Title: The Natural Course of IgE-mediated Food Allergy in Children

Running title: The Natural Course of Food Allergy

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Abstract

The prevalence of food allergy and food-induced anaphylaxis in children is increasing worldwide. Cow’s milk, hen’s egg, and wheat allergies in young children have more favorable prognosis with relatively early outgrow, while allergies to peanut, tree nuts, and seafood have higher tendency to be persistent. Although we still have an inadequate understanding about the mechanism underlying the resolution of food allergy, the roles of dendritic cells, regulatory T cells, and regulatory B cells are known to be important. Many past studies on the natural course of food allergy have been retrospective analyses of specific study groups, but recently, large-scale population-based prospective studies are being published. This review includes a summary of recent studies on the natural course of cow’s milk, hen’s egg, wheat, peanut, tree nuts, soy, sesame, and seafood allergies. The potential factors affecting the natural course of food allergy would be the symptom severity on ingestion, age at diagnosis, allergic comorbidities, skin prick test size or serum food-specific immunoglobulin (Ig) E levels, the change in the degree of sensitization, IgE epitope specificity, the ratio of food-specific IgE to IgG4, food-specific IgA levels, component-resolved diagnostics profile, diet, gut microbiome, and interventions such as immunotherapy. Since food allergy places a significant burden on patients and their caregivers in their daily life, clinicians should be able to provide relevant knowledge on the natural course of food allergy, appropriately evaluate the resolution of food allergy, and offer therapeutic options if possible.

Keywords

Allergens, Anaphylaxis, Food hypersensitivity, Immunoglobulin E, Natural history
**Key message**

- The roles of dendritic cells, regulatory T cells, and regulatory B cells are known to play significant roles in the natural course of food allergy.

- Allergies to cow’s milk and hen’s egg are known to outgrow in earlier childhood, but studies show that about 50% of patients still have their allergies even into school age.

- The potential factors affecting the natural course of food allergy are age at diagnosis, symptom severity, sensitization status and its change rate, and external factors such as diet and interventions.

- There is a considerable possibility of food allergy outgrow if specific IgE levels are 2~5 kU/L or less, but other factors such as age and recent symptoms should be considered together.

- With a clear understanding of the natural course of food allergy, pediatricians can provide appropriate assessment and interventions to our patients, and consequently can help patients overcome their food allergy and improve the social safety net.
Introduction

The prevalence of immunoglobulin (Ig) E-mediated food allergy in children has increased remarkably worldwide in recent decades, placing a substantial burden on patients, their caregivers, and health care systems. The results of food allergy epidemiologic studies vary depending on the study method, such as whether the diagnosis is based on oral food challenges, clinician’s history taking, or self-reported questionnaire, but it is apparent that the prevalence of IgE-mediated food allergy in children is on the rise even considering the variances in research designs.\(^1\) Large scale population-based studies in Australia reported that the prevalence of food allergy was more than 10% in infants and 4% to 5% in older children.\(^2,3\) In the United States, the prevalence of IgE-mediated food allergy in children was 7.6% based on a cross-sectional population-based survey.\(^4\) In a Korean birth cohort study, the prevalence of immediate-type food allergy was 5.3% in infants.\(^5\) Potentially life-threatening food-induced anaphylaxis is of greater importance, especially in the younger age group, where a sharp increase has been observed compared to older age groups. The annual admission rates due to food-induced anaphylaxis in Australia has increased 9-fold between 1998-1999 and 2018-2019, with the highest rates in those younger than 1 year.\(^6\) According to the national big data analysis in Korea, the prevalence of all-cause anaphylaxis increased 1.7-fold from 2010 to 2014, and the increase was highest in the 0-2 year old group, where food-induced anaphylaxis was most frequent.\(^7\)

