Review / Обзор

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

REV — обзорная статья

https://doi.org/10.53529/2500-1175-2024-3-19-29

Date of receipt: 23.07.2024
Date of acceptance: 31.08.2024
Date of publication: 30.09.2024

Albina A. Galimova, Svetlana G. Makarova

National Medical Research Center of Children's Health of the Ministry of Health of the Russian Federation, 119296, Lomonosovsky Prospekt, 2, building 1, Moscow, Russia

Albina Albertovna Galimova — Junior Researcher at the Laboratory of Clinical Immunology and Nutritional Science of National Medical Research Center of Children's Health, ORCID ID: 0000-0002-6701-3872, e-mail: albina86@yandex.ru.

Svetlana Gennadyevna Makarova — Dr. Sci., Professor, Deputy Director of National Medical Research Center of Children's Health. ORCID ID: 0000-0002-3056-403X, e-mail: sm27@yandex.ru.

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.

For citation: Galimova A.A., Makarova S.G. Reintroduction of excluded food triggers as a crucial step in managing patients with food allergies. *Allergology and Immunology in Pediatrics*. 2024; 22(3): 19–29. https://doi.org/10.53529/2500-1175-2024-3-19-29

For correspondence:
Albina Albertovna Galimova, junior researcher at the Laboratory of Clinical Immunology and Nutritional Science of National Medical Research Center of Children's Health.

Address: 119296, Moscow, Lomonosovsky Prospect, 2, bldg. 1, Russia.

E-mail: albina86@yandex.ru.

Для корреспонденции:
Галимова Альбина Альбертовна, младший научный сотрудник лаборатории клинической иммунологии и нутрициологии, врач аллерголог-иммунолог отделения стационар-замещающих технологий ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Минздрава России.

Адрес: 119296, г. Москва, Ломоносовский проспект, 2, стр. 1, Россия.

E-mail: albina86@yandex.ru.

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

https://doi.org/10.53529/2500-1175-2024-3-19-29

УДК 616-08-031.81
Дата поступления: 23.07.2024
Дата принятия: 31.08.2024
Дата публикации: 30.09.2024

Галимова А. А., Макарова С. Г.

ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Министерства здравоохранения Российской Федерации, 119296, Ломоносовский проспект, 2, стр. 1, г. Москва, Россия

Галимова Альбина Альбертовна — младший научный сотрудник лаборатории клинической иммунологии и нутрициологии ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Минздрава России, ORCID ID: 0000-0002-6701-3872, e-mail: albina86@yandex.ru.

Макарова Светлана Геннадиевна — д. м. н., доцент, заместитель директора по научной работе ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Минздрава России, ORCID ID: 0000-0002-3056-403X, e-mail: sm27@yandex.ru.

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

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

Для цитирования: Галимова А.А., Макарова С.Г. Реинтродукция исключенных пищевых триггеров как важный этап ведения пациентов с пищевой аллергией. *Аллергология и иммунология в педиатрии*. 2024; 22 (3): 19–29. https://doi.org/10.53529/2500-1175-2024-3-19-29

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.

REFERENCES

1. Burney P.G., Potts J., Kummeling I., et al. The prevalence and distribution of food sensitization in European adults. Allergy. 2014; 69 (3): 365–371. https://doi.org/10.1111/all.12341.
2. Muraro A., Roberts G., Worm M., et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy. 2014; 69 (8): 1026–1045. https://doi.org/10.1111/all.12437.
3. Clinical guidelines. Food allergy [internet]. 2021. (In Russ.)
4. Makarova S.G., Balabolkin I.I., Fisenko A.P. Food allergy in children and adolescents: monograph. Moscow: FGAU "NMIC of Children's Health" of the Ministry of Health of Russia; 2021. 288 p. (Informational materials) (In Russ.)
5. Dambacher W.M., de Kort E.H., Blom W.M., Houben G.F., de Vries E. Double-blind placebo-controlled food challenges in children with alleged cow's milk allergy: prevention of unnecessary elimination diets and determination of eliciting doses. Nutr J. 2013; 12 (1): 12–22. https://doi.org/10.1186/1475-2891-12-22.

