of ventilatory disorders occurs in case of normal VLC index, normal or decreased FEV_1, decreased FEV_1/VLC [20]. Thus, in our study, no ventilation disorders were found in children with BA. Assessment of periostin levels in serum may help us to better study the possibilities of BA control in children.

CONCLUSIONS:

1. Periostin concentration in serum increased in proportion to the severity of BA.
2. Periostin levels varied according to the degree of BA control and frequency of disease exacerbations during the year.
3. A moderate correlation between serum periostin level and FEV_1 was revealed.
4. It is advisable to determine serum periostin levels in children with BA to assess the activity of allergic inflammation in atopic BA.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted taking into account the requirements of the Helsinki Declaration of the World Association "Ethical Principles of Conducting Scientific Medical Research with human Participation" as amended in 2000 and the "Rules of Clinical Practice in the Russian Federation" approved by Order of the Ministry of the Russian Federation dated 06/19/2003, No. 266. This study was approved by the local Ethics Committee of

the Federal State Budgetary Educational Institution of the Ryazan State Medical University of the Ministry of Health of the Russian Federation (Protocol dated 03/09/2021).

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THE AUTHORS' CONTRIBUTION TO THE WORK

Natalia A. Belykh — conceptualization, formal analysis, visualization, writing — review & editing.
Inna V. Pisnyur — formal analysis, investigation, visualization, writing — original draft.
Aleksandr A. Nikiforov, Larisa V. Nikiforova — investigation.

ВКЛАД АВТОРОВ В РАБОТУ

Белых Н. А. — разработка концепции, формальный анализ, подготовка текста — оценка и редактирование.
Пизнюр И. В. — проведение исследования, формальный анализ, работа с данными, подготовка текста.
Никифоров А. А., Никифорова Л. В. — проведение исследования, работа с данными.

Во 2 номере неверно указаны электронные идентификаторы статей.

Исправленный вариант:

1. Локальные проявления перекрестной пищевой аллергии у детей с клиническими симптомами респираторной аллергии на пыльцу березы: пути решения

Т. С. Лепешкова

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2. Пациент с коморбидной патологией: возможна ли АСИТ?

Е. А. Орлова, Ю. А. Кандрашкина, Е. Ю. Трушина, Е. М. Костина

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3. Опыт аллерген-специфической иммунотерапии у пациента с оральными и системными проявлениями аллергии к пыльце березы

Е. Ю. Трушина, Е. М. Костина, Е. А. Орлова, А. А. Туровская, Т. А. Нефедова

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