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Food Allergy: Epidemiology and Natural History

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Synopsis

The prevalence of food allergy is rising for unclear reasons, with prevalence estimates in the developed world approaching 10%. Knowledge regarding the natural course of food allergies is important because it can aid the clinician in diagnosing food allergies and in determining when to consider evaluation for food allergy resolution. Many food allergies with onset in early childhood are outgrown later in childhood, although a minority of food allergy is persistent into adolescence and even adulthood. More research is needed to improve food allergy diagnosis, treatment, and prevention.

Keywords

food allergy; epidemiology; natural history; peanut; milk; egg

Introduction

This chapter reviews the epidemiology and natural history of IgE mediated food allergy with emphasis on recent advances in these areas. For several years, it has been suggested that the prevalence of food allergy is rising, and we review the most recent literature to provide supportive evidence including trends by race/ethnicity and geography. The natural history of food allergy refers to both the acquisition of clinical allergy and its resolution or persistence. The timing of the onset of allergy and likelihood and timing of tolerance development varies depending on the food in question, and therefore, the natural history section is organized by specific food allergen (**Table 1**). We review the development of food allergy and the natural history of food allergy with an emphasis on when it is appropriate to assess for resolution of the allergy with a physician-supervised oral food challenge (OFC)[1, 2], the gold standard for diagnosis of food allergy.

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The majority of studies of the epidemiology and natural history of food allergy have inherent limitations in their study design. Precise evaluation of the prevalence and natural history of food allergy on a population level requires prospective ascertainment with confirmatory oral food challenges of a representative sample of infants and young children at predetermined intervals over time. Studies such as this are rarely performed in the United States due to feasibility and ethical issues. However, recent efforts in Australia have begun to meet this need. Generally speaking, however, it is important to recognize that much of the currently available data on the epidemiology and natural course of food allergy is by necessity imprecise. Furthermore, published studies typically come from selected populations, such as from a particular clinic or referral population, and may not be representative of the general food allergic population. These limitations are highlighted in this Chapter.

Epidemiology

Prevalence

Estimates of food allergy prevalence vary widely, likely because of differences in study methodology including use of different definitions of food allergy, and different geographic area studied. In the United States, prevalence estimates range from 1-2% to 10% and most are derived from self- or parent-report of allergy.[3] A recent study reporting on a nationally representative, population-based survey (the National Health and Nutrition Examination Survey, NHANES), found the prevalence of self-reported food allergy in children to be 6.53%[4] from 2007-2010. The most common childhood food allergies reported were to milk (1.94% of children surveyed), peanut (1.16%), and shellfish (0.87%). Another United States population-based study reported a slightly higher estimate of childhood food allergy prevalence (8%).[5] This survey was internet-based, which may have resulted in selection bias, contributing to the higher prevalence estimate. Nonetheless, the most commonly reported food allergies were similar[5]. The importance of the method of ascertaining food allergy in generating prevalence estimates was highlighted by a recent meta-regression using only US survey data from 1988-2011. Roughly half of between-study variability was explained by method of identifying food allergy alone, and because of this and other sources of heterogeneity, the authors were unable to provide a point estimate for current food allergy prevalence in the US.[6]

In other developed countries, overall prevalence estimates are in general within the range of US estimates. The overall rate of food allergy was estimated at 6.7% in Canada (7.1% for children and 6.6% for adults) in a population-based self-report study using random digit telephone sampling and adjusting for non-response, with cow's milk, peanut, and tree nut allergy being the most common allergens among children.[7] A recent meta-analysis of European food allergy prevalence found an overall prevalence of self-reported food allergy of 5.9% from 2000 to 2012, though many of the primary studies had at least moderate potential for bias.[8]

Estimates relying on self-report are of course limited in part by the subjective nature of the data. Other more objective methods include measuring sensitization using food allergen-specific serum IgE. In a US based study, again using NHANES data, prevalence estimates

for sensitization were 7.6% to peanut, 5.9% to shrimp, 4.8% to milk, and 3.4% to egg in the overall population aged 6 and over, and 6.8% to peanut, 21.8% to milk, and 14.2% to egg in children aged 1-5. These are certainly over-estimates of true clinical food allergy prevalence, but are valuable because they provide some objectivity.[9]

The gold standard for food allergy diagnosis is the OFC, but prevalence of OFC-confirmed allergy has not been widely studied on a population level, and there are no US studies using OFC to determine food allergy prevalence. A population-based study of 12-month old Australian infants using predetermined challenge criteria identified prevalence estimates of 3.0% to peanut, 8.9% to raw egg, and 0.8% to sesame based on OFC. Overall, over 10% of subjects had allergy to peanut, egg, or sesame.[10] This is moderately higher than recent prevalence estimates from the United States that rely on self-report, suggesting either variation in food allergy prevalence throughout the developed world, perhaps due to different exposures, or higher than previously estimated levels of transient food allergy.

