Curr Allergy Asthma Rep (2011) 11:465–472
DOI 10.1007/s11882-011-0219-2

PEDIATRIC ALLERGY AND IMMUNOLOGY (JAY M. PORTNOY AND CHRISTINA E. CIACCIO, SECTION EDITORS)

Oral Food Challenges in Children: Review and Future Perspectives

Matthew Greenhawt

Published online: 8 September 2011

Abstract Food allergy is a lifelong condition with no known treatment or cure. Allergy tests such as skin tests and blood tests are not always accurate when positive and are not necessarily diagnostic of a food allergy. A food allergy takes into consideration both the history of exposure and the testing. The food challenge is considered the diagnostic gold standard for food allergy. However, recent evidence suggests that not enough challenges are being performed. Several techniques exist with which clinicians can challenge patients. Providers who perform challenges should be familiar with assessing signs and symptoms of a potential reaction and must be prepared to treat anaphylaxis. The magnitude of the serum and skin tests may be of assistance in stratifying a patient's risk of passing a challenge, and newer diagnostic tests may help better stratify such risk of based on particular epitope recognition.

Keywords Food allergy · Oral food challenge · Children · Pediatric · DPBCFC · Single-blinded challenge · Open challenge · Allergy diagnosis · ImmunoCAP · Diagnostic cutoff points · Anaphylaxis · Component resolved diagnostic testing

M. Greenhawt (✉)
Division of Allergy and Clinical Immunology,
The University of Michigan Food Allergy Center,
24 Frank Lloyd Wright Drive, Lobby H 2100, Box 442,
Ann Arbor, MI 48106, USA
e-mail: mgreenha@med.umich.edu

M. Greenhawt
The University of Michigan Health System,
24 Frank Lloyd Wright Drive, Lobby H 2100, Box 442,
Ann Arbor, MI 48106, USA

Introduction

Food allergy is a lifelong condition that has no known cure and no known present treatment [1••]. Food allergy can decrease a family's quality of life and lead to anxiety, stress, and depression [2]. Fatalities from food allergy occur at a frequency of about 150 per year, and disproportionately so among teens and young adults [3–5]. Using all the diagnostic tools at one's disposal to make the correct diagnosis is essential. The oral food challenge is perhaps the most useful of all such tools.

While the literature suggests an "epidemic" of food allergy is occurring in US society, a great deal of misunderstanding of food allergy still exists among the unaffected [6]. This has involved bullying, public displays of insensitivity, as well as frank declarations of "hysteria" by members of the media and academic community [7–9]. This creates an incredible onus to make the proper diagnosis. This review focuses on oral food challenges, their role in enhancing the accuracy of food allergy diagnosis, and how allergy tests can be used to enhance the provider's ability to perform a challenge.

How Is Food Allergy Defined?

A food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food through an IgE- or non-IgE–mediated mechanism (per the most current National Institute of Allergy and Infectious Diseases definition) [1••]. Distinguishing sensitization from clinical allergy is difficult and often not well-understood. Sensitization refers to the body's ability to make detectable specific IgE against a food protein in vivo or in vitro. Sensitization is reflected

by positive serum (eg, ImmunoCAP; Phadia AB, Uppsala, Sweden) or skin tests but is not pathognomonic for allergy [10]. Allergy is defined by a clear history of reaction with typical symptoms (eg, urticaria, wheezing, angioedema) in the context/setting of a relative sensitization. Thus, the clinical context under which allergy tests are run and interpreted must be carefully considered.

Allergy tests are highly sensitive but often nonspecific, meaning that false-positive rates are high [10]. This lack of precision is why allergy tests are not performed for widespread population screening but rather in response to a particular event or history of symptoms. In fact, many individuals make specific IgE against food that carries no clinical relevance. Unfortunately, many providers may not necessarily understand the limitations of interpreting allergy tests, and may perform indiscriminate food allergen testing without good indication. Such practice yields misleading results that if taken too literally can lead to the practice of widespread elimination diets. Nutritional deficiencies have been documented in children subjected to such diets [11]. Newer molecular level tests, called *component resolved diagnostics*, may offer future insight through targeting specific epitope recognition of cross-reactive moieties that may help explain why some recognition is asymptomatic [12••].

