UDC 616.248-053.2-082.3-056.3-084+615.874.2+613.24
DOI: 10.56871/CmN-W.2024.26.75.001

UNSOLVED PROBLEMS OF FOOD ALLERGY IN CHILDREN

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For citation: Trusova OV, Kamaev AV. Unsolved problems of food allergy in children. Children's Medicine of the North-West. 2024;12(2):7–18. DOI: https://doi.org/10.56871/CmN-W.2024.26.75.001

Received: 15.01.2024 **Revised: 06.03.2024** **Accepted: 05.06.2024**

Abstract. ***Introduction.*** The article discusses the most significant problems faced by a pediatrician, family medicine physician, and allergist-immunologist when caring for children with food allergy (FA). Unsolved problems of FA still include the heterogeneity of information about its prevalence and age dynamics. The clinical value of various examination methods are discussed, revealing the main common errors in the interpretation of tests. Cases of unjustified prescription of elimination diets in children with unproven PA are considered. We present our own data obtained during observation of cohorts of pediatric patients in the city allergology office of St. Petersburg. Among 263 children diagnosed with bronchial asthma, in 91 cases (34.6%) positive (>0.35 IU/ml) specific IgE was found in the blood serum to food products (in descending order of frequency): chicken egg white, milk, cod, wheat, soy, oats. The development of respiratory symptoms when consuming certain products was recorded in 16 people (6.1% of the sample). The paper provides clinical characteristics of this small subgroup of children with bronchial asthma who are indicated for an individually selected elimination diet. The advantages and disadvantages of a promising method of treating FA — oral immunotherapy with food allergen — are considered. The method provides protection against the development of a severe and life-threatening episode if the patient accidentally consumes food allergen. The advantages and disadvantages of the most popular strategies in the prevention of FA in children, starting from the prenatal period, including the use of hydrolyzed formulas and the introduction of potentially allergenic products into complementary foods, were assessed. ***Conclusion.*** In the field of prevention, diagnosis and treatment of food allergies in children at the present stage, there are significant unresolved problems. The development and approval of recommendations for conducting food challenge tests is required. Interpretation of tests can only be carried out in direct connection with knowledge of the history and clinical picture of the disease in the child. The problem of food allergies continues to focus the efforts of both the international community and domestic scientists.

Keywords: *children, food allergy, diet therapy, prevention, clinical manifestations of food allergy*

НЕРЕШЕННЫЕ ПРОБЛЕМЫ ПИЩЕВОЙ АЛЛЕРГИИ У ДЕТЕЙ

© Ольга Валерьевна Трусова, Андрей Вячеславович Камаев

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Для цитирования: Трусова О.В., Камаев А.В. Нерешенные проблемы пищевой аллергии у детей // Children's Medicine of the North-West. 2024. Т. 12. № 2. С. 7–18. DOI: https://doi.org/10.56871/CmN-W.2024.26.75.001

Поступила: 15.01.2024 **Одобрена: 06.03.2024** **Принята к печати: 05.06.2024**

Резюме. ***Введение.*** В статье рассмотрены наиболее значимые проблемы, с которыми сталкивается педиатр, врач семейной медицины, аллерголог-иммунолог при ведении детей с жалобами на пищевую аллергию (ПА). К нерешенным проблемам ПА по-прежнему относят разнородность сведений о ее распространенности и возрастной динамике. Обсуждается информативность и клиническая ценность различных

 ISSN 2221-2582

методов обследования, с раскрытием основных типичных ошибок при интерпретации анализов. Рассмотрены случаи необоснованного назначения элиминационных диет у детей при недоказанной ПА. Приведены собственные данные, полученные при наблюдении когорт пациентов детского возраста в городском аллергологическом кабинете Санкт-Петербурга. У 263 детей с диагнозом «бронхиальная астма» в 91 случае (34,6%) обнаруживали положительные (>0,35 МЕ/мл) специфические IgE в сыворотке крови к пищевым продуктам (в порядке убывания частоты): белок куриного яйца, молоко, треска, пшеница, соя, овес. Развитие респираторных симптомов при употреблении определенных продуктов фиксировали у 16 человек (6,1% выборки). В работе дана клиническая характеристика этой небольшой подгруппы детей с бронхиальной астмой, которым показана индивидуально подобранная элиминационная диета. Рассмотрены преимущества и недостатки перспективного метода лечения ПА — оральной иммунотерапии с пищевым аллергеном. Метод дает защиту от развития тяжелого и жизнеугрожающего эпизода при случайном употреблении пищевого аллергена пациентом. Оценены преимущества и недостатки наиболее популярных стратегий в профилактике ПА у детей, начиная с внутриутробного периода, в том числе, применение профилактических гидролизных смесей, введение потенциально аллергенных продуктов в прикорм. ***Заключение.*** В области профилактики, диагностики и лечения пищевой аллергии у детей на современном этапе существуют значимые нерешенные проблемы. Требуется разработка и утверждение рекомендаций по проведению провокационных пищевых проб. Интерпретацию анализов можно проводить только в непосредственной связи со знанием анамнеза и клинической картины заболевания у ребенка. Проблема пищевой аллергии продолжает концентрировать усилия и мирового сообщества, и отечественных ученых.

Ключевые слова: *дети, пищевая аллергия, диетотерапия, профилактика, клинические проявления пищевой аллергии*

INTRODUCTION

Food allergy (FA) is a food-induced pathological reaction based on immune mechanisms [1]. The immune mechanisms of allergic reaction are mediated by specific immunoglobulins E (IgE-mediated reactions) or have a cellular mechanism (non-IgE-mediated) [2]. Several mechanisms may be involved in the pathogenesis of FA-associated disease (so-called mixed-type reactions), but allergen-specific IgG of any subclass (including IgG4) is not clinically relevant in any of the described FA-associated conditions [1]. The term "food hypersensitivity" does not show anything about the mechanisms of pathogenesis of reactions to some food, so its application to immunologically determined reactions to food is inappropriate [1]. However, a clear distinction should be made between cases of "food intolerance" in which, despite the certain association of clinical manifestations with food intake, there is no reproducibility and consistency of the reaction or any immunologic mechanisms [1, 3].

