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Oral food challenges in clinical practice: a missing element of food allergy diagnosis in Russia

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Food allergy is one of the most prevalent allergic conditions, causing reduction in patient quality of life. It is linked with high levels of anxiety due to potential life-threatening reactions, and high economic burden for a healthcare system. Food allergy affects approximately 5 to 10% of children around the world. In Russian Federation the diagnosis of food allergy is primarily based on clinical history, laboratory test results, examination and elimination of suspected food. Meanwhile oral food challenge (OFC) is considered a “gold standard” of food allergy diagnosis by most of professional bodies nationally and internationally. OFC is a diagnostic procedure involving administration of a causative allergen in gradually increasing amount under a close medical supervision. The method is safe, highly specific and sensitive and is widely used around the world for more than 45 years. The main goals of OFC include food allergy diagnosis and presence of tolerance evaluation, which may result in diet expansion. OFC may also help establishing both, reaction severity and dose needed to elicit reaction, which may further assist with alleviation of patients' anxiety. In this paper we discuss existing approaches to the diagnosis of food allergy in Russian Federation and review available recommendations on OFC outlined in international guidelines.

Keywords: oral food challenge, food allergy, egg, milk, peanut, allergy diagnosis, quality of life

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Провокационные пробы в клинической практике: недостающее звено в диагностике пищевой аллергии в России

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Пищевая аллергия – заболевание, оказывающее негативное влияние на качество жизни миллионов человек, а также представляющее огромное физическое и экономическое бремя как для пациента и его семьи, так и для государства. Распространенность пищевой аллергии среди детского населения составляет в среднем от 5 до 10%. Основным методом диагностики пищевой аллергии в Российской Федерации является тщательный анализ данных анамнеза, клинической картины и результатов лабораторных исследований, а универсальным методом подтверждения диагноза является диагностическая элиминационная диета, в то время как «золотым стандартом» диагностики в протоколах зарубежных профессиональных сообществ является проведение провокационных проб. Данный метод заключается в употреблении в пищу «подозреваемого» продукта в возрастающем количестве под контролем медицинского персонала. При четком следовании протоколу проведения он является безопасным и благодаря своей высокой диагностической значимости широко используется во многих странах мира более 45 лет. Проведение провокационных проб может быть использовано с целью расширения диеты пациента с подтвержденной пищевой аллергией, а возможность оценить точную дозу аллергена, необходимую для возникновения реакции, вместе с употреблением продукта под контролем медицинского персонала снижает уровень тревожности как самого пациента, так и его семьи. Таким образом, провокационные пробы являются достоверным, безопасным, широко применяемым методом диагностики пищевой аллергии. В данном литературном обзоре обсуждаются недостатки рутинных методов диагностики [проведения кожных проб, определения

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аллерген-специфического IgE (allergen-specific IgE – asIgE)], а также проводится сравнение методик выполнения провокационных проб в разных странах мира, подходов к их использованию, расчету дозы аллергена и интерпретации результатов провокационной пробы.

Ключевые слова: провокационные пробы, пищевая аллергия, аллергология, белок коровьего молока, яйцо, арахис, диагностика аллергии, качество жизни

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Introduction

Food allergy (FA) is a common chronic disease associated with a negative impact on the quality of life. It represents a significant physical and economic burden, both for the patients, their families, and health care system [1, 2]. An approximate of 7 million people in Europe suffer from food allergies, and one in ten of food allergic patients report anaphylaxis [3]. The prevalence of the disease among children is higher than in adults [4] and varies between 5 and 10%, depending on the country of residence [5–9]. The number of adults believing that they have an allergic reaction to food is approximately 17% [10]. In the absence of the large epidemiological studies, data on the prevalence of allergic diseases in the Russian Federation are very limited, with an estimated 5 and 30% [11].

The correct diagnosis is important both, to avoid inappropriate elimination diet in tolerant individuals and to prevent reactions in people who suffer from FA. The main approach to FA diagnosis in the Russian Federation remains a thorough analysis of clinical history, symptoms, and laboratory test results, with the elimination of the causative food used as a universal method for diagnosis confirmation [12, 13]. This approach is far from perfection, however, due to the frequent discrepancy between the clinical picture and laboratory tests results and the likelihood of symptoms misinterpretation by patients and their families. It should also be noted, that skin prick tests (SPT) and measurement of specific IgE (sIgE) in blood serum, do not always possess sufficient prognostic value [14]. It is worth noting, that SPT are still not widely used in the Russian Federation, and data on the predictive value of the commonly used skin scarification tests are quite limited. Diagnostic elimination diet, remaining an important part of routine clinical practice is associated with reduced quality of life for patients and their families, takes a long time, and is not always accurate due to potential accidental exposure.