Changes over time

While the overall prevalence of food allergy seems to be increasing, objective data on this are scarce. Because many estimates of food allergy prevalence are derived from self-report, assessment of changes over time is limited by the potential for increased food allergy awareness in the media and other sources influencing responses over time. Several well designed studies of self-reported food allergy have supported a worrisome increase in food allergy prevalence over a recent time period. Using meta-regression of 20 US based surveys conducted by the Centers for Disease Control representing nearly 400,000 children covering the period 1988-2011, Keet et al estimated an overall increase in childhood prevalence of self reported food allergy of 1.2 percentage points per decade. Interestingly, the increase in food allergy prevalence was nearly twice as high in non-Hispanic black children (2.1 percentage points per decade) compared to white children (1.0 percentage points) and Hispanic children (1.2 percentage points).[6] Several US and international studies suggest that peanut allergy diagnoses are increasing: in a United States telephone-based population survey that was repeated three times between 1997 and 2008, estimates of the prevalence of peanut allergy increased significantly from 0.4% to 1.4% and estimates of tree nut allergy prevalence increased from 0.2% to 1.1%.[11] Similar trends have been reported from the UK.[12] Hospitalizations for food-induced anaphylaxis are also rising[13, 14]. Overall, these results support a concerning trend over time and by race/ethnicity, and reasons for these increases should be identified, so that prevention strategies can be developed.

Risk Factors

Many risk factors for food allergy have been identified, although it is not clear what is driving the observed rise in prevalence. As in other atopic diseases, a family history of atopy is a strong risk factor. In a population-based study of one-year-old infants diagnosed via oral food challenge with food allergy (primarily egg or peanut), the risk of food allergy was increased by 40% in patients with one immediate family member with any allergic disease and by 80% in patients with two immediate family members with any allergic disease compared to children without a family history of allergy.[15] Race/ethnicity and other demographic characteristics are also associated with food allergy: non-Hispanic black

ethnicity[4, 5, 16, 17], Asian ethnicity[5], and male sex in children[18,16] have all been associated with higher risk of food allergy. Overall, these findings suggest a genetic predisposition; however, the genetic determinants of food allergy are largely undefined.

While there is some evidence implicating specific genes in food allergy susceptibility, studies have not been replicated on a wide scale. Loss-of-function mutations in the filaggrin gene have been associated with peanut allergy independent of atopic dermatitis, implicating the skin as a potential route of sensitization.[3] Filaggrin mutations have also been associated with self-reported allergy to eggs, milk, wheat, and fish in a Danish population and with positive specific IgE levels to milk.[19] However, another study reported that while filaggrin mutations do increase the likelihood of sensitization to food-specific IgE in children in the first year of life, they are not associated with an increased risk of clinical allergy among children already sensitized.[20] Polymorphisms in the STAT6 gene have been associated with an increase in the age of tolerance in cow's milk allergy,[21] food sensitization[22], and risk for nut allergy.[23] While it seems likely that there is a genetic basis to food allergy development, further studies are needed to identify the specific loci involved.

Environmental factors are also associated with food allergy risk.[3] Children with older siblings[24] and pets in the home may be at lower risk of egg allergy at age 12 months, supporting the hypothesis that increased microbial stimulation in infancy may have a protective effect in terms of developing allergy.[18] Parental nativity has also been implicated: in a study of the 2005-2006 NHANES, US-born children and children immigrating to the US in early childhood had higher odds of sensitization to milk, peanut, or egg than foreign-born children, and among children born in the US, those children born to immigrant parents had higher odds of sensitization.[25] Vitamin D insufficiency has been associated with an increased risk of food allergy[26-28]; however, these associations are controversial and need further exploration as Vitamin D sufficiency has also been associated with an increased risk of allergic sensitization.[29] Increased food diversity in infancy may have a protective effect on food sensitization as well as clinical food allergy later in childhood.[30] Atopy, including comorbid atopic dermatitis and doctor-diagnosed asthma,[16] has also been associated with an increased risk of food allergy. Whether this represents a more severe allergic phenotype or food allergy arises due to impaired barrier function is unknown.

