Oral Tolerance and Prognosis in Food Allergy

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Introduction

A diagnosis of IgE-mediated food allergy is life altering. As discussed in detail earlier in this book, children with food allergies need to strictly avoid their allergen at all times. Successful avoidance requires communication with food handlers and caregivers and reading labels on packaged products. In addition, families with food-allergic children need to be well versed in the recognition and treatment of allergic reactions. This can result in significant burden, cost, psychosocial impact, and decreased quality of life [1].

While the overarching themes surrounding successful management of IgE-mediated food allergies are similar regardless of specific food, the prognosis differs greatly. A deeper understanding of IgE-mediated food allergies demonstrates that prognosis can differ greatly for one child compared with another. This is an important area for physicians and families to understand as a diagnosis of food allergy during childhood should not be communicated as an absolute need for lifelong avoidance. As with any chronic medical condition, food allergies should be monitored routinely with at least annual office visits to review management strategies, accidental exposures, and to discuss anticipatory guidance, which varies based upon age, specific food allergen, and circumstances specific to each family (Table 16.1). In addition, repeat skin prick or serum food-specific IgE testing should be performed over time to help determine prognosis and identify those children who will naturally develop oral tolerance.

This chapter discusses specific aspects that can help predict which child may develop tolerance to their food allergen over time. Most of the research surrounding this topic has been conducted for a few specific highly allergenic foods including peanut, milk, and egg, but general concepts can be applied to children with other food allergies.

Case Study

A 9-month-old boy developed facial hives and two episodes of emesis after eating scrambled egg for the first time. Symptoms resolved without any treatment. Follow-up skin prick testing 2 months later revealed a 10-mm wheal to egg and his family was instructed on avoidance measures. He returns for follow-up evaluation at 24 months of age. Parents report successful avoidance of any egg-containing foods, and he has not had reactions suggestive for food allergy to any other foods. At this visit, parents inquire about ongoing

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Table 16.1 Food allergy discussion topics at annual physician visits

Age	Topic
All	Accidental ingestion or reactions since last visit Prior test results and consideration for repeat testing Challenges in management, including exclusion from social interactions, reading labels, dining out at restaurants Signs/symptoms of an allergic reaction Indications for using epinephrine Proper epinephrine auto-injector technique with hands-on-practice through a training device Misconceptions surrounding epinephrine Update written food allergy/anaphylaxis treatment plan
Infant/ toddler	Allergen exposure in the home Normal development/exploration of environment with mouths Discussion points with caregivers, babysitters, family members Comorbid conditions such as atopic dermatitis
School age	Management in the classroom and cafeteria Preparation for new school year, teachers, nurses Classroom celebrations with food School bus, field trips
Teenagers	Self-carry of epinephrine Peer pressure, communication with friends and significant others Common occurrence and risks of not having epinephrine available at all times Practice scenarios involving dining out, dating, alcohol Preparation for transition to independent living

avoidance of all egg products, or if they can try to introduce baked egg into his diet. They also have questions about repeat skin prick testing and if he will ever be able to eat egg without having a reaction.

- What is the best advice regarding baked egg in a child with egg allergy?
- What is the natural history of egg allergy in the majority of children?

Differences Between Food Allergens

While any food can potentially cause an IgE-mediated food allergy, the eight most common allergenic foods (cow's milk, hen's egg, soy, wheat, peanut, tree nut, finfish, and shellfish) account for more than 90% of all reactions. Food allergies can be transient for many children, particularly to milk, egg, wheat, and soy [2]. Approximately 85% of children with these food allergies will naturally develop oral tolerance, often by school age. Recent research has demonstrated that egg and milk allergies may be more persistent than previously believed, and some children are not developing tolerance until adolescence [3]. Additionally, milk seems to persist into adolescence and adulthood frequently and is reported to be the second most common food allergy among both children and adults [4]. Unfortunately, only about 20% of children with peanut, tree nut, or seafood allergy will develop tolerance with age [3]. There are limited, if any, data surrounding most other foods, or adults who develop food allergies later in life. Thus, the prognosis for a child diagnosed with allergies to foods including seeds, fruits, vegetables, grains, poultry, and red meat remains largely unknown.