The Food Challenge

In 1976, May [13] described a challenge of 38 asthmatics with suspected food hypersensitivity through use of graduated doses of food or placebo, establishing the double-blind, placebo-controlled food challenge (DBPCFC) as the gold standard for diagnosing food allergy. This procedure allows for objectively observed challenge to definitively prove or disprove tolerance. Although the May [13] study was hospital based, challenge has evolved into an office-based procedure with less labor-/time-intensive technique variations (single-blinded and open challenges) that are more practical to perform within the clinic setting [14•].

Choosing the Type of Challenge

Although DBPCFC provides the most objective evaluation, it may be impractical for the busy office setting [14•]. Several staff are required to maintain blinding, and this can be a labor intensive process. DBPCFCs require a vehicle to disguise the food item which also serves as the placebo. Use of capsules as a vehicle has fallen out of favor except for limited use in dye/additive challenge. Capsules prolong digestion time, require use of dehydrated or powdered foods, and limit assessment for oral symptoms given that digestion of the capsule starts in the stomach [14•]. Proper masking vehicles must be carefully prepared to ensure that the food is truly camouflaged. Vehicle choice recommendations are nicely summarized elsewhere [14•]. One additional limitation of the DPBCFC to consider is timing. Essentially, three challenges are necessary: the placebo challenge, the active challenge, and the observed open feeding. Although some centers will perform active and placebo challenges in different sessions on the same day, other centers prefer to space these out by several days.

Single-blinded challenges offer the compromise of objectivity by using placebo with the logistical simplicity of the provider being aware. Single-blinded challenges are very useful with suggestive or anxious patients, in whom subjective symptoms are a concern. However, provider bias could influence the results. Similar considerations for use of the food vehicle and timing exist with single-blinded challenges, as described above. Dosing graduations used are identical to those of the DBPCFC [15].

Open challenges do not use a placebo, which can lead to subjective symptom development and a biased procedure. This may necessitate a subsequent blinded challenge. However, a clearly negative open challenge is generally confirmatory, and in certain cases, a clearly positive challenge may be as well. The benefits of the open challenge are that no complex food preparation is required, and that it is logistically easy for office medical staff to perform. Feeding is still generally done in graduated intervals but could be accomplished as a single step under the right clinical circumstances [15].

The recent American Academy of Allergy Asthma and Immunology Work Group report on oral food challenge and the recent National Institutes of Health/National Institute of Allergy and Infectious Diseases food allergy guidelines have fostered more acceptance of open and single-blinded challenges. Although the DPBCFC is still the diagnostic gold standard and the most preferred technique (especially in the research setting), experts have acknowledged the high utility of the alternative techniques as acceptable methods given the logistical difficulty of performing the DBPCFC in the office setting [14•, 15]. The type of challenge must be carefully considered and matched to the type of allergen, the patient's age and emotional demeanor, staff comfort/expertise, location considerations, and the underlying clinical context of the suspected allergy. Irrespective of the setting or type of challenge, staff should be prepared to treat and manage a potentially life-threatening anaphylactic event. If necessary, emergency medical services should be on standby to respond.

Selection of Challenge Candidates Using Diagnostic Decision Points

Challenge candidates are chosen after considering both the clinical history and allergy testing as part of a basic allergy

evaluation. Serum tests have evolved from the radioallergosorbent test, which was replaced in the late-1980s with fluorescent enzyme-based systems allowing more sensitive, quantified, accurate binding on a solid-phase cellulose assay without radioactivity [10, 16, 17]. This is sold as the ImmunoCAP system. Siemens (IMMULITE 2000; Deerfield, IL) and HYCOR Biomedical (Turbo RAST; Garden Grove, CA) sell fluorescent immunoassays as well [10]. Researchers using the ImmunoCAP system have been able to determine 95% positive predictive values (PPVs) for the likelihood of passing or failing a challenge based on the quantity of a particular food-specific IgE, called *diagnostic cutoff values*. These are generated by comparing the ratio of true to false-positive tests based on challenge outcomes and have best been established for milk, egg, and peanut. Less reliable levels exist for fish, wheat, soy, and tree nut [18, 19]. Similar cutoff points have been generated for skin tests based on millimeters of wheal [20]. Thus, these measures can be used to screen out candidates with the highest probability or expectation to react upon challenge. However, caution is warranted. The established serum cutoff levels only apply to the ImmunoCAP platform, not the Siemens or HYCOR platforms. Siemens and HYCOR reporting levels may appear similar to ImmunoCAP but are not equivalent [1••, 19, 21]. Very recently, one single-center study suggested that although IMMULITE levels are different, the IMMULITE values correlated with ImmunoCAP levels in predicting peanut and milk candidates who failed the challenge [22]. Importantly, cutoff values only predict the probability of passing a challenge, not the severity of the reaction that may ensue. No such measure exists that can predict severity [1••, 10, 14•, 19, 23].

