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REVIEW

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IgE-mediated allergy to egg protein

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Abstract
Egg allergy is one of the most common food allergies in the pediatric population. It significantly impacts the quality of life of patients and their families. Egg allergy is an adverse reaction mediated by an immune mechanism. There are different mechanisms involved. This review refers to immunoglobulin E (IgE)-mediated egg allergy. The prevalence of egg sensitization and allergy is higher in children with cow's milk allergy and in those with atopic dermatitis. The prognosis for egg allergy in young children is generally good, although in some cases it tends to persist at adult age. The main allergens in egg white are ovomucoid and ovalbumin. Diagnosis is based on the suggestive clinical history and the study of specific positive egg allergy. Oral food challenge test is the gold standard test to confirm diagnosis. Egg allergy, like other food allergies, is primarily managed with the avoidance diet and symptomatic treatment in case of an allergic reaction. The current approach emphasizes minimizing restrictive diets, if possible. Therefore, obtaining an accurate diagnosis through

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component-resolved diagnostics is essential, and whenever necessary, confirming tolerance through oral challenge tests. Food immunotherapy can be potentially curative and can be regarded as a therapeutic option for IgE-mediated egg allergy. It increases the amount of food tolerated and reduces the risk of a life-threatening anaphylactic reaction. There are different approaches: orally, sublingually, subcutaneous, or via epicutaneous. Among these, oral immunotherapy is the most extensively studied and widely used approach in clinical practice.

Introduction

Egg allergy is one of the most common food allergies in the pediatric population.[1] It significantly impacts the quality of life of patients and their families because of the need to adapt the diet and monitor the food ingested to avoid accidental exposure.[2]

Eggs are among the most widely consumed foods globally.[1] Hen eggs, commonly introduced in the first year of child's life, are affordable, rich in protein, and packed with essential amino acids. These are consumed in different ways, both cooked and raw, and are extensively used in the food industry. As a result, exposure to egg proteins is common and can sometimes occur unexpectedly.

Definition

According to the latest classification proposed by the European Academy of Clinical Immunology (EAACI),[3] egg allergy is an adverse reaction mediated by an immune mechanism that occurs by the intake or any type of contact with hen's egg proteins. There are different mechanisms involved.[3] This review refers only to immunoglobulin E (IgE)-mediated egg allergy, which is the most frequent and studied adverse reaction.

Epidemiology and Natural History

In Spain, hen's egg is the leading cause of food allergy in children aged <5 years.[4] In the Euro Prevall study,[5] the adjusted mean incidence of egg allergy during the first 2 years of life was estimated at 1.25% (95% CI: 0.57–2.36%), and in the overall European cohort, it was 1.23% (95% CI: 0.98–1.51%). In the US children cohort, the prevalence of egg allergy was 1.3% in children aged ≤5 years.[6] Egg allergy typically presents before the age of 2 years, coinciding with the introduction of egg into the diet. In a Spanish study (which included 355 children), 56.5% of the patients had symptoms between 6 and 12 months of age and in 97% of cases symptoms appeared in the first 2 years of age.[7]

The prevalence of egg sensitization and allergy is higher in children with cow's milk allergy and in those with atopic dermatitis. In infants with cow's milk allergy, sensitization to eggs[8,9] is observed and up to 30–67% are sensitized to hen's egg before it is introduced in their diet, and 36% of them had a positive oral food challenge (OFC). In infants with atopic dermatitis,[10,11] sensitization to egg proteins is observed in 61% before introducing it into the diet, and allergy with a positive challenge test was observed in 27–67% of patients. Asthma is more prevalent in children with egg allergy than in children with other food allergies.[6]

The prognosis for egg allergy in young children is generally good, although in some cases it tends to persist for years. The development of tolerance to boiled eggs precedes that to raw eggs.[6,12] In three studies carried out in Spain, 50% of the patients with egg allergy reached tolerance at 3–5 years of age, and 64–74% at 9 years of age.[13–15]

Factors of poor prognosis are the persistence of clinical reactivity[16] at 9 years of age, high values of specific IgE, especially ovomucoid (OVM), and previous severe reactions. Specifically, white eggs IgE level of more than 18–24 kU/L is associated with maintained clinical reactivity,[17] and patients[18] with specific serum IgE >50 kU/L were unable to develop egg tolerance at 18 years of age. Nakamura's study found that children with FLG mutations (genetic variation in the *filaggrin* gene) had an approximately four-fold increased the risk of suffering persistent egg sensitization ($P < 0.05$).[19]

Pathogenic Mechanism: IgE-Mediated Reactions

Egg allergens

Hen's eggs contain more than 20 high biological value proteins, but only few[20,21] are usually involved in egg allergy (Table 1).

