

RECOMMENDATIONS FOR PREVENTING, DIAGNOSING, AND TREATING FOOD ALLERGY IN CHILDREN

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RECOMMENDATIONS FOR PREVENTING, DIAGNOSING, AND TREATING FOOD ALLERGY IN CHILDREN

Sara Martín Armentia. Pediatría. Centro de Salud Delicias II. Valladolid
smarmentia@hotmail.com

Alicia Armentia Medina. Alergología. Universidad de Valladolid. Hospital Rio Hortega
aliciaarmentia@gmail.com

Abstract: There is a wide range of adverse food reactions. Allergic reactions must be distinguished from toxic reactions and non-toxic reactions, which are not-immune mediated. Food allergies may be divided into two groups: IgE-mediated food allergies, in which immediate clinical features appear on contact with the allergen, and non-IgE-mediated food allergies, which have a prolonged latent period and a more insidious onset.

Most cases of food allergy develop in the first two years of age, with a peak of 8% in one-year-olds. The main causative foods in children are milk, eggs, and fish.

The basis for diagnosing an allergy is the clinical record, in which suspicious allergy symptoms must be registered: hives, asthma, atopic dermatitis, anaphylaxis, etc., as well as in vivo complementary tests (prick tests, provocation tests, elimination diet) and in vitro complementary tests: specific IgE determination and molecular diagnostics. The therapeutic options are based on a diet of elimination of the causative food. After the diagnosis, patients should be monitored until the natural acquisition of tolerance to food is verified and, should this not be achieved, hyposensitisation treatment, such as allergen-specific oral immunotherapy, should be initiated.

It must be borne in mind that patients with food allergy may become sensitive to other foods. In children allergic to milk, a plan must be established for the progressive introduction of solid foods, and the appearance of allergy symptoms must be monitored.

The optimal follow-up of a child with food allergy requires the collaboration of the paediatrician and the allergist, and in order to find the correct aetiology, valid diagnostic techniques must be used.

Keywords: allergy, foods, children, IgE, prick test, immunotherapy, tolerance.

ALERGIA ALIMENTARIA EN LA INFANCIA. RECOMENDACIONES PARA PREVENIR, DIAGNOSTICAR Y TRATAR

Resumen. Existen diferentes reacciones adversas a los alimentos. Las reacciones alérgicas deben distinguirse de las reacciones tóxicas y de las reacciones no tóxicas, sin mediación inmunitaria. La alergia alimentaria se divide en dos grupos: la alergia alimentaria mediada por IgE en la que se produce una clínica inmediata al contacto con el alérgeno y la alergia alimentaria no mediada por IgE, en la que los síntomas son más tardíos e insidiosos.

La mayoría de los casos de alergia alimentaria se desarrollan en los primeros dos años de edad, siendo el pico del 8% a la edad de un año. Los principales alimentos causales en los niños son la leche, el huevo y el pescado.

La base del diagnóstico en alergia es la historia clínica en la que se debe registrar sintomatología sospechosa de alergia: urticaria, asma, dermatitis atópica, anafilaxia... seguida de las pruebas complementarias in vivo (prick test, provocación, dieta de eliminación) e in vitro: determinación de IgE específica y diagnóstico molecular. Las opciones terapéuticas se basan en la dieta de eliminación del alimento causal. Tras el diagnóstico se debe seguir al paciente hasta comprobar la adquisición natural de tolerancia al alimento y si esta no se consigue, se ha de iniciar un tratamiento de hiposensibilización como son la inmunoterapia oral específica.

No se debe olvidar que el paciente con alergia alimentaria puede sensibilizarse a otros alimentos. En los niños alérgicos a la leche hay que establecer un plan para la introducción de la alimentación sólida de manera progresiva y se debe vigilar la aparición de sintomatología alérgica.

Para el seguimiento óptimo de un niño con alergia alimentaria se requiere la colaboración del pediatra y del alergólogo y llegar a la etiología correcta con las técnicas diagnósticas válidas.

Palabras clave: alergia, alimentos, niños, IgE, prick test, inmunoterapia, tolerancia.

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ALERGIA ALIMENTAR NA INFÂNCIA. RECOMENDAÇÕES PARA PREVENIR, DIAGNOSTICAR E TRATAR

Resumo. Existem diferentes reações adversas aos alimentos. As reações alérgicas devem ser diferenciadas das reações tóxicas e das reações não tóxicas, sem mediação imunitária. A alergia alimentar divide-se em dois grupos: a alergia alimentar mediada pela IgE, na qual se produz uma clínica imediata quando se entra em contacto com o alérgeno e a alergia alimentar não mediada pela IgE, na qual os sintomas são posteriores e insidiosos.