6. Miceli Sopo S., Monaco S., Greco M., Onesimo R. Prevalence of adverse reactions following a passed oral food challenge and factors affecting successful re-introduction of foods. A retrospective study of a cohort of 199 children. Allergol Immunopathol (Madr). 2016; 44 (1): 54–58. https://doi.org/10.1016/j.aller.2015.04.010.
7. van der Valk J.P., Gerth van Wijk R., Dubois A.E., de Groot H., de Jong N.W. Failure of introduction of cashew nut after a negative oral food challenge test in children. Pediatr Allergy Immunol. 2016; 27 (6): 654–658. https://doi.org/10.1111/pai.12591.
8. Oole-Groen C.J., Brand P.L. Double-blind food challenges in children in general paediatric practice: useful and safe, but not without pitfalls. Allergol Immunopathol (Madr). 2014; 42 (4): 269–274. https://doi.org/10.1016/j.aller.2013.06.005.
9. Strinnholm A., Winberg A., Hedman L., Ronmark E., Lindh V. Reintroduction failure is common among adolescents after double-blind placebo-controlled food challenges. Acta Paediatr. 2017; 106 (2): 282–287. https://doi.org/10.1111/apa.13673.
10. Meyer R., Venter C., Bognanni A., et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guideline update - VII - Milk elimination and reintroduction in the diagnostic process of cow's milk allergy. World Allergy Organ J. 2023; 16 (7): 100785. https://doi.org/10.1016/j.waojou.2023.100785.
11. Gau J., Wang J. Rate of food introduction after a negative oral food challenge in the pediatric population. J Allergy Clin Immunol Pract. 2017; 5 (2): 475–476. https://doi.org/10.1016/j.jaip.2016.06.027.
12. Fiocchi A., Bognanni A., Brożek J., Ebisawa M., Schünemann H.; WAO DRACMA guideline group. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines update - I - Plan and definitions. World Allergy Organ J. 2022; 15 (1): 100609. https://doi.org/10.1016/j.waojou.2021.100609.
13. Wambre E., Jeong D., Tordesillas L., Berin M.C. Oral Tolerance Development and Maintenance. Immunol Allergy Clin North Am. 2018; 38 (1): 27–37. https://doi.org/10.1016/j.iac.2017.09.003.
14. Satitsuksanoa P., Jansen K., Głobińska A., et al. Regulatory immune mechanisms in tolerance to food allergy. Front Immunol. 2018; 9: 2939. https://doi.org/10.3389/fimmu.2018.02939.
15. Ho H.E., Bunyavanich S. Role of the microbiome in food allergy. Curr Allergy Asthma Rep. 2018; 18 (4): 27. doi:10.1007/s11882-018-0780-z.
16. Du Toit G., Sampson H.A., Plaut M., Burks A.W., Akdis C.A., Lack G. Food allergy: Update on prevention and tolerance. J Allergy Clin Immunol. 2018; 141 (1): 30–40. https://doi.org/10.1016/j.jaci.2017.11.010.
17. Ditlof C., Hummel R., Wong S., Alexanian-Farr M., et al. Food reintroduction after passing an oral food challenge: A cross-sectional structured interview-based assessment of barriers, challenges, and impact on quality of life. J Allergy Clin Immunol. 2021; 147 (2 Suppl). https://doi.org/10.1016/j.jaci.2020.12.057.
18. Vandenplas Y., Broekaert I., Domellöf M., et al. An ESPGHAN position paper on the diagnosis, management and prevention of cow's milk allergy. J Pediatr Gastroenterol Nutr. Published online July 26, 2023. https://doi.org/10.1097/MPG.0000000000003897.
19. Aguirre C.P.M., Vasconcelos P.D.S.P., Caldas J.P.S., Lomazi E.A., Bellomo-Brandão M.A. Induced proctocolitis - oral food challenge should be done to confirm the diagnosis of cow's milk allergy in neonates? Arq Gastroenterol. 2022; 59 (3): 365–369. https://doi.org/10.1590/S0004-2803.202203000-66.
20. Martin V.M., Virkud Y.V., Phadke N.A., Su K.W., Seay H., Atkins M.R., Keet C., Shreffler W.G., Yuan Q. Increased IgE-mediated food allergy with food protein-induced allergic proctocolitis. Pediatrics. 2020; 146 (3). https://doi.org/10.1542/peds.2020-0202.
21. Emelyashenkov E.E., Makarova S.G., Murashkin N.N., Galimova A.A., Pronina I.Y., Yasakov D.S. Influence of an elimination diet on the quality of life and eating behavior of children with severe atopic dermatitis and food allergies. Med Al'fab. 2023; (8): 69–74. https://doi.org/10.33667/2078-5631-2023-8-69-74. (In Russ.)
22. Athanasopoulou P., Deligianni E., Dean T., Dewey A., Venter C. Use of baked milk challenges and milk ladders in clinical practice: a worldwide survey of healthcare professionals. Clin Exp Allergy. 2017; 47 (3): 430–434. https://doi.org/10.1111/cea.12890.
23. Nowak-Wegrzyn A., Bloom K.A., Sicherer S.H., Shreffler W.G., Noone S., Wanich N., Sampson H.A. Tolerance to extensively heated milk in children with cow's milk allergy. J Allergy Clin Immunol. 2008; 122 (2): 342–347.e2. https://doi.org/10.1016/j.jaci.2008.05.043.
24. Monaco S., Russo G., Romano A., et al. Yogurt is tolerated by the majority of children with IgE-mediated cow's milk allergy. Allergol Immunopathol. 2019; 47: 322–327. https://doi.org/10.1016/j.aller.2018.10.005.
25. Ayats-Vidal R., Valdesoiro-Navarrete L., García-González M., Asensio-De la Cruz O., Larramona-Carrera H., Bosque-García M. Predictors of a positive oral food challenge to cow's milk in children sensitized to cow's milk. Allergol Immunopathol (Madr). 2020; 48 (6): 568–575. https://doi.org/10.1016/j.aller.2020.03.007.
26. Ogata M., Yoshida T., Kido J., et al. Safety of oral food challenge for individuals with low egg white and ovomucoid-specific IgE antibodies. Int Arch Allergy Immunol. 2024; 185 (1): 33–42. https://doi.org/10.1159/000531955.