HOW COMMON IS FOOD ALLERGY IN CHILDREN?

The overall prevalence of FA is thought to be increasing everywhere, and the spectrum of its clinical manifestations is also expanding [4]. A meta-analysis of 23 studies conducted between 2000 and 2012 in Europe showed that the frequency of FA found in patient at any time during his or her life was 17.3% according to questionnaire data. The prevalence of sensitization by detection of specific IgE (sIgE) to food was 10.1%, proportion of patients with positive allergy skin tests (AST) with food was 2.7%, and probability of a positive result of provocative test for food allergy diagnosis (PT) was only 0.9%. At the same time, significant regional differences in the incidence of FA were noted [5]. Data revision was done in 2023 and linked the results of studies conducted between 2000 and 2021 in all European countries, including the Russian Federation and Turkey, showed an increase in the prevalence of FA, using a questionnaire, and the detection of sensitization. The prevalence of FA noted ever in life was 19.9%, according to questionnaire data, the frequency of laboratory-detected sensitization (sIgE) to food increased to 16.6%; a proportion of positive ASTs to food increased to 5.7%, and the probability of receiving a positive PT did not change significantly, only 0.8% [6]. Thus, the "incidence of FA" has significant differences depending on how it is confirmed. The detection of food sensitization by AST and sIgE has increased over the last decades, possibly reflecting a true increase in FA, but may also be a consequence of the increased vigilance and coverage of allergy screening methods in different countries and general increase in the number of studies on FA. The most recent and comprehensive meta-analysis suggests that large, well-coordinated studies of rigorous de-

sign, including mandatory confirmation of the diagnosis by double-blind, placebo-controlled PT, are needed to more accurately determine the incidence of PA [6].

WHICH FOOD IS THE MOST ALLERGENIC?

At first, the concept of the "Big Eight" (a list of foods that are the most common causes of FA) was proposed in 2014 by the European Academy of Allergy and Clinical Immunology (EAACI) based on research data conducted in 2000–2012. According to current clinical recommendations, the Russian "Big Eight" foods that most often is the cause of allergic reactions include cow milk proteins (CMP), chicken eggs, peanuts, nuts, fish, seafood, wheat and soy [1]. A review and meta-analysis of publications from 2000 to 2021 (total number of studies — 93) showed that the "Big Eight" has not changed during this time [6]. Data from the meta-analysis on the frequency of FAs for G8 foods are presented in Figure 1.

In the study of the sensitization spectrum in children, who lived in Ekaterinburg, aged from 4 months to 16 years and had anaphylaxis due to allergic reaction to food, causative allergens were identified in 100% of cases. CMP (51.67%), various types of nuts (33%), egg (16.67%), walnuts (16.67%), fish (15%), kiwi (11.67%), peanuts (11.67%) were the leading causes of anaphylaxis. Children who suffered anaphylaxis due to allergic reaction to food were also sensitized to non-food allergens: birch pollen (68.33%), cat fur (40.0%), dog fur (16.6%), and grass pollen (13.3%) [7].

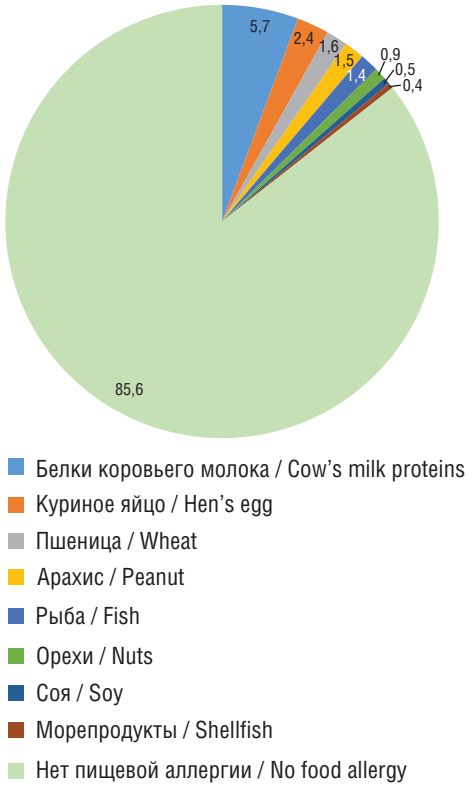

Fig. 1. The prevalence of food allergies according to research data [6]

Рис. 1. Распространенность видов пищевой аллергии в популяции по данным [6]

DOES THE AGE OF A PATIENT MATTER

The frequency of allergies to various foods changes with age. Moreover, for the most important and allergenic products, positive dynamics are expected in the form of the formation of tolerance or "outgrowing" allergies. In many cases, this is exactly what happens, and the child begins to tolerate foods such as cow milk, chicken eggs, and wheat without developing a reaction. It is known that the most significant food allergen in young children, CMP, causes allergic reactions in 2–3% of infants, and by the age of 5, approximately 80% of patients develop tolerance. Therefore, the prevalence of FA to CMP allergens at the age of 6 years decreases and is less than 1% [1].

ARE THERE ANY METHODS FOR TREATMENT OF SEVERE FOOD ALLERGY?

In case of confirmed severe FA, patients are forced to strictly avoid the allergen for a life. In many cases, it is necessary to control the intake of even the smallest trace amounts of product.

The question arises about the possibility of curative treatment. Specific immunotherapy with food allergens is being widely studied around the world as a method that provides protection against the development of a severe and life-threatening episode if the allergen is accidentally consumed by a patient who generally follows a strict elimination diet.

Oral immunotherapy (OIT) is the administration of a causative food allergen to a patient with proven sensitization and allergy on a regular basis in quantities. It is not cause a severe reaction, with a gradual increase in the dose of the product in order to achieve tolerance. OIT has been widely studied around the world, and it is clear that although it may generally have the desired effect, but the risk of developing an anaphylaxis reaction to OIT itself must be kept in mind [8].