Practical Points About the Use of Decision Points in Food Challenge

Understanding the research that established the ImmunoCAP and skin test levels as a diagnostic aid is crucial to using them properly as such. The studies by Sampson and Ho [18] in 1997 and by Sampson [19] in 2001 involved children referred to a university center for atopic dermatitis and suspected food allergy, who underwent DPBCFC. However, aspects of these studies may limit the application of these values. Foremost, the cutoff values may not apply to patients without a history of reaction (eg, those who are only sensitized) [19]. In the 2001 study, the author notes that many patients in excess of the 1997 cutoffs refused challenge, which prevented firm validation of the previously established decision points. Plausibly, some of them may have passed, which may have affected the predictive values. The perceived prevalence of food allergy used in the study was adjusted to 10%, which is higher than recent estimates, and the high prevalence of subjects with atopic dermatitis in the reference population may have been unique to the study center and not necessarily reflect the characteristics of the general food allergy population [6, 18, 19]. Subsequent studies have shown international differences in the cutoff points, which suggest that cutoffs may be regionally or institutionally dependent [24, 25, 26]. Children younger than 2 years of age have smaller cutoff points that still indicate significant allergy, and levels are adjusted for age [20, 27, 28].

Interestingly, few studies have focused on levels indicative of when one should consider challenge. As opposed to when challenge would be prohibitive Perry et al. [28] described 50% predictive levels of 2 kUA/L for milk-, egg-, and peanut-allergic patients with a convincing history (5 kUA/L if the peanut reactivity was unclear). Their reference population was similar to that of Sampson, and the use of open challenges may have been attributable to some false-positive challenges [28]. However, this study highlights the full scope of how one can utilize testing results to help guide decision making.

How to Perform an Oral Food Challenge

Screening Protocol and Practical Considerations

It is crucial to select an appropriate patient/family. Considerations in whom to offer a challenge include the child's verbal ability; the date of the patient's last reaction; the anticipated effect on the patient's quality of life (in someone unlikely to eat a food again despite passing a challenge, is it worth performing); and, most importantly, what were the reported symptoms of reaction (subjective or objective, IgE mediated or atypical). These will all influence challenge type [14•, 15, 29].

The procedure should be reviewed with the family in advance of arrival, and one should verify that the patient is not ill within 24 to 48 h of the challenge to avoid confounding factors. A starting dose should be determined in advance, as should a designated set of "stop" versus "continue-on" criteria (eg, how to proceed in the event of subjective or atypical symptoms). An algorithm for which medication should be used to treat specific symptoms should be created. Emergency medications and resuscitation equipment must be on hand (eg, "crash cart"), and doses of epinephrine and antihistamine must be prepared ahead of time. For consistency, a single person should be tasked with assessing and recording symptoms. A dedicated room is needed for 4 to 6 h. It is recommended to provide entertainment (eg, books, games, DVDs) for children to help pass the time. Many practices also elect to obtain informed consent for the challenge procedure [14•].

Specific Protocols

General target dose recommendations are 8 to 10 g of protein for dry foods, 16 to 20 g for meats, and 100 mL for wet food [14•, 30]. Graduated measuring devices and/or scales are strongly recommended to ensure precision. Items should be prepared and doses measured in advance of the patient's arrival. Patients should be tolerant of any vehicle being used. It is advisable to pretest any vehicle used to mask the taste of the food to ensure that it can do so effectively [30].

Increments of food are given every 15 to 20 min until the cumulative target dose is met. The choice of a starting dose is somewhat complex. These range from 0.1% to 1% of the target dose, but no official guidelines exist for the quantity of each increment (eg, double vs logarithmic) [14•, 30]. The recommended starting dose may be lower in certain countries than what is customarily used in the United States, such as those proposed by the European Academy of Allergy and Clinical Immunology [31]. However, the choice of the starting dose may be a more patient-specific factor after the history of past reaction threshold is considered.