27. Kabil N., Stokes J. Cracking the Egg: Predictors of Baked Egg Oral Food Challenge Outcomes. Ann Allergy Asthma Immunol. 2018; 121 (5 Suppl).
28. Venter C., Meyer R., Ebisawa M., Athanasopoulou P., Mack D.P. Food allergen ladders: A need for standardization. Pediatr Allergy Immunol. 2022; 33 (1). https://doi.org/10.1111/pai.13714.
29. Meyer R., De Koker C., Dziubak R., Godwin H., Reeve K., Chebar-Lozinsky A., Foong R.-X., Skrapac A.-K., Ellmer M., Shah N. The Challenge of Home Allergen Reintroductions Using the Ladder Approach in Children With Non-IgE Mediated Gastrointestinal Food Allergy. Front Allergy. 2021; 2: 721686. https://doi.org/10.3389/falgy.2021.721686.
30. Ye L., Wong T., Lavine E., Cook V.E., Erdle S.C. Using the Canadian egg ladder in children with food protein-induced enterocolitis syndrome: a case series. Allergy Asthma Clin Immunol. 2023; 19 (1): 87. https://doi.org/10.1186/s13223-023-00843-x.
31. Bognanni A., Chu D.K., Firmino R.T., et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guideline update - XIII - Oral immunotherapy for CMA — Systematic review. World Allergy Organ J. 2022; 15 (9): 100682. https://doi.org/10.1016/j.waojou.2022.100682.
32. Pajno G.B., Fernandez-Rivas M., Arasi S., et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy. 2018; 73 (4): 799–815. https://doi.org/10.1111/all.13319.
33. Guillaume P., Guillaume L. Oral immunotherapy for food allergy: Translation from studies to clinical practice? World Allergy Organ J. 2023; 16 (2): 100747. doi:10.1016/j.waojou.2023.100747.
34. Brozek J.L., Firmino R.T., Bognanni A., et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guideline update - XIV — Recommendations on CMA immunotherapy. World Allergy Organ J. 2022; 15 (4): 100646. https://doi.org/10.1016/j.waojou.2022.100646.