ISSN 2221-2582

OIT is the most promising technique in the treatment of severe FA, but difficulties in its use are associated with many reasons:

- the risk of development of acute allergic reactions at the initial stage of treatment;
- differences in protocols (dose and rate of its increase);
- a lack of commercially available OIT drugs;
- a difficulty in diagnosing the onset of tolerance (as well as for allergen-specific immunotherapy with inhaled allergens, reliable and safe markers for testing the onset of effect have not been developed) [8].

There is an opinion that after achieving clinical success, OIT should be continued for a life, because a loss of effect is likely after ending of the therapy [8]. The possibilities of improving OIT by combining it with the administration of biological therapy (monoclonal antibodies: omalizumab, dupilumab) and with probiotics are also being studied. A final opinion on this issue has not yet been formed [8].

High-risk factors of undesirable consequences of OIT include:

- high degree of sensitization to the allergen, anaphylaxis in anamnesis (i.e., actually a direct indication for OIT);
- uncontrolled course of allergic disease;
- low compliance to the treatment regimen;
- presence of gastrointestinal forms of FA (eosinophilic esophagitis, food protein-induced enterocolitis syndrome) [8].

Due to these reasons, OIT is currently not authorized for use in the Russian Federation [1].

During childhood, patients with food anaphylaxis inevitably raise the question of the possibility of "disease outgrowth" and, consequently, of discontinuation of the diet, which is no longer required.

There are no reliable and highly safe methods either for diagnosing tolerance formation or for predicting the course of the disease as the child grows up.

ARE THERE RELIABLE METHODS FOR DIAGNOSIS OF FOOD ALLERGY?

The first and often most reliable way to diagnose FA is a structured anamnesis [9].

To complete the anamnesis data, methods for confirming sensitization are used, i.e. detection of specific IgE, free in serum or attached to effector immunocompetent cells, both *in vivo* and *in vitro*:

- AST;
- sIgE;
- basophil activation test (BAT), etc.

You must always remember that:

- these diagnostic methods confirm sensitization, and not the allergic disease itself.
- the cut-off level above which the test result in most cases is actually associated with the presence of an allergy to the product is only being studied for some of the most significant food allergens, such as CMP, egg [10];
- for different food products, the information content of the methods will be different; not all types of tests are available in a doctor's practice [9];
- none of the examination methods available in practice are without drawbacks; in addition, for a full interpretation of the results, studies performed on a local population are highly desirable [11].

The informativeness of methods for confirming sensitization depends naturally on the mechanism of FA in patient.

In the development of type 1 hypersensitivity reactions (atopic, IgE-mediated mechanism) to a food allergen, a typical pattern of clinical manifestations of the reaction is observed. The above-mentioned diagnostic tests for detection of IgE-sensitization in these situations are often highly informative and provide results that are easy to interpret and explain the patient's anamnesis [9].

Clinical characteristics of IgE-mediated food allergy include rapid onset of symptoms (from minutes to 2 hours after ingestion of the food allergen) reproducibility of reactions in dynamics with repeated contact with the same product and typical symptoms:

- urticaria, angioedema, itching of the skin, ears, palms, feeling of heat, hyperemia in pre-existing foci of dermatitis;
- itching, swelling of mucous membranes of an oral cavity, pharynx, nausea, vomiting, spasmodic abdominal pain, diarrhea;
- itching, swelling of conjunctivae, lacrimation;
- rhinorrhea, sneezing, nasal congestion, nasal itching, hoarseness of voice, stridor, cough, difficulty breathing, wheezing, cyanosis;
- pallor, cold sweat, palpitations, loss of consciousness and shock, tachycardia, arterial hypotension;
- anxiety, behavioral disturbances, irritability, apathy, lethargy, seizures, tremors, metrorrhagia;
- polysystemic reactions, including many of the above symptoms, up to lethal outcome (anaphylaxis).

The symptoms of IgE-mediated immediate-type FA are varied and Its interpretation depends on the clinical case. For example, the development of isolated seizures against the background of complete health is unlikely to make one suspect FA in the first place. Sneezing fits after consumption of a certain product are quite characteristic, although are not very common [9].

Clinical manifestations that develop by non-IgE-mediated and mixed mechanisms are more difficult to interpret. Based on the patient's complaints and anamnesis, a physician can identify a potential food allergen as the cause of symptom. But the informativeness of methods for detecting IgE-sensitization will be highly questionable.

Symptoms of non-IgE-mediated or mixed mechanisms of FA include [9]:

- contact dermatitis;
- gastrointestinal forms of FA (food protein-induced enterocolitis, allergic proctocolitis, allergic enteropathy);
- exacerbation of atopic dermatitis;
- eosinophilic esophagitis, gastritis, enteritis;
- exacerbation of bronchial asthma.

In clinical practice, it is not uncommon for patients with atopic dermatitis, suspecting food allergy, to have various tests to detect IgE-sensitization to food allergens by themselves, and upon receipt of the results exclude a number of foods from the child's diet. Based on this knowledge, the failure of this approach becomes clear. Particularly alarming are the situations when strict elimination diets are prescribed and number of important foods are excluded from the child's diet based only on laboratory tests, without sufficient analysis of clinical picture [9].

Patient education should emphasize that many variants of atopic dermatitis are not associated with FA. The search for causative food allergens is justified in patients with early-onset atopic dermatitis, in patients with severe atopic dermatitis at any age, and in patients with direct anamnesis data indicating a provocative role of food in the development of exacerbations [12]. However, it should be remembered that the absence of specific IgE does not exclude the diagnosis of FA [1].

In foreign practice, provocative test for food allergy diagnosis (PT) is often used after the sensitization confirmation step, which demonstrate the reaction to the suspected product under controlled conditions. PT is undoubtedly the "gold standard" in the diagnosis of FA. A particularly useful function of PT is to demonstrate tolerance to a product that has been excluded for a long time from the child's diet and feared to be introduced [9]. For practical purposes, an open PT is sufficient. In complex expert cases and in scientific studies, double-blind placebo-controlled PT is also used [9].

Due to technical complexity, lack of approved protocols for PT, and lack of standardized food preparations for PT, these tests are not performed in the Russian Federation [1].