Factors Associated with Prognosis

While it is generally accepted that milk, egg, wheat, and soy allergies are the most likely to be transient, and peanut, tree nut, fish, and shellfish allergies are more likely to remain lifelong, the ability to predict which child may or may not develop tolerance remains challenging. In general, children with a history of severe early-onset atopic dermatitis, multiple food allergies, and severe anaphylactic reactions to their food allergen are most likely to have persistent food allergies [2]. At the time of initial food allergy diagnosis, it is important to discuss prognosis with every family. Thus, an understanding of how

the natural history differs by food allergen and factors associated with development of tolerance is useful. Physicians should anticipate questions from families regarding long-term prognosis, future need for repeat testing, and the manner of determining whether tolerance has occurred.

The specific size of initial skin prick and serum food-specific IgE testing that predicts future tolerance have not been established for any food allergen. However, in general, when the initial IgE test result is very elevated, this suggests that it is less likely for tolerance to develop over time. Ongoing assessment is useful to detect trends in IgE levels. For milk, egg, peanut, and tree nuts, skin prick wheal diameter >15 mm and/or serum IgE >25 kU/L suggests persistent allergy. Conversely, some children only demonstrate mild elevations in IgE testing, regardless of the severity of their reaction, and maintain persistent food allergy for years. As discussed in the section regarding food allergy diagnosis, the clinical history is the most important "test" to consider and can also help guide discussion regarding the potential for developing tolerance. Children who experience severe reactions (respiratory distress, anaphylaxis, need for epinephrine) are less likely to develop tolerance in the future compared with those who have mild symptoms such as skin rash or who have never experienced a clinical reaction but were diagnosed through testing alone.

The monitoring of serum IgE testing over time is more indicative of prognosis and future tolerance compared with skin prick testing [3]. Several studies have evaluated the usefulness of comparing food-specific IgE levels with prior test results to determine suitability for reintroduction. It merits mention that the research studies evaluating this concept vary widely according to population, methodology, cutoff points, and use of oral food challenges. In an ideal research setting, every child with food allergy would be followed longitudinally and undergo a supervised oral food challenge at specific intervals as they age along with skin prick and serum food-specific IgE testing at the time of challenge. This is the best way to not only determine prognosis and acquisition of tolerance, but to develop predictive cutoff values that may offer benefit on a population level. Unfortunately, this approach is not feasible for many reasons.

The HealthNuts study, a large prospective longitudinal cohort of thousands of food-allergic children in Australia, offers one of the best attempts at this approach and has revealed useful information about the natural history of peanut, egg, and milk allergy [5]. HealthNuts researchers evaluated patients longitudinally through serial IgE measurements and oral food challenges. Among 1-year-old infants with challenge-confirmed peanut allergy (n = 156) enrolled in this cohort, 103 underwent repeat oral challenge and IgE measurements at 4 years of age [6]. They found that peanut allergy resolved in 22% of children by age four and a decreasing wheal size on skin testing predicted tolerance, whereas an increasing wheal size predicted unsuccessful challenge on persistent allergy. Thresholds for 95% positive predictive value (PPV) of peanut allergy at 1-year of age were a ≥13 mm wheal and serum IgE ≥5 kU/L. At 4 years of age, these 95% PPV thresholds were wheal size ≥8 mm and serum IgE ≥2.1 kU/L.

The HealthNuts researchers took a similar approach for children with egg allergy (n = 140) who were challenged at both 1 and 2 years of age [7]. They found that egg allergy resolved in 47% of children by 2 years of age. Interestingly, the development of tolerance varied according to the ability to ingest baked egg, which will be discussed later in this chapter. At 1 year of age, infants with a skin prick wheal size ≥4 mm or serum IgE ≥1.7 kU/L were more likely to have persistent egg allergy at age 2.

A large research network in the United States employed a similar approach in determining the natural history of milk and egg allergy [8, 9]. The Consortium of Food Allergy Research enrolled 293 children with milk allergy between 3 and 15 months of age and followed them longitudinally. In this cohort, milk allergy resolved in 53% of participants at a median age of 63 months. Smaller skin prick (<5 mm compared with ≥10 mm) and serum IgE (<2 kU/L compared

with ≥10 kU/L) milk levels at baseline were associated with higher likelihood for developing tolerance. Among infants enrolled with egg allergy ($n = 213$), 49% experienced resolution at a median age of 72 months. Similar to milk, smaller skin prick (<5 mm compared with ≥10 mm) and serum IgE (<2 kU/L compared with ≥10 kU/L) egg levels at baseline were associated with higher likelihood for developing tolerance.