Natural Course

Knowledge about the natural history of food allergy is important for the allergist to guide use of elimination diets and when it may be appropriate to consider liberalizing the diet to include a food that previously caused allergic symptoms. Here we discuss the clinical and laboratory factors associated with the natural history of food allergy, the natural history of the most common food allergens, and strategies to assess for resolution of food allergy.

Clinical and laboratory factors associated with the natural history of food allergy

Several clinical and laboratory factors have been associated with development of tolerance or persistence of an allergy to an allergenic food. These have been most studied in association with egg, milk, and peanut allergy, the most common childhood food allergens. Factors associated with the timing of resolution of allergy to these foods include severity of

symptoms on ingestion[31-35], skin prick test (SPT) size[31, 33, 36, 37], age at diagnosis[31, 38], comorbid allergic disease[39-42] and severity[31, 33], food specific IgE levels[21, 31-33, 36, 39, 43-45], rate of change of food specific IgE levels[38] or SPT sizes [36], IgE epitope specificity[46], IgE/IgG_4 ratio[47], and specific IgA and IgA2 levels[48]. While these were identified in children with egg, milk, or peanut allergy, it is likely that these principles are generalizable to other food allergens, and this warrants further study. Unfortunately, IgE based methods are imprecise, and oral food challenge is usually necessary to confirm resolution of allergy. New methods such as allergen component testing-determination of individual allergens to which a patient's IgE is directed- or cellular based studies, may help improve the diagnosis of food allergy[49], but their role in assessing resolution of allergy is not clear.

Egg Allergy

Egg allergy is one of the most common IgE mediated childhood food allergies with a reported prevalence of 1.3-1.6%[51, 52]. Most egg allergy develops in the first year of life[53]. Several prospective studies have attempted to address the natural history of egg allergy[32, 37, 44, 54-56]. Although families have generally been advised that most children will outgrow their allergy by the early school-age years[57], recent studies suggest that this is not the current case.

In a retrospective review of 881 patients with egg allergy, the median age at egg allergy resolution was 9 years when tolerance was defined as passing an egg challenge or having a last recorded egg IgE level of <2kUA/L and no reported symptomatic accidental ingestions in the last year[39]. However, this study was limited by its retrospective design and its focus on a highly allergic referral population. Further, it was conducted at a time before it was common to introduce baked egg into the diet of children who could tolerate baked egg but not concentrated egg (see below) which has been hypothesized to affect the natural history of egg allergy. In a more recent prospective study of egg-allergic children recruited from primary care offices, the median age of resolution (defined by oral food challenge and successful home introduction of whole egg) was 6 years with a rate of resolution of nearly 50%. Of those children with unresolved allergy, 38.1% were able to tolerate some baked egg products.[33] These studies highlight the importance of the study population in influencing the observed natural history of food allergy.

Although most consumers of egg generally eat cooked eggs, the length and degree of heating can reduce the allergenicity of egg[58]. A majority of children (over 70% in some series) who react to concentrated egg (lightly heated egg such as French toast or scrambled egg) can tolerate baked egg in the form of a muffin or waffle[10, 59, 60]. However, the role of baked egg consumption in the resolution of egg allergy is unknown. One prospective study which assessed tolerance to both baked and concentrated egg demonstrated a median age at baked egg allergy resolution of 5.6 years, and after introduction of baked egg into the diet, a median age at concentrated egg allergy resolution of 10.6 years, suggesting that introduction of baked egg may not hasten the resolution of egg allergy.[54] Similarly, a retrospective chart review demonstrated that the rate of decline of skin prick test size was not associated with frequency of baked egg consumption.[61] However, other recent prospective studies have

shown increased likelihood of[62] and accelerated development of concentrated egg tolerance with frequent ingestion of baked egg.[43]

Milk Allergy

Milk is the most common childhood food allergy with a prevalence of up to 2.5% when both IgE and non-IgE mediated reactions are considered[63-66], and accounts for about one-fifth of all childhood food allergy, according to a national cross-sectional survey of parents.[67] Most milk allergy typically presents in the first year of life[53, 68]. Like egg allergy, most studies have shown the prognosis of developing tolerance to cow's milk to be favorable, with the majority outgrowing their allergy throughout childhood and early adolescence[44, 55, 63, 64, 69-74]. However, a minority of milk-allergic children become milk-allergic adults.