In Russian practice, the so-called diagnostic introduction of a product is recommended as a diagnostic technique, i.e. trial introduction of small amounts of product previously excluded from the diet to assess clinical symptoms. Diagnostic administration is not used in children with anaphylaxis, when even minimal (trace) amounts of an allergenic product cause complaints. For diagnostic administration, a small amount of the product containing the suspected causative allergen is used, based on the anamnesis (the amount of the product for which the development of complaints was noted, the severity of the reaction to this amount). Start should be with a dose significantly lower than the one that led to the clinical manifestations of the allergic disease. The period of observation of the patient after diagnostic administration of the product depends also on the nature of previous reactions to this product and ranges from 2 hours in case of hypersensitivity of immediate type (urticaria, rhinitis, asthma) and to 2 days in case of hypersensitivity of delayed type (atopic dermatitis, gastrointestinal manifestations) in the anamnesis. If diagnostic introduction of the product did not lead to the development of symptoms, the product is introduced into the diet in gradually increasing amounts [1].

DOES A CHILD WITH BRONCHIAL ASTHMA NEED AN ELIMINATION DIET?

The prescription of diets with the elimination of a number of "highly allergenic" foods to children with bronchial asthma, allergic rhinitis and other respiratory allergic pathologies seems to be an important problem.

Bronchial asthma in childhood most often has an atopic mechanism. In some cases, the child's parents believe that food allergens provoke the symptoms of the disease. Thus, 180 children (of total 362 children aged from 6 to 18 years with atopic bronchial asthma) noted a provocative role of food in anamnesis. Among them, 70 children

ISSN 2221-2582

were found to have positive sIgE to food allergens, and only 20 children had a positive PT [13].

Food allergens are seriously inferior to inhalant allergens (house dust, pollen, fur) [14, 15]. Even though the frequency of sensitization to this group varies from 0.8 to 25%. A significant proportion of these patients do not have clinical manifestations of food allergy, despite the detection of specific IgE in blood serum [14].

We present our own data on the analysis of the dispensary group of patients observed in the City Allergy Clinic of St. Petersburg (SPbFBO "Children's City Clinic No. 44"). The data of case histories and results of repeated examinations of 263 children diagnosed with bronchial asthma (BA, J45.0) at least 1 year ago were studied. The distribution of patients by age groups, comorbid diseases and severity is presented in Table 1.

After analysis of the data from case histories, it was found that 91 (34.6%) patients had positive (>0.35 IU/ml) specific IgE in serum to a small list of products (in descending order of frequency): chicken egg protein, milk (more often casein), cod, wheat, soy, and oats. During the directed questionnaire survey of patients (older than 7 years) and/or their parents, it was found that when consuming certain foods, the development of respiratory symptoms was repeatedly recorded in 16 people (6.1% of the examined sample), of whom 3 (18.75%) had no specific IgE detected in serum (reactions to fish and milk). Meanwhile, only nasal itching, serial sneezing, and watery rhinorrhea developed in 5 patients (31.25%) of the subgroup. All of them had positive specific IgE in serum. The remaining 11 patients (68.75%) had distant wheezing, dyspnea, serial cough in addition to rhinitis symptoms. Table 2 shows the clinical characteristics of subgroups of patients: patients in whom food consumption causes only an exacerbation of allergic rhinitis (AR) and comorbid bronchial asthma (BA) is exacerbated by inhalant allergens ("food AR"), patients in whom food consumption causes a combined exacerbation of both AR and BA ("food BA"), and patients without clinically significant FA ("no food allergy").

For patients in whom food consumption does not lead to respiratory symptoms, anaphylactic reactions have been described to insect stings and penicillin antibiotics. Patients with reproducible respiratory manifestations of food allergy (exacerbation of AR and/or an attack of BA) are usually younger and have polysensitization. Food sensitization has a delineated clinical picture even in the absence of specific IgE. Multisystemic manifestations in the structure of food anaphylaxis are more characteristic for "food BA" than for "food AR" (45.5% vs. 20%, a correct statistical

Table 1. Clinical features and medical history in examined patients

Таблица 1. Клинико-анамнестическая характеристика обследованных пациентов

Характеристика / Sign		Бронхиальная астма (263 пациентов), n (%) / Bronchial asthma (263 patients), n (%)
Возрастной интервал / Age interval	До 3 лет Under 3 years	22 (8,3)
	3–6 лет 3–6 years	71 (27,0)
	7–11 лет 7–11 years	97 (36,9)
	12–17 лет 12–17 years	73 (27,8)
Степень тяжести основного заболевания / Severity of the disease	Легкая / Mild	154 (58,6)
	Средняя / Moderate	81 (30,8)
	Тяжелая / Severe	28 (10,6)
Коморбидные заболевания / Comorbid diseases	Аллергический ринит / Allergic rhinitis	247 (93,9)
	Атопический дерматит / Atopic dermatitis	69 (26,2)

Table 2. Clinical features in patients with respiratory food allergy

Таблица 2. Клинические характеристики пациентов с респираторными проявлениями пищевой аллергии

Показатель / Indicator	Пищевой аллергический ринит, n=5 Food-induced allergic rhinitis, n=5	Пищевая бронхиальная астма, n=11 Food-induced bronchial asthma, n=11	Нет пищевой аллергии, n=247 No food allergy, n=247
Возраст, лет, Me [Q25; Q75] / Age in years, Me [Q25; Q75]	5,2 [4,1; 9,3]	7,3 [5,2; 14,6]	8,9 [6,5; 15,1]
Доля пациентов с атопическим дерматитом, n (%) / Patients with atopic dermatitis, n (%)	1 (20)	5 (45,5)	63 (25,5)
Доля пациентов с анафилаксией, n (%) / Patients with anaphylaxis, n (%)	1 (20)	4 (36,4)	2 (0,8)
Средняя суточная доза иГКС*, мкг, M±σ / Mean daily dose of inhaled glucocorticosteroid, mcg, M±σ	178,4±94,7	396,8±72,4	217,5±146,3

* Доза ингаляционных глюкокортикостероидов рассчитана по будесониду, согласно таблице эквипотентных доз GINA 2023 [16].