A maioria dos casos de alergia alimentar desenvolve-se nos dois primeiros anos de idade, sendo o pico de 8% registado ao ano de idade. Nas crianças, os principais alimentos causais são o leite, o ovo e o peixe.

Na alergia, a base do diagnóstico é o historial clínico no qual devem ser registados os sintomas suspeitos de alergia: urticária, asma, dermatite atópica, anafilaxia... seguidos de testes complementares *in vivo* (teste de punção cutânea, provocação, dieta de eliminação) e *in vitro*: determinação da IgE específica e diagnóstico molecular. As opções terapêuticas baseiam-se na dieta de eliminação do alimento causal. Após o diagnóstico, deve-se fazer o seguimento do doente até à aquisição natural de tolerância ao alimento e, se a mesma não for alcançada, deve ser iniciado um tratamento de hipossensibilização tal como a imunoterapia oral específica.

Não se deve esquecer que o doente com alergia alimentar pode ser sensibilizado a outros alimentos. Em crianças alérgicas ao leite, deve ser definido um plano de introdução de alimentação sólida de maneira progressiva e o aparecimento de sintomas alérgicos deve ser monitorizado.

Para o seguimento ótimo de uma criança com alergia alimentar, é necessária a colaboração do pediatra e do alergologista e descobrir a etiologia correta por meio das técnicas de diagnóstico válidas.

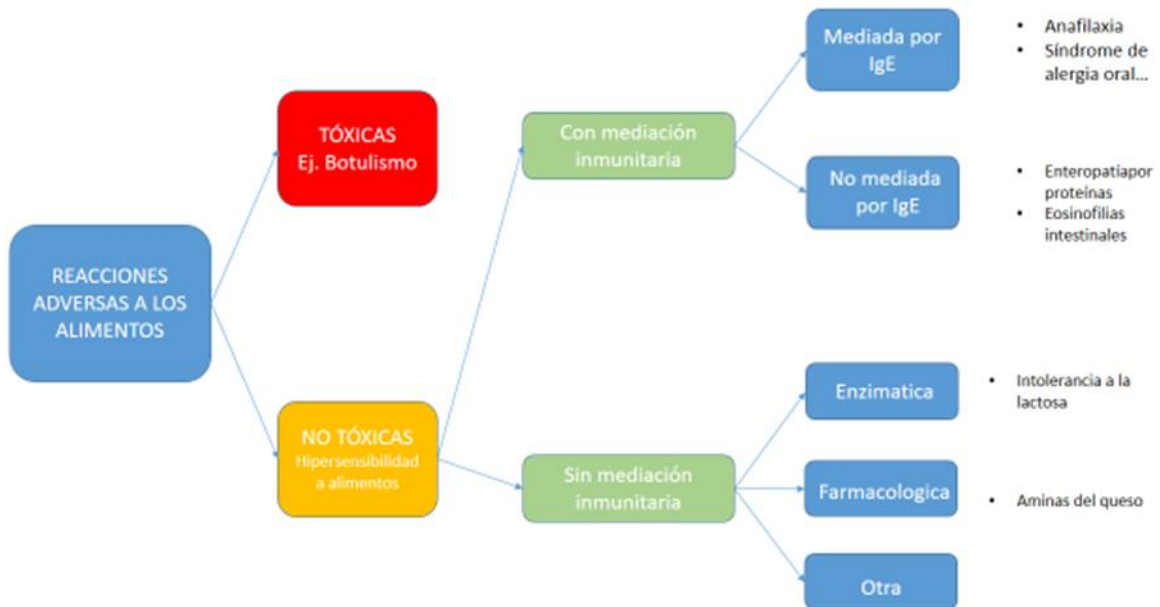
Palavras-chave: alergia, alimentos, crianças, IgE, teste de punção cutânea (*prick test*), imunoterapia, tolerância.

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INTRODUCTION

Recently, the Nomenclature Committee of the European Academy of Allergy and Clinical Immunology (Worm, 2014) proposes that any adverse reaction to food be defined as food hypersensitivity. Allergic reactions should be distinguished from toxic food reactions (botulism, toxic oil syndrome, etc.) and from non-toxic, non-immune-mediated reactions (previously known as food intolerance), such as lactose intolerance, or metabolic conditions, such as phenylketonuria (Figure 1). A particular characteristic of the latter two is that they depend on the dose ingested, i.e. the intensity of clinical features depends on the amount of food the individual has been exposed to. Other examples in this group are drug hypersensitivity reactions to natural adjuvants or compounds added during food processing.