Data from a large population based cohort in Israel demonstrated that only 57% of children with milk allergy resolved their allergy prior to the study completion by age 4-5 years, and the majority of these did so by age 2[40]. However, clinic based studies, which may include children at higher risk for allergic disease, suggest a worse prognosis. In a recent prospective study from Europe, only 43% had outgrown their allergy by the age of 10, when food challenges were performed after the SPT size to milk had decreased [75]. These data are consistent with a retrospective study of milk allergy in a referral population demonstrating that the median age to outgrow milk allergy is 10 years when allergy is defined as passing an open food challenge, or having a milk specific IgE < 3 kUA/L at the last visit, and no reported symptomatic accidental ingestions in the last year[41], consistent with the possibility that the natural history of food allergy may be lengthening over time.

Similar to egg allergy, baked milk is tolerated in a majority (75%) of children who are reactive to uncooked milk. Baked milk consumption may affect the natural history of milk allergy. Ingestion of baked milk for 3 months led to significantly decreased milk SPT size and increase in casein-IgG_4[76]. A follow-up study suggested that ingestion of baked milk accelerated the resolution of milk allergy, as patients who incorporated baked milk into their diet were more likely to become milk tolerant compared to children who underwent clinic standard of care with strict avoidance of milk[77]. Ingestion of extensively hydrolyzed casein formula as opposed to rice hydrolyzed formula, soy formula, and amino acid-based formula has also been demonstrated to increase the rate of milk tolerance acquisition, although other smaller studies have not found such an association.[78] While it is often incredibly helpful to food allergic patients and families to introduce foods when they are safely tolerated, larger studies are needed to determine if ingestion of baked milk is solely a marker of transient milk allergy, or an effective treatment to induce tolerance.

Peanut allergy

The prevalence of childhood peanut allergy is estimated around 2%[79], and studies from North America and Europe suggest it is increasing rapidly[12, 80]. Interestingly, peanut allergy appears to be more common in Western-born children than in Asian children, according to a population survey of both local and Western-born Singapore and Philippine schoolchildren.[81] While risk factors for peanut allergy are not well-defined outside of the

aforementioned risk factors for general food allergy, the Learning Early About Peanut Allergy (LEAP) study, based in the UK, has recently associated egg allergy and severe atopic dermatitis, or both, with an increased risk of peanut sensitization in infancy.[17] The most common age for the presentation of peanut allergy is 18 months, although peanut allergy can present later in childhood or adulthood, most often as part of the pollen-food allergy syndrome[82-84].

Unlike the previously discussed foods, the majority of childhood onset peanut allergy is not outgrown prior to adulthood[85]. Estimates of tolerance development rates vary with study design[82, 85]. The largest study to date reported that 21.5% of patients had become peanut tolerant when patients aged 4-20 years with a history of peanut allergy and peanut sIgE less than 20 kUA/L were offered a food challenge[86]. Another study demonstrated a similar rate of tolerance acquisition (20% by age five) in preschool-aged children by offering an oral challenge to children whose peanut SPT size had decreased to less than the 95% positive predictive value for peanut allergy[36]. The timing of peanut allergy resolution is not clearly defined, but cases of resolution in adulthood have been reported[84] suggesting that patients can benefit from long term follow up for peanut allergy. In rare cases, symptomatic peanut allergy has been demonstrated to recur after passing an open challenge. This has been seen especially in patients who do not introduce peanut into their diets after a negative peanut challenge[89, 90].