* Daily dose of inhaled glucocorticosteroid was calculated as budesonide equivalent, according to GINA 2023 dosing table [16].

comparison is impossible due to the small number of observations). Such clinical picture makes it necessary to strictly exclude the "guilty" product from the patient's diet for many years. However, in some children with normalization of laboratory parameters, trial allergen administration is possible.

Patients with respiratory complaints but without signs of food anaphylaxis often show a decrease or even absence of reaction to products after several years of elimination measures. In the study group, we identified 8 adolescent patients (12–17 years of age) with no dietary restrictions, clinical reactions to food and specific IgE to food allergens, who had a history of transient respiratory complaints to egg, milk, or fish during preschool age.

SHOULD HYDROLYZED ADAPTED FORMULA BE USED IN ARTIFICIAL FEEDING TO PREVENT FOOD ALLERGIES?

There are no absolutely effective techniques in the prevention of food allergy in young children. The most discussed measures for the prevention of FA are the support of breastfeeding until the age of 4–6 months, need for dietary restrictions for the expectant mother and lactating woman, and administration of hydrolyzed and partially hydrolyzed formula to children at risk (with aggravated heredity) who are artificially or mixed-fed. There are pros and cons for each intake, and the most balanced is the agreed position of domestic pediatricians, presented in the national clinical recommendations:

- there is no convincing evidence for the preventive effect of a strict hypoallergenic diet for a mother during pregnancy; a varied and nutritious diet is recommended for the expectant mother;
- exclusion of causative allergens is recommended for a mother if *she* suffers from an allergic disease;
- a breastfeeding mother of a child, who is at risk group, should be given a varied and complete diet with *restriction*, but not exclusion, of the most common allergens, including products containing CMP [1].

In 2020, the European Academy of Allergology and Clinical Immunology conducted a review of the evidence for FA prevention in children, excluding those recommendations for which the evidence base was not considered strong [17].

The experts support breastfeeding. They acknowledge with a low level of evidence the undesirability of introducing milk-based formula, but only for the time period in the first week of life. In fact, they explain that in the first 1–3 days of life, until the colostrum synthetized, if necessary, the baby should not be supplemented with milk-based formula without a recommendation. So what should be supplemented and how to continue feeding a newborn in the absence of breastfeeding after the age of 7 days?

The recommendations also include, with a moderate level of evidence, the introduction of

potentially allergenic foods such as chicken eggs and peanuts in the 1st year of life [18]. A systematic review of the literature did not show any adverse events or signs of any harm to children from feeding partially hydrolyzed formulas. The use of partially hydrolyzed formulas is associated with normal growth rates in children [19]. Thus, the recommendation to prescribe formulas based on partially hydrolyzed milk protein for prophylactic purposes to high-risk children who require artificial feeding is currently not supported or prohibited by European guidelines. The volume of evidence-based research is considered insufficient to produce any type of conclusion: neither pros nor cons. The "partial hydrolyzed" formula provides the same indicators of child growth and development as the standard formula, and is characterized by a high level of safety.

The agreed opinion of domestic experts is presented in the methodological recommendations of the Union of Pediatricians of Russia. There is currently no convincing evidence that hydrolyzed formula prevents the development of FA. Nevertheless, some studies demonstrate a reduction in the risk of atopic diseases in some children. In children at risk for atopy who are artificially or mixed-fed before 6 months of age, it is possible to use formula with reduced allergenic properties, particularly those based on moderately hydrolyzed milk protein. The effectiveness of such an intervention in children older than 6 months of age (e.g., after lactation cessation) has not been studied [20].

IS LATE INTRODUCTION OF COMPLEMENTARY FOOD JUSTIFIED FOR PREVENTION OF FOOD ALLERGY?

The opinion about the protective role of exclusive breastfeeding for the prevention of FA and the advisability of introducing the first complementary foods no earlier than the age of 6 months is widespread in different countries of the world.

In the French ELFE cohort (6662 children), the feeding patterns of children aged from 3 to 10 months were studied and information was collected on allergic diseases that developed by the age of 5.5 years. In this large cohort of children at both high and low risk of allergic disease, there was evidence that *failure* to introduce at least two "highly allergenic" foods by 10 months of age resulted in an increased risk of allergic conjunctivitis and food allergy (the reverse of the relationship, when allergenic foods are not introduced, because the child already had a food allergy, was controlled for in this study as a separate type of statistical error) [21].

Many experts believe that the introduction of complementary foods within the "window of tolerance" (from 4 to 6 months of age) helps to reduce the risk of developing atopy in subsequent years of a child's life [22, 23]. The key rule for the careful introduction of complementary foods in children at high risk of developing atopy is to prescribe monocomponent products of no more than 1 product per week. In general, the timing of introducing complementary foods should be the same as in healthy children [1, 23, 24]. From a "window of tolerance" perspective, oral tolerance induction should begin as soon as the child is able to accept foods other than breast milk (or formula), but before food allergy manifests. To start eating solid food, it is necessary to develop an interest in food, hold the head, sit with support, and lose the reflex of "pushing out the spoon" with the tongue. These conditions usually develop between 4 and 6 months of age. However, by this age the child may already be sensitized to food allergens and manifest an allergic disease. Thus, for some children the "window of opportunity" may be very narrow [25]. It is also unknown whether oral tolerance to non-IgE-mediated forms of FA can develop [25].

Key international studies, the 2015 LEAP and 2016 EAT studies, showed a reduction in the risk of development of peanut food allergy with early (4 to 11 months of age) introduction of peanuts into complementary foods in children at high and normal risk for allergic diseases, respectively [26, 27]. A meta-analysis of early egg introduction included 5 studies (1915 study participants) and found that introducing eggs into complementary foods between 4 and 6 months of age is associated with a lower risk of development of allergy to egg [28].