Both egg white and yolk proteins can trigger allergies,[20] but reactions are more often associated with egg white proteins. Yolk allergies mainly affect adults and are uncommon in children.

The main allergens in egg white are OVM and ovalbumin (OVA). OVM is resistant to heat and enzymatic digestion. Persistent sensitization and/or elevated levels of specific IgE to OVM are markers of poor prognosis and lack of tolerance to cooked eggs. Patients only sensitized to OVA often tolerate well-cooked eggs.[19–21]

Conalbumin (Gal d 3) and lysozyme (Gal d 4) are thermolabile; however, the consumption of raw egg white can sometimes induce allergic reactions.[20] Sensitization to specific IgE for lysozyme or ovotransferrin, a protein found in egg whites, may be responsible for allergic reactions to medications or foods containing these proteins. Hen's egg proteins cross-react with eggs from other birds, so their avoidance is recommended.

Egg yolk contains three distinct protein fractions, among which alpha-livetin (Gal d 6) is considered the most

Table 1 Egg protein composition. (Modified from EAACI Molecular Allergology User's Guide 2.0.[20])

Protein name	MW (kDa)	Composition %	Protein family	Biological function	Resistance to heating and chemical denaturation	Clinical relevance
Egg white proteins						
OVM (Gal d 1)	28	11%	Kazal-type serine protease inhibitor	Serin proteasa inhibitor Antibacterial activity	High	Heat-stable Risk for reaction to all forms of egg
OVA (Gal d 2)	45	54%	Serine proteasa inhibitor	Storage protein	Low	Heat-labile Risk for clinical reaction to raw or slightly heated egg
Ovotransferrin or conalbumina (Gal d 3)	76–77	12%	Transferrin	Iron-binding capacity with antimicrobial activity	Low	Heat-labile. Risk for clinical reaction to raw or slightly heated egg
Egg lysozyme (Gal d 4)	14.3	3.5%	Glycoside hydrolase family 22 (GH22)	Antibacterial activity	Moderate	Risk for clinical reaction to raw or slightly heated egg
Ovomucin	165	1.5%	Contains trypsin inhibitor-like (TIL) domains	Heavilyglycosylated proteinwith potent antiviral activities	N.A.	
Egg yolk proteins						
∝-livetina (Gal d 5)	65–70		Serum albumin	Bind ions, fatty acids, hormones in physiological conditions	N.A.	
Gal d 6	35		Vitellogenin	Storage protein	High	

clinically significant allergen.[22,24] It is known to be resistant to heat and enzymatic digestion.[22-24] Currently, there is no standardized method available for its detection in clinical practice.

Alpha-livetin (Gal d 6), which is also present in chicken meat and feathers, is responsible for cross-reactivity between avian and egg proteins, giving rise to bird-egg syndrome. In this condition, patients exhibit clinical symptoms upon inhalation of feather particles or ingestion of chicken meat or eggs.[24-27] Sensitization may initially occur via inhalation of avian proteins.

Clinical Manifestations

Clinical manifestations of egg allergy typically develop within the first 2 years of life,[4] coinciding with the introduction of egg white in diet, and rarely occur beyond this age.

Allergic reactions to egg are most commonly IgE-mediated,[5,14,28] although non-IgE-mediated reactions have been reported as well. Up to 90% reactions involve the skin,[29] followed by the gastrointestinal system (up to 60%) and the respiratory system (up to 40%). Egg allergy is a leading cause of severe anaphylaxis.[30,31]

Non-IgE-mediated egg allergy[32] is much less common than IgE-mediated allergy. Also, egg may be implicated in conditions such as eosinophilic esophagitis (EoE), gastroenterocolitis, and proctocolitis.

In some individuals, cofactors, such as fever, viral infections, nonsteroidal anti-inflammatory drugs, physical exercise, sleep deprivation, and alcohol consumption, can lower the reaction threshold and trigger allergic symptoms to egg.[29] These factors may unmask sensitization or contribute to the loss of oral tolerance, even in previously asymptomatic patients.