ЛИТЕРАТУРА

35. Burney P.G., Potts J., Kummeling I., et al. The prevalence and distribution of food sensitization in European adults. Allergy. 2014; 69 (3): 365–371. https://doi.org/10.1111/all.12341.
36. Muraro A., Roberts G., Worm M., et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy. 2014; 69 (8): 1026–1045. https://doi.org/10.1111/all.12437.
37. Клинические рекомендации. Пищевая аллергия [интернет]. 2021.
38. Макарова С.Г., Балаболкин И.И., Фисенко А.П. Пищевая аллергия у детей и подростков: монография. Москва: ФГАУ «НМИЦ здоровья детей» Минздрава России; 2021. 288 с. (Информационные материалы)
39. Dambacher W.M., de Kort E.H., Blom W.M., Houben G.F., de Vries E. Double-blind placebo-controlled food challenges in children with alleged cow's milk allergy: prevention of unnecessary elimination diets and determination of eliciting doses. Nutr J. 2013; 12 (1): 12–22. https://doi.org/10.1186/1475-2891-12-22.
40. Miceli Sopo S., Monaco S., Greco M., Onesimo R. Prevalence of adverse reactions following a passed oral food challenge and factors affecting successful re-introduction of foods. A retrospective study of a cohort of 199 children. Allergol Immunopathol (Madr). 2016; 44 (1): 54–58. https://doi.org/10.1016/j.aller.2015.04.010.
41. van der Valk J.P., Gerth van Wijk R., Dubois A.E., de Groot H., de Jong N.W. Failure of introduction of cashew nut after a negative oral food challenge test in children. Pediatr Allergy Immunol. 2016; 27 (6): 654–658. https://doi.org/10.1111/pai.12591.
42. Oole- Groen C.J., Brand P.L. Double-blind food challenges in children in general paediatric practice: useful and safe, but not without pitfalls. Allergol Immunopathol (Madr). 2014; 42 (4): 269–274. https://doi.org/10.1016/j.aller.2013.06.005.
43. Strinnholm A., Winberg A., Hedman L., Ronmark E., Lindh V. Reintroduction failure is common among adolescents after double-blind placebo-controlled food challenges. Acta Paediatr. 2017; 106 (2): 282–287. https://doi.org/10.1111/apa.13673.
44. Meyer R., Venter C., Bognanni A., et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guideline update - VII - Milk elimination and reintroduction in the diagnostic process of cow's milk allergy. World Allergy Organ J. 2023; 16 (7): 100785. https://doi.org/10.1016/j.waojou.2023.100785.
45. Gau J., Wang J. Rate of food introduction after a negative oral food challenge in the pediatric population. J Allergy Clin Immunol Pract. 2017; 5 (2): 475–476. https://doi.org/10.1016/j.jaip.2016.06.027.
46. Fiocchi A., Bognanni A., Brożek J., Ebisawa M., Schünemann H.; WAO DRACMA guideline group. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines update - I - Plan and definitions. World Allergy Organ J. 2022; 15 (1): 100609. https://doi.org/10.1016/j.waojou.2021.100609.
47. Wambre E., Jeong D., Tordesillas L., Berin M.C. Oral Tolerance Development and Maintenance. Immunol Allergy Clin North Am. 2018; 38 (1): 27–37. https://doi.org/10.1016/j.iac.2017.09.003.