Regarding the early introduction of other complementary foods, there are mixed results from studies. The most studied allergenic complementary foods, peanuts, are not very important for Russia either as a cause of allergies or as a component of complementary feeding in the first year of a child's life. There are no guidelines for the early introduction of allergenic foods into the diet of children. There are also no commercially available dosed food supplements containing allergenic foods. There are no drugs to induce oral tolerance.

The global community is in the process of development an evidence-based, practical strategy for feeding of infants in the first year of life aimed at preventing of FA. Moreover, one of the important components of this strategy may, over time, be the early introduction of highly allergenic products [29]. Interventions aimed at the formation of oral tolerance through early dosed systematic introduction of highly allergenic foods into the diet of a child in the first half of the year have not currently been introduced in Russian pediatric practice [1].

Exposing the body to a variety of food antigens at a certain age may stimulate the formation of immunological tolerance. However, the protective effect of timely introduction of complementary foods can also be realized through the so-called Diet diversity, which is defined as the number of types of foods or food groups in a person's diet over a certain period of time. Studies, conducted in infants at the age of introduction of complementary foods, show a greater diversity of microbiota with a greater variety of diet, which, in turn, can lead to a decrease in the risk of allergies [30].

CONCLUSION

In the field of prevention, diagnosis and treatment of food allergies in children at the present time, there are significant unresolved problems.

1. Low awareness of primary care physicians about the difference between the detection of specific IgE and clinically significant food allergies.

2. Lack of protocols and approved recommendations for conducting PT in outpatient clinics.

3. Insufficient data on clinical and laboratory markers of the formation of food tolerance in patients with different mechanisms of pathogenesis (IgE-dependent and independent forms) and different clinical manifestations (gastrointestinal, skin, respiratory, systemic) of food allergy.

4. Limited therapeutic arsenal for acute allergic reactions to food (in particular, the lack of adrenaline autoinjectors).

5. Limited use of staged dietary expansion in patients who have achieved clinical remission of food allergy as a result of an elimination diet.

Nevertheless, the problem of food allergy continues to concentrate the efforts of both the international community and domestic scientists to conduct research and subsequently develop recommendations for the implementation of the results obtained in real clinical practice.

ADDITIONAL INFORMATION

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

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

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

REFERENCES

1. Pischevaya allergiya. [Food allergy]. Klinicheskie rekomendatsii. Sojuz pediatrov Rossii. 2021. Available at https://www.pediatr-russia.ru/information/klinrek/proekty-klinicheskikh-rekomendatsiy/index.php (accessed 01.02.2024). (in Russian).
2. Jutel M., Agache I., Zemelka-Wiacek M. et al. Nomenclature of allergic diseases and hypersensitivity reactions: Adapted to modern needs: An EAACI position paper. Allergy. 2023;78:2851–2874. DOI: 10.1111/all.15889.
3. Pischevaya neperenosimost u detey. Sovremennye aspekty diagnostiki, lecheniya, profilatiki i dietoterapii. [Food intolerance in children. Modern aspects of diagnosis, treatment, prevention and diet therapy]. Pod red. Ivanova D.O., Novikovoi V.P., Kosenkovoi T.V. Санкт-Петербург; 2018. (in Russian).
4. Savage J., Johns C.B. Food Allergy: Epidemiology and Natural History. Immunol Allergy Clin North Am. 2015;35(1):45–59.
5. Nwaru B.I., Hickstein L., Panesar S.S. et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. Allergy. 2014;69(1):62–75.
6. Spolidoro G.C.I., Ali M.M., Amera Y.T. et al. Prevalence estimates of eight big food allergies in