Oral food challenge (OFC) is considered a “gold standard” approach for food allergy diagnosis in many countries [9, 15–17]. This method allows not only to assess allergic reaction presence or absence but also gives a better understanding of the dose of the allergen required to elicit a reaction. This may decrease the fear of accidental exposure

to an allergen in the future and reduces the anxiety [18]. OFC can also be used to monitor tolerance development, which is very useful for the diet expansion.

This manuscript reviews different approaches to OFC in different countries.

Food allergy diagnosis in the Russian Federation

According to the clinical recommendations of the Russian Pediatric Union, the diagnosis is made on the basis of the clinical history, symptoms evaluation and determination of the sIgE levels, skin testing, and diagnostic elimination diet. The authors of this document emphasize that the elimination diet is the only method that can be used for the diagnosis of both IgE-mediated and non-IgE-mediated FA [12].

Unfortunately, in routine clinical practice, physician often faces unclear clinical picture and ambiguous results of clinical examination and laboratory tests. Recent systematic review assessed prognostic abilities of SPT and sIgE antibodies and found substantial variations in the test sensitivity and specificity, depending on the specific allergen (Table 1). Although sensitivity was high, the specificity remains relatively low [14]. Given widespread use of the scarification skin tests in Russian Federation it is not possible to extrapolate outcomes of the systematic review, collating evidence on SPT, on the predictive value of scarification tests. Therefore, the prognostic value of scarification tests remains unclear.

The prognostic value of SPT and sIgE can be influenced by a number of factors, such as patient’s age and ethnicity, site of SPT performance, the presence of dermatographism, time of the day, technique of diagnostic test performance and the quality of allergen solutions used [19, 20]. It is also important to note, that studies validating SPT and sIgE in the Russian population are lacking and the exact cut-off values remain unclear.

Despite being easy and fast to conduct, both SPT and sIgE may lead to false-positive results and positive test result may serve a sign of sensitization, but not allergy [20].

Oral food challenge is a “gold standard” for food allergy diagnosis. During the procedure, a patient is asked to consume a potential causative allergen food in increasing quantities under medical supervision. This

Table 1. Sensitivity and specificity of the diagnostic tests used for food allergy diagnosis [14]

Allergen	Skin prick test (d ≥3 mm)		Serum sIgE (with different cutoff's)	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Cow's milk	87,9 (75,6–94,4)	67,5 (56,0–77,2)	87,3 (75,2–93,9)	47,7 (36,4–59,2)
Hen's egg	92,4 (79,9–97,4)	58,1 (49,1–66,6)	93,4 (82,1–97,8)	49,2 (40,2–58,1)
Peanut	94,7 (87,9–97,8)	61,0 (46,6–73,6)	96,3 (91,6–98,4)	59,3 (45,4–72,0)

stepwise diagnostic procedure is carried out with all necessary precautions, in the hospital settings and with access to the intensive care unit.

There are several types of OFC:

- open OFC, in which both the patient and the doctor performing the procedure know which food and in what quantity is being tested;
- single-blind OFC, in which a patient is blinded to this information;
- double-blind placebo-controlled OFC, which is considered the “gold standard” of diagnosis due to the minimal risk of the patient’s subjective symptoms misinterpretation.

OFC is not given enough attention in the Russian clinical guidelines: “Open and blind oral food challenges, including a double-blind placebo-controlled OFC, which is considered to be the gold standard for FA diagnosis are associated with a high risk for the patient and carried out quite rarely around the world” [12]. However, existing evidence suggests that OFC is a common diagnostic approach, widely used in routine clinical practice around the globe. It should also be noted that the risk associated with this procedure is extremely low. Akuete and co-authors found that from 2008 to 2013, 6377 OFC were carried out in 5 allergy centers in the United States and 84% of patients did not have any allergic reaction with only 2% reporting anaphylaxis [21]. In a 45-year history only 2 deaths were recorded during the OFC [22, 23]. Despite low incidence of death, those cases require special attention, a detailed analysis of the circumstances, and indicate the need in meticulous following the protocol when conducting the challenge.