Factors associated with higher risk challenges include the following: experiencing a reaction within the past year, a past history of anaphylaxis to the food, sensitization in excess of the diagnostic cutoffs, asthma, allergy to peanut/tree nut/seed/seafood, and use of a β-blocker. Factors associated with lower risk challenges include the following: a history of recently tolerated ingestion, foods not typically associated with anaphylaxis (eg, dyes, meats, vegetables), favorable sensitization levels, and challenge for a history of symptoms not typical of an allergic reaction (eg, fatigue, headache, indigestion) [14•].

What Is on the Horizon for Food Allergy Diagnosis, and How Can Challenge Be an Aid?

"Just Do It!": Open and Single-Blind Challenges Are Acceptable Alternatives

Both the 2009 American Academy of Allergy Asthma and Immunology Work Group report and the 2010 National Institutes of Health/National Institute of Allergy and Infectious Diseases food allergy guidelines recommend open and single-blinded challenges as acceptable alternatives to the DBPCFC [1••, 14•]. The Work Group report, as addressed previously, was instrumental in forwarding the opinion that the DBPCFC is not the only viable option. Although many in practice had already embraced this, such acceptance was not previously reflected in the literature [10, 15, 23, 29, 30]. The report does specify that the DBPCFC is still preferred in certain circumstances (eg, research, or when subjective symptoms are present). Similarly, guideline 11, section 4.2.2.8. of the National Institutes of Health/National Institute of Allergy and Infectious Diseases guidelines echoes these sentiments [14•, 21].

Thus, the consensus expert opinion states that food challenge is of high importance in the diagnosis of food allergy and highlights that open and single-blind challenges are acceptable alternatives to DBPCFC. Even if limited to use as a confirmatory measure of tolerance, these types of challenges are invaluable options to academic and nonacademic providers that can be easily performed in the office [1]. A more direct and far less labor-intensive technique should create an appealing opportunity to increase the number of providers willing to conduct challenges. More food challenges need to be conducted, a shortcoming acknowledged by the field's experts.

How Good Is Our Literature, and How Can We Improve Upon It?

In parallel with the National Institutes of Health/National Institute of Allergy and Infectious Diseases food allergy guideline development, a meta-analysis was commissioned to evaluate the current state of the food allergy literature. Just 72 of 12,378 literature citations met inclusion criteria. After reviewing more self-reported prevalence studies than studies involving food challenge, the authors determined that the evidence is unclear as to whether the prevalence of food allergies is increasing. This is in contrast to the recent Centers for Disease Control and Prevention report [6, 32•]. Similarly, neither skin prick tests nor serum food-specific IgE to food challenge showed statistical superiority for diagnosis, and the authors found that elimination diets rarely have been studied for efficacy despite their widespread use. Thus, the authors found a lack of uniformity for criteria for making a diagnosis, and that studies specifically using oral challenge were few in number, which highlights the need for use of definitive tests such as the oral food challenge [32•]. This analysis is important, as it should motivate creation of better study design to target specifically the shortcomings that the meta-analysis unearthed. The National Institute of Allergy and Infectious Diseases had separately released guidelines for food allergy study design prior to the release of these guidelines [33].

The Case of Multisensitized Patients With Atopic Dermatitis: A Shift in Paradigm?

Fleischer et al. [34••] recently undertook an important study that highlights the extreme usefulness of the oral food challenge in determining a true diagnosis in multisensitized

children practicing elimination diets. They retrospectively reviewed 125 such children, the majority of whom had atopic dermatitis (96%), and all of whom were diagnosed as food allergic by skin or serum tests. Upon completion of 364 challenges, 89% were negative despite specific food sensitization, which highlights that challenge is an essential tool to help determine the extent to which food elimination is necessary. Of note, this group excluded cases in which the values to egg, milk, or peanut exceeded the age-specific diagnostic cutoff value, as well as patients with a history of recent reaction or of a prior severe reaction. Although this may have excluded further candidates who may have proven themselves to be tolerant, this study has exceptional utility in highlighting how useful challenge can be to ascertain the correct diagnosis, and provides an excellent example of how providers should be utilizing this diagnostic modality [34••]. Furthermore, it highlights the message echoed in the National Institutes of Health/National Institute of Allergy and Infectious Diseases guidelines and elsewhere, that past overreliance upon diagnostic testing alone to determine if someone is food allergic leads to nonspecific and potentially false-positive results [35–37].