Europe: Updated systematic review and meta-analysis. Allergy. 2023;78:2361–2417. DOI: 10.1111/all.15801.
7. Lepeshkova T.S. Prichinno-zhnachimye allergeny i spektr sensibilizatsii detey, perenesshikh pischevuju anafilaksiju. [Causative allergens and sensitization spectrum in children with the history of food-induced anaphylaxis]. Rossiyskiy meditsinskiy zhurnal. Meditsinskoe obozrenie. 2023;7(2):75–80. DOI: 10.32364/2587-6821-2023-7-2-75-80. (in Russian).
8. Locke A., Hung L., Upton J.E.M., O'Mahony L., Hoang J., Eiwegger T. An update on recent developments and highlights in food allergy. Allergy. 2023;78:2344–2360. DOI: 10.1111/all.15749.
9. Santos A.F., Riggioni C., Agache I. et al. EAACI guidelines on the diagnosis of IgE-mediated food allergy. Allergy. 2023;78:3057–3076. DOI: 10.1111/all.15902.
10. Luyt D., Ball H., Makwana N., Green M.R., Bravin K., Nasser S.M., Clark A.T. BSACI guideline for the diagnosis and management of cow's milk allergy. Clinical & Experimental Allergy. 2014;44:642–672.
11. Riggioni C., Ricci C., Moya B. et al. Systematic review and meta-analyses on the accuracy of diagnostic tests for IgE-mediated food allergy. Allergy. 2024;79:324–352. DOI: 10.1111/all.15939.
12. Campbell D.E. Role of food allergy in childhood atopic dermatitis. Journal of Paediatrics and Child Health. 2012;48:1058–1064.
13. Krogulska A., Dynowski J., Funkowicz M., Małachowska B., Wąsowska-Królikowska K. Prevalence and Clinical Impact of IgE-Mediated Food Allergy in School Children With Asthma: A Double-Blind Placebo-Controlled Food Challenge Study. Allergy Asthma Immunol Res. 2015;7(6):547–56. DOI: 10.4168/aair.2015.7.6.547.
14. Geppe N.A., Kolosova N.G., Kondjurina E.G., Malakhov A.B., Revyakina V.A. i dr. Natsionalnaya Programma. Bronchialnaya astma u detey. Strategya lechenija i proilaktika. [Bronchial asthma in children. Treatment and prophylaxis strategy]. 6 izd., pererab. i dop. Moskva: MedKom-Pro Publ.; 2021. (in Russian).
15. Shakhova N.V., Kamaltynova E.M., Lobanov Ju.F., Kashinskaya T.S. Rasprostranennost allegicheskoy i neallegicheskoy bronkhialnoy astmy i spektr sensibilizatsii sredi detey doshkolnogo vozrasta, prozhivajuschikh v gorodskikh uslovijakh Altaiskogo kraja: populjatsionnoe odnomomentnoe issledovanie. [The prevalence of allergic and non-allergic bronchial asthma and the spectrum of sensitization among children of preschool age living in urban areas of the Altai Territory: a momentary population study]. Rossiyskiy vestnik perinatologii i pediatrii. 2019;64(1):88–93. DOI: 10.21508/1027-4065-2019-64-1-88-93. (in Russian).
16. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA). 2023. Available at: https://ginasthma.org/2023-gina-main-report/. (accessed 01.02.2024).
17. De Silva D., Halken S., Singh C. et al. on behalf of European Academy of Allergy, Clinical Immunology Food Allergy, Anaphylaxis Guidelines Group. Preventing food allergy in infancy and childhood: Systematic review of randomised controlled trials. Pediatr Allergy Immunol. 2020;31:813–826. DOI: 10.1111/pai.13273.
18. Halken S., Muraro A., de Silva D., Khaleva E., Angier E., Arasi S. et al. European Academy of Allergy and Clinical Immunology Food Allergy and Anaphylaxis Guidelines Group. EAACI guideline: Preventing the development of food allergy in infants and young children (2020 update). Pediatr Allergy Immunol. 2021;32(5):843–858. DOI: 10.1111/pai.13496.
19. Vandenplas Y., Latiff A.H.A., Fleischer D.M., Gutiérrez-Castrellón P., Miqdady M.-I.S., Smith P.K. et al. Partially hydrolyzed formula in non-exclusively breastfed infants: A systematic review and expert consensus. Nutrition. 2019;57:268–274. DOI: 10.1016/j.nut.2018.05.018.
20. Metodicheskie rekomendatsii po primeneniju u detey smesey na osnove chastichno gidrolizovannogo belka. [Guidelines for the use of formulas based on partially hydrolyzed protein in children]. Sojuz pediatrov Rossii. 2023. Available at https://www.pediatr-russia.ru/upload/%D0%A7%D0%93%D0%A1%2020.01.2023.pdf (accessed 01.02.2024). (in Russian).
21. Adam T., Divaret-Chauveau A., Roduit C. et al. Complementary feeding practices are related to the risk of food allergy in the ELFE cohort. Allergy. 2023; 78:2456–2466. DOI: 10.1111/all.15828.
22. Makarova S.G., Lavrova T.E., Vishyeva E.A., Turti T.V., Akoev Ju.S., Petrovskaya M.I. Pervichnaya profilaktika kak effektivny otvet na epidemiju allergicheskikh bolezney. [Primary Prevention as an Effective Response to the Epidemic of Allergic Diseases]. Pediatricheskaya farmakologija. 2015;12(1):67–74. (in Russian).
23. Revyakina V.A., Melnikova K.S. Sovremennyi podkhod k formirovaniju ratsiona pitanija rebenka pervogo goda zhizni. [A modern approach to shaping the diet of a child in the first year of life]. Doktor.Ru. 2020; 19(3): 44–47. DOI: 10.31550/1727-2378-2020-19-3-44-47. (in Russian).
24. Sicherer S.H., Sampson H.A. Food allergy: A review and update on epidemiology, pathogenesis,

diagnosis, prevention, and management. J Allergy Clin Immunol. 2018; 141(1):41–58. DOI: 10.1016/j.jaci.2017.11.003.
25. Fisher H.R., Toit G.D., Bahnson H.T., Lack G. The challenges of preventing food allergy. Annals of Allergy, Asthma & Immunology. 2018; 121(3):313–319. DOI: 10.1016/j.anai.2018.06.008
26. Du Toit G., Roberts G., Sayre P.H. et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015; 372(9):803–813.
27. Perkin M.R., Logan K., Tseng A. et al. Randomized trial of introduction of allergenic foods in breastfed infants. N Engl J Med. 2016; 374(18):1733–1743.
28. Ierodiakonou D., Garcia-Larsen V., Logan A. et al. Timing of allergenic food introduction to the infant diet and risk of allergic or autoimmune disease: a systematic review and meta-analysis. JAMA. 2016; 316(11):1181–1192.
29. McWilliam V., Venter C., Greenhawt M. et al. A pragmatic approach to infant feeding for food allergy prevention. Pediatr Allergy Immunol. 2022; 33:e13849. DOI: 10.1111/pai.13849.
30. Venter C., Greenhawt M., Meyer R.W. et al. EAACI position paper on diet diversity in pregnancy, infancy and childhood: Novel concepts and implications for studies in allergy and asthma. Allergy. 2019; 75:497–523. DOI: 10.1111/all.14051.