OFC methodology

1. OFC indications

According to national and international consensus documents on the diagnosis of FA, the use of OFC is most appropriate under the following circumstances [24]:

- after acute reactions (urticaria, anaphylaxis, etc.) if medical history is unclear and/or in the presence of the SPT and sIgE results;

- in the presence of chronic course of the disease (atopic dermatitis, GI manifestations, etc.) to confirm the diagnosis if outcomes of elimination diet are inconclusive or if SPT and/or sIgE are positive but below the threshold;
- in patients with confirmed food allergy, to establish the development of tolerance, following and/or sIgE testing.

Thus, OFC do not replace the standard patient examination protocol (clinical history taking, SPT, sIgE and elimination diet), but serve as an additional step of allergy diagnosis aiming to confirm the diagnosis or expand the patient’s diet.

Approaches to OFC vary between different geographical locations and some local specifics can be applied. For example, in Japan [9], in addition to the abovementioned indications for the OFC, it can be also carried out for the following reasons:

- FA diagnosis confirmation (identification of a causal allergen, both already consumed and not present in the patient’s diet);
 - verification of the diagnosis in patients with infant form of atopic dermatitis associated with food allergy;
 - to establish a specific amount of the food required for eliciting a reaction;
- and to assess the probability of tolerance development.

2. Pre-OFC considerations

The most common approach to OFC preparation elimination diet prescription, with the exclusion of the “suspected” allergen for at least 14 days. Patient should also be advised to stop taking antihistamines, beta-agonists, beta-blockers (including eye drops and other treatment forms), as well as other medication potentially able to affect the occurrence of allergic reaction (e.g. benzodiazepines, tricyclic antidepressants). The time of intake avoidance should be at least five elimination half-lives of the medication, but it varies between active substances [15]. In some countries, like Japan complete elimination of the suspected food is not recommended; on the contrary, the patient is advised to eat the food in low doses or a less “allergenic” (thermally processed) form [9].

3. Food options and portions sizes

Despite OFC procedure being standardized around the globe, portion sizes, number of doses, and time intervals between them vary from one country to another.

Tables 2 and 3 describe common protocols used for the OFC with milk, hen's eggs, and peanuts in Japan, the USA, and Europe.

symptoms occur (Table 6). The occurrence of one or more subjective symptoms (tingling/itching in the throat and mouth, a feeling of suffocation, nausea, abdominal pain) may be a reason for discontinuing the test if they arose after taking at least 3 doses of the product or persist for at least 40 minutes. The final decision to terminate the challenge is made by the physician on an individual

Table 2. Common approaches for the OFC in different countries

Japanese Society of Allergology [9]	The American Academy of Allergy, Asthma, and Immunology [15]	European Academy of Allergy and Clinical Immunology [4, 16]
One of the following approaches is used: 1) One dose 2) Two doses with 60 minutes interval $1/4 - 3/4$ or $1/3 - 2/3$ 3) Three doses 30-60 minutes interval $1/8 - 3/8 - 1/2$ 4) Five doses 20-40 minutes interval $1/16 - 1/16 - 1/8 - 1/4 - 1/2$	One of the following approaches is used: 1) Four doses $1/12 - 1/6 - 1/4 - 1/2$ 2) Six doses $1\% - 4\% - 10\% - 20\% - 30\% - 35\%$ The standard interval between the doses varies from 15 to 30 minutes	One of the following approaches is used: 1) A doubling of the dose until the top dose has been reached or the patient react 2) A increment using logarithmic mean ie 1, 3, 10, 30, 100, etc. The standard interval between the doses varies from 15 to 30 minutes

“Stepwise scheme” for conducting OFC is used in Japan with OFC being the first step. However, in patients with a high likelihood of a reaction (high sIgE level, a history of anaphylaxis and a low eliciting dose), a low dose allergen test is considered, as a first OFC dose [25].

The danger of accidental exposure to an allergen is one of the major problems patients with FA face. In many countries, mandatory product labeling has been introduced, obligating manufacturer clearly identify any ingredients that are one of the major food allergens or contain any protein derived from a major food allergen. The level of labeling depends on the amount of protein the food contains and whether this amount is sufficient to elicit a reaction in an allergic person. The eliciting dose is calculated based on the large dataset of OFC from around the globe. Calculations of the minimum dose causing an allergic response in 5% of individuals (ED_{05}) and the minimum dose causing an allergic response in 1% of individuals (ED_{01}). Table 4 outlines these values for the main food allergens according to the the Voluntary Incidental Trace Allergen Labeling (VITAL 3.0) database [26].