Figure 1. Classification of the main adverse food reactions.



Source: Compiled by the authors.

Spanish	English
REACCIONES ADVERSAS A LOS ALIMENTOS	ADVERSE FOOD REACTIONS
TÓXICAS	TOXIC
Ej. Botulismo	e.g. botulism
NO TÓXICAS	NÃO TÓXICAS
Hipersensibilidad a los alimentos	Food hypersensitivity
Con mediación inmunitaria	Immune-mediated
Sin mediación inmunitaria	Non-immune mediated
Mediada por IgE	IgE-mediated

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No mediada por IgE	Non-IgE-mediated
Enzimática	Enzymatic
Farmacológica	Drug-related
Otra	Other
- Anafilaxia	- Anaphylaxis
- Síndrome de alergia oral...	- Oral allergy syndrome...
- Enteropatía por proteínas	- Protein enteropathy
- Eosinofilia intestinal	- Intestinal eosinophilia
- Intolerancia a la lactosa	- Lactose intolerance
- Aminas del queso	- Amines in cheese

However, in immune-mediated hypersensitivity reactions (food allergy), very small doses of food may result in exaggerated clinical features. Food allergies may be divided into two groups, depending on whether or not the symptoms are IgE-mediated. IgE mediated food allergies often produce immediate clinical features on contact (by ingestion or inhalation) with the allergen: hives, angioedema, asthma. Non-IgE-mediated food allergies have a prolonged latent period and a more insidious onset, mainly affecting the digestive tract (Martín Mateos, 2011).

STRUCTURED QUESTION

What would be the most appropriate management of a suspected food allergy in children?

EPIDEMIOLOGY OF FOOD ALLERGY

Up to one-third of all families have visited the paediatrician at some time on suspicion of an adverse reaction to food (Leung, Yung, Wong, Lam, & Wong, 2009; Pyrhönen, Näyhä, Kaila, Hiltunen, & Läärä, 2009; Venter et al., 2006). An estimated 10% of these visits may be due to an immune reaction. Data on food allergy prevalence are limited due to the disparity of criteria, survey methodologies, and populations. Most food allergies appear in the first two years of life, with a peak of 8% in one-year-olds, as it is during the first years of life that most potentially allergenic foods are introduced into the diet and when immune tolerance mechanisms are established. This prevalence decreases as the child grows older, remaining at 3-4% in adulthood (Nwaru et al., 2014).

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Etiology

According to data from the Spanish multicentre study Alergológica (SEAIC, 2015), the main food allergens in children are milk (82%), eggs (76%), and fish (50%). In adults, nuts (35%), fresh fruit (31%), fish, shellfish, and eggs (10%). However, these percentages differ according to specific geographical areas and dietary habits.

Diagnosis

The clinical record and complementary tests are the basis for the diagnosis of food allergies.

Clinical features in relation to food allergy:

- *Hives and/or angioedema* are the most frequent signs. Hives (urticaria) usually appear suddenly, together with intense itching, mainly affecting the skin that has been in contact with the food (face, mouth, and hands). Oedema and swelling of soft tissues (angioedema) may also occur, with glottic oedema being the most dangerous, as it compromises the respiratory tract.
- *Acute gastrointestinal symptoms*: nausea, vomiting, abdominal pain, or sudden-onset diarrhoea after eating the food. Generally in infants, rare in older children. Special mention should be made of the Food Protein-Induced Enterocolitis Syndrome (FPIES) or food-induced enterocolitis, which is a non-IgE mediated allergy.
- *Oral allergy syndrome*: Oral or oropharyngeal pruritus after eating certain foods, usually fresh fruits and vegetables. This syndrome occurs very frequently in patients with allergies to pollen (grasses) and sometimes precedes a more serious condition: anaphylaxis. It can be prevented if vegetables are cooked.
- *Atopic dermatitis*: Dryness, erythema, and skin irritation. In atopic dermatitis, it is common to find IgE-mediated hypersensitivity to various foods and inhalants, although the severity of dermatitis is not associated with food. It is necessary to establish the true clinical meaning of these lesions via elimination diet and the subsequent controlled provocation.
- *Bronchial asthma*: Dyspnoea during bronchoconstriction and hissing respiration during auscultation. In highly food-allergic patients, asthma or pharyngo-conjunctival symptoms (conjunctivitis, rhinitis) may occur after inhalation of volatile food products that are more intensely released during handling or cooking.
- *Anaphylaxis*: Up to 1% of patients sensitised to food may present with anaphylaxis. This is a very serious allergic reaction: it should be suspected when there is skin impairment immediately after the ingestion of a food (hives, angioedema). Associated clinical features in other systems: respiratory system (asthma, uvular oedema), digestive system (diarrhoea, vomiting). Sometimes

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several systems can be affected and lead to shock, so it is necessary to be familiar with anaphylaxis to treat it before it escalates to shock.