ЛИТЕРАТУРА

1. Пищевая аллергия. Клинические рекомендации. Союз педиатров России. 2021. Доступен по: https://www.pediatr-russia.ru/information/klinrek/proekty-klinicheskikh-rekomendatsiy/index.php (дата обращения 01.02.2024).
2. Jutel M., Agache I., Zemelka-Wiacek M. et al. Nomenclature of allergic diseases and hypersensitivity reactions: Adapted to modern needs: An EAACI position paper. Allergy. 2023;78:2851–2874. DOI:10.1111/all.15889.
3. Пищевая непереносимость у детей. Современные аспекты диагностики, лечения, профилактики и диетотерапии. Под ред. Д.О. Иванова, В.П. Новиковой, Т.В. Косенковой. СПб.; 2018.
4. Savage J., Johns C.B. Food Allergy: Epidemiology and Natural History. Immunol Allergy Clin North Am. 2015;35(1):45–59.
5. Nwaru B.I., Hickstein L., Panesar S.S. et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. Allergy. 2014;69(1):62–75.
6. Spolidoro G.C.I., Ali M.M., Amera Y.T. et al. Prevalence estimates of eight big food allergies in Europe: Updated systematic review and meta-analysis. Allergy. 2023;78:2361–2417. DOI: 10.1111/all.15801.
7. Лепешкова Т.С. Причинно-значимые аллергены и спектр сенсибилизации детей, перенесших пищевую анафилаксию. РМЖ. Медицинское обозрение. 2023;7(2):75–80. DOI: 10.32364/2587-6821-2023-7-2-75-80.
8. Locke A., Hung L., Upton J.E.M., O'Mahony L., Hoang J., Eiwegger T. An update on recent developments and highlights in food allergy. Allergy. 2023;78:2344–2360. DOI: 10.1111/all.15749.
9. Santos A.F., Riggioni C., Agache I., et al. EAACI guidelines on the diagnosis of IgE-mediated food allergy. Allergy. 2023;78:3057–3076. DOI: 10.1111/all.15902.
10. Luyt D., Ball H., Makwana N., Green M.R., Bravin K., Nasser S.M., Clark A.T. BSACI guideline for the diagnosis and management of cow's milk allergy. Clinical & Experimental Allergy. 2014;44:642–672.
11. Riggioni C., Ricci C., Moya B. et al. Systematic review and meta-analyses on the accuracy of diagnostic tests for IgE-mediated food allergy. Allergy. 2024;79:324–352. DOI: 10.1111/all.15939.
12. Campbell D.E. Role of food allergy in childhood atopic dermatitis. Journal of Paediatrics and Child Health. 2012;48:1058–1064.
13. Krogulska A., Dynowski J., Funkowicz M., Małachowska B., Wąsowska-Królikowska K. Prevalence and Clinical Impact of IgE-Mediated Food Allergy in School Children With Asthma: A Double-Blind Placebo-Controlled Food Challenge Study. Allergy Asthma Immunol Res. 2015;7(6):547–56. DOI: 10.4168/aair.2015.7.6.547.
14. Геппе Н.А., Колосова Н.Г., Кондюрина Е.Г., Малахов А.Б., Ревякина В.А. и др. Национальная программа. Бронхиальная астма у детей. Стратегия лечения и профилактика. 6 изд., перераб. и доп. М.: МедКом-Про; 2021.
15. Шахова Н.В., Камалтынова Е.М., Лобанов Ю.Ф., Кашинская Т.С. Распространенность аллергической и неаллергической бронхиальной астмы и спектр сенсибилизации среди детей дошкольного возраста, проживающих в городских условиях Алтайского края: популяционное одномоментное исследование. Рос. вестн. перинатол. и педиатр. 2019;64(1):88–93. DOI: 10.21508/1027-4065-2019-64-1-88-93.
16. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2023. Available at: https://ginasthma.org/2023-gina-main-report/. (accessed 01.02.2024).
17. De Silva D., Halken S., Singh C., et al. on behalf of European Academy of Allergy, Clinical Immunology Food Allergy, Anaphylaxis Guidelines Group. Preventing food allergy in infancy and childhood:

Systematic review of randomised controlled trials. Pediatr Allergy Immunol. 2020;31:813–826. DOI: 10.1111/pai.13273.
18. Halken S., Muraro A., de Silva D., Khaleva E., Angier E., Arasi S. et al. European Academy of Allergy and Clinical Immunology Food Allergy and Anaphylaxis Guidelines Group. EAACI guideline: Preventing the development of food allergy in infants and young children (2020 update). Pediatr Allergy Immunol. 2021;32(5):843–858. DOI: 10.1111/pai.13496.
19. Vandenplas Y., Latiff A.H.A., Fleischer D.M., Gutiérrez-Castrellón P., Miqdady M.-I.S., Smith P.K. et al. Partially hydrolyzed formula in non-exclusively breastfed infants: A systematic review and expert consensus. Nutrition. 2019;57:268–274. DOI: 10.1016/j.nut.2018.05.018.
20. Методические рекомендации по применению у детей смесей на основе частично гидролизованного белка. Союз педиатров России. 2023. Доступен по: https://www.pediatr-russia.ru/upload/%D0%A7%D0%93%D0%A1%2020.01.2023.pdf (дата обращения 01.02.2024).
21. Adam T., Divaret-Chauveau A., Roduit C. et al. Complementary feeding practices are related to the risk of food allergy in the ELFE cohort. Allergy. 2023;78:2456–2466. DOI: 10.1111/all.15828.
22. Макарова С.Г., Лаврова Т.Е., Вишнева Е.А., Турти Т.В., Акоев Ю.С., Петровская М.И. Первичная профилактика как эффективный ответ на эпидемию аллергических болезней. Педиатрическая фармакология. 2015;12(1):67–74.
23. Ревякина В.А., Мельникова К.С. Современный подход к формированию рациона питания ребенка первого года жизни. Доктор.Ру. 2020;19(3):44–47. DOI: 10.31550/1727-2378-2020-19-3-44-47.
24. Sicherer S.H., Sampson H.A. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J Allergy Clin Immunol. 2018;141(1):41–58. DOI: 10.1016/j.jaci.2017.11.003.
25. Fisher H.R., Toit G.D., Bahnson H.T., Lack G. The challenges of preventing food allergy. Annals of Allergy, Asthma & Immunology. 2018;121(3):313–319. DOI: 10.1016/j.anai.2018.06.008.
26. Du Toit G., Roberts G., Sayre P.H. et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015;372(9):803–813.
27. Perkin M.R., Logan K., Tseng A. et al. Randomized trial of introduction of allergenic foods in breast-fed infants. N Engl J Med. 2016;374(18):1733–1743.
28. Ierodiakonou D., Garcia-Larsen V., Logan A. et al. Timing of allergenic food introduction to the infant diet and risk of allergic or autoimmune disease: a systematic review and meta-analysis. JAMA. 2016;316(11):1181–1192.
29. McWilliam V., Venter C., Greenhawt M. et al. A pragmatic approach to infant feeding for food allergy prevention. Pediatr Allergy Immunol. 2022;33:e13849. DOI: 10.1111/pai.13849.
30. Venter C., Greenhawt M., Meyer R.W. et al. EAACI position paper on diet diversity in pregnancy, infancy and childhood: Novel concepts and implications for studies in allergy and asthma. Allergy. 2019;75:497–523. DOI: 10.1111/all.14051.