Food allergies to peanut, tree nuts, and seafood have higher tendency to be persistent, whereas allergies to cow’s milk, hen’s egg, wheat, and soy are typically known to have more favorable prognosis with relatively early outgrow in preschool ages. However, some studies suggest that resolution timing of these food allergies may have been delayed compared with impressions from past decades.\(^8,9\) Food allergy patients and/or their caregivers often experience a
significant decrease in their quality of life, especially if they have experienced severe symptoms, have multiple food allergies, or have allergies to staple foods that are more difficult to avoid, such as cow’s milk, hen’s egg, or wheat.\textsuperscript{10, 11) Therefore, it is important for clinicians to equip ourselves with the up-to-date knowledge about the natural course of food allergy for the relevant guidance of elimination diets as well as to evaluate food allergy resolution at appropriate timing during the follow-up process of our patients. In this review, the natural course of major IgE-mediated food allergies in children will be discussed.

**Mechanisms related to resolution of IgE-mediated food allergy**

Currently, we still have a poor understanding of why some food allergies outgrow earlier and some food allergies persist longer. Tolerance to food allergens can be driven mainly by antigen presenting cells within the gut lamina propria by promoting T cell differentiation. CX3CR1\textsuperscript{+} dendritic cells directly uptake antigens from the intestinal lumen and take more inflammatory potential, whereas CD103\textsuperscript{+}CX3CR1\textsuperscript{-} dendritic cells have tolerogenic properties.\textsuperscript{12) Goblet-cell-associated antigen passages deliver antigens to CD103\textsuperscript{+}CX3CR1\textsuperscript{-} dendritic cells and therefore are associated with the oral tolerance induction.\textsuperscript{13) Migratory CD103\textsuperscript{+} dendritic cells from the lamina propria in the mesenteric lymph nodes can promote the development of gut-homing regulatory T cells through multiple mechanisms involving TGF-β, retinoic acid, transmembrane proteins, and enzymes involved in tryptophan catabolism.\textsuperscript{14-16) Regulatory T cells, especially Foxp3\textsuperscript{+} regulatory T cells characterized by the expression of CD25 plays an essential role in oral tolerance. Foxp3 knockout mice developed multi-organ allergic inflammatory responses, whereas adoptive transfer of regulatory T cells could suppress anaphylaxis in a food allergy animal model.\textsuperscript{17, 18) Higher numbers of milk-specific CD4\textsuperscript{+} CD25\textsuperscript{+}
Regulatory T cells can also produce several inhibitory cytokines, such as IL-10 and TGF-β. IL-10 has a role in suppressing Th2 immune reactions and allergic inflammation by reducing activation of IgE production and promoting allergen-specific IgG4 responses. Children who developed natural tolerance to hen’s egg or peanut had considerably increased levels of IL-10 expressed by CD4⁺ T regulatory cells, CD25⁺ CD127lo cell, and Foxp3⁺ cells.\(^{21,22}\)

Immunosuppressive regulatory B cells regulate the immune responses by suppressing effector T cells via the production of suppressor cytokines such as IL-10 and TGF-β.\(^ {23}\) Also, IL-10 secreting regulatory B cells produce IgG4, a non-inflammatory isotype that prevents IgE-mediated mast cell and basophil degranulation.\(^ {24}\)

**Natural course of specific food allergies**

Numerous studies have shown that IgE-mediated allergies to cow’s milk, hen’s egg, wheat, and soy are more likely to resolve in childhood, while allergies to peanut, tree nuts and seafood tend to persist.\(^ {25-30}\) However, majority of studies on the natural course of food allergy have inherent limitations in their design because population-based prospective studies using oral food challenges at predetermined intervals are almost impossible. Many of past studies are retrospective analyses that include both oral food challenges and medical history for the assessment of tolerance acquisition, but recent studies in Australia have been releasing longitudinal population-level, challenge-based results on the natural course of food allergy in children.\(^ {3,26,29}\) The factors suggested to affect the tolerance development or persistence of food allergy are the severity of symptoms on ingestion, age at diagnosis, comorbid allergic diseases, and various immune-related markers that will be described later.\(^ {31}\) As the current status and
results of studies related to the natural course of food allergy vary widely depending on the food in question, large-scale recent studies have been mainly described in the text, and other various research results including Korean data are listed in Table 1 and Table 2 for the reference for each major food allergen.