Similarly, Spergel and colleagues [38••] recently investigated the accuracy of ImmunoCAP predictive values in a large, prospective cohort of children with atopic dermatitis. This cohort was unique in that these children were unselected for food allergy. These children (n=1,065) were observed for 36 months to determine if they developed food allergy. Only 15.9% developed food allergy, which was assessed by clinical history but not confirmed with challenge [38••]. Importantly, their ImmunoCAP levels were noticeably less predictive of food allergy despite strong sensitization compared with previously published values [19].

At baseline, the established cutoff values for milk, peanut, and egg white showed a PPV for food allergy of 0.26, 0.2, and 0.1, respectively. After 36 months, these same cutoff points showed a PPV of 0.56 for milk, 0.48 for peanut, and 0.13 for egg white, which are significantly lower than previously published levels [38••]. Children with atopic dermatitis and food sensitization are often diagnosed as food allergic because test levels exceed the cutoffs—even despite questionable history of how the food affects their skin—given that most experts consider atopic dermatitis a strong risk factor for food allergy. Although this study was observational and different than that of Sampson (his population was largely suspected of having food allergy because of the atopic dermatitis, and most of his patients were challenged), they represent similar "at-risk" populations [18]. The Spergel et al. [38••] study demonstrates that decision points may not be absolute, depending on the population. This offers hope that perhaps investigators will be more willing to challenge patients to determine an outcome rather than assume what will happen based on probability.

Component Resolved Diagnostic Testing and Food Challenge Applications

Molecular diagnostic allergy testing is now commercially available for food allergens. Two products from a single testing company are available, though just one is presently US Food and Drug Administration approved. For many years, this type of clinical tool had been limited to the research setting [12••]. The utility of molecular testing is that it shows that allergen recognition can be highlighted at the epitope level, allowing isolation of the individual site at which IgE can bind. Much like separating out a bag of M&M's into its color groupings, component tests show the individual contribution of a particular epitope recognition to sensitization. Present skin/serum tests only allow for binary recognition (eg, yes or no) and do not provide any information about which component of the allergen is involved. Not all recognized parts are equally important or even clinically relevant [12••].

Component testing has shown early utility in highlighting how epitope/component recognition can predict clinical reaction phenotype through the use of oral food challenge. Two studies have independently demonstrated that recognition of Ara h 2, even at 0.35 kUA/L (the lower limit of observed quantity), had exceptionally high specificity in identifying peanut-sensitized patients who were challenge positive or who had strongly supportive clinical history of symptom development [12••, 26••, 39, 40]. Similarly, in other studies, identification of high sensitization to Ara h 8 with low sensitization to Ara h 1 to Ara h 3 was associated with lack of symptom development [40–42]. Similar patterns have been discerned for hazelnut based on epitope recognition, which is of high potential utility in birch-endemic areas [43]. For nonplant food allergy, αs1/αs2/κ-casein and ovomucoid have been identified as risk factors for individuals with persistent milk and egg allergy, respectively, in some of the earliest studies involving component testing [44, 45]. Component resolved diagnostic testing holds potential to be a highly utilized tool in refining diagnostic accuracy, better identifying candidates for challenge, and allowing for enhanced longitudinal patient tracking in much the same way that the standard ImmunoCAP assay has been used for years.

Fear and Loathing of Strong Sensitization: Have Decision Points Created Risk-Averse Allergists?

In the past decade, the rise in number of food-allergic children has been mirrored by a rise in availability of

allergy diagnostic testing [1••, 6]. It is established that there is overreliance upon serum or skin testing as a sole means of diagnosis. This point was specifically alluded to in the National Institutes of Health/National Institute of Allergy and Infectious Diseases guidelines. Many practitioners, particularly when assessing young children with atopic dermatitis, have overattributed the role of food allergy and prescribed avoidance diets as management, based on these children having multiple sensitivities. Literature supportive of this practice was commonplace in the late-1990s and early-2000s, and this was furthered with the advent of the diagnostic cutoff points [19, 37, 46, 47].