Diagnosis

The diagnosis of egg allergy,[5,33,34] as with all food allergies, is based on a suggestive clinical history, a positive allergy test result, and, when appropriate, a controlled challenge test, which is the gold standard for diagnosis of food allergy (Figure 1). Half (50%) of children suspected of having egg allergy at initial screening had a negative controlled challenge test.

Clinical History

Clinical diagnosis requires a detailed history (Table 2), including information about the culprit food, manifestations, and personal and familiar medical history and a physical examination.

About the culprit food: There must be a causality between the intake of food and allergic reaction. Symptoms

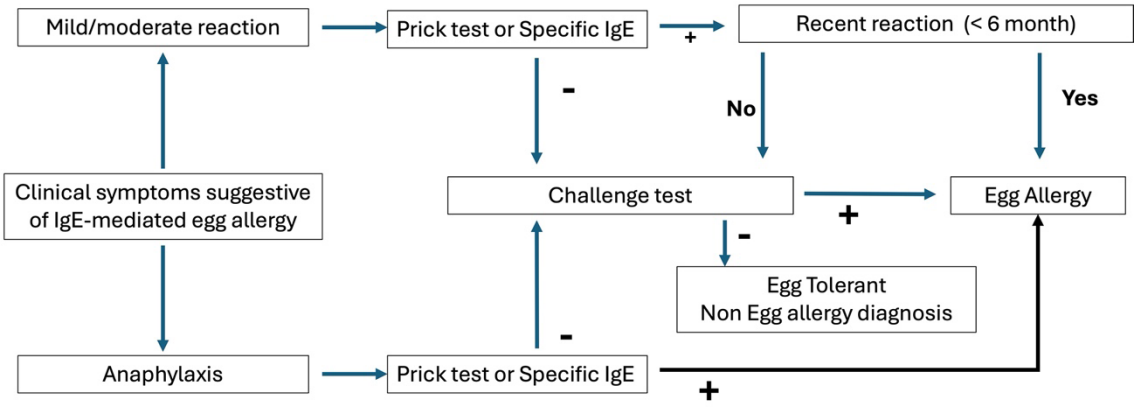

Figure 1 Diagnosis algorithm of egg allergy.[34]

Table 2 Clinical history items.[29]

Recommended egg allergy clinical history items
About the culprit food: egg
• The age at which whole egg, yolk, and egg white were introduced.
• The age at which the first reaction occurred, specifying whether it was the apparent first exposure.
• Tolerance or intolerance to whole egg, yolk, and egg white.
• Tolerance to different preparations (cooked, raw, omelette, semi-raw, flour-baked), along with the assessment of subsequent tolerance following the clinical manifestations that prompted consultation.
• The quantity of food that triggered the reaction is indicative of the allergy's severity.
About the Symptoms
A precise description of the symptoms is required.
• The time interval between food ingestion (or contact) and onset of symptoms.
• Treatment required and the time for the resolution of symptoms, which indirectly indicate the severity of the condition. However, if symptoms persist for more than 12 h or worsen later, other conditions should be considered.
• The number and description of episodes. Multiple episodes related to egg consumption provide the strongest diagnostic evidence.
• Time elapsed since the last symptoms. Recent symptoms suggest a current allergy. Revaluation is needed if symptoms occurred long ago.
About the patient and familiar medical history
Data should be collected referring to the following:
• Family history of atopy.
• Another food allergy.
• Another atopic manifestation, such as asthma, wheezing, rhinoconjunctivitis, or atopic dermatitis, is frequently associated with egg allergy.

are usually caused by oral ingestion or by the presence of egg in other foods as a hidden allergen; however, it can also result from direct or indirect skin contact with egg or exposure to volatile particles of beaten egg.

Clinical differential diagnosis

Food allergy should be carefully distinguished from the manifestations of viral infections, which are quite common during early childhood.[29,33,34]

The following factors strongly indicate an allergy:

- A brief latency period between egg consumption and the onset of symptoms.
- Absence of fever or other signs suggestive of an infection.
- Resolution of clinical manifestations within a few hours, with or without treatment.
- If the triggering factor is allergenic, the patient remains symptom-free unless there is repeated exposure to the food.