**Cow’s milk, hen’s egg, and wheat allergy**

The EuroPrevall birth cohort study from nine countries across Europe revealed that 56.5% of children with IgE-associated cow’s milk allergy passed double-blind placebo-controlled food challenge at re-evaluation one year after the initial diagnosis.\(^{32}\) From a relatively large-scale retrospective analysis of children with cow’s milk allergy in the United States with the median follow-up duration of 54 months, the resolution rates of cow’s milk allergy were 19% by 4 years, 42% by 8 years, 64% by 12 years, and 79% by 16 years.\(^{25}\) From a retrospective analysis in Korean children, half of children with cow’s milk allergy outgrew at a median age of 8.7 years.\(^{33}\)

The resolution of challenge-proven hen’s egg allergy from a population-based prospective study in Australia was 89% by 6 years of age.\(^{34}\) In Japan, where hen’s egg accounts for the highest frequency of all food allergies, the resolution rates were 30% by 3 years of age, 59% by 5 years of age, and 73% at 6 years of age in a retrospective analysis.\(^{35}\) From a recent prospective report as a continuation of the previous study, the estimated acquired resolution rates were 14.6% by 7 years, 40.8% by 9 years, and 60.5% by 12 years.\(^{36}\) In Korean children with immediate-type hen’s egg allergy, the median age of tolerance acquisition in 50% of patients was 5.6 years.\(^{33}\) This result shows that the age of resolution of hen’s egg allergy is slightly younger than those reported in the United States, and a similar trend to that of Japan.
A prospective study with a larger scale will be needed in Korea in the future.

In Thailand, where wheat allergy is particularly common and the research is actively conducted, oral food challenge was performed for evaluation of wheat allergy resolution if the patients’ specific IgE levels to wheat and ω-5 gliadin were ≤ 26 kU/L and ≤ 1.06 kU/L, respectively.\textsuperscript{37)}

In this study, the proportion of children with wheat tolerance was 14.7\% by 2 years of age, 27\% by 4 years, 45.7\% by 5 years, and 69\% by 9 years of age. Another prospective analysis of fifty challenge-proven wheat-allergic children in Poland revealed that the resolution rates by ages were 20\% by 4 years, 52\% by 8 years, 66\% by 12 years, and 76\% by 18 years.\textsuperscript{38)}

As described above and summarized in Table 1, allergies to cow’s milk, hen’s egg, and wheat often outgrow before school age, but not rarely persist into late childhood, so clinicians need to pay attention to each individual patient when managing these allergies.

\textit{Legume, tree nut, and seed allergy}

There are relatively few studies on the natural course of soy allergy compared to other food allergies. A retrospective analysis in a tertiary clinic in the United States reported that the resolution rates for soy allergy in children were 25\% by age 4 years, 45\% by age 6 years, and 69\% by age 10 years.\textsuperscript{28)} Peanut allergy is a very active research field especially in the West, and according to the latest Australian population-based prospective study, peanut allergy had resolved in 29\% by 6 years of age.\textsuperscript{34)} As reported by the same research team, the rate of resolution of peanut allergy by the age of 4 was reported at 22\% in 2015.\textsuperscript{29)} A retrospective analysis conducted at 3 hospitals in Korea reported that the probabilities of peanut allergy resolution were 10.3\% at age 6 years, and 32.8\% at age 10 years.\textsuperscript{39)}

Tree nut allergy accounts for a considerable portion of food allergy in children and frequently
cause severe reactions, but the natural course of tree nut allergy remains understudied compared
to other major food allergies.\textsuperscript{40, 41} A study published in 2005, which is still consistently cited
when referring to the natural course of tree nuts, reported a resolution rate of 8.9% among
children with previous clinical reactivity and evidence of tree nut sensitization.\textsuperscript{30}