However, the concept of diagnostic decision points being able to accurately diagnose a food allergy when the patient's level is in excess of the 95th percentile predicted range may be imperfect. These levels are not necessarily absolute and by definition only define the odds of success or failure. They do not "automatically" predict the outcome. A problem arises when these levels are applied to patients with questionable history of reaction or no history of prior reaction to the particular item, or simply used as a "line in the sand" that excludes the possibility of challenge even being offered to certain patients. The practice of withholding challenge due to a high ImmunoCAP level or large skin test is not uncommon and may preclude strongly sensitized patients from definitively ascertaining (through challenge) if they truly react.

No single value can accurately predict challenge outcome consistently, much in the same way that a baseball batting average cannot accurately predict in each at-bat if the player will get a hit, or the odds in a casino game predict that the house will win with each individual hand wagered. These values may represent an overall expectation of success across a large number of similar data points but should not serve as a surrogate crystal ball to predict the outcome in any single particular situation. Given that several studies have shown discrepancies between centers and nations in the upper-limit cutoff values for certain foods, this alone is proof that the concept is good for approximate risk stratification but not precise enough to deny otherwise willing and able candidates the opportunity to undergo challenge [18, 19, 24, 25, 26••, 27, 38••].

The crux of this matter may resolve around avoiding failed challenges. A negative anticipated outcome of a challenge should not necessarily be a reason to withhold the procedure from a family that understands the risks and benefits of the procedure, is willing to consent a child, and trusts the provider could treat any symptoms that may (or may not) result. Challenge is defined by the fact that the outcome is not necessarily known. Otherwise, the procedure becomes a confirmation. Strict interpretation of these levels as fail-safe predictors may have inadvertently created a risk-averse standard of care and communicated to providers that avoiding a failed challenge is the goal. The cutoff levels then only serve to stratify patients we are most comfortable in challenging—those with the highest expectation of passing. This over-selects for cases that are confirmatory and excludes cases in which risk would be ventured and an accurate outcome actually ascertained. At some point, if patients with higher degrees of sensitization are never challenged, these values will perpetuate a management strategy that is not subjected to periodic testing and re-evaluation, and the process becomes a catch-22 situation. While most will concur that higher levels of food sensitization do correlate with higher risk of challenge failure, it is of paramount importance for more investigators to continue to conduct well-designed trials to continually re-evaluate this relationship. There is evidence that this is not a "one-level-fits-all" scenario, and that cross-reactivity can potentially overcall allergy. Component resolved diagnostics do offer some hope to enhance and redefine this relationship [26••, 40]. As well, more integrative methods are being developed that may better predict risk and expectation of food challenge than skin or blood test levels alone [48].

Conclusions

The oral food challenge is an essential tool for diagnosing food allergy. The DPBCFC remains the diagnostic gold standard, but more practical methods such as open and single-blinded challenges will allow for greater acceptance of providing this service to food-allergic patients. It is clear that we can no longer rely solely upon positive skin or serum tests to diagnose allergy, as they are imprecise and nonspecific. We are learning that prior thinking and practice pertaining to diagnostic decision points may represent an overly risk-averse strategy that may limit the ability to accurately diagnose food allergy in otherwise willing but strongly sensitized candidates. Component resolved diagnostic testing is the wave of the future in allergy testing and offers a multitude of possibilities to enhance diagnostic accuracy in early studies that use oral food challenge to test how epitope-specific recognition may be predictive of one's reaction phenotype.