Apart from these clinical features, there are multiple food allergy-related conditions, generally non-IgE-mediated (Table 1. Examples of non-IgE-mediated food allergies.)

Table 1. Examples of non-IgE-mediated food allergies.

<p>Coeliac disease Dermatitis herpetiformis Food enteropathy Intestinal eosinophilias (gastritis, eosinophilic oesophagitis) Allergic proctocolitis</p>	<p>Pneumopathy due to hypersensitivity to cow's milk Thrombocytopaenias Some connective tissue diseases</p>
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Source: Compiled by the authors.

Complementary tests:

- **Skin tests (prick tests)** consist of exposing patients to the suspected allergen through a micro-puncture made with a lancet in the skin, usually in the forearm. They are safe and specific, with an elevated negative predictive value (NPV). The size of a positive reaction gives us some idea of the patient's degree of sensitivity to a specific allergen; however, this varies greatly from patient to patient. In addition, extracts can be made for testing for a large group of allergens, which is very useful if we want to test for an atypical allergen. The preparation of diagnostic food extracts complicates the diagnosis. Purified allergens are better than recombinants, which are obtained by recombining nucleic acids in vitro. However, the latter are replicable and can be easily standardised.

With fruits and vegetables, the prick by prick test is preferable, bearing in mind that the peel is more allergenic than the pulp, and that there are different levels of allergenicity between varieties of the same species. If the reaction was anaphylactic, it is better to avoid the tests and measure the specific IgE instead. *Intradermal reaction tests* are not used in food allergy testing because they have not been shown to have diagnostic value and because they are also dangerous, as they may trigger a systemic reaction (Sicherer & Teuber, 2004). Patch testing, useful for assessing the cause of contact dermatitis, is also not commonly used in the diagnosis of food allergy.

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- **IgE quantification:** There is a correlation between the severity of clinical features and the presence of *specific IgE* against a wide variety of foods. These “in vitro” tests do not pose a risk of allergic reaction, are not affected by the medication the patient may be taking (antihistamines), and do not depend on the characteristics of the skin. This is very useful in paediatrics, especially in infants under 12 months of age, where sensitisation is not clearly reflected on the skin using the prick test. Specific IgE should not be confused with the measurement of *total IgE*. Patients with any type of allergic condition usually have very high levels of IgE in comparison to the rest of the healthy population. Although an elevated total IgE rate indicates that the patient may be atopic, this rate does not provide information about the patient's condition or which allergens the patient is sensitive to. The usefulness of this measure is limited, except for the diagnosis and follow-up of some diseases, such as parasite infections, broncho-pulmonary aspergillosis, hyperimmunoglobulin E syndrome, etc.

Food-specific IgE is measured in levels of kU/L. Even if the test is positive, the patient may not be allergic (average levels may be found in food-tolerant patients). This is why clinical records are essential. However, these tests have a high positive predictive value in children (Sampson & Ho, 1997).

- **Molecular diagnostics (component-resolved diagnostics):** Advances in recombinant protein research have made it possible to identify different types of IgE that bind to different epitopes or proteins in the same food. Molecular diagnostics are a set of highly sensitive and specific techniques that allow us to identify different types of IgE against different molecules of a single food (while distinguishing the potentially anaphylactic ones). These techniques also allow us to establish a prognosis of allergic symptoms. For instance, a patient may be hypersensitive to hazelnut and have different types of IgE. If the patient has a positive response to IgE Cor1, the patient will have very mild oropharyngeal symptoms or will even be tolerant to hazelnut. However, if the patient tests positive for IgE Cor 8, the symptoms are likely to be more severe and the patient may become anaphylactic because this protein is a lipid transfer protein (LTP) (De Knop et al., 2011; Hansen et al., 2009).

While molecular diagnostics techniques for plant foods are very advanced, much remains to be done in the field of allergies to animal foods. This is the most specific type of testing and is highly sensitive, so the results obtained must be assessed by an expert.