Diagnostic Testing

The most commonly used and widely available food-specific IgE tests use commercial extracts that contain combinations of multiple proteins within each food. However, not all proteins are associated with the same risk for clinical food allergy reaction. Both over diagnosis and misdiagnosis of food allergies occur based upon IgE testing alone, particularly through the use of widely marketed food allergy panel testing, which includes various numbers of unrelated foods which can be analyzed through one blood sample [10]. Newer component testing can isolate the specific protein that IgE is directed towards and is available for a few specific foods. The most widespread example of component testing is for peanut. Patients who have IgE directed towards the proteins Ara h 1, 2, or 3 are at highest risk for clinical allergy compared with those who are sensitized towards Ara h 8, which represents cross-sensitization with birch tree pollen [11]. As component testing becomes more widely available for peanut and other foods, these tests must be used and interpreted in the proper context [12]. For instance, it is not useful to obtain peanut component testing on a patient who has already had clear anaphylaxis from peanut ingestion as the component test will not predict future tolerance or severity of future reactions. Most importantly, component testing should not be routinely obtained in the diagnosis or follow-up of food allergy. Use of these tests warrants careful consideration of their cost, limitations, performance characteristics, differing results in various populations, and always must be interpreted in the proper clinical context.

The proteins in cow's milk and egg offer two examples of how testing beyond the routine commercial testing reagents may offer insight into prognosis. Markers for persistent cow's milk allergy include children with higher IgE binding towards casein as compared with whey [13]. Markers for persistent egg allergy include children with higher IgE towards ovomucoid compared with egg white, egg yolk, ovalbumin, and lysozyme [14]. In addition, patients may react to three-dimensional conformational epitopes, whereas others react to linear segments which are much more resistant to degradation through cooking or food production. It is well established that egg and milk allergic children may only react to conformational epitopes, which can be destroyed through extensive heating [15]. Recent research conducted in infants with peanut allergy found that those with persistent allergy developed specific IgE towards linear epitopes, as opposed to conformational epitopes [16]. At this time, there are no commercially available tests to distinguish conformational versus linear epitopes, but this concept is important to understand for future applications and individualized management options.

Can the Natural Development of Oral Tolerance Be More Rapidly Acquired?

Other chapters in this textbook address the use of immunotherapy to assist the development of tolerance to food allergens. However, the question that many parents and researchers have asked is: Can we help a child who will naturally develop tolerance to a food allergen achieve this more rapidly? The alternate question that may be asked is: Are there factors that may slow the development of tolerance? To answer the second question, there do not appear to be any factors that will hasten natural resolution. As discussed at the end of this chapter, oral food challenges are the best predictors for resolution of food allergy. However, not all food challenges are successful and may induce reactions in children with ongoing allergy. Fortunately, there is no evidence that unsuccessful food challenges, or reactions to foods through accidental ingestion, will cause someone to "hold onto" their food allergy any

longer than they would through strict avoidance. This is useful information to share with parents who may be concerned that they harmed their child through a supervised challenge or accidental exposure at some point. One study demonstrated that the mean age of reported outgrown food allergy is 5.4 years old and children that experienced earlier allergy onset were more likely to report developing food allergy tolerance compared to later onset [17]. While it is discouraged to counsel patients they have a "mild" allergy due to concern they will not follow stringent avoidance measures, patients with a milder phenotype exist [11]. These are likely the same patients that have transient IgE-mediated food allergies and naturally develop oral tolerance over time. Given our limitations in reliably identifying these individuals at this time, we are relegated to offer the same management strategies of strict avoidance for anyone with a diagnosis of IgE-mediated food allergy. However, as our understanding of mechanisms involved in the pathogenesis and manifestations of food allergy continues to evolve, a more individualized approach to management may be applicable in the near future.