Disclosure Dr. Greenhawt has served on a specialty advisory board for Phadia AB; served on speakers' bureaus for Phadia AB and Nutricia; served on a medical advisory board for Kids With Food Allergies Foundation; received grant support from the American College of Allergy, Asthma & Immunology; received honoraria from Medscape/WebMD; is supported by the National Institutes of Health Clinical and Translational Science Award grant number UL1RR024986; and received payment for development of educational presentations (including service on speakers' bureaus) from Sunovion Pharmaceuticals.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. •• Boyce JA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126(6 Suppl):S1-58. *This article is of exceptional importance as it is the most comprehensive, up-to-date peer review of food allergy and its management, from an expert panel assembled by the National Institute of Allergy and Infectious Diseases.*
2. Primeau MN et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. Clin Exp Allergy. 2000;30(8):1135–43.
3. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol. 2001;107(1):191–3.
4. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001–2006. J Allergy Clin Immunol. 2007;119(4):1016–8.
5. Yocum MW et al. Epidemiology of anaphylaxis in Olmsted County: a population-based study. J Allergy Clin Immunol. 1999;104(2 Pt 1):452–6.
6. Branum AM, Lukacs SL. Food allergy among children in the United States. Pediatrics. 2009;124(6):1549–55.
7. Christakis N. This allergies hysteria is just nuts. BMJ. 2008;337: a2880.
8. Stein J. Nut allergies: a yuppie invention. Los Angeles Times, January 9, 2009. Accessed June 20, 2011.
9. Peanut allergy stirs controversy at Florida school. Available at http://news.yahoo.com/s/nm/20110322/hl_nm/us_peanut_allergy>. Accessed April 4. 2011.
10. Bernstein IL et al. Allergy diagnostic testing: an updated practice parameter. Ann Allergy Asthma Immunol. 2008;100(3 Suppl 3): S1–S148.
11. Noimark L, Cox HE. Nutritional problems related to food allergy in childhood. Pediatr Allergy Immunol. 2008;19(2):188–95.
12. •• Shreffler WG. Microarrayed recombinant allergens for diagnostic testing. J Allergy Clin Immunol. 2011;127(4):843–9; quiz 850–1. *This is an exceptional review of a new and exciting technique that will prove to be of exceptional utility in the future diagnosis of food allergy and help explain a great deal of clinically relevant cross-reactivity.*
13. May CD. Objective clinical and laboratory studies of immediate hypersensitivity reactions to foods in asthmatic children. J Allergy Clin Immunol. 1976;58(4):500–15.
14. • Nowak-Wegrzyn A., et al. Work Group report: oral food challenge testing. J Allergy Clin Immunol. 2009;123(6 Suppl): S365-83. *This is a well-written, comprehensive review and working manual for the allergy practitioner on how to conduct oral food challenges. It is a must read*.
15. Sicherer SH. Food allergy: when and how to perform oral food challenges. Pediatr Allergy Immunol. 1999;10(4):226–34.
16. Wraith DG et al. Recognition of food-allergic patients and their allergens by the RAST technique and clinical investigation. Clin Allergy. 1979;9(1):25–36.
17. Axen R., et al. A new laboratory diagnostic system applied to allergy testing. In: Johansson SGO, editor. Clinical Workshop: IgE Antibodies and the Pharmacia CAP System in Allergy Diagnosis. Uppsala: Sweden: Pharmacia Diagnostics AB; 1988. p. 3–4.
18. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. J Allergy Clin Immunol. 1997;100 (4):444–51.
19. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol. 2001;107(5):891–6.
20. Wang J, Sampson HA. Food anaphylaxis. Clin Exp Allergy. 2007;37(5):651–60.
21. Maloney JM et al. The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. J Allergy Clin Immunol. 2008;122(1):145–51.
22. Hamilton RG, et al. Extension of food allergen specific IgE ranges from the ImmunoCAP to the IMMULITE systems. Ann Allergy Asthma Immunol. 2011.
23. Sicherer SH, Sampson HA. Food allergy. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S116–25.
24. Rance F, Abbal M, Lauwers-Cances V. Improved screening for peanut allergy by the combined use of skin prick tests and specific IgE assays. J Allergy Clin Immunol. 2002;109(6):1027–33.
25. Roberts G, Lack G. Diagnosing peanut allergy with skin prick and specific IgE testing. J Allergy Clin Immunol. 2005;115 (6):1291–6.
26. •• van Nieuwaal NH, et al. Utility of peanut-specific IgE levels in predicting the outcome of double-blind, placebo-controlled food challenges. J Allergy Clin Immunol. 2010;125(6):1391–2. *This is a very important article detailing the potential application for how Ara h 2 recognition is a highly specific factor for distinguishing truly clinically reactive peanut-allergic patients from those with more clinically irrelevant sensitization. This is a sentinel article for how new-generation component resolved diagnostic testing can be used.*
27. Komata T et al. The predictive relationship of food-specific serum IgE concentrations to challenge outcomes for egg and milk varies by patient age. J Allergy Clin Immunol. 2007;119(5):1272–4.
28. Perry TT et al. The relationship of allergen-specific IgE levels and oral food challenge outcome. J Allergy Clin Immunol. 2004;114 (1):144–9.
29. Sicherer SH, Morrow EH, Sampson HA. Dose-response in double-blind, placebo-controlled oral food challenges in children with atopic dermatitis. J Allergy Clin Immunol. 2000;105(3):582–6.
30. Mofidi S, Bock SA, editors. A health professional's guide to food challenges. Fairfax, VA. The Food Allergy & Anaphylaxis Network, 2004.
31. Bindslev-Jensen C et al. Standardization of food challenges in patients with immediate reactions to foods—position paper from the European Academy of Allergology and Clinical Immunology. Allergy. 2004;59(7):690–7.
32. • Chafen JJ, et al. Diagnosing and managing common food allergies: a systematic review. JAMA 2010;303(18):1848–56. *This is a National Institutes of Health–commisioned meta-analysis of the food allergy literature by an independent authorship group of nonfood allergists. It is an honest, critical appraisal of the strengths and weaknesses of the food allergy literature to date.*
33. Plaut M, Sawyer RT, Fenton MJ. Summary of the 2008 National Institute of Allergy and Infectious Diseases-US Food and Drug Administration Workshop on Food Allergy Clinical Trial Design. J Allergy Clin Immunol. 2009;124(4):671–678 e1.
34. •• Fleischer DM, et al. Oral food challenges in children with a diagnosis of food allergy. J Pediatr. 2011;158(4):578–83 e1. *This was an interesting and timely study highlighting the importance of challenging children with suspected food allergy and sensitization to food to prevent unnecessary elimination diets.*
35. Burks AW et al. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. J Pediatr. 1988;113(3):447–51.