Evidence of IgE mechanism: Allergy test

Skin tests/serum-specific IgE

Evidence of an IgE-mediated mechanism can be collected through *in vivo* (Prick test) and *in vitro* tests.[29,32,33] Regarding *in vitro* tests, we measure specific IgE for the

whole egg and a component-resolved diagnosis must be performed.

In many patients, egg has not been introduced in the diet, and the positive test results only indicate sensitization.[33] Assume sensitization allergy unless symptoms are present.

The allergens to be tested[20] include whole egg, OVM (OVM Gal d 1), OVA (OVA Gal d 2), egg white, and yolk. Testing for other minor allergens, such as conalbumin and lysozyme, can provide additional insights and may be particularly important in cases of discordance between the whole egg test and component-based diagnosis.

Intraepidermal testing—prick test

The antigens used for skin tests could be commercial extracts or fresh food.[20,28,29] Commercial allergenic extracts of egg offer high diagnostic sensitivity. Glycerinated extracts are used at a concentration of 10 mg/mL for egg white and yolk, and 1 mg/mL for OVA and OVM. The test is considered positive if a wheal measuring ≥3 mm (with respect to the negative control) in size is produced, and the positive and negative control are assessed as correct.

Skin tests performed using the prick technique have high but variable sensitivity and lower specificity.[29,33,34] The positive predictive value is low, while the negative predictive value is very high; as a result, a negative skin test using an adequate extract practically rules out egg allergy.

The determination of serum-specific IgE has the same limitations as skin tests. A negative determination for OVA and OVM has a high negative predictive value but does not exclude clinical reactivity.

Basophil Activation Test (BAT)

The basophil activation test is a laboratory test used to assess allergic reactions by measuring the activation of basophils by flow cytometry.[33] BAT is useful in diagnosing allergies, particularly in cases where skin prick tests or specific IgE tests may be inconclusive. BAT is making transition to clinical practice and may not be widely available. There is no evidence of its usefulness in egg allergy.

Other tests, while not yet supported by sufficient evidence to be recommended for routine clinical practice,[33] show promise and warrant further research as specific IgE testing for allergen peptides, epitope profiling, and the Mast Cell Activation Test (MAT).

Oral food challenge test

The controlled challenge test is the gold standard for confirming or excluding a food allergy diagnosis.[33-35] We recommend adhering to the methods and conditions outlined in the position statements of the European Academy of Allergology and Clinical Immunology (EAACI).[33,35-37]

Informed consent must be obtained and documented in the patient's medical history before the procedure. Patients should be asymptomatic, and not on antihistamines for at least 7–10 days according to PRACTALL consensus before testing.[35] Patients must be in a comfortable environment where trained personnel can monitor them for early detection and management of any symptoms that may arise.

Indications

The procedure is indicated in all patients with suspected allergy to egg in whom diagnostic confirmation is necessary (Table 3).

Contraindications

Severe anaphylaxis because of egg allergy is not an absolute contraindication for testing. However, it requires a more thorough review of the interval since the initial episode, and a rigorous assessment of skin tests, IgE level variations, and other diagnostic methods.[33,35]

Oral Controlled Challenge Test Technique[35]

The choice between open, single-blind, or double-blind OFC depends on the patient's age and symptomatology. In the pediatric population and patients presenting with objective clinical symptoms, open provocation testing may be employed for practical considerations. Double-blind testing is particularly crucial in a research context. The challenge test should begin with the administration of cooked egg whites; raw egg, white, or pasteurized egg white is tested

Table 3 Indications of oral food challenge test for diagnosis of food allergy.[33,35]

Indications of oral food challenge test
• Suspected egg allergy based on clinical history, positive skin tests, and positive IgE; diagnosed confirmation is essential to prevent misdiagnosis of food allergy and avoid unnecessary elimination diet.
• IgE sensitization, but food never consumed or previously tolerated but avoided for a significant period.
• The test result is below the validated cut-off* point for that specific food. It is necessary to confirm or exclude the diagnosis.
• Patient's clinical history does not align with the test result, despite it being above the validated cut-off point.
• Patient and/or parents exhibit significant anxiety and/or avoid multiple foods without a confirmed allergy diagnosis.

Note. *The mentioned IgE cut-offs can be used as an orientation but always considering that they are group-predictive, not predictive of individual cases, and that other above-mentioned diagnostic tests must be used for confirmation purposes.

only if the results are negative. Some patients exhibit tolerance to fully cooked eggs but may experience severe reactions when exposed to raw eggs. The maximum initial dose for provocation testing has been established as 100 mg; however, the starting dose should be tailored to the individual patient's clinical condition.