Most studies on sesame allergy have been published in Israel, and as a result of a retrospective
observation of 45 sesame allergy patients for 6 years, 20% achieved tolerance.\textsuperscript{42} In a more
recent retrospective analysis of 190 children with sesame allergy, 32.1% had spontaneous
resolution during the mean follow-up period of 3.86 ± 4.43 years.\textsuperscript{43}

Among allergies to legumes, tree nuts, and seeds, only soy allergy seems to have good
prognosis, but there is no Korean data dealing with the natural course of soy allergy so far.
Even though walnuts are the most common cause of anaphylaxis in children aged 2-12 in Korea,
there is also no study on the natural course of walnut allergy in Korean children, strongly
suggesting the need for additional research in this field in the future.\textsuperscript{44}

\textbf{Seafood allergy}

Studies on the natural course of seafood allergy in children are relatively rare, compared to
other food allergies. A recently published prospective study examining the natural course of
IgE-mediated fish allergy in Greek children reported 22% tolerance development to cod during
the follow-up period.\textsuperscript{45} Complete tolerance to fish increased with age, from 3.4% in preschool
children to 45% in adolescents in this study. According to a longitudinal cohort study including
49 children and 14 adults with seafood allergy in Canada, the resolution rate was 0.6% per
person-year for fish and 0.8% per person-year for shellfish.\textsuperscript{46} Reports on the natural course of
shellfish allergy are rare, and no studies have been conducted in Asian children. In 11 adults
with shrimp allergy, the levels of shrimp-specific IgE remained constant over a 24 month period suggesting persistence of allergy.\textsuperscript{47)} Studies related to the natural course of seafood allergy in Korean children have not been published so far. Contrary to the point that seafood allergy generally persists into adulthood, in actual clinical practice, it seems not very rare for young children with fish allergy to improve within a few years from the diagnosis, suggesting the necessity for the future research in the natural course of seafood allergy in Korean children.

Factors associated with persistent food allergy

The evidence for markers predicting the resolution or persistency of food allergy is still insufficient at this stage. Factors associated with the timing of food allergy resolution include age at diagnosis, comorbid allergic diseases and their severity, symptom severity on ingestion, skin prick test size, food-specific IgE levels, rate of change of food-specific IgE levels or skin prick test sizes, ratio of specific IgE to IgG4, diet, gut microbiome, and interventions such as oral immunotherapy (Figure 1). The degree of sensitization to the specific food, either by serum specific IgE levels or skin prick test is almost the only available tool that can be repeated performed in the actual clinical setting to monitor the natural course of food allergy. Diagnostic cutoff levels for predicting the persistency of food allergy have been suggested by numerous studies, but the results vary widely according to age, region, and study design, bearing considerable limits when applied in clinical practice.\textsuperscript{48-51)} The extensive research results related to specific IgE for the prediction of oral food challenge outcomes at specific time points are not covered in detail in this article as they are more referring to the diagnosis of food allergy. In this review we mainly examined and summarized
the findings related to the prediction of persistent food allergy in studies that prospectively or retrospectively followed the natural course of food allergy over a period of time (Table 3). Studies showed that the persistency of food allergy was considerably associated with either the baseline, peak (highest at all ages), and/or time-point food-specific IgE levels. The resolution rates of cow’s milk allergy by 10 years was 87% with a peak cow’s milk-specific IgE < 2 kU/L and 5% with a peak level ≥ 50 kU/L.²⁵

Component resolved data in some foods may provide additional information for more precise diagnosis as well as for persistency prediction of food allergy. High levels of ovomucoid-specific IgE and casein-specific IgE were associated with persistent hen’s egg allergy and cow’s milk allergy, respectively, but specific cutoff levels for ovomucoid-specific IgE or casein-specific IgE for prediction of persistent food allergy have not been reported so far.³⁵, ⁵²

High IgE levels to gliadins were correlated with persistent wheat allergy and the development of asthma in children.⁵³ Other components such as Ara h 2 and Ara h 6 from peanut, Jug r 1 from walnut, Cor a 9 and Cor a 14 from hazelnut, and Ana o 3 from cashew nut have been studied for their useful value in the diagnosis of food allergy, but the role of these components with regard to the natural course of food allergy should be further investigated.⁵⁴-⁵⁷