Tree nut allergy

Relatively little is known about the natural course of tree nut allergy, but it can present in both childhood and adulthood. One OFC-based study on children and young adults with tree nut IgE levels below 10 kUA/L found that 9% of 101 patients with prior reactions to tree nuts had resolved their allergy, while 74% of 19 patients who had never ingested tree nuts but were diagnosed on the basis of an elevated tree nut IgE passed a challenge.[91] . They also found that no subject who was allergic to more than two tree nuts outgrew their allergy. Adult tree nut allergy is presumed to represent a mixture of late onset IgE mediated allergy to tree nuts as well as allergy due to cross reactivity with inhalant allergens (pollen-food allergy syndrome), though little is known about its natural course.

Soy allergy

Soy is another common childhood allergen[92] and may be more common in children with concomitant peanut allergy. Soy allergy is typically considered to have its onset in infancy. One study reported a peak incidence of soy sensitization around age 2 [53]. Early prospective studies of children with soy allergy and concomitant eczema demonstrated a relatively good prognosis, with a 50% rate of resolution at 1 year of follow-up and 67% rate at 2 years of follow-up[55, 93]. However, a retrospective study conducted on soy-allergic patients at a tertiary referral center reported that the allergy was outgrown in 45% of children by age 6, suggesting a less-promising prognosis. Soy IgE level was a useful predictor of the speed of tolerance acquisition: by age 6, 59% of children with a peak soy IgE level <5 kUA/L were soy-tolerant compared to only 18% of children with a peak soy IgE level >50 kUA/L[94].

A phenotype of late-onset soy allergy has been described where some patients develop typical IgE mediated symptoms to soy after tolerating it as a regular part of their diet. This phenomenon may be more common in patients with persistent peanut allergy[94] or may be related to pollen-food allergy syndrome due to cross-reactivity with birch pollen[95].

Wheat allergy

Wheat is another common childhood food allergen, but little is known about its natural history. Studies on the prognosis of patients with wheat allergy and concomitant atopic dermatitis suggest that 25-33% of patients become tolerant by follow-up 1 to 2 years later [55, 93]. In a prospective study of 50 Polish children with positive wheat specific IgE and food challenge results along with predominant gastrointestinal symptoms, 20% of children had resolved allergy by age 4, 52% by age 8, 66% by age 12, and 76% by age 18. Similar results have been obtained by retrospective studies. One such study of children with OFC-proven wheat allergy indicated that 84% had gained tolerance by age 10 when wheat allergy cases included both IgE mediated and non-IgE mediated reactions[96]. A larger retrospective study, estimated a median age at resolution of wheat allergy of 6.5 years, but 35% of patients remained allergic into their teens[97]. Peak wheat specific IgE is somewhat useful in determining the age at which tolerance develops, and higher levels may be related to allergy persistence.[98] However, high levels of wheat IgE do not preclude resolution of the allergy[97].

Other Foods

The natural history of other foods such as sesame and other seeds, seafood, meats, and fruits has not been well described. These food allergies can present both in childhood and adulthood. In general, childhood onset allergy to seeds, seafood, and meats, has a poor prognosis, with the minority outgrowing their food allergies during childhood, [44, 99-101] and adult onset allergy to these foods is thought to be persistent. Recently, a syndrome of delayed allergy to meats caused by reactivity to galactose-alpha-1,3-galactose has been described [102]. The natural history of this entity is currently unknown.

Allergic reactions to fruits and vegetables can also have their onset at any age. In early childhood, adverse reactions to fruits and vegetables are common and are typically short lived, although some children do have IgE mediated allergies to these foods[44, 63, 64]. Later in childhood and into adulthood, some proportion of fruit and vegetable reactions are most certainly associated with pollen-food allergy syndrome secondary to cross reactivity with inhalant allergens, which can develop after clinical sensitivity to seasonal inhalants has developed. The natural history of pollen-food allergy syndrome has not been investigated.

Assessing for resolution of food allergy—Once the diagnosis of food allergy is confirmed, the role of the allergist becomes to guide the assessment for resolution of food allergy. Some food allergens are difficult to avoid and fortunately have a generally high likelihood of resolution (e.g. milk and egg). Safely liberalizing the diet to include these foods has important nutritional and quality of life benefits.