Treatment

Egg allergy, like other food allergies, is primarily managed with an avoidance diet and symptomatic treatment in case of an allergic reaction.[29,34] Over the past two decades, oral tolerance induction, or oral immunotherapy (OIT), has emerged as an effective clinical treatment for egg, milk, and, more recently, peanut allergies.

A significant advancement is the recommendation to avoid overly restrictive diets.[34,38,39] These diets should be as minimally restrictive as possible, aiming to improve the patient's quality of life (QoL). avoidence selective depends on tolerance to different egg preparations. The aim is to have a less restrictive diet as possible. The challenge test is contraindicated if the reaction was severe and/or recent and specific IgE levels or the skin prick test results are clearly positive (Figure 2).

An additional therapeutic option involves monoclonal antibodies.[39,40] Recently, the use of omalizumab (OMZ) for the treatment of food allergies has been approved in the United States.[39.]

Avoidance diet

The current approach emphasizes minimizing restrictive diets whenever possible.[39] Therefore, obtaining an accurate diagnosis through component-resolved diagnostics is essential (Figure 2), and, when necessary, confirming tolerance through oral provocation tests. Maternal egg avoidance is not recommended because the probability of IgE-mediated allergic reactions to food proteins in breast feeding is low.[41]

If it is confirmed that the child tolerates cooked eggs, then they may also safely consume foods containing baked eggs. In this case, they would only need to avoid raw eggs (e.g., ice cream, mayonnaise, and toppings) or partially cooked eggs, such as undercooked omelets. We recommend[34,39] testing tolerance to baked eggs in children who do not recognize thermo-resistant proteins, such as OVM (Gal d 1), or partially heat-resistant proteins, such as conalbumin (Gal d 3) or ovotransferrin.

If children are sensitized to egg but it has already been introduced in the diet and tolerated, it is important that they continue eating it.[42-44] We must be careful because after a period of exclusion, reintroduction may trigger immediate allergic reactions because of loss of tolerance.

Strict avoidance of egg is difficult in normal daily life, and in most cases an allergic reaction occurs at home or at school.[45] The minimum dose of egg protein capable of triggering an allergic reaction[46] could be as low as 2 mcg in approximately one in a million patients, and as low as 3.4 mg in about one in every 100 cases.[47]

Eggs from other bird species should also be avoided initially due to the high degree of protein cross-reactivity with hen's egg proteins.

In the pediatric population, clinical cross-reactivity between egg and chicken meat—previously referred to as bird-egg syndrome—is extremely rare;[25] therefore, routine avoidance of chicken meat is generally not necessary.

Therapeutic education is a cornerstone in the treatment of egg allergy.[34] Each patient must have a written individualized action plan for treating an allergic reaction, including anaphylaxis. The medication and action plan should be available to the family, school, and after-school activity centers. They must be trained to administer treatment if needed.

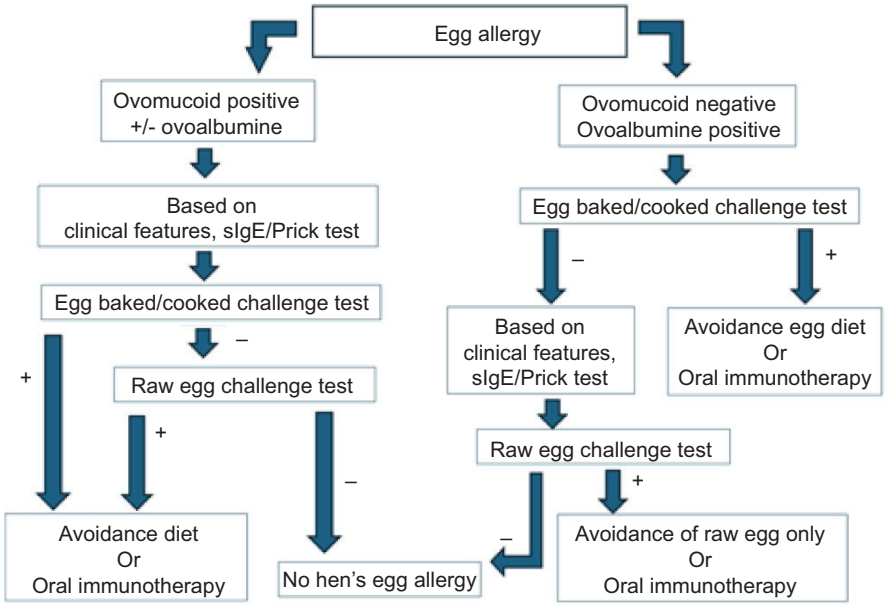

Figure 2 Selective avoidance depends on tolerance to different egg preparations. (Based on EAACI and SEICAP recommendations.)