Diet and gut microbiome also influence the persistency of food allergy by influencing mucosal immune tolerance.⁵⁸ Recently it is suggested that regular consumption of the food in the form of reduced allergenicity, such as baked products containing egg and/or milk, or in an amount that does not induce symptoms, may improve the prognosis of food allergy.⁵⁹ Certain strains such as Bifidobacterium longum and Bacteroides fragilis can induce the intestinal regulatory T cells possibly by pattern-recognition receptor activation on dendritic cells.⁶⁰ The bacterial metabolites such as short-chain fatty acids produced by bacteria after digestion of dietary fibers, play an important role in enhancing the regulatory activity of dendritic cells, leading to the
Assessment for resolution of food allergy and possible interventions

It is imperative for clinicians to aptly guide the timing to assess for food allergy resolution using appropriate parameters. As the course of food allergy can vary substantially depending on the type of food, the patient’s age, and the test results, clinicians would have to integrate all available information to evaluate the patient’s food allergy resolution status. By incorporating the results of various studies as listed in Table 3, Santos et al. recently suggested the approach for assessment of food allergy resolution as follows; for cow’s milk and hen’s egg, the baseline specific IgE < 2 kU/L, > 50% decrease in specific IgE levels over > 12 months, and specific IgE < 3 kU/L (cow’s milk) or < 2 kU/L (hen’s egg) at other time points were associated with likely resolution; for peanut, the baseline specific IgE < 2 kU/L and other time-point specific IgE < 2 kU/L (if reaction) or < 5 kU/L (if no reaction) were associated with likely resolution; for tree nuts, the baseline specific IgE < 2 kU/L was associated with likely resolution whereas skin prick test ≥ 13 mm and/or specific IgE ≥ 5 kU/L at other time points were associated with likely persistence. When considering oral food challenges for assessment of food allergy resolution, the clinicians should consider the multifaceted factors such as patient’s age, the importance of the food in the diet, previous history of reactions, potential for risk, comorbidities especially severe atopic dermatitis, uncontrolled asthma, or eosinophilic gastrointestinal diseases, and preferences of the patient and family (Figure 3).

The leading treatment for modifying the natural course of food allergy at current stage is oral immunotherapy, which is an allergen-specific approach based on progressive increment in the food allergen doses until reaching a daily maintenance dosage to achieve desensitization.
Although oral immunotherapy still has some issues to be addressed, such as adverse events occurring not rarely during the treatment and achievement of continued tolerance, its implementation is gradually expanding worldwide, and studies proving its efficacy are abounding. Epicutaneous immunotherapy has been actively studied particularly in peanut allergy, and has shown safe and modest treatment response especially in younger children. In severe or multiple food allergy, studies on the allergen-specific immunotherapy combined with biologics such as omalizumab have been reported, enabling faster dose escalation and lower rates of adverse reactions during immunotherapy. The purpose of allergen-specific immunotherapy in food allergy may be sufficient tolerance induction in some patients, or the increase of the tolerated dose to improve the quality of life in others, which will not be discussed in detail here. Besides immunotherapy, other aspects which may affect the natural course of food allergy are dietary pattern, gut microbial modulation, skin barrier management, psychological state, and other environmental factors, which are outlined in Figure 2.

Conclusion

In order to provide the optimal treatment to patients with food allergy and help improve their quality of life, it is essential for clinicians to understand the natural course of individual food allergies. At this point it is still not clear why some children outgrow their food allergy and others do not. Past studies on the natural course of food allergy are heterogeneous and bear limitations in terms of study design, but lately, population-based prospective data are becoming available. Based on the various factors associated with the persistency of food allergy, health care practitioners should offer relevant information to patients and their caregivers, and provide relevant assessments to evaluate food allergy resolution at an appropriate timing. Through therapeutic tools including allergen-specific immunotherapy, gut microbial modulation and...
other potential therapeutics to be developed, we may gradually approach altering the course of food allergy in future.