In general, we recommend yearly evaluation by food specific IgE or SPT. We prefer to use specific IgE testing because it provides more prognostic information regarding the long term

timing of tolerance acquisition[39] and the short term likelihood of passing a food challenge. In general we use a specific IgE cutoff that provides a 50% positive predictive value of passing a food challenge. Values have been published for some foods (**Table 2**), but these should be interpreted with caution because studies are small and other factors beside IgE influence the outcome of a challenge. In those patients without a history of previous reaction, whose diagnosis was made on the basis of sensitization alone, higher IgE cutoffs may be appropriate[87]. In patients with persistent allergy with unchanged specific IgE levels for several years, testing can be performed less frequently over time[88]. Factors to consider before deciding to pursue an OFC include the chance of success, the potential for risk, and the preferences of the patient and family including the importance of the food to the diet[103]. Other important considerations may include patient age, history of reactions, family characteristics, and comorbidities (e.g. severe atopic dermatitis or eosinophilic esophagitis).

Current controversies

The observation that children with milk and egg allergy may tolerate extensively heated forms of these allergens has challenged previous food allergy dogma of strict allergen avoidance. Fortunately, this has allowed many patients to safely incorporate these foods into their diets, where just a decade ago strict avoidance of even cooked forms would have been recommended. However, this breakthrough, combined with observations that delayed introduction of food may actually increase the rate of food allergy[81, 86, 87, 89, 104] has complicated the management of food allergy. The optimal time to introduce allergenic foods during infancy is not known, and the American Academy of Pediatrics currently does not recommend delaying the introduction of highly allergenic complimentary foods to prevent the development of food allergy. A committee from the American Academy of Allergy, Asthma and Immunology has published advice for complimentary food introduction including scenarios where allergy evaluation may be helpful.[104] In general, they recommend introduction of complementary foods between the ages of 4-6 months, with highly allergenic foods introduced in small quantities at home, once other foods are tolerated. However, young infants may demonstrate clinical allergy to foods on their first exposure. This was highlighted in a recent study that tried to determine whether early egg introduction in children with moderate to severe eczema could prevent the development of egg allergy. Although they were able to show that early egg exposure was associated with a non-significant reduction in egg allergy defined by failing an oral food challenge at one year, a third of subjects reacted to early egg exposure, including one case of anaphylaxis.[105] More research is certainly needed to better identify those infants that may benefit from early allergen exposure, and those in whom clinical allergy has already developed.

Future directions

Despite the dismal observation that food allergy prevalence is rising rapidly, several interventions are on the horizon that may favorably impact the natural history of food allergy. Small scale studies have demonstrated that it is possible to induce desensitization to specific foods using oral and sublingual immunotherapy, with tolerance induced in a subset[106-109]. These treatments are still under active research investigation and will hopefully be available widely in the next several years. Improved diagnostic testing for food

allergy with epitope specific testing[110], component-resolved diagnostics [111], or cellular methods[112] will allow for more precise identification of young patients with food allergy, and will ideally provide insight into the natural course of food allergy on an individual level While these efforts are promising for established disease, primary and secondary prevention efforts have had limited success and are needed to stem the rapid rise in food allergy prevalence world-wide.

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Key points

- Food allergy prevalence is between 5-10% throughout the developed world, and is rising at an alarming rate, for unclear reasons.
- The natural history of childhood food allergy varies by food, and can guide the clinician in determining when it may be safe to introduce a food that was previously not tolerated.
- Further research is needed on the optimum time to introduce complimentary allergenic foods, and methods for prevention and treatment of food allergy.

Table 1

Common Allergenic Foods with General Age of Onset of Clinical Allergy and Resolution

Food	Age of Onset	Age of Resolution
Egg	Infant/toddler	Early to late childhood
Milk	Infant/toddler	Early to late childhood
Peanut	Infant/toddler Adulthood	Early to late childhood-uncommon Unknown
Tree nuts	Toddler/early childhood Adulthood	Early to late childhood-uncommon Unknown
Soy	Infant/toddler Adulthood (rare)	Early to late childhood Unknown
Wheat	Infant/toddler	Early to late childhood

Table 2

Specific IgE levels associated with a 50% positive predictive value for clinical allergy. In general we use the 50% positive predictive value to guide the timing of an oral food challenge, but caution should always be used in considering when to perform a food challenge.

	50% Positive Predictive Value	
Food Allergen	**Age, if investigated**	**sIgE Value (kUA/L)**
Egg	-	2[113]
Milk	-	2[113]
Peanut	-	2[113]
Wheat	<1 >1	1 20[114]
Soy	-	20-30[114]
Tree Nuts	-	N/A