Oral tolerance induction or oral immunotherapy with egg

Until two decades ago, the only treatment for food allergy was the avoidance diet, treating adverse reactions when they occurred, and waiting for spontaneous tolerance to be achieved over time.

Food immunotherapy can be potentially curative.[49,50] It increases the amount of food tolerated and reduces the risk of a life-threatening anaphylactic reaction. Treatment consists on the administration of progressively increasing doses of the food,[49] following a maintenance phase.[50] There are different approaches: orally, sublingually, subcutaneously, or fixed doses via epicutaneous. Among these, OIT is the most extensively studied and widely used in clinical practice.

It is important to distinguish between desensitization and tolerance.[50] Desensitization[51,52] refers to a temporary and reversible reduction in clinical reactivity achieved through regular intake of allergenic food. This state is usually dependent on continued exposure and may disappear within days or weeks after discontinuing regular intake of allergenic food.[50,51,53] Tolerance is a permanent state in which a person no longer experiences clinical reactivity to the food, even after periods without exposure or regular intake.

The Cochrane meta-analysis,[54] published in 2014 and the one carried out later by the European Academy of Allergy and Clinical Immunology [EAACI][55] show the efficacy of ITO in achieving desensitization in most patients, although its efficacy in achieving long-term tolerance is still unknown.

A randomized multicenter trial by SEICAP (Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica) showed that 82% of children receiving OIT to egg achieved full desensitization, versus only 16% in the control group after 1 year on an elimination diet.[52,56]

The immunological mechanisms involved in OIT are not fully understood, although a reduction in the activation and release of mast cell and basophil mediators, an increase in specific IgG4 levels, a decrease in specific IgE levels, and the activation of specific regulatory T cells have been observed, inhibiting the T helper 2 (Th2) immune response.[57–60]

The factors influencing permanent tolerance acquisition remain unclear.[61] Egg OIT promotes desensitization, but its long-term safety and efficacy are uncertain.[62]

The precise time to achieve tolerance to food or why some people do not acquire it is unknown. Factors such as sensitization level, dosage, duration, and adherence to treatment would be implicated.[51] Most treatment failures occur during the maintenance phase because of discontinuation.[40,53]

Allergic reactions are common during OIT, particularly in the escalation phase, although they may also occur during maintenance. Most are mild to moderate but 3.5–5% may require epinephrine.[52,56,62] In the SEICAP study, 75% of patients experienced reactions during induction but 4.97% due to the administered doses, mostly mild and linked to increase in dose and cofactors.[52,56]

Cofactors that lower the reaction threshold must be considered during the OIT.

Eosinophilic esophagitis is reportedly associated to food OIT,[63] although causality remains unclear. In many cases, EoE was not excluded before therapy. A recent review reported a 2.7% prevalence of EoE after OIT for milk, peanut, or wheat.

The EAACI OIT guidelines recommend this therapeutic option in children,[55,64] aged 4–5 years, with persistent egg allergy, with an evidence level I and recommendation grade B.[55] The ITEMS (**I**dentifying, **T**reating, **E**ducating, and **M**anaging reaction) Guidelines[49,50] recommend OIT as an alternative to the elimination diet (Table 4). The current trend is to initiate OIT as early as possible.[64]

The treatment should be accepted by the patient and their family after providing thorough information about its risks, benefits, and the importance of continuing maintenance therapy.

There are specific contraindications to initiating the treatment (Table 5). Coexistence of uncontrolled asthma is an absolute contraindication,[49,50] as it significantly increases the risk of anaphylaxis.