48. Satitsuksanoa P., Jansen K., Głobińska A., et al. Regulatory immune mechanisms in tolerance to food allergy. Front Immunol. 2018; 9: 2939. https://doi.org/10.3389/fimmu.2018.02939.
49. Ho H.E., Bunyavanich S. Role of the microbiome in food allergy. Curr Allergy Asthma Rep. 2018; 18 (4): 27. doi:10.1007/s11882-018-0780-z.
50. Du Toit G., Sampson H.A., Plaut M., Burks A.W., Akdis C.A., Lack G. Food allergy: Update on prevention and tolerance. J Allergy Clin Immunol. 2018; 141 (1): 30–40. https://doi.org/10.1016/j.jaci.2017.11.010.
51. Ditlof C., Hummel R., Wong S., Alexanian-Farr M., et al. Food reintroduction after passing an oral food challenge: A cross-sectional structured interview-based assessment of barriers, challenges, and impact on quality of life. J Allergy Clin Immunol. 2021; 147 (2 Suppl). https://doi.org/10.1016/j.jaci.2020.12.057.
52. Vandenplas Y., Broekaert I., Domellöf M., et al. An ESPGHAN position paper on the diagnosis, management and prevention of cow's milk allergy. J Pediatr Gastroenterol Nutr. Published online July 26, 2023. https://doi.org/10.1097/MPG.0000000000003897.
53. Aguirre C.P.M., Vasconcelos P.D.S.P., Caldas J.P.S., Lomazi E.A., Bellomo-Brandão M.A. Induced proctocolitis - oral food challenge should be done to confirm the diagnosis of cow's milk allergy in neonates? Arq Gastroenterol. 2022; 59 (3): 365–369. https://doi.org/10.1590/S0004-2803.202203000-66.
54. Martin V.M., Virkud Y.V., Phadke N.A., Su K.W., Seay H., Atkins M.R., Keet C., Shreffler W.G., Yuan Q. Increased IgE-mediated food allergy with food protein-induced allergic proctocolitis. Pediatrics. 2020; 146 (3). https://doi.org/10.1542/peds.2020-0202.
55. Емельяшенков Е.Е., Макарова С.Г., Мурашкин Н.Н., Галимова А.А., Пронина И.Ю., Ясаков Д.С. Влияние элиминационной диеты на качество жизни и пищевое поведение детей с тяжелой формой атопического дерматита и пищевой аллергией. Медицинский алфавит. 2023; (8): 69–74. https://doi.org/10.33667/2078-5631-2023-8-69-74.
56. Athanasopoulou P., Deligianni E., Dean T., Dewey A., Venter C. Use of baked milk challenges and milk ladders in clinical practice: a worldwide survey of healthcare professionals. Clin Exp Allergy. 2017; 47 (3): 430–434. https://doi.org/10.1111/cea.12890.
57. Nowak-Wegrzyn A., Bloom K.A., Sicherer S.H., Shreffler W.G., Noone S., Wanich N., Sampson H.A. Tolerance to extensively heated milk in children with cow's milk allergy. J Allergy Clin Immunol. 2008; 122 (2): 342–347.e2. https://doi.org/10.1016/j.jaci.2008.05.043.
58. Monaco S., Russo G., Romano A., et al. Yogurt is tolerated by the majority of children with IgE-mediated cow's milk allergy. Allergol Immunopathol. 2019; 47: 322–327. https://doi.org/10.1016/j.aller.2018.10.005.
59. Ayats-Vidal R., Valdesoiro-Navarrete L., García-González M., Asensio-De la Cruz O., Larramona-Carrera H., Bosque-García M. Predictors of a positive oral food challenge to cow's milk in children sensitized to cow's milk. Allergol Immunopathol (Madr). 2020; 48 (6): 568–575. https://doi.org/10.1016/j.aller.2020.03.007.
60. Ogata M., Yoshida T., Kido J., et al. Safety of oral food challenge for individuals with low egg white and ovomucoid-specific IgE antibodies. Int Arch Allergy Immunol. 2024; 185 (1): 33–42. https://doi.org/10.1159/000531955.
61. Kabil N., Stokes J. Cracking the Egg: Predictors of Baked Egg Oral Food Challenge Outcomes. Ann Allergy Asthma Immunol. 2018; 121 (5 Suppl).
62. Venter C., Meyer R., Ebisawa M., Athanasopoulou P., Mack D.P. Food allergen ladders: A need for standardization. Pediatr Allergy Immunol. 2022; 33 (1). https://doi.org/10.1111/pai.13714.
63. Meyer R., De Koker C., Dziubak R., Godwin H., Reeve K., Chebar-Lozinsky A., Foong R.-X., Skrapac A.-K., Ellmer M., Shah N. The Challenge of Home Allergen Reintroductions Using the Ladder Approach in Children With Non-IgE Mediated Gastrointestinal Food Allergy. Front Allergy. 2021; 2: 721686. https://doi.org/10.3389/falgy.2021.721686.
64. Ye L., Wong T., Lavine E., Cook V.E., Erdle S.C. Using the Canadian egg ladder in children with food protein-induced enterocolitis syndrome: a case series. Allergy Asthma Clin Immunol. 2023; 19 (1): 87. https://doi.org/10.1186/s13223-023-00843-x.
65. Bognanni A., Chu D.K., Firmino R.T., et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guideline update - XIII - Oral immunotherapy for CMA — Systematic review. World Allergy Organ J. 2022; 15 (9): 100682. https://doi.org/10.1016/j.waojou.2022.100682.
66. Pajno G.B., Fernandez-Rivas M., Arasi S., et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy. 2018; 73 (4): 799–815. https://doi.org/10.1111/all.13319.
67. Guillaume P., Guillaume L. Oral immunotherapy for food allergy: Translation from studies to clinical practice? World Allergy Organ J. 2023; 16 (2): 100747. https://doi.org/10.1016/j.waojou.2023.100747.
68. Brozek J.L., Firmino R.T., Bognanni A., et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guideline update - XIV — Recommendations on CMA immunotherapy. World Allergy Organ J. 2022; 15 (4): 100646. https://doi.org/10.1016/j.waojou.2022.100646.

FINANCING SOURCE

The authors state that there is no external funding for the study.

ИСТОЧНИК ФИНАНСИРОВАНИЯ

Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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.