- **Elimination diets** of various types. *Elimination diets of the suspected food:* improvement of the symptoms is observed at 2 weeks if the allergy is IgE mediated. In non-IgE mediated allergies, improvement can be observed after

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several weeks of exclusion (Lozinsky et al., 2015). This type of diet is practised in paediatrics, especially when milk allergy is suspected, as shown below. *Empiric elimination diet*: The most potentially allergenic foods are removed from the diet and then introduced one by one. This diet is mainly used in chronic conditions (eosinophilic oesophagitis, chronic idiopathic hives, etc.). This type of diet should only be prescribed by a professional and should be monitored by a nutritionist, especially in children, as the exclusion of certain foods could affect their growth. *Elemental diet*: food is replaced by extensively hydrolysed amino acid formulas. It is used in very severe cases of food allergy.

- **Food-controlled provocation tests** are highly diagnostic techniques (gold standard), but they involve risks. They should not be performed in case of anaphylaxis or severe systemic reaction, or in case the clinical record is highly suggestive, repeated, recent, and consistent with a previous allergological analysis.
- **Testing techniques that have not been shown to be useful in the diagnosis of food allergy**: The *determination of specific IgG, IgA, and IgM* is of no use. Cytotoxic testing techniques (ALCAT) are not replicable and are not supported by the scientific literature. Other testing techniques, such as *kinesiology, neutralisation, and electrothermal pulse* have no value.

Food Allergy Treatment

Elimination diet: The current options available for treating food allergy are based on avoiding the allergen and waiting for the patient to become tolerant to the food over time. In the natural course of food allergy, the period of clinical sensitisation is followed by a period of asymptomatic sensitisation, until total tolerance is achieved and specific IgE antibodies disappear. Not all food allergy sufferers become tolerant, in some cases, allergy tends to persist for years and the longer symptomatic sensitisation is maintained, the less likely it is to heal.

Substitution diet in food allergies: There are some circumstances in which the use of special substitute foodstuffs is necessary, as in the case of allergy to cow's milk proteins in infants. In this case, we will use a cow's milk protein hydrolysate until tolerance is achieved.

Periodic checks that tolerance has developed: In young children, every 6-12 months. The periodicity varies according to the clinical features of the allergy and the food involved. This is necessary in order to establish whether it is necessary to continue with the exclusion diet or, if the food is tolerated, to add it to the diet safely.

Hyposensitisation: The food elimination diet has many drawbacks in terms of compliance (many foods have hidden allergens, especially the most processed),

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nutrition (by depriving the child of certain foods), as well as the drawbacks arising from family distress and the child rejecting the food itself once tolerance has developed.

- *Specific oral immunotherapy (OIT) treatments* are based on introducing the food orally at very small doses tolerated by the patient, while the doses are progressively increased. Thus, tolerance can be achieved while the amount of specific IgE decreases. These protocols last approximately 3-6 months, but may last longer if the patient is very allergic. These guidelines have been shown to be very effective for the treatment of milk and egg allergies.
- *Conventional immunotherapy*. Immunotherapy has been successfully tested in some types of allergy to plant foods and has yielded good results in the treatment of eosinophilic oesophagitis (Armentia A, 2018).

Prevention

Primary prevention (before the onset of allergy) consists of the implementation of measures aimed at preventing sensitisation to food allergens and the development of allergic manifestations ensuing from such sensitisation. These measures are particularly important in patients with a history of atopy. Children with food allergy often develop atopic dermatitis and other conditions that manifest over time (allergic conjunctivitis, asthma, etc.). This is called the “allergic march.” For this reason, the professional in charge of these high-risk children should propose dietary standards aimed at avoiding sporadic contact with minimum doses of potentially sensitising foods. In addition, this professional should be the first person in the lookout in the event of an allergic reaction to food.

Secondary prevention: Elimination diet is not the only element to take into account when monitoring an allergic patient, but also the occurrence of new sensitivities on contact with new foods. One case in point is that of children allergic to cow’s milk: exclusive breastfeeding up to 6 months (or, alternatively, hydrolysed milk) should be promoted, after which the foods should be introduced progressively and separately (one or two weeks must pass between each food), with repeated daily portions. Subsequently, it is necessary to maintain contact with all the foods that the child eats at least two days a week.

BRIEF RECOMMENDATION IN RESPONSE TO THE ORIGINAL QUESTION

The optimal follow-up of a child with food allergy requires the collaboration of the paediatrician and the allergist, and in order to find the correct aetiology, valid diagnostic techniques must be used. Oral food immunotherapy is to be performed in Allergy Units.

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RINSAD

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