OIT with omalizumab (anti-IgE) as an adjuvant

Desensitization is achieved in most patients, but about 20% fail because of allergic reactions.[49,50] OMZ is a humanized anti-IgE monoclonal antibody that binds to free IgE, reducing the expression of high-affinity IgE receptors on mast cells, basophils, and antigen-presenting cells. When combined with OIT, OMZ increases the tolerance threshold, particularly in patients with anaphylaxis or those not progressing with OIT alone. Studies have demonstrated that OMZ improves the safety of OIT, reducing adverse reactions and their severity, especially in patients with high IgE levels. A recent placebo-controlled study confirmed that combining OIT with OMZ reduces adverse effects and facilitates successful treatment completion in previously non-responsive patients.[65]

The combination of OMZ and OIT[39] significantly increases the tolerated dose of various foods and enhanced

Table 4 Indications for initiation of oral immunotherapy to egg. (According to the recommendations of the ITEMS Guide.[48,49])

Indications for initiation of oral immunotherapy to egg (food)
1. People with IgE-mediated egg allergy who maintain clinical reactivity to cooked eggs at 5 years of age.
2. They tolerate cooked eggs, but have symptoms with small amounts of raw or undercooked eggs.
3. Any patient, regardless of age, with poor prognostic factors to achieve spontaneous tolerance and/or risk of serious reactions could be a candidate to initiate OIT without age limit.

Table 5 Contraindications to starting oral immunotherapy with food. (Modified from ITEMS Guide recommendations.)

1. Uncontrolled asthma. It must be controlled before starting OIT.
2. Severe atopic dermatitis. It must be controlled before starting OIT.
3. Uncontrolled eosinophilic esophagitis. It must be controlled before starting OIT.
4. Diseases or treatments that contraindicate the use of adrenaline.
5. Non-IgE-mediated egg allergy.
6. Family or social situation that may affect compliance with the treatment.
7. Lack of human and material resources or training to safely address this treatment. It applies to the health center and staff, and the family environment.
8. Inability of guardians to follow rules, identify reactions, and administer treatments (adrenaline).
9. Treatment with immunosuppressants.
10. Inflammatory bowel disease.
11. Mastocytosis. Assess benefit/risk in selected patients
12. Inflammatory bowel disease. Assess benefit/risk in selected patients

desensitization, with improvements in both quality of life and IgG4 levels (all $P \leq 0.01$). However, some patients relapse when discontinuing OMZ, likely due to the factors such as symptom severity, sensitization, treatment duration, and adherence to daily food administration.[40,66,67] Non-adherence is a common cause of failure in OIT, accounting for up to 50% of reactions.[40] OMZ is approved in Spain for allergic asthma, nasal polyposis, and chronic urticaria, and in the United States for food allergies from 1 year of age, unlike other indications that start at 6 years of age.[67]

Prevention of primary and secondary egg allergy

Traditional guidelines advised delaying egg introduction and avoiding it during breastfeeding. Since the publication of the Learning Early About Peanut Allergy (LEAP)[68] and Enquiring About Tolerance (EAT),[69] numerous studies have supported the benefits of early introduction of potentially allergenic foods—such as egg—into infant's diet.

Avoiding potentially allergenic foods—such as eggs or peanuts—during pregnancy, breastfeeding, and early childhood may promote the development of food allergies, rather than prevent them. There is no evidence to prevent food allergy with avoidance during pregnancy, lactation, or the first year of life.

The most recent clinical guidelines recommend introducing hen's egg between 4 and 6 months of age, depending on the infant's developmental readiness. Routine screening with skin prick tests or specific IgE measurement is not required prior to introduction.[31,32,42,69] Although egg sensitization is more prevalent in children with atopic dermatitis and cow's milk allergy, studies show that up to 69% of these children exhibit sensitization to eggs even before their first dietary exposure, with confirmed egg allergy in approximately 71% of those sensitized. If sensitization is known, then introduction of egg must be through an OFC conducted in hospital settings.[44]

We recommend introducing well-cooked egg white (e.g., hard-boiled egg) 2– 3 times a week, along with other fully cooked egg-containing foods.[43] Once tolerance to hard-boiled egg is established, progressively less cooked forms—such as omelets, scrambled eggs, or poached eggs—could be gradually incorporated into the regular diet.

A key element is maintaining regular and sustained consumption over time, as this supports the development of long-term tolerance.

Drugs and vaccines containing egg proteins

Preventive vaccines in children with egg allergy proteins

Severe and anaphylaxis reactions to vaccines are rare but can occur, regardless of allergy history. All vaccines should be administered in the settings equipped to manage acute hypersensitivity reactions.