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References


Table 1. Studies on the natural course of cow’s milk, hen’s egg, and wheat allergy in children

Table 2. Studies on the natural course of legume, tree nuts, seed, and seafood allergy in children

Table 3. Factors associated with persistent food allergy

Figure 1. Suggested elements associated with the natural course of food allergy

Figure 2. Possible measures to affect the future of food allergy in children

Figure 3. Factors related to the natural course of major food allergies
<table>
<thead>
<tr>
<th>Food</th>
<th>Age or rates of resolution</th>
<th>Criteria for resolution</th>
<th>Study type, country</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow’s milk</td>
<td>19% by 4 years, 42% by 8 years, 64% by 12 years, and 79% by 16 years (^{25})</td>
<td>Passed OFC or sIgE &lt; 3 kU/L with no symptoms within 12 months</td>
<td>Retrospective, US</td>
<td>2007</td>
</tr>
<tr>
<td></td>
<td>57.4% during 48-60-month follow-up (^{69})</td>
<td>Passed OFC or successful consumption history</td>
<td>Prospective, Israel</td>
<td>2012</td>
</tr>
<tr>
<td></td>
<td>52.6% at a median age of 63 months (^{9})</td>
<td>Passed OFC or ingestion of uncooked milk products in serving size quantities</td>
<td>Observational cohort, US</td>
<td>2013</td>
</tr>
<tr>
<td></td>
<td>57% after 1 year from the diagnosis (^{32})</td>
<td>Passed OFC</td>
<td>Birth cohort, Europe</td>
<td>2015</td>
</tr>
<tr>
<td></td>
<td>25% by 43 months, 50% by 104.8 months (^{33})</td>
<td>Passed OFC or successful consumption history</td>
<td>Retrospective, Korea</td>
<td>2020</td>
</tr>
<tr>
<td></td>
<td>81.8% by 6 years (^{70})</td>
<td>Passed OFC or successful consumption history</td>
<td>Retrospective, Singapore</td>
<td>2022</td>
</tr>
<tr>
<td>Hen’s egg</td>
<td>11% by 4 years, 41% by 8 years, 65% by 12 years, 82% by 16 years (^{8})</td>
<td>Passed OFC or sIgE &lt; 2 kU/L with no symptoms within 12 months</td>
<td>Retrospective, US</td>
<td>2007</td>
</tr>
<tr>
<td></td>
<td>49.3% at a median age of 74 months (^{71})</td>
<td>Passed OFC or ingestion of whole, concentrated egg products in serving size quantities</td>
<td>Observational cohort, US</td>
<td>2014</td>
</tr>
<tr>
<td></td>
<td>30% by 3 years, 59% by 5 years, and 73% by 6 years (^{35})</td>
<td>Passed OFC</td>
<td>Retrospective, Japan</td>
<td>2016</td>
</tr>
<tr>
<td></td>
<td>83.9% by 4 years (^{26})</td>
<td>Passed OFC</td>
<td>Longitudinal cohort, Australia</td>
<td>2019</td>
</tr>
<tr>
<td></td>
<td>25% by 46.7 months, 50% by 67.6 months (^{33})</td>
<td>Passed OFC or successful consumption history</td>
<td>Retrospective, Korea</td>
<td>2020</td>
</tr>
<tr>
<td></td>
<td>14.6% by 7 years, 40.8% by 9 years, 60.5% by 12 years (^{13})</td>
<td>Passed OFC</td>
<td>Prospective, Japan</td>
<td>2022</td>
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<tr>
<td></td>
<td>Percentage</td>
<td>Study Details</td>
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<tr>
<td>Wheat</td>
<td>89% by 6 y</td>
<td>Passed OFC or SPT &lt; 3 mm or SPT 3-7 mm with successful consumption history</td>
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<tr>
<td></td>
<td></td>
<td>Longitudinal cohort, Australia 2022</td>
<td></td>
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<tr>
<td></td>
<td>29% by 4 y, 56% by 8 y, 65% by 12 y</td>
<td>Passed OFC or successful consumption history</td>
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<td></td>
<td></td>
<td>Retrospective, US 2009</td>
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<tr>
<td></td>
<td>20% by 4 y, 52% by 8 y, 66% by 12 y, 76% by 18 y</td>
<td>Passed OFC</td>
<td></td>
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<td></td>
<td></td>
<td>Prospective, Poland 2014</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>14.7% at 2 y, 27% at 4 y, 45.7% at 5 y, 69% at 9 y</td>
<td>Passed OFC</td>
<td></td>
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<td></td>
<td></td>
<td>Prospective, Thailand 2017</td>
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</table>