Baked Milk and Baked Egg

Milk and egg allergies are two of the most common IgE-mediated food allergies in young children. Dietary avoidance can be challenging given the ubiquitous nature of these food proteins as ingredients in a wide variety of products. As discussed previously, the natural history of milk and egg allergy is favorable with most patients developing oral tolerance by later in childhood. However, the ability to incorporate these foods into the diet in some form has many positive advantages.

Interestingly, approximately 70% of children with milk and egg allergies can tolerate these proteins in the baked, or extensively heated, form [18]. As introduced earlier, some food allergies are caused by three-dimensional conformational epitopes as opposed to linear structures. These conformational epitopes are subject to degradation through heating. This change in conformation alters the recognition by the immune system and in many cases no longer causes an IgE-mediated reaction. It is recommended that only foods cooked at high enough temperatures, such as 350 degrees Fahrenheit, in an oven for 30 minutes be considered safe for ingestion. Stove top preparation, boiling, or frying has not been demonstrated to sufficiently heat or denature these proteins. In addition, the interactions with other ingredients involved in the food matrix that constitutes a food product appears to be of significance, thus boiling milk alone is not likely enough to denature the proteins rendering it safe for consumption.

The predominant protein in egg allergy is ovalbumin, which is a heat-labile conformational epitope. The other major allergen is ovomucoid, which is a heat-resistant linear epitope. Similarly, whey proteins in cow's milk allergy are heat labile whereas casein is heat resistant. Interestingly, the level of specific IgE towards these specific proteins may predict which child is more likely to have persistent allergy but have not been shown to be as reliable at predicting which child may tolerate baked milk (Table 16.2) or baked egg (Table 16.3).

Table 16.2 Predictors of baked milk tolerance [18]

Specific IgE (kU/L) NPV	Specific IgE (kU/L) PPV	Skin prick test wheal (mm) NPV	Skin prick test wheal (mm) PPV
[19] Cow's milk <0.35, 100%	Cow's milk ≥0.35, >50%	Cow's milk <5, 100%	Cow's milk ≥15, >5 0%
[20] casein <0.35, 100% Casein 0.94, 95% Casein 4.95, 89% Cow's milk 1.21, 94% Cow's milk 9.97, 86%	Casein 20.2, 69% Cow's milk 24.5, 69%	N/A	N/A
[21] casein 0.9, >90% Cow's milk 1.0, >90%	Casein >10.3, 100% Cow's milk >20.6, 100%	Casein <9, 92% Cow's milk <7, 100% Cow's milk <13, 91%	Casein >15, 100%

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NPV negative predictive value, *PPV* positive predictive value

Table 16.3 Predictors of baked egg tolerance [18]

Specific IgE (kU/L) NPV	Specific IgE (kU/L) PPV	Skin prick test wheal (mm) NPV	Skin prick test wheal (mm) PPV
[22] OM <0.35, 10%	OM 50, 90% EW 25, 30% EW 50, 40% EW 75, >50%	N/A	EW 0, 5% EW 15, 60%
[23] EW 0.85, 96% OM 1.16, 97%	EW 30.7, 84% OM 10.8, 88%	N/A	N/A
[24] EW 2.5, 89% EW 5, 77% EW 10, 71%	EW 10, 60%	N/A	N/A
[25] N/A	N/A	N/A	OM ≥11, 100%
[26] EW 6, >90% OM 0.35, >90%	EW 9.65, 59% OM 3.38, 42%	EW <3, 100% EW <11, >90%	N/A

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NPV negative predictive value, *PPV* positive predictive value, *OM* ovomucoid, *EW* egg white

In addition, the size of skin prick wheal or serum IgE testing to egg or milk also does not reliably predict which children may tolerate in the baked form, i.e., children with very large skin test reactions may tolerate and vice versa.

Given the limited predictive capabilities of available testing and the potential for approximately 30% of children with milk or egg allergy to react upon ingestion of baked forms, there is debate as to whether it is safe to introduce at home or if it should always be done in an office setting through an oral food challenge. For children who have already eaten and tolerated baked forms, they should be encouraged to continue to expand their diet with these foods at home. Other considerations for at home versus in office introduction include the severity of prior reactions, size of IgE testing, comorbid conditions such as severe atopic dermatitis that may make interpretation of potential reaction difficult, and parental comfort. Any child with a history of anaphylaxis, respiratory or severe gastrointestinal symptoms, or underlying asthma should have baked milk or egg introduced under physician supervision in the office setting.