Viral vaccines produced using chicken embryo cultures may contain trace amounts of egg proteins. This applies to vaccines, such as the measles, mumps, and rubella (MMR), influenza, yellow fever, rabies, certain formulations of hepatitis A, and a few others that are rarely administered.

MMR (triple viral vaccine)

This vaccine is a live attenuated virus vaccine, cultured in fibroblasts derived from chicken embryos. The recommendation is that children with egg allergy, even with prior anaphylaxis, can safely receive the MMR vaccine at standard centers.[70] If anaphylaxis followed a previous MMR dose, future doses should be administered under the supervision of a pediatric allergist. Reactions are usually due to components such as gelatin or neomycin.

Influenza vaccine

Egg allergy does not indicate additional safety measures for flu vaccination beyond those recommended for a recipient of any vaccine,[71,72] regardless of the severity of previous reaction to egg. The incidence of allergic reactions following influenza vaccination in egg-allergic individuals is exceedingly low, as evidenced by the data supporting the safety of both inactivated and live attenuated formulations.

Current inactivated influenza vaccines produced using egg-based manufacturing processes contain only trace amounts of egg protein (less than 1 mcg of OVA per dose; Table 6).[71]

Yellow fever vaccine

This vaccine contains live attenuated virus, without thermal processing. Yellow fever viruses are cultured in chicken embryos and can contain significant amounts of egg proteins. It is contraindicated in patients allergic to eggs.[11,70,71] If its administration is required, children should undergo an allergological study and assess its administration in a hospital center.[70,71]

Anti-Rabies vaccine

In some countries, the only commercially available rabies vaccine is Rabipur, which is cultured in chicken embryo fibroblasts. This vaccine is contraindicated for individuals with severe egg allergy. However, given the high lethality of the disease, there is no absolute contraindication.[70,71] Merieux rabies vaccine does not contain egg in its composition, but its availability is limited.

Another vaccine containing egg

Hepatitis A vaccine, Epaxal®, contains OVA. It is contraindicated in patients having a previous anaphylactic allergic reaction to eggs or vaccine doses. In such cases, it is recommended to use vaccines that do not contain eggs, such as Havrix® or Vaqta®.

Tick-borne Central European encephalitis vaccine

FSME-IMMUN® and Encepur® de GSK: These contain viruses cultured in chicken embryo fibroblasts. They are of little use in Spain, and if necessary, the risk–benefit ratio should be weighed.[70,71]

Drugs containing egg proteins

Some medications may contain egg-derived proteins in their composition and should therefore be avoided in children with egg allergy.

Table 6 Influenza vaccines that are currently available in Spain.

Influenza vaccines and their corresponding egg protein concentrations
Fluarix Tetra: ≤0.05 mcg/dose
Influvac Tetra: ≤0.1 mcg/dose
Vaxigrip Tetra: ≤0.05 mcg/dose
Fluenz Tetra: <0.024 mcg/dose

Lysozyme is an enzyme with bactericidal activity against anaerobic bacteria, and is obtained from egg whites, although it can also be produced by biofermentation. Some medications, vitamin preparations, or nasal drops to relieve congestion contain lysozyme.[73] These lysozyme-containing medicines should be avoided in egg allergies, especially those applied to mucous membranes because of their rapid absorption.

Some medications, such as Ferroprotina®, Kilor®, Syron®, and Profer®, contain OVA, but no allergic reactions are reported.[73]

Lecithin is obtained from eggs or soybeans. It is present in propofol and lipid emulsions for parenteral nutrition. Based on the published data, there is no contraindication for propofol in patients with non-anaphylactic egg allergy.[74-76] Patients with a history of anaphylaxis because of egg might start with a small trial dose of propofol. The full anesthetic dose can be reached gradually if this is well tolerated.[74,77]

Future Perspective

The food allergy approach has changed in last two decades. There are ongoing studies on food allergy, specifically egg allergy, new protein components and their relevance, and new treatments.

Conclusion

Egg allergy is one of the most frequent causes of food allergy in Spain and globally. It affects the quality of life of allergic people and their families. New advances in prevention, less restrictive diets, and therapeutic options, such as the OIT, have opened new perspectives. Therefore, we must do more research to achieve no-allergy status among children.

Author Contributions

All authors contributed equally to this manuscript.

Conflict of Interest

The authors had no conflict of interest to declare about this manuscript.

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