a) Among children with a definitive immediate-type reaction to hen’s egg when they turned 6 years.
Table 2. Studies on the natural course of legume, tree nuts, seed, and seafood allergy in children

<table>
<thead>
<tr>
<th>Food</th>
<th>Age or rates of resolution</th>
<th>Criteria for resolution</th>
<th>Study type, country</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>13.2% at 3 years, 21.4% at 5 years, 34.2% at 7 years&lt;sup&gt;72)&lt;/sup&gt;</td>
<td>Passed OFC</td>
<td>Longitudinal cohort, Australia</td>
<td>2008</td>
</tr>
<tr>
<td></td>
<td>10% by 4 years, 18% by 6 years, 22% by 8 years, 26% by 10 years&lt;sup&gt;73&lt;/sup&gt;</td>
<td>Passed OFC</td>
<td>Prospective, Canada</td>
<td>2013</td>
</tr>
<tr>
<td></td>
<td>22% by 4 years&lt;sup&gt;29)&lt;/sup&gt;</td>
<td>Passed OFC</td>
<td>Longitudinal cohort, Australia</td>
<td>2015</td>
</tr>
<tr>
<td></td>
<td>10.3% by 6 years, 32.8% by 10 years&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Passed OFC or successful consumption history</td>
<td>Retrospective, Korea</td>
<td>2021</td>
</tr>
<tr>
<td></td>
<td>29% by 6 years&lt;sup&gt;34)&lt;/sup&gt;</td>
<td>Passed OFC or SPT &lt; 3 mm or SPT 3-7 mm with successful consumption history</td>
<td>Longitudinal cohort, Australia</td>
<td>2022</td>
</tr>
<tr>
<td>Tree nuts</td>
<td>8.9% among children with previous clinical reactivity and evidence of tree nut sensitization&lt;sup&gt;30)&lt;/sup&gt;</td>
<td>Passed OFC</td>
<td>Retrospective, US</td>
<td>2005</td>
</tr>
<tr>
<td>Soy</td>
<td>25% by 4 years, 45% by 6 years, 69% by 10 years&lt;sup&gt;28)&lt;/sup&gt;</td>
<td>Passed OFC or successful consumption history</td>
<td>Retrospective, US</td>
<td>2010</td>
</tr>
<tr>
<td>Sesame</td>
<td>20% during 6.4-year follow-up&lt;sup&gt;72)&lt;/sup&gt;</td>
<td>Successful consumption history</td>
<td>Retrospective, Israel</td>
<td>2007</td>
</tr>
<tr>
<td></td>
<td>32.1% during 3.86 ± 4.43-year follow-up&lt;sup&gt;31)&lt;/sup&gt;</td>
<td>Passed OFC or successful consumption history</td>
<td>Retrospective, Israel</td>
<td>2022</td>
</tr>
<tr>
<td>Seafood</td>
<td>0.6% per person-year for fish, 0.8% per person-year for shellfish&lt;sup&gt;346)&lt;/sup&gt;</td>
<td>Successful consumption history or decision of resolution by a physician</td>
<td>Longitudinal cohort, Canada</td>
<td>2019</td>
</tr>
<tr>
<td></td>
<td>Complete fish tolerance 3.4% in preschool children, 45% in adolescents&lt;sup&gt;45)&lt;/sup&gt;</td>
<td>Passed OFC</td>
<td>Prospective, Greece</td>
<td>2021</td>
</tr>
</tbody>
</table>