5. Evaluation of the results

Evaluation of OFC results is based on clinical symptoms, which are normally divided into objective and subjective (Table 5) [27].

6. Stopping the challenge, result's interpretation, and further instruction for patients

According to the American Academy of Allergology Asthma and Immunology (AAAAI) guidelines [15], the challenge should be stopped if one or two objective

basis based on an assessment of the clinical data and the patient's history. When symptoms appear and the challenge is stopped it is considered positive, which indicates the presence of FA. The patient also remains under the supervision of medical personnel for 1–2 hours after the total dose is reached. If no reaction occurs, the challenge is considered negative.

If OFC is negative, the patient should avoid the food for 24 hours to monitor for the potential delayed reactions. It is recommended to include the food in the diet on a regular basis in the amount of a standard portion 24 hours after the challenge. However, there is a very small probability of symptoms occurrence even after a negative OFC. With that in mind, patients and their families should carefully monitor the reaction and contact physician if symptoms appear. If OFC is positive, the patient is advised to continue food avoidance [15].

European Academy of Allergology and Clinical Immunology (EAACI) guidelines suggests inclusion of the food in the diet in case of the negative test result and strict avoidance if OFC is positive. Double-blind, placebo-controlled OFC is recommended if subjective symptoms or a delayed reaction occurred during an open OFC [4].

A slightly different approach is outlined in the Japanese guidelines [9] with OFC being considered positive if objective symptoms appear within a few hours after the OFC. If symptoms were subjective or their manifestation was insignificant, a second OFC should be carried out, and home food challenge may be considered. If OFC is negative it is recommended to take the dose equivalent to the dose used during the challenge at home

Table 3. Top doses of common allergens used in the protocols from EAACI, AAAAI and JSA

Cow's milk			
Japanese Society of Allergology [9]	Low dose – about 3 ml Medium dose – 15–50 ml Full dose – 200 ml*		
European Academy of Allergy and Clinical Immunology [4, 16]	Equivalent to an 'age-appropriate' portion, containing around 3 g of food protein		
The American Academy of Allergy, Asthma, and Immunology [15]	4–11 months	1–8 years	9 years and older
	113.4–226.8 g (cow's milk formula is preferred at this age)	113.4–226.8 g	226.8 g
Hen's egg			
Japanese Society of Allergology [9]	Low dose – one cooked egg yolk, about 1/32 cooked whole egg Medium dose – about 1/8–1/2 cooked whole egg Full dose – one cooked whole egg (around 50 g)*		
European Academy of Allergy and Clinical Immunology [4, 16]	Equivalent to an 'age-appropriate' portion, containing around 3 g of food protein		
The American Academy of Allergy, Asthma, and Immunology [15]	4 months – 3 years	4–8 years	9 years and older
	1/2 – 1 egg**	1 egg**	1–2 eggs**
Peanut			
Japanese Society of Allergology [9]	0.1–10 g As a measure against accidental ingestion, the test may be conducted with a total challenge dose of 0.1–0.5 g. Food elimination can be released at school in a case that patients can intake 10 g. Each peanut weighs approximately 1 g		
European Academy of Allergy and Clinical Immunology [4, 16]	Equivalent to an 'age-appropriate' portion, containing around 3 g of food protein		
The American Academy of Allergy, Asthma, and Immunology [15]	4–11 months	1–8 years	9 years and older
	1 rounded tbsp	1–2 rounded tbsp	2 rounded tbsp

* The low challenge dose is used in patients with a high possibility to react, the low and full doses are used in patients with low possibility to react; ** either hard-boiled or scrambled egg is used; *** peanut butter is used.

Table 4. Minimal eliciting [26]

Allergen	ED ₀₁ (mg)	ED ₀₅ (mg)
Cow's milk protein	0.2	2.4
Hen's egg protein	0.2	2.3
Peanut protein	0.2	2.1

for final result confirmation. In the absence of reaction, the patient can consume the food in a volume equal to the volume of the total dose used during the test. If this dose was not the maximum possible according to the protocol a repeated OFC can be performed with a larger amount of the food at patient's request. The tolerated allergen dose may increase over time, therefore, repeated OFCs with an increased maximum dose are recommended to assess the development of tolerance. Furthermore, the patient may be advised to consume the product in a small amount even if symptoms appear during the test and were very mild.