36. Eigenmann PA, Calza AM. Diagnosis of IgE-mediated food allergy among Swiss children with atopic dermatitis. Pediatr Allergy Immunol. 2000;11(2):95–100.
37. Eigenmann PA et al. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. Pediatrics. 1998;101(3): E8.
38. •• Spergel JM, Bogunewicz M, et al. Specific IgE levels in a cohort of infants with atopic dermatitis do not predict the development of food allergy (abstract). Ann Allergy Asthma Immunol. 2010;105(5):A106. *This is an interesting and much overdue re-evaluation of the relationship between serum-specific IgE levels and food allergy that shows these levels to be far less predictive than originally thought.*
39. Nicolaou N et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. J Allergy Clin Immunol. 2010;125(1):191–7. e1-13.
40. Johnson K et al. Predictive value of peanut component specific IgE in a clinical population. J Allergy Clin Immunol. 2011;127(2):AB71.
41. Asarnoj A et al. IgE to peanut allergen components: relation to peanut symptoms and pollen sensitization in 8-year-olds. Allergy. 2010;65(9):1189–95.
42. Vereda A et al. Peanut allergy: clinical and immunologic differences among patients from 3 different geographic regions. J Allergy Clin Immunol. 2011;127(3):603–7.
43. De Knop KJ et al. Age-related sensitization profiles for hazelnut (Corylus avellana) in a birch-endemic region. Pediatr Allergy Immunol. 2011;22(1pt2):e139–49.
44. Jarvinen KM et al. B-cell epitopes as a screening instrument for persistent cow's milk allergy. J Allergy Clin Immunol. 2002;110 (2):293–7.
45. Jarvinen KM et al. Specificity of IgE antibodies to sequential epitopes of hen's egg ovomucoid as a marker for persistence of egg allergy. Allergy. 2007;62(7):758–65.
46. Jones SM, Burks AW. Chapter 51 in Pediatric Allergy: Principles and Practice. In: Donald YM, Leung DYM, Sampson HA, Geha RS, Szefler SJ. St. Louis, Mosby; 2003.
47. Sampson HA. The evaluation and management of food allergy in atopic dermatitis. Clin Dermatol. 2003;21(3):183–92.
48. DunnGalvin A et al. Highly accurate prediction of food challenge outcome using routinely available clinical data. J Allergy Clin Immunol. 2011;127:633–9.