<sup>6)</sup>Study participant composed of 49 children and 14 adults.
Table 3. Factors associated with persistent food allergy

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<tr>
<td>Cow’s milk</td>
<td>Baseline milk-sIgE level (&gt; 10 kU/L), SPT wheal size (&gt; 10 mm), moderate/severe AD&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Observational cohort, US</td>
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<td>Reaction to &lt; 10 mL on OFC, SPT wheal size (&gt; 6 mm), age of ≤ 30 days at first reaction&lt;sup&gt;69&lt;/sup&gt;</td>
<td>Prospective, Israel</td>
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<td>Peak milk-sIgE within the first 24 months of birth (&gt; 15 kU/L)&lt;sup&gt;c&lt;/sup&gt;/4)</td>
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<td>High milk-sIgE at the first reaction&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Retrospective, Korea</td>
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<tr>
<td>Hen’s egg</td>
<td>Initial reaction profile (presentations other than isolated urticarial/angioedema), baseline egg white-sIgE levels (&gt; 10 kU/L), baseline SPT wheal size (&gt; 10 mm), moderate/severe AD, baseline egg-sIgG4 levels (&lt; 0.1 mg/L)&lt;sup&gt;21&lt;/sup&gt;)</td>
<td>Observational cohort, US</td>
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<td>High egg white-sIgE at the first reaction, positive family history of allergic diseases&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Retrospective, Korea</td>
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<td>Previous history of egg-induced anaphylaxis before 6 years of age, symptoms to small amounts of heated egg by 6 years of age, higher ovomucoid-sIgE levels at 6 years of age (&gt; 12.5 kU/L)&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Prospective, Japan</td>
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<td>Ovomucoid sensitization at 12 months&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Longitudinal cohort, Australia</td>
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<td>High peak egg white-sIgE, presence of other atopic disease, presence of other food allergy&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Retrospective, US</td>
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<tr>
<td>Wheat</td>
<td>α-5-gliadin-sIgE (&gt; 0.35 kU/L)&lt;sup&gt;37&lt;/sup&gt;</td>
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<td>High peak wheat-sIgE (&gt; 50 kU/L)&lt;sup&gt;27&lt;/sup&gt;</td>
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<tr>
<td>Peanut</td>
<td>Peanut-sIgE at diagnosis (&gt; 1 kU/L)&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Retrospective, Korea</td>
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<tr>
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<td>SPT wheal size (&gt; 6mm), peanut-sIgE (&gt; 3 kU/L)&lt;sup&gt;72&lt;/sup&gt;</td>
<td>Longitudinal cohort, Australia</td>
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<td></td>
<td>Increasing SPT wheal size &lt;sup&gt;29&lt;/sup&gt;</td>
<td>Longitudinal cohort, Australia</td>
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<tr>
<td>Soy</td>
<td>High peak soy-sIgE (&gt; 50 kU/L)&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Retrospective, US</td>
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<tr>
<td>Seafood</td>
<td>Prechallenge cod-sIgE (&gt; 4.87 kU/L), SPT to sardine (&gt; 6.5 mm)&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Prospective, Greece</td>
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<sup>3</sup>Children with AD
Figure 1. Suggested elements associated with food allergy progression.
Figure 2. Possible measures to affect the factors in eczema resolution and persistency.
Factors related to the natural course of major food allergies

<table>
<thead>
<tr>
<th>Specific IgE (sIgE)</th>
<th>Component sIgE</th>
<th>Baseline SPT</th>
<th>Comorbidity</th>
<th>Amount</th>
<th>Symptom profile</th>
<th>Onset age</th>
<th>Family history</th>
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<tr>
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<td><img src="image2" alt="Cow's milk baseline" /></td>
<td><img src="image3" alt="Cow's milk SPT" /></td>
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<td><img src="image5" alt="Cow's milk amount" /></td>
<td><img src="image6" alt="Cow's milk symptom profile" /></td>
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