OFC impact on anxiety and quality of life

Children living with FA feel lonely, get bullied, and experience high levels of stress and anxiety. This leads to a decrease in quality of life [1]. The presence of FA affects not only child's life but also the entire family. The recently published study examining the level of anxiety among mothers of children with food allergies in the Russian Federation has shown that one in five mothers suffers from a generalized anxiety disorder, which is three times higher than in general population norms [28]. Patients living with FA are constantly facing a large number of restrictions and constant feeling of uncertainty [29]. Oral food challenge under the supervision of the medical personnel, may clearly demonstrate the amount of the food that child is able to consume without any clinical symptoms as well as severity of potential symptoms. Recent systematic review, looked at the impact of the OFC on the quality of life of patients and their families. The data on 1370 patients showed that OFC is associated with an improved food allergy-specific quality of life and

Table 5. Most common signs and symptoms of allergic reactions to food [27]

Organ system	Objective symptoms	Subjective symptoms
Skin	Urticaria Angioedema Flush Erythema (redness)	Pruritus (itching)
Oral cavity	Lip swelling Redness/swelling of the oral mucosa Blisters of the oral mucosa Urticaria	Pruritus (itching) and paresthesia (tingling sensation) of the oral cavity, pharynx and/or lips (so-called oral allergy symptoms)
Gastrointestinal	Diarrhea Vomiting*	Dysphagia Abdominal/gastric pain** Cramps Nausea Bloating
Respiratory	Sneezing Rhinorrhea Laryngeal edema Dysphonia Wheezing Reduced peak expiratory flow/FEV1 decrease Silence (in lung auscultation) Breathless to speak Rapid breath Chest retractions Cough	Pruritus (itching) Laryngeal/throat tightness Thoracic/chest tightness Dyspnea/shortness of breath
Cardiovascular	Change in heart rate/tachycardia Hypotension/ blood pressure decrease Change in consciousness	Faintness Tiredness
Neurological	Seizures	Headache Dizziness Anxiety Tension/agitation
Eyes	Red eye/conjunctival hyperemia Tearing	Pruritus (itching)
Other		Uterine cramps/contractions

* Vomiting is not considered an objective symptom in children less than 1 year of age unless the clinician stops the challenge because of the vomiting. If vomiting occurs at the final dose of the challenge, it is not considered an objective symptom in children less than 1 year old unless additional objective symptoms are present; ** abdominal pain and gastric pain are considered objective symptoms provided they are observed in children less than 3 years old.

Table 6. Suggested Stopping Criteria [15]

The OFC should be stopped if any 1 of the following symptoms is present during the OFC	If 2 or more of the following are present, the OFC should be stopped
Skin <ul style="list-style-type: none"> • 3 urticarial lesions • Angioedema • Confluent erythematous, pruritic rash 	Skin <ul style="list-style-type: none"> • Persistent scratching for ≥3 min
Respiratory <ul style="list-style-type: none"> • Wheezing • Difficulty breathing/increased work of breathing • Repetitive cough • Stridor • Dysphonia • Aphonia 	Respiratory <ul style="list-style-type: none"> • Persistent rubbing of the nose or eyes for ≥3 min • Persistent rhinorrhea for ≥3 min
Gastrointestinal <ul style="list-style-type: none"> • Vomiting alone not associated with gag reflex Severe abdominal pain (such as abnormal stillness, inconsolable crying, or drawing legs up to abdomen) that persists for ≥3 min 	Gastrointestinal <ul style="list-style-type: none"> • Diarrhea
Cardiovascular <ul style="list-style-type: none"> • Hypotension for age not associated with vasovagal episode 	

reduced parental burden of food allergy [18]. Therefore, conducting an OFC can be both a diagnostic and therapeutic procedure that provides patients and their families a sense of certainty and improves the quality of life [29].

Conclusion

Oral food challenge is a widely used method for food allergy diagnosis with high sensitivity and specificity. Being used for more than 45-years, this diagnostic procedure has proven its safety and effectiveness not only for the diagnosis but also for tolerance assessment and diet expansion in patients of all ages. It is also associated with the quality of life improvement in patients and their families. Oral food challenge may help to reduce the number of unnecessarily prescribed elimination diets and also helps patients to have a better idea of the dose required to elicit reaction and reduces the fear of facing an allergen in everyday life. A standardized technique under careful supervision reduces anxiety. Therefore, OFC is a reliable, safe, widely used method for food allergy diagnosis. With that in mind, we consider the possibility of standardizing this method and introducing it into clinical practice in the Russian Federation.

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