Once a child is tolerating baked milk or egg, parents should be instructed to maintain it in the child's diet. There are several published recipes [7] that ensure sufficient amounts of baked protein both during challenge and once at home. Store-bought baked products can be included in the diet as well, so long as milk or eggs are not the first or second ingredient listed. Parents should be counseled to continue to read labels and avoid stove top or raw forms of milk and egg to prevent reactions from occurring.

In addition to liberalizing the diet and affording additional choices for feeding children with milk and egg allergy, inclusion of baked milk and egg into the diet may offer additional benefits. Tolerance of baked milk and egg is safe and does not increase the risk of reaction for children with milk or egg allergy. In addition, studies have shown that this may accelerate development of tolerance to unheated milk and egg. Whether the inclusion of baked milk and egg acts as a form of immunotherapy or marks children who are "less allergic" to begin with, this discussion should be a routine part of management of all children with milk and egg allergy [27]. Ongoing evaluation of existing milk and egg allergy should continue to occur in children who tolerated baked milk and baked egg along with the same provisions for repeat testing and consideration for supervised oral food challenge to determine future tolerance.

Case Study

A 12-month-old boy develops rapid onset emesis and generalized hives after ingestion of yogurt. Skin prick testing 1 month later reveals an 11-mm wheal diameter. The family is counseled regarding milk avoidance and he does well

without any accidental ingestion or subsequent reactions. Follow-up skin prick testing at 2, 3, and 4 years of age reveals a slightly declining wheal diameter of 9 mm, 8 mm, and then 6 mm. He is now 5 years old and parents would like to clarify his milk allergy diagnosis prior to starting kindergarten.

- What other tests can be considered to help determine his need to continue milk avoidance?

Long-Term Follow-Up

Every child who is diagnosed with IgE-mediated food allergies should have at least annual follow-up visits to discuss food allergen avoidance, challenges with management, and to repeat testing (Table 16.1). There are no well-established guidelines regarding the use of repeat skin prick or serum IgE tests in patients who have established food allergy but it is important to consider the utility and limitations of both types of tests. In general, the trends of IgE values over time are useful in predicting the likelihood that allergy may be dissipating. If skin prick and/or serum IgE levels increase over time, this indicates persistent allergy. If these levels decrease over time, or if they are relatively low at baseline and remain low with increasing age, this indicates possible tolerance.

As discussed previously in this book, neither skin prick or serum IgE tests by themselves are diagnostic for food allergy. Neither test result can predict the severity of future reactions. Both tests are associated with high rates of falsely elevated results and must be used and interpreted with caution and in the proper clinical context. The availability and use of each test will vary by physician, access to allergists, and parental preference. The positive and negative predictive values for skin prick and serum IgE tests have not been well established other than for the most highly allergenic foods and also vary significantly by food. Most clinicians who manage food allergy use established 95% PPV cutoffs to determine not only the likelihood of a food allergy being present at the time of diagnosis, but also whether tolerance may be possible over time (Table 16.4) [28, 38]. Unfortunately, cutoff values have only been established for a few select foods. A general approach to long-term monitoring of children with food allergy is highlighted in Fig. 16.1.

Table 16.4 Predictive values of IgE testing [28–36]

	>95% PPV		~50% NPV	
Food	Serum IgE	Skin prick (mm)	Serum IgE	Skin prick (mm)
Egg white	≥7	≥7	≤2	≤3
	≥2 if age <2 years old			
Cow's milk	≥15	≥8	≤2	
	≥5 if age <1 years old			
Peanut	≥14	≥8	≤2 = prior reaction	≤3
			≤5 = no prior reaction	
Fish	≥20			

Reprinted from Sampson et al. [37], with permission from Elsevier [28]
PPV positive predictive value, *NPV* negative predictive value

There are several nuances to the data surrounding cutoffs that must be appreciated prior to application in clinical practice [39]. Previous studies have significant limitations in methodology including lack of food challenges to confirm diagnosis, retrospective application of cutoff levels, and variances in study population, age of participants, and length of time between follow-up visits. In addition, the diagnostic cutoffs were established in children of different ages, and clinical applicability will vary by age. Studies investigating PPV and NPV of skin prick and serum IgE testing to peanut, egg, and milk found variable results or no correlation of test results with the development of tolerance. Most studies reliably determined the persistence of allergy to these foods through higher skin prick/serum IgE values but could not reliably identify cutoff values that demonstrated tolerance. Ultimately, this circles back to the need for longitudinal studies that incorporate serial food challenges and skin prick/serum IgE testing at various ages. In the meantime, skin prick and serum IgE tests can be utilized to determine trends over time and

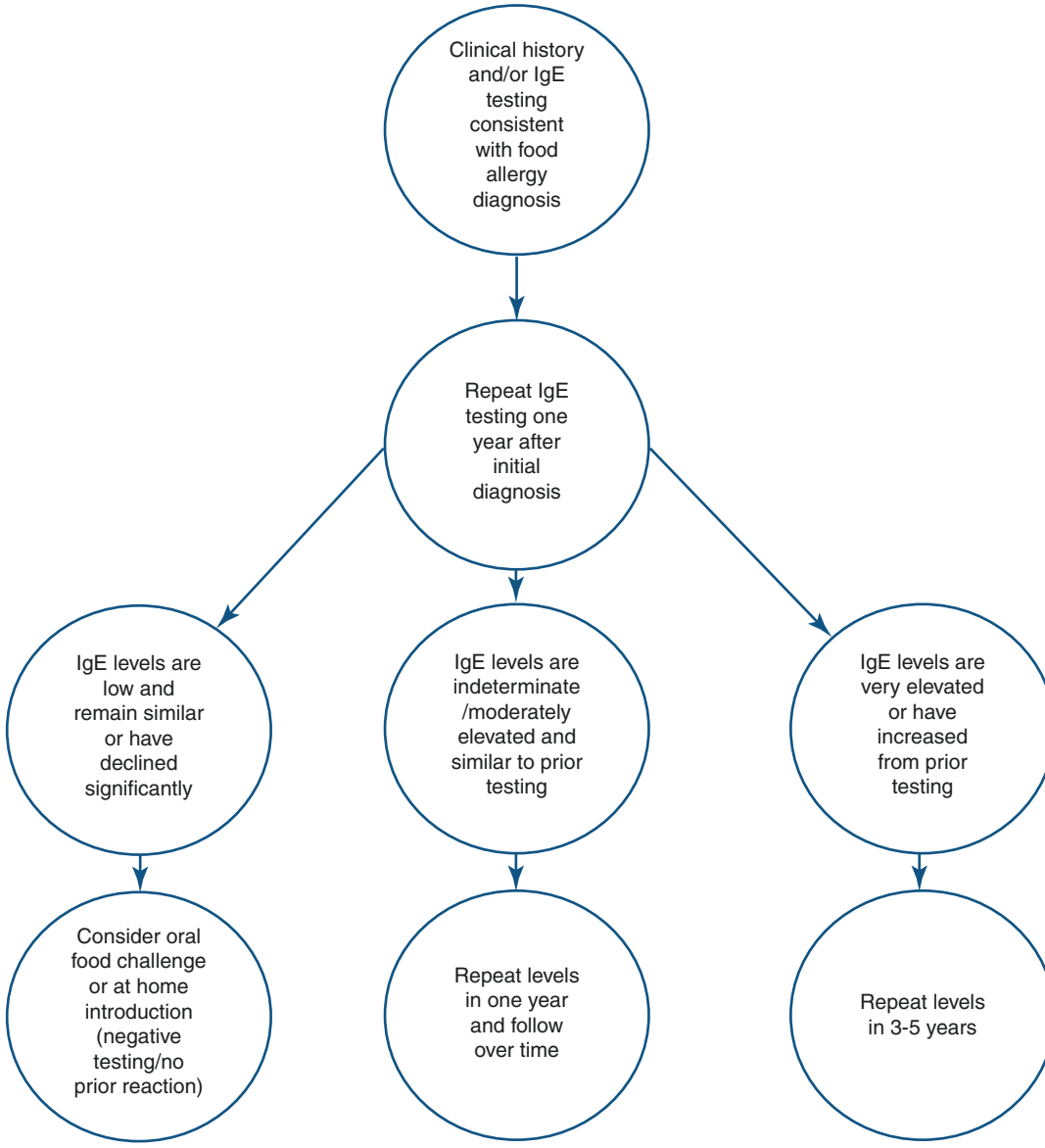

Fig. 16.1 Approach to long-term follow-up and repeat IgE testing

patients with decreasing values should be considered the best candidates to develop tolerance with age.

Oral Food Challenges

The only manner to truly determine if oral tolerance has developed is through ingestion of the food. For children who have had prior clinical reactions and/or IgE testing that highly suggests likelihood for clinical reaction, reintroduction of the food is safest through a physician-supervised oral challenge. During this procedure, small amounts of the food are ingested with gradual increases in the amount given until a cumulative dose of 6–10 grams (or 1–2 servings) are eaten. Medical supervision is important in case signs or symptoms of an allergic reaction occur. Physicians who administer oral food challenges must be versed in the recognition

and treatment of anaphylaxis, have resuscitation equipment immediately available in their office including epinephrine, and should obtain informed written consent from families prior to administration of the first dose.

Reasons to consider an oral food challenge include determining if a prior food allergy has resolved, as suggested by reassuring and declining repeat IgE testing over time. Oral food challenges are useful at the time of initial diagnosis as well, particularly when the clinical history and/or IgE test results are indeterminate. At times, patients who are likely to react with ingestion may still wish to undergo an oral food challenge. An example is an adolescent who has not ingested or reacted to a food for years but desires to better understand if they are still allergic or what signs/symptoms may occur during a reaction.

In clinical practice, most oral food challenges are open with both the patient and provider knowing what food is being ingested. This is the easiest method for conducting a challenge. The potential downside for the open challenge is the development of subjective symptoms in a patient who is very anxious. Children and families should be counseled ahead of time that anxiety is a normal and expected occurrence during oral food challenges, as well as what to expect during the challenge. Blinded challenges mask the food being ingested so the patient is not aware of what they are ingesting. If symptoms occur after ingestion of a placebo dose, this can assist the patient and family in better understanding the role that anxiety is contributing to their suspected reactions. Double-blind oral food challenges are considered the gold standard but are often limited to research studies due to the technical demands of preparation and lack of necessity for the majority of patients.

Consideration of whom and when to perform an oral food challenge varies, and conversations should be individualized. See Table 16.5 for talking points to consider in this discussion with patients and their families. There are many benefits to oral food challenges. If no symptoms occur, then the patient can incorporate the food back into their diet and no longer needs to follow strict avoidance measures. Even when symptoms occur, including anaphylaxis and the need for epinephrine, patients and families benefit by increasing their understanding of how a reaction will present, observing how rapidly symptoms improve with proper treatment, and confirming that they need to continue ongoing avoidance of that food. When done properly under medical supervision with small starting doses and gradual escalation, the oral food challenge is a safe and beneficial procedure to consider and is the gold standard method to determine the development of oral tolerance.

Table 16.5 Discussion points to determine readiness for an oral food challenge

How severe was the prior reaction?
How long has it been since the last reaction?
Has there been accidental ingestion and if so, what happened?
What do the most recent IgE results predict?
Is the patient interested and/or willing to ingest the food and incorporate it into their diet?
Does the family have significant anxiety or decreased quality of life due to food avoidance?
How much of a burden is it to avoid the food(s)?
What are the patient/family reasons for wanting or not wanting to pursue an oral food challenge?

Summary

IgE-mediated food allergies have a heterogeneous clinical presentation, severity, and prognosis. The majority of children with milk, egg, wheat, and soy allergies are expected to develop oral tolerance as they age, whereas those with peanut, tree nut, and seafood allergies are more likely to have persistent allergies. Unfortunately, our ability to accurately predict which children with existing food allergy have developed tolerance is limited by current research and imperfect performance characteristics of IgE testing. Each child who has been diagnosed with food allergy should be monitored longitudinally with repeat IgE testing and consideration of an oral food challenge when results indicate that their food allergy may no longer be present. An informed and comprehensive approach can assist families in better understanding their child's food allergy, prognosis, and